

**SEPTEMBER 2014**  
**STAFF REPORT to the NIDA DIRECTOR**



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## **RESEARCH FINDINGS**

### **BASIC AND BEHAVIORAL RESEARCH**

#### **Separate GABA Afferents to Dopamine Neurons Mediate Acute Action of Opioids, Development of Tolerance, and Expression of Withdrawal**

Matsui A, Jarvie BC, Robinson BG, Hentges ST, Williams JT. *Neuron*. 2014 Jun 18; 82(6): 1346-56. doi: 10.1016/j.neuron.2014.04.030. Epub 2014 May 22.

GABA release from interneurons in VTA, projections from the nucleus accumbens (NAc), and rostromedial tegmental nucleus (RMTg) was selectively activated in rat brain slices. The inhibition induced by  $\mu$ -opioid agonists was pathway dependent. Morphine induced a 46% inhibition of IPSCs evoked from the RMTg, 18% from NAc, and IPSCs evoked from VTA interneurons were almost insensitive (11% inhibition). In vivo morphine treatment resulted in tolerance to the inhibition of RMTg, but not local interneurons or NAc, inputs. One common sign of opioid withdrawal is an increase in adenosine-dependent inhibition. IPSCs evoked from the NAc were potently inhibited by activation of presynaptic adenosine receptors, whereas IPSCs evoked from RMTg were not changed. Blockade of adenosine receptors selectively increased IPSCs evoked from the NAc during morphine withdrawal. Thus, the acute action of opioids, the development of tolerance, and the expression of withdrawal are mediated by separate GABA afferents to dopamine neurons.

#### **Chronic Cannabinoid Receptor 2 Activation Reverses Paclitaxel Neuropathy Without Tolerance or Cannabinoid Receptor 1-Dependent Withdrawal**

Deng L, Guindon J, Cornett BL, Makriyannis A, Mackie K, Hohmann AG. *Biol Psychiatry*. 2014 Apr 25. pii: S0006-3223(14)00274-1. Doi: 10.1016/j.biopsych.2014.04.009. [Epub ahead of print].

Mixed cannabinoid receptor 1 and 2 (CB<sub>1</sub> and CB<sub>2</sub>) agonists such as  $\Delta^9$ -tetrahydrocannabinol ( $\Delta^9$ -THC) can produce tolerance, physical withdrawal, and unwanted CB<sub>1</sub>-mediated central nervous system side effects. Whether repeated systemic administration of a CB<sub>2</sub>-preferring agonist engages CB<sub>1</sub> receptors or produces CB<sub>1</sub>-mediated side effects is unknown. The authors evaluated antiallodynic efficacy, possible tolerance, and cannabimimetic side effects of repeated dosing with a CB<sub>2</sub>-preferring agonist AM1710 in a model of chemotherapy-induced neuropathy produced by paclitaxel using CB<sub>1</sub>knockout (CB<sub>1</sub>KO), CB<sub>2</sub> knockout (CB<sub>2</sub>KO), and wild-type (WT) mice. Comparisons were made with the prototypic classiccannabinoid  $\Delta^9$ -THC. The authors also explored the site and possible mechanism of action of AM1710. Paclitaxel-induced mechanical and cold allodynia developed to an equivalent degree in CB<sub>1</sub>KO, CB<sub>2</sub>KO, and WT mice. Both AM1710 and  $\Delta^9$ -THC suppressed established paclitaxel-induced allodynia in WT mice. In contrast to  $\Delta^9$ -THC, chronic administration of AM1710 did not engage CB<sub>1</sub> activity or produce antinociceptive tolerance, CB<sub>1</sub>-mediatedcannabinoid withdrawal, hypothermia, or motor dysfunction. Antiallodynic efficacy of systemic administration of AM1710 was absent in CB<sub>2</sub>KO mice and WT mice receiving the CB<sub>2</sub> antagonist AM630, administered either systemically or intrathecally. Intrathecal administration of AM1710 also attenuated paclitaxel-induced allodynia in WT mice, but not CB<sub>2</sub>KO mice, implicating a possible role for spinal CB<sub>2</sub> receptors in AM1710 antiallodynic efficacy. Finally, both acute andchronic administration of AM1710 decreased messenger RNA levels of tumor necrosis factor- $\alpha$  and monocyte chemoattractant protein 1 in lumbar spinal cord of paclitaxel-treated WT mice. These results highlight the potential of prolonged use of CB<sub>2</sub> agonists for managing chemotherapy-induced allodynia with a favorable therapeutic ratio marked by sustained efficacy and absence of tolerance, physical withdrawal, or CB<sub>1</sub>-mediated side effects.

**G9a Influences Neuronal Subtype Specification In Striatum** Maze I, Chaudhury D, Dietz DM, Von Schimmelmann M, Kennedy PJ, Lobo MK, Sullivan SE, Miller ML, Bagot RC, Sun H, Turecki G, Neve RL, Hurd YL, Shen L, Han MH, Schaefer A, Nestler EJ. *Nat Neurosci.* 2014 Apr; 17(4): 533-9. doi: 10.1038/nn.3670. Epub 2014 Mar 2.

Cocaine-mediated repression of the histone methyltransferase (HMT) G9a has recently been implicated in transcriptional, morphological and behavioral responses to chronic cocaine administration. Here, using a ribosomal affinity purification approach, the authors found that G9a repression by cocaine occurred in both Drd1-expressing (striatonigral) and Drd2-expressing (striatopallidal) medium spiny neurons. Conditional knockout and overexpression of G9a within these distinct cell types, however, revealed divergent behavioral phenotypes in response to repeated cocaine treatment. These studies further indicated that such developmental deletion of G9a selectively in Drd2 neurons resulted in the unsilencing of transcriptional programs normally specific to striatonigral neurons and in the acquisition of Drd1-associated projection and electrophysiological properties. This partial striatopallidal to striatonigral 'switching' phenotype in mice indicates a new role for G9a in contributing to neuronal subtype identity and suggests a critical function for cell type-specific histone methylation patterns in the regulation of behavioral responses to environmental stimuli.

**The Effects Of Social Learning on the Acquisition Of Cocaine Self-Administration** Smith MA, Lacy RT, Strickland JC. *Drug Alcohol Depend.* 2014 Aug 1; 141: 1-8. doi: 10.1016/j.drugalcdep.2014.04.025. Epub 2014 May 14.

Social learning models of substance use propose that drug-use behaviors are learned by observing and mimicking the behavior of others. The aim of this study was to examine the acquisition of cocaine self-administration in three groups of experimentally naïve rats: rats that were tested in isolation, rats that were tested in the presence of another rat that had access to cocaine and had previously been trained to self-administer cocaine, and rats that were tested in the presence of another rat that did not have access to cocaine. Male rats were reared in isolated or pair-housed conditions and implanted with intravenous catheters. Pair-housed rats were then assigned to drug-experienced or drug-naïve conditions. In the drug-experienced condition, one rat of each pair was trained to self-administer cocaine in isolation before the reintroduction of its partner. In the drug-naïve condition, one rat of each pair did not have access to cocaine for the duration of the study. For each group, the acquisition of cocaine self-administration was measured over 15 days in rats with access to cocaine but no prior operant training. Rats tested with a drug-experienced partner were faster to acquire cocaine self-administration and emitted more active lever presses than rats tested with a cocaine-naïve partner. Data for the isolated control group fell between the other two groups on these measures. These data indicate that the acquisition of cocaine self-administration can either be facilitated or inhibited by social contact. Collectively, these results support a social learning model of substance use.

**Miswiring the Brain:  $\Delta$ 9-Tetrahydrocannabinol Disrupts Cortical Development By Inducing An SCG10/Stathmin-2 Degradation Pathway** Tortoriello G, Morris CV, Alpar A, Fuzik J, Shirran SL, Calvigioni D, Keimpema E, Botting CH, Reinecke K, Herdegen T, Courtney M, Hurd YL, Harkany T. *EMBO J.* 2014 Apr 1; 33(7): 668-85. doi: 10.1002/embj.201386035. Epub 2014 Jan 27.

Children exposed in utero to cannabis present permanent neurobehavioral and cognitive impairments. Psychoactive constituents from Cannabis spp., particularly  $\Delta$ (9)-tetrahydrocannabinol (THC), bind to cannabinoid receptors in the fetal brain. However, it is unknown whether THC can trigger a cannabinoid receptor-driven molecular cascade to disrupt neuronal specification. Here, the

authors show that repeated THC exposure disrupts endocannabinoid signaling, particularly the temporal dynamics of CB1 cannabinoid receptor, to rewire the fetal cortical circuitry. By interrogating the THC-sensitive neuronal proteome we identify Superior Cervical Ganglion 10 (SCG10)/stathmin-2, a microtubule-binding protein in axons, as a substrate of altered neuronal connectivity. The authors find SCG10 mRNA and protein reduced in the hippocampus of midgestational human cannabis-exposed fetuses, defining SCG10 as the first cannabis-driven molecular effector in the developing cerebrum. CB1 cannabinoid receptor activation recruits c-Jun N-terminal kinases to phosphorylate SCG10, promoting its rapid degradation in situ in motile axons and microtubule stabilization. Thus, THC enables ectopic formation of filopodia and alters axon morphology. These data highlight the maintenance of cytoskeletal dynamics as a molecular target for cannabis, whose imbalance can limit the computational power of neuronal circuitries in affected offspring.

**Fragile X Mental Retardation Protein Regulates Synaptic and Behavioral Plasticity To Repeated Cocaine Administration**

Smith LN, Jedynak JP, Fontenot MR, Hale CF, Dietz KC, Taniguchi M, Thomas FS, Zirlin BC, Birnbaum SG, Huber KM, Thomas MJ, Cowan CW. *Neuron*. 2014 May 7; 82(3): 645-58. doi: 10.1016/j.neuron.2014.03.028.

Repeated cocaine exposure causes persistent, maladaptive alterations in brain and behavior, and hope for effective therapeutics lies in understanding these processes. The authors describe here an essential role for fragile X mental retardation protein (FMRP), an RNA-binding protein and regulator of dendritic protein synthesis, in cocaine conditioned place preference, behavioral sensitization, and motor stereotypy. Cocaine reward deficits in FMRP-deficient mice stem from elevated mGluR5 (or GRM5) function, similar to a subset of fragile X symptoms, and do not extend to natural reward. The authors find that FMRP functions in the adult nucleus accumbens (NAc), a critical addiction-related brain region, to mediate behavioral sensitization but not cocaine reward. FMRP-deficient mice also exhibit several abnormalities in NAc medium spiny neurons, including reduced presynaptic function and premature changes in dendritic morphology and glutamatergic neurotransmission following repeated cocaine treatment. Together, these findings reveal FMRP as a critical mediator of cocaine-induced behavioral and synaptic plasticity.

**Excessive Cocaine Use Results From Decreased Phasic Dopamine Signaling In The Striatum**

Willuhn I, Burgeno LM, Groblewski PA, Phillips PE. *Nat Neurosci*. 2014 May; 17(5): 704-9. doi: 10.1038/nn.3694. Epub 2014 Apr 6.

Drug addiction is a neuropsychiatric disorder marked by escalating drug use. Dopamine neurotransmission in the ventromedial striatum (VMS) mediates acute reinforcing effects of abused drugs, but with protracted use the dorsolateral striatum is thought to assume control over drug seeking. The authors measured striatal dopamine release during a cocaine self-administration regimen that produced escalation of drug taking in rats. Surprisingly, they found that phasic dopamine decreased in both regions as the rate of cocaine intake increased, with the decrement in dopamine in the VMS significantly correlated with the rate of escalation. Administration of the dopamine precursor L-DOPA at a dose that replenished dopamine signaling in the VMS reversed escalation, thereby demonstrating a causal relationship between diminished dopamine transmission and excessive drug use. Together these data provide mechanistic and therapeutic insight into the excessive drug intake that emerges following protracted use.

**PIP2 Regulates Psychostimulant Behaviors Through Its Interaction With A Membrane Protein**

Hamilton PJ, Belovich AN, Khelashvili G, Saunders C, Erreger K, Javitch JA, Sitte HH, Weinstein H, Matthies HJ, Galli A. *Nat Chem Biol.* 2014 Jul; 10(7): 582-9. doi: 10.1038/nchembio.1545. Epub 2014 Jun 1.

Phosphatidylinositol (4,5)-biphosphate (PIP2) regulates the function of ion channels and transporters. Here, the authors demonstrate that PIP2 directly binds the human dopamine (DA) transporter (hDAT), a key regulator of DA homeostasis and a target of the psychostimulant amphetamine (AMPH). This binding occurs through electrostatic interactions with positively charged hDAT N-terminal residues and is shown to facilitate AMPH-induced, DAT-mediated DA efflux and the psychomotor properties of AMPH. Substitution of these residues with uncharged amino acids reduces hDAT-PIP2 interactions and AMPH-induced DA efflux without altering the hDAT physiological function of DA uptake. The authors evaluated the significance of this interaction in vivo using locomotion as a behavioral assay in *Drosophila melanogaster*. Expression of mutated hDAT with reduced PIP2 interaction in *Drosophila* DA neurons impairs AMPH-induced locomotion without altering basal locomotion. They present what is to their knowledge, the first demonstration of how PIP2 interactions with a membrane protein can regulate the behaviors of complex organisms.

**Post-Retrieval Extinction Attenuates Cocaine Memories**

Sartor GC, Aston-Jones G. *Neuropsychopharmacology.* 2014 Apr; 39(5): 1059-65. doi: 10.1038/npp.2013.323. Epub 2013 Nov 21.

Recent studies have shown that post-retrieval extinction training attenuates fear and reward-related memories in both humans and rodents. This noninvasive, behavioral approach has the potential to be used in clinical settings to treat maladaptive memories that underlie several psychiatric disorders, including drug addiction. However, few studies to date have used a post-retrieval extinction approach to attenuate addiction-related memories. In the current study, the authors attempted to disrupt cocaine-related memories by using the post-retrieval extinction paradigm in male Sprague Dawley rats. Results revealed that starting extinction training 1 h after cocaine contextual memory was retrieved significantly attenuated cocaine-primed reinstatement of conditioned place preference (CPP) and relapse of cocaine CPP (drug-free and cocaine-primed) following 30 days of abstinence. However, animals that did not retrieve the contextual cocaine memory before extinction training, or animals that began extinction training 24 h after retrieval (outside of the reconsolidation window), demonstrated normal cocaine CPP. Conversely, animals that received additional CPP conditioning, rather than extinction training, 1 h after reactivation of cocaine memory showed enhanced cocaine CPP compared with animals that did not reactivate the cocaine memory before conditioning. These results reveal that a behavioral manipulation that takes advantage of reconsolidation and extinction of drug memories may be useful in decreasing preference for, and abuse of, cocaine.

**Designer Receptors Show Role For Ventral Pallidum Input To Ventral Tegmental Area In Cocaine Seeking**

Mahler SV, Vazey EM, Beckley JT, Keistler CR, McGlinchey EM, Kaufling J, Wilson SP, Deisseroth K, Woodward JJ, Aston-Jones G. *Nat Neurosci.* 2014 Apr; 17(4): 577-85. doi: 10.1038/nn.3664. Epub 2014 Mar 2.

The ventral pallidum is centrally positioned within mesocorticolimbic reward circuits, and its dense projection to the ventral tegmental area (VTA) regulates neuronal activity there. However, the ventral pallidum is a heterogeneous structure, and how this complexity affects its role within wider reward circuits is unclear. The authors found that projections to VTA from the rostral ventral pallidum (RVP), but not the caudal ventral pallidum (CVP), were robustly Fos activated during cue-induced reinstatement of cocaine seeking--a rat model of relapse in addiction. Moreover, designer

receptor-mediated transient inactivation of RVP neurons, their terminals in VTA or functional connectivity between RVP and VTA dopamine neurons blocked the ability of drug-associated cues (but not a cocaine prime) to reinstate cocaine seeking. In contrast, CVP neuronal inhibition blocked cocaine-primed, but not cue-induced, reinstatement. This double dissociation in ventral pallidum subregional roles in drug seeking is likely to be important for understanding the mesocorticolimbic circuits underlying reward seeking and addiction.

**The Effect Of Naltrexone On Neuropathic Pain In Mice Locally Transfected With the Mutant Mu-Opioid Receptor Gene In Spinal Cord**

Kao JH, Gao MJ, Yang PP, Law PY, Loh HH, Tao PL. Br J Pharmacol. 2014 May 28. doi: 10.1111/bph.12790. [Epub ahead of print].

Opioid antagonists, such as naloxone and naltrexone, exhibit agonistic properties at the mutated mu-opioid receptor MOR-S196ACSTA. In the authors' previous study, systemic naloxone (10 mg/kg, s.c.) elicited antinociceptive effect without the induction of tolerance, dependence, or rewarding effect in mice 2 weeks after intrathecal administration of dsAAV2-MOR-S196ACSTA-EGFP. In the present study, they further investigated whether this antinociceptive paradigm could be effective in mice with neuropathic pain. Spinal nerve ligation surgery was performed on male C57BL/6 mice (25-30 g) 3 or 4 weeks after intrathecal injection of the lentivirus encoding the construct of MOR-S196ACSTA-EGFP (LV-MOR-S196ACSTA). The von Frey test was used to detect the anti-allodynic effects of systemic saline, naltrexone (10 mg/kg, s.c., q.d.), and morphine (10 mg/kg, s.c., q.d.). After 14 days of treatment with saline, naltrexone, or morphine, the natural withdrawal signs were measured at 22 and 46 h after the last injection. To determine the rewarding effects induced by morphine or naltrexone, the conditioned place preference test was carried out. Paw withdrawal pressure, as measured by von Frey test, increased after naltrexone (10 mg/kg, s.c.) or morphine (10 mg/kg, s.c.) treatment in mice transfected with LV-MOR-S196ACSTA in spinal cord. Chronic treatment of morphine but not naltrexone induced natural withdrawal and rewarding effects. Systemic injection of naltrexone after the expression of MOR-S196ACSTA in the spinal cord may have therapeutic potential for chronic neuropathic pain without the development of dependence/addiction.

**Persistent Pain Facilitates Response To Morphine Reward By Downregulation Of Central Amygdala Gabaergic Function**

Zhang Z, Tao W, Hou YY, Wang W, Lu YG, Pan ZZ.

Neuropsychopharmacology. 2014 Aug;39(9): 2263-71. doi:10.1038/npp.2014.77. Epub 2014 Apr 1.

Opioid-based analgesics are widely used for treating chronic pain, but opioids are highly addictive when repeatedly used because of their strong rewarding effects. In recent years, abuse of prescription opioids has dramatically increased, including incidences of misuse of opioid drugs prescribed for pain control. Despite this issue in current clinical pain management, it remains unknown how pain influences the abuse liability of prescription opioids. Pain as aversive experience may affect opioid reward of positive emotion through common brain sites involved in emotion processing. In this study, on a rat model of chronic pain, the authors determined how persistent pain altered behavioral responses to morphine reward measured by the paradigm of unbiased conditioned place preference (CPP), focusing on GABAergic synaptic activity in neurons of the central nucleus of the amygdala (CeA), an important brain region for emotional processing of both pain and reward. The authors found that pain reduced the minimum number of morphine-conditioning sessions required for inducing CPP behavior. Both pain and morphine conditioning that elicited CPP inhibited GABA synaptic transmission in CeA neurons. Pharmacological activation of CeA GABAA receptors reduced the pain and inhibited CPP induced both by an effective dose of morphine and by a sub-threshold dose of morphine under pain condition. Furthermore, inhibition of CeA GABAA receptors mimicked the pain effect, rendering the sub-

threshold dose of morphine effective in CPP induction. These findings suggest that pain facilitates behavioral responses to morphine reward by predisposing the inhibitory GABA function in the CeA circuitry involved in the behavior of opioid reward.

**Pharmacological Characterization In the Rat Of a Potent Analgesic Lacking Respiratory**

**Depression, 3'-iodobenzoyl-6 $\beta$ -naltrexamide (IBNtxA)** Grinnell SG, Majumdar S, Narayan A, Le Rouzic V, Ansonoff M, Pintar JE, Pasternak GW. J Pharmacol Exp Ther. 2014 Jun 26. pii: jpet.114.213199. [Epub ahead of print].

3'-Iodobenzoyl-6 $\beta$ -naltrexamide (IBNtxA) is a potent analgesic in mice lacking many traditional opioid side-effects. In mice, it displays no respiratory depression, does not produce physical dependence with chronic administration, and shows no cross tolerance to morphine. It has limited effects on gastrointestinal transit and shows no reward behavior. Biochemical studies indicate its actions are mediated through a set of MOR-1 splice variants associated with exon 11 that lack exon 1 and contain only six transmembrane domains. Like the mouse and human, rats express exon 11-associated splice variants that also contain only six transmembrane domains, raising the question of whether or not IBNtxA would have a similar pharmacological profile in rats. Given systemically, IBNtxA is a potent analgesic in rats, with an ED<sub>50</sub> value of 0.89 mg/kg, s.c., approximately 4-fold more potent than morphine. It shows no analgesic cross tolerance in morphine-pelleted rats. IBNtxA displays no respiratory depression as measured by blood oxygen saturation. In contrast, oximetry shows an equianalgesic dose of morphine lowers blood oxygen saturation values by 30%. IBNtxA binding is present in a number of brain regions, with the thalamus standing out with very high levels and the cerebellum with low levels. In conclusion, as in mice, IBNtxA is a potent analgesic in rats with a favorable pharmacological profile and reduced side-effects.

**Roles of Heat Shock Factor 1 In Neuronal Response To Fetal Environmental Risks And Its Relevance To Brain Disorders**

Hashimoto-Torii K, Torii M, Fujimoto M, Nakai A, El Fatimy R, Mezger V, Ju MJ, Ishii S, Chao SH, Brennand KJ, Gage FH, Rakic P. Neuron. 2014 May 7; 82(3): 560-72. doi: 10.1016/j.neuron.2014.03.002. Epub 2014 Apr 10.

Prenatal exposure of the developing brain to various environmental challenges increases susceptibility to late onset of neuropsychiatric dysfunction; still, the underlying mechanisms remain obscure. Here the authors show that exposure of embryos to a variety of environmental factors such as alcohol, methylmercury, and maternal seizure activates HSF1 in cerebral cortical cells.

Furthermore, Hsf1 deficiency in the mouse cortex exposed in utero to subthreshold levels of these challenges causes structural abnormalities and increases seizure susceptibility after birth. In addition, the authors found that human neural progenitor cells differentiated from induced pluripotent stem cells derived from schizophrenia patients show higher variability in the levels of HSF1 activation induced by environmental challenges compared to controls. The authors propose that HSF1 plays a crucial role in the response of brain cells to prenatal environmental insults and may be a key component in the pathogenesis of late-onset neuropsychiatric disorders.

**Environmental Enrichment Reduces Methamphetamine Cue-Induced Reinstatement But Does Not Alter Methamphetamine Reward Or VMAT2 Function**

Hofford RS, Darna M, Wilmouth CE, Dwoskin LP, Bardo MT. Behav Brain Res. 2014 Aug 15; 270: 151-8. doi: 10.1016/j.bbr.2014.05.007. Epub 2014 May 10.

Environmental factors influence a variety of health-related outcomes. In general, being raised in an environment possessing social, sensory, and motor enrichment reduces the rewarding effects of various drugs, thus protecting against abuse vulnerability. However, in the case of methamphetamine (METH), which acts at the vesicular monoamine transporter 2 (VMAT2) to

enhance dopamine release from the cytosol, previous evidence suggests that METH reward may not be altered by environmental enrichment. This study examined the influence of an enriched environment on measures of METH reward, METH seeking, and VMAT2 function. Rats were raised from weaning to adulthood in either an enriched environment (presence of social cohorts and novel objects) or an isolated environment (no cohorts or novel objects). Rats in these two conditions were subsequently tested for their acquisition of conditioned place preference (CPP), METH self-administration, maintenance of self-administration at various unit doses of METH (0.001-0.5mg/kg/infusion), and cue-induced reinstatement. VMAT2 function in striatum from these two groups also was assessed. No significant environment effects were found in CPP or METH self-administration, which paralleled a lack of effect in VMAT2 function between groups. However, cue-induced reinstatement was reduced by environmental enrichment. Together, these results suggest that environmental enrichment does not alter VMAT2 function involved in METH reward. However, the enrichment-induced decrease in cue-induced reinstatement indicates that enrichment may have a beneficial effect against relapse following a period of extinction via a neural mechanism other than striatal VMAT2 function.

### **Mutation of Putative GRK Phosphorylation Sites In the Cannabinoid Receptor 1(CB1R) Confers Resistance To Cannabinoid Tolerance and Hypersensitivity To Cannabinoids In Mice**

Morgan DJ, Davis BJ, Kearn CS, Marcus D, Cook AJ, Wager-Miller J, Straiker A, Myoga MH, Karduck J, Leishman E, Sim-Selley LJ, Czyzyk TA, Bradshaw HB, Selley DE, Mackie K. J Neurosci. 2014 Apr 9; 34(15): 5152-63. doi: 10.1523/JNEUROSCI.3445-12.2014.

For many G-protein-coupled receptors (GPCRs), including cannabinoid receptor 1 (CB1R), desensitization has been proposed as a principal mechanism driving initial tolerance to agonists. GPCR desensitization typically requires phosphorylation by a G-protein-coupled receptor kinase (GRK) and interaction of the phosphorylated receptor with an arrestin. In simple model systems, CB1R is desensitized by GRK phosphorylation at two serine residues (S426 and S430). However, the role of these serine residues in tolerance and dependence for cannabinoids in vivo was unclear. Therefore, the authors generated mice where S426 and S430 were mutated to nonphosphorylatable alanines (S426A/S430A). S426A/S430A mutant mice were more sensitive to acutely administered delta-9-tetrahydrocannabinol ( $\Delta(9)$ -THC), have delayed tolerance to  $\Delta(9)$ -THC, and showed increased dependence for  $\Delta(9)$ -THC. S426A/S430A mutants also showed increased responses to elevated levels of endogenous cannabinoids. CB1R desensitization in the periaqueductal gray and spinal cord following 7 d of treatment with  $\Delta(9)$ -THC was absent in S426A/S430A mutants.  $\Delta(9)$ -THC-induced downregulation of CB1R in the spinal cord was also absent in S426A/S430A mutants. Cultured autaptic hippocampal neurons from S426A/S430A mice showed enhanced endocannabinoid-mediated depolarization-induced suppression of excitation (DSE) and reduced agonist-mediated desensitization of DSE. These results indicate that S426 and S430 play major roles in the acute response to, tolerance to, and dependence on cannabinoids. Additionally, S426A/S430A mice are a novel model for studying pathophysiological processes thought to involve excessive endocannabinoid signaling such as drug addiction and metabolic disease. These mice also validate the approach of mutating GRK phosphorylation sites involved in desensitization as a general means to confer exaggerated signaling to GPCRs in vivo.

### **Identification Of Novel Functionally Selective K-Opioid Receptor Scaffolds** White KL, Scpton AP, Rives ML, Bikbulatov RV, Polepally PR, Brown PJ, Kenakin T, Javitch JA, Zjawiony JK, Roth BL. Mol Pharmacol. 2014 Jan; 85(1): 83-90. doi: 10.1124/mol.113.089649. Epub 2013 Oct 10.

The  $\kappa$ -opioid receptor (KOR)-dynorphin system has been implicated in the control of affect, cognition, and motivation, and is thought to be dysregulated in mood and psychotic disorders, as

well as in various phases of opioid dependence. KOR agonists exhibit analgesic effects, although the adverse effects produced by some KOR agonists, including sedation, dysphoria, and hallucinations, have limited their clinical use. Interestingly, KOR-mediated dysphoria, assessed in rodents as aversion, has recently been attributed to the activation of the p38 mitogen-activated protein kinase pathway following arrestin recruitment to the activated KOR. Therefore, KOR-selective G protein-biased agonists, which do not recruit arrestin, have been proposed to be more effective analgesics, without the adverse effects triggered by the arrestin pathway. As an initial step toward identifying novel biased KOR agonists, the authors applied a multifaceted screening strategy utilizing both in silico and parallel screening approaches. They identified several KOR-selective ligand scaffolds with a range of signaling bias in vitro. The arylacetamide-based scaffold includes both G protein- and  $\beta$ -arrestin-biased ligands, while the endogenous peptides and the diterpene scaffolds are G protein biased. Interestingly, the authors found scaffold screening to be more successful than library screening in identifying biased ligands. Many of the identified functionally selective ligands are potent selective KOR agonists that are reported to be active in the central nervous system. They therefore represent excellent candidates for in vivo studies aiming at determining the behavioral effects mediated by specific KOR-mediated signaling cascades.

**Cell-Type Specific Expression of p11 Controls Cocaine Reward** Arango-Lievano M, Schwarz JT, Vernov M, Wilkinson MB, Bradbury K, Feliz A, Marongiu R, Gelfand Y, Warner-Schmidt J, Nestler EJ, Greengard P, Russo SJ, Kaplitt MG. *Biol Psychiatry*. 2014 Feb 26. pii: S0006-3223(14)00107-3. doi:10.1016/j.biopsych.2014.02.012. [Epub ahead of print].

The high rate of comorbidity between depression and cocaine addiction suggests shared molecular mechanisms and anatomical pathways. Limbic structures, such as the nucleus accumbens (NAc), play a crucial role in both disorders, yet how different cell types within these structures contribute to the pathogenesis remains elusive. Downregulation of p11 (S100A10), specifically in the NAc, elicits depressive-like behaviors in mice, but its role in drug addiction is unknown. The authors combined mouse genetics and viral strategies to determine how the titration of p11 levels within the entire NAc affects the rewarding actions of cocaine on behavior (six to eight mice per group) and molecular correlates (three experiments, five to eight mice per group). Finally, the manipulation of p11 expression in distinct NAc dopaminergic neuronal subsets distinguished cell-type specific effects of p11 on cocaine reward (five to eight mice per group). The authors demonstrated that p11 knockout mice have enhanced cocaine conditioned place preference, which is reproduced by the focal downregulation of p11 in the NAc of wild-type mice. In wild-type mice, cocaine reduced p11 expression in the NAc, while p11 overexpression exclusively in the NAc reduced cocaine conditioned place preference. Finally, they identified dopamine receptor-1 expressing medium spiny neurons as key mediators of the effects of p11 on cocaine reward. These data provide evidence that disruption of p11 homeostasis in the NAc, particularly in dopamine receptor-1 expressing medium spiny neurons, may underlie pathophysiological mechanisms of cocaine rewarding action. Treatments to counter maladaptation of p11 levels may provide novel therapeutic opportunities for cocaine addiction.

**Initial Uncertainty In Pavlovian Reward Prediction Persistently Elevates Incentive Salience and Extends Sign-Tracking To Normally Unattractive Cues** Robinson MJ, Anselme P, Fischer AM, Berridge KC. *Behav Brain Res*. 2014 Jun 1; 266: 119-30. doi: 10.1016/j.bbr.2014.03.004. Epub 2014 Mar 11.

Uncertainty is a component of many gambling games and may play a role in incentive motivation and cue attraction. Uncertainty can increase the attractiveness for predictors of reward in the Pavlovian procedure of autoshaping, visible as enhanced sign-tracking (or approach and nibbles) by

rats of a metal lever whose sudden appearance acts as a conditioned stimulus (CS+) to predict sucrose pellets as an unconditioned stimulus (UCS). Here the authors examined how reward uncertainty might enhance incentive salience as sign-tracking both in intensity and by broadening the range of attractive CS+s. They also examined whether initially induced uncertainty enhancements of CS+ attraction can endure beyond uncertainty itself, and persist even when Pavlovian prediction becomes 100% certain. These results show that uncertainty can broaden incentive salience attribution to make CS cues attractive that would otherwise not be (either because they are too distal from reward or too risky to normally attract sign-tracking). In addition, uncertainty enhancement of CS+ incentive salience, once induced by initial exposure, persisted even when Pavlovian CS-UCS correlations later rose toward 100% certainty in prediction. Persistence suggests an enduring incentive motivation enhancement potentially relevant to gambling, which in some ways resembles incentive-sensitization. Higher motivation to uncertain CS+s leads to more potent attraction to these cues when they predict the delivery of uncertain rewards. In humans, those cues might possibly include the sights and sounds associated with gambling, which contribute a major component of the play immersion experienced by problematic gamblers.

**Loss of BDNF Signaling in D1R-Expressing NAc Neurons Enhances Morphine Reward by Reducing GABA Inhibition** Koo JW, Lobo MK, Chaudhury D, Labonté B, Friedman A, Heller E, Peña CJ, Han MH, Nestler EJ. *Neuropsychopharmacology*. 2014 May 23. doi: 10.1038/npp.2014.118. [Epub ahead of print].

The nucleus accumbens (NAc) has a central role in the mechanism of action of drugs of abuse. The major neuronal type within the NAc is the GABAergic medium spiny neuron (MSN), with two major subpopulations defined—termed D1-type and D2-type MSNs—based on the predominant dopamine receptor expressed. However, very little is known about the contribution of altered GABAergic function in NAc MSNs to the neural and behavioral plasticity that contributes to the lasting actions of drugs of abuse. In the present study, the authors show that GABAergic activity is selectively modulated in D1-type MSNs of the NAc by signaling of brain-derived neurotrophic factor (BDNF) and its receptor, tyrosine receptor kinase B (TrkB), and that such adaptations control rewarding responses to morphine. Optical activation of D1-type MSNs, or the knockout of TrkB from D1-type MSNs (D1-TrkB KO), enhances morphine reward, effects not seen for D2-type MSNs. In addition, D1-TrkB KO mice, but not D2-TrkB KO mice, display decreased GABA<sub>A</sub> receptor (GABAAR) subunit expression and reduced spontaneous inhibitory postsynaptic currents (sIPSCs) in D1-type, but not D2-type, MSNs in the NAc. Furthermore, the authors found that GABAAR antagonism in the NAc enhances morphine reward and that morphine exposure decreases TrkB expression as well as GABAergic activity in D1-type MSNs. Together, these data provide evidence for the enhancement of morphine reward through reduction of inhibitory GABAAR responses, an adaptation mediated by morphine-induced reduction of BDNF-TrkB signaling in D1-type MSNs.

**Natural Neural Projection Dynamics Underlying Social Behavior** Gunaydin LA, Grosenick L, Finkelstein JC, Kauvar IV, Fenno LE, Adhikari A, Lammel S, Mirzabekov JJ, Airan RD, Zalocusky KA, Tye KM, Anikeeva P, Malenka RC, Deisseroth K. *Cell*. 2014 Jun 19; 157(7): 1535-51. doi: 10.1016/j.cell.2014.05.017.

Social interaction is a complex behavior essential for many species and is impaired in major neuropsychiatric disorders. Pharmacological studies have implicated certain neurotransmitter systems in social behavior, but circuit-level understanding of endogenous neural activity during social interaction is lacking. The authors therefore developed and applied a new methodology,

termed fiber photometry, to optically record natural neural activity in genetically and connectivity-defined projections to elucidate the real-time role of specified pathways in mammalian behavior. Fiber photometry revealed that activity dynamics of a ventral tegmental area (VTA)-to-nucleus accumbens (NAc) projection could encode and predict key features of social, but not novel object, interaction. Consistent with this observation, optogenetic control of cells specifically contributing to this projection was sufficient to modulate social behavior, which was mediated by type 1 dopamine receptor signaling downstream in the NAc. Direct observation of deep projection-specific activity in this way captures a fundamental and previously inaccessible dimension of mammalian circuit dynamics.

**3-Aminoazetididin-2-one Derivatives as N-Acylethanolamine Acid Amidase (NAAA) Inhibitors Suitable for Systemic Administration** Fiasella A, Nuzzi A, Summa M, Armirotti A, Tarozzo G, Tarzia G, Mor M, Bertozzi F, Bandiera T, Piomelli D. *ChemMedChem*. 2014 Jul; 9(7): 1602-14. doi: 10.1002/cmdc.201300546. Epub 2014 May 14.

N-Acylethanolamine acid amidase (NAAA) is a cysteine hydrolase that catalyzes the hydrolysis of endogenous lipid mediators such as palmitoylethanolamide (PEA). PEA has been shown to exert anti-inflammatory and antinociceptive effects in animals by engaging peroxisome proliferator-activated receptor  $\alpha$  (PPAR- $\alpha$ ). Thus, preventing PEA degradation by inhibiting NAAA may provide a novel approach for the treatment of pain and inflammatory states. Recently, 3-aminooxetan-2-one compounds were identified as a class of highly potent NAAA inhibitors. The utility of these compounds is limited, however, by their low chemical and plasma stabilities. In the present study, the authors synthesized and tested a series of N-(2-oxoazetididin-3-yl)amides as a novel class of NAAA inhibitors with good potency and improved physicochemical properties, suitable for systemic administration. Moreover, the authors elucidated the main structural features of 3-aminoazetididin-2-one derivatives that are critical for NAAA inhibition.

**Developmental But Not Adult Cannabinoid Treatments Persistently Alter Axonal and Dendritic Morphology Within Brain Regions Important For Zebra Finch Vocal Learning**

Gilbert MT, Soderstrom K. *Brain Res*. 2014 Apr 16;1558:57-73. doi: 10.1016/j.brainres.2014.02.039. Epub 2014 Mar 2.

Prior work shows developmental cannabinoid exposure alters zebra finch vocal development in a manner associated with altered CNS physiology, including changes in patterns of CB1 receptor immunoreactivity, endocannabinoid concentrations and dendritic spine densities. These results raise questions about the selectivity of developmental cannabinoid effects: are they a consequence of a generalized developmental disruption, or are effects produced through more selective and distinct interactions with biochemical pathways that control receptor, endogenous ligand and dendritic spine dynamics? To begin to address this question the authors have examined effects of developmental cannabinoid exposure on the pattern and density of expression of proteins critical to dendritic (MAP2) and axonal (Nf-200) structure to determine the extent to which dendritic vs. axonal neuronal morphology may be altered. Results demonstrate developmental, but not adult cannabinoid treatments produce generalized changes in expression of both dendritic and axonal cytoskeletal proteins within brain regions and cells known to express CB1 cannabinoid receptors. Results clearly demonstrate that cannabinoid exposure during a period of sensorimotor development, but not adulthood, produce profound effects upon both dendritic and axonal morphology that persist through at least early adulthood. These findings suggest an ability of exogenous cannabinoids to alter general processes responsible for normal brain development. Results also further implicate the importance of endocannabinoid signaling to peri-pubertal periods of adolescence, and underscore potential consequences of cannabinoid abuse during periods of late-postnatal CNS development.

### **Distinct Lineage-Dependent Structural and Functional Organization of the Hippocampus**

Xu HT, Han Z, Gao P, He S, Li Z, Shi W, Kodish O, Shao W, Brown KN, Huang K, Shi SH. *Cell*. 2014 Jun 19;157(7):c1552-64. doi: 10.1016/j.cell.2014.03.067.

The hippocampus, as part of the cerebral cortex, is essential for memory formation and spatial navigation. Although it has been extensively studied, especially as a model system for neurophysiology, the cellular processes involved in constructing and organizing the hippocampus remain largely unclear. Here, the authors show that clonally related excitatory neurons in the developing hippocampus are progressively organized into discrete horizontal, but not vertical, clusters in the stratum pyramidale, as revealed by both cell-type-specific retroviral labeling and mosaic analysis with double markers (MADM). Moreover, distinct from those in the neocortex, sister excitatory neurons in the cornu ammonis 1 region of the hippocampus rarely develop electrical or chemical synapses with each other. Instead, they preferentially receive common synaptic input from nearby fast-spiking (FS), but not non-FS, interneurons and exhibit synchronous synaptic activity. These results suggest that shared inhibitory input may specify horizontally clustered sister excitatory neurons as functional units in the hippocampus.

### **Pharmacology and Anti-Addiction Effects of the Novel $\kappa$ Opioid Receptor Agonist Mesyl Sal B, A Potent and Long-Acting Analogue Of Salvinorin A**

Simonson B, Morani AS, Ewald AW, Walker L, Kumar N, Simpson D, Miller JH, Prisinzano TE, Kivell BM. *Br J Pharmacol*. 2014 Mar 18. Doi: 10.1111/bph.12692. [Epub ahead of print].

Acute activation of  $\kappa$  opioid (KOP) receptors results in anticocaine-like effects, but adverse effects, such as dysphoria, aversion, sedation and depression, limit their clinical development. Salvinorin A, isolated from the plant *Salvia divinorum*, and its semi-synthetic analogues have been shown to have potent KOP receptor agonist activity and may induce a unique response with similar anticocaine addiction effects as the classic KOP receptor agonists, but with a different side effect profile. The authors evaluated the duration of effects of Mesyl Sal B in vivo utilizing antinociception assays and screened for cocaine-prime induced cocaine-seeking behaviour in self-administering rats to predict anti-addiction effects. Cellular transporter uptake assays and in vitro voltammetry were used to assess modulation of dopamine transporter (DAT) function and to investigate transporter trafficking and kinase signalling pathways modulated by KOP receptor agonists. Mesyl Sal B had a longer duration of action than SalA, had anti-addiction properties and increased DAT function in vitro in a KOP receptor-dependent and Pertussis toxin-sensitive manner. These effects on DAT function required ERK1/2 activation. The authors identified differences between Mesyl Sal B and SalA, with Mesyl Sal B increasing the  $V_{max}$  of dopamine uptake without altering cell-surface expression of DAT. SalA analogues, such as Mesyl Sal B, have potential for development as anticocaine agents. Further tests are warranted to elucidate the mechanisms by which the novel salvinorin-based neoclerodane diterpene KOP receptor ligands produce both anti-addiction and adverse side effects.

### **Nicotine and Methamphetamine Disrupt Habituation Of Sensory Reinforce Effectiveness In**

**Male Rats** Lloyd DR, Hausknecht KA, Richards JB. *Exp Clin Psychopharmacol*. 2014 Apr; 22(2): 166-75. doi: 10.1037/a0034741.

The reinforcing effectiveness of a sensory stimulus such as light-onset rapidly habituates (Lloyd, Gancarz, Ashrafioun, Kausch, & Richards, 2012). According to memory-based theories, habituation occurs if a memory exists for perceived stimulation, and dishabituation occurs if a memory does not exist and the stimulation is "unexpected." According to Redgrave and Gurney (2006), unexpected response-contingent sensory stimuli increase phasic firing of dopamine neurons, providing a sensory error signal that reflects the difference between perceived and expected stimuli. Together, memory-based theories of habituation and the sensory error signal hypothesis predict a disruption

(slowing) of habituation rate by novel response-contingent sensory stimulation or by artificial increases in dopamine neurotransmission by stimulant drugs. To test these predictions, the authors examined the effects of stimulant drugs on both the operant level of responding (snout-poking) and operant responding for a sensory reinforcer (light-onset) presented according to a fixed ratio 1 schedule. Robust within-session decreases in responding indicating habituation were observed. The effects of stimulant drugs (saline, n = 10; nicotine, 0.40 mg/kg, n = 10; and methamphetamine, 0.75 mg/kg, n = 9) on habituation in rats were determined. Nicotine was found to decrease habituation rate and did not affect response rate, while methamphetamine decreased habituation rate and increased response rate. In addition, introduction of a novel visual stimulus reinforcer decreased habituation rate and increased responding. These findings show that habituation of reinforcer effectiveness modulates operant responding for sensory reinforcers, and that stimulant drugs may disrupt normally occurring habituation of reinforcer effectiveness by increasing dopamine neurotransmission.

**Retromer Mediates A Discrete Route Of Local Membrane Delivery To Dendrites** Choy RW, Park M, Temkin P, Herring BE, Marley A, Nicoll RA, von Zastrow M. *Neuron*. 2014 Apr 2; 82(1):55-62. doi: 10.1016/j.neuron.2014.02.018.

A fundamental and still largely unresolved question is how neurons achieve rapid delivery of selected signaling receptors throughout the elaborate dendritic arbor. Here the authors show that this requires a conserved sorting machinery called retromer. Retromer-associated endosomes are distributed within dendrites in ~2  $\mu\text{m}$  intervals and supply frequent membrane fusion events into the dendritic shaft domain immediately adjacent to (<300 nm from) the donor endosome and typically without full endosome discharge. Retromer-associated endosomes contain  $\beta$ -adrenergic receptors as well as ionotropic glutamate receptors, and retromer knockdown reduces extrasynaptic insertion of adrenergic receptors as well as functional expression of AMPA and NMDA receptors at synapses. The authors propose that retromer supports a broadly distributed network of plasma membrane delivery to dendrites, organized in micron-scale axial territories to render essentially all regions of the postsynaptic surface within rapid diffusion distance of a localexocytic event.

**Social Stress and CRF-Dopamine Interactions in the VTA: Role In Long-Term Escalation Of Cocaine Self-Administration** Boyson CO, Holly EN, Shimamoto A, Albrechet-Souza L, Weiner LA, DeBold JF, Miczek KA. *J Neurosci*. 2014 May 7; 34(19): 6659-67. doi: 10.1523/JNEUROSCI.3942-13.2014.

The nature of neuroadaptations in the genesis of escalated cocaine taking remains a topic of considerable interest. Intermittent social defeat stress induces both locomotor and dopaminergic cross-sensitization to cocaine, as well as escalated cocaine self-administration. The current study examines the role of corticotropin releasing factor receptor subtypes 1 and 2 (CRFR1, CRFR2) within the ventral tegmental area (VTA) during social defeat stress. This study investigated whether injecting either a CRFR1 or CRFR2 antagonist directly into the VTA before each social defeat would prevent the development of later (1) locomotor sensitization, (2) dopaminergic sensitization, and (3) escalated cocaine self-administration in rats. CRFR1 antagonist CP376395 (50 or 500 ng/side), CRFR2 antagonist Astressin2-B (100 or 1000 ng/side), or vehicle (aCSF) was microinjected into the VTA 20 min before social defeat stress (or handling) on days 1, 4, 7, and 10. Ten days later, rats were injected with cocaine (10 mg/kg, i.p.) and assessed for either locomotor sensitization, measured by walking activity, or dopaminergic sensitization, measured by extracellular dopamine (DA) in the nucleus accumbens shell (NAcSh) through in vivo microdialysis. Locomotor sensitization testing was followed by intravenous cocaine self-administration. Intra-VTA antagonism of CRFR1, but not CRFR2, inhibited the induction of

locomotor cross-sensitization to cocaine, whereas both prevented dopaminergic cross-sensitization and escalated cocaine self-administration during a 24 h "binge." This may suggest dissociation between locomotor sensitization and cocaine taking. These data also suggest that interactions between CRF and VTA DA neurons projecting to the NAcSh are essential for the development of dopaminergic cross-sensitization to cocaine.

**Multiple Distinct CHRN3-CHRNA6 Variants Are Genetic Risk Factors For Nicotine Dependence in African Americans and European Americans**

Culverhouse RC, Johnson EO, Breslau N, Hatsukami DK, Sadler B, Brooks AI, Hesselbrock VM, Schuckit MA, Tischfield JA, Goate AM, Saccone NL, Bierut LJ. 13. *Addiction*. 2014 May; 109(5): 814-22. doi: 10.1111/add.12478. Epub 2014 Feb 18.

Studies have shown association between common variants in the  $\alpha 6\text{-}\beta 3$  nicotinic receptor subunit gene cluster and nicotine dependence in European ancestry populations. The authors investigate whether this generalizes to African Americans, whether the association is specific to nicotine dependence and whether this region contains additional genetic contributors to nicotine dependence. They examined consistency of association across studies and race between the  $\alpha 6\beta 3$  nicotinic receptor subunit locus and nicotine, alcohol, marijuana and cocaine dependence in three independent studies in the U.S. Participants comprised European Americans and African Americans from three case-control studies of substance dependence. Subjects were evaluated using the Semi-Structured Assessment for the Genetics of Alcoholism. Nicotine dependence was determined using the Fagerström Test for Nicotine Dependence. The single nucleotide polymorphism rs13273442 was associated significantly with nicotine dependence across all three studies in both ancestry groups [odds ratio (OR) = 0.75,  $P = 5.8 \times 10^{-4}$  European Americans; OR = 0.80,  $P = 0.05$  African Americans]. No other substance dependence was associated consistently with this variant in either group. Another SNP in the region, rs4952, remains modestly associated with nicotine dependence in the combined data after conditioning on rs13273442. The common variant rs13273442 in the CHRN3-CHNRA6 region is associated significantly with nicotine dependence in European Americans and African Americans across studies recruited for nicotine, alcohol and cocaine dependence. Although these data are modestly powered for other substances, our results provide no evidence that correlates of rs13273442 represent a general substance dependence liability. Additional variants probably account for some of the association of this region to nicotine dependence.

**"Deconstruction" of the Abused Synthetic Cathinone Methylenedioxypropylamphetamine (MDPV) and An Examination of Effects At the Human Dopamine Transporter**

Kolanos R(1), Solis E Jr, Sakloth F, De Felice LJ, Glennon RA. *ACS Chem Neurosci*. 2013 Dec 18; 4(12): 1524-9. doi: 10.1021/cn4001236. Epub 2013 Oct 31.

Synthetic cathinones,  $\beta$ -keto analogues of amphetamine (or, more correctly, of phenylalkylamines), represent a new and growing class of abused substances. Several such analogues have been demonstrated to act as dopamine (DA) releasing agents. Methylenedioxypropylamphetamine (MDPV) was the first synthetic cathinone shown to act as a cocaine-like DA reuptake inhibitor. MDPV and seven deconstructed analogues were examined to determine which of MDPV's structural features account(s) for uptake inhibition. In voltage-clamped (-60 mV) *Xenopus* oocytes transfected with the human DA transporter (hDAT), all analogues elicited inhibitor-like behavior shown as hDAT-mediated outward currents. Using hDAT-expressing mammalian cells the authors determined the affinities of MDPV and its analogues to inhibit uptake of [3H]DA by hDAT that varied over a broad range (IC<sub>50</sub> values ca. 135 to >25,000 nM). The methylenedioxy group of MDPV made a minimal contribution to affinity, the carbonyl group and a tertiary amine are more important, and the

extended  $\alpha$ -alkyl group seems most important. Either a tertiary amine, or the extended  $\alpha$ -alkyl group (but not both), are required for the potent nature of MDPV as an hDAT inhibitor.

**A Cocaine Context Renews Drug Seeking Preferentially in a Subset of Individuals** Saunders BT, O'Donnell EG, Aurbach EL, Robinson TE. *Neuropsychopharmacology*. 2014 Jun 4. doi: 10.1038/npp.2014.131. [Epub ahead of print].

Addiction is characterized by a high propensity for relapse, in part because cues associated with drugs can acquire Pavlovian incentive motivational properties, and acting as incentive stimuli, such cues can instigate and invigorate drug-seeking behavior. There is, however, considerable individual variation in the propensity to attribute incentive salience to reward cues. Discrete and localizable reward cues act as much more effective incentive stimuli in some rats ('sign-trackers', STs), than others ('goal-trackers', GTs). The authors asked whether similar individual variation exists for contextual cues associated with cocaine. Cocaine context conditioned motivation was quantified in two ways: (1) the ability of a cocaine context to evoke conditioned hyperactivity and (2) the ability of a context in which cocaine was previously self-administered to renew cocaine-seeking behavior. Finally, the authors assessed the effects of intra-accumbens core flupenthixol, a nonselective dopamine receptor antagonist, on context renewal. In contrast to studies using discrete cues, a cocaine context spurred greater conditioned hyperactivity, and more robustly renewed extinguished cocaine seeking in GTs than STs. In addition, cocaine context renewal was blocked by antagonism of dopamine receptors in the accumbens core. Thus, contextual cues associated with cocaine preferentially acquire motivational control over behavior in different individuals than do discrete cues, and in these individuals the ability of a cocaine context to create conditioned motivation for cocaine requires dopamine in the core of the nucleus accumbens. The authors speculate that different individuals may be preferentially sensitive to different 'triggers' of relapse.

**Significant Associations of CHRNA2 and CHRNA6 with Nicotine Dependence in European American and African American Populations** Wang S, D van der Vaart A, Xu Q, Seneviratne C, Pomerleau OF, Pomerleau CS, Payne TJ, Ma JZ, Li MD. *Hum Genet*. 2014 May; 133(5): 575-86. doi: 10.1007/s00439-013-1398-9. Epub 2013 Nov 20.

The direct physiological effects that promote nicotine dependence (ND) are mediated by nicotinic acetylcholine receptors (nAChRs). In line with the genetic and pharmacological basis of addiction, many previous studies have revealed significant associations between variants in the nAChR subunit genes and various measures of ND in different ethnic samples. In this study, the authors first examined the association of variants in nAChR subunits  $\alpha 2$  (CHRNA2) and  $\alpha 6$  (CHRNA6) genes on chromosome 8 with ND using a family sample consisting of 1,730 European Americans (EAs) from 495 families and 1,892 African Americans (AAs) from 424 families (defined as the discovery family sample). ND was assessed by two standard quantitative measures: smoking quantity (SQ) and the Fagerström Test for ND (FTND). The authors found nominal associations for all seven tested SNPs of the genes with at least one ND measure in the EA sample and for two SNPs in CHRNA2 in the AA sample. Of these, associations of SNPs rs3735757 with FTND ( $P = 0.0068$ ) and rs2472553 with both ND measures (with a  $P$  value of 0.0043 and 0.00086 for SQ and FTND, respectively) continued to be significant in the EA sample even after correction for multiple tests. Further, they found several haplotypes that were significantly associated with ND in the EA sample in CHRNA6 and in the both EA and AA samples in CHRNA2. To confirm the associations of the two genes with ND, the authors conducted a replication study with an independent case-control sample from the SAGE study, which showed a significant association of the two genes with ND, although the significantly associated SNPs were not always the same in the two samples. Together, these findings indicate that both CHRNA2 and CHRNA6 play a significant

role in the etiology of ND in AA and EA smokers. Further replication in additional independent samples is warranted.

**Kappa Opioid Receptor-Mediated Antinociception Is Blocked By A Delta Opioid Receptor**

**Agonist** Taylor AM1, Roberts KW, Pradhan AA, Akbari HA, Walwyn W, Lutfy K, Carroll FI, Cahill CM, Evans CJ. Br J Pharmacol. 2014 Jun 12. doi: 10.1111/bph.12810. [Epub ahead of print]. The opioid receptor family is made up of four structurally homologous but functionally distinct receptors, the mu (MOP), delta (DOP), kappa (KOP), and nociceptin (NOP). Given that most opioid agonists are selective but not specific, a broad spectrum of behaviors due to activation of different opioid receptors is expected. In this study, the authors examine whether other opioid receptor systems influence KOP-mediated antinociception. They use a tail withdrawal assay in C57Bl/6 mice to assay the antinociceptive effect of systemically administered opioid agonists with varying selectivity at the KOP. Pharmacological and genetic approaches were used to dissect out the interaction of the other opioid receptors in modulating KOP mediated antinociception. Etorphine, a potent agonist at all 4 opioid receptors, was not antinociceptive in MOP knock out (KO) mice. This result was unexpected since etorphine is an efficacious KOP agonist and specific KOP agonists remain analgesic in MOP KO mice. Given that KOP agonists are aversive, we considered KOP-mediated antinociception might be a form of stress-induced analgesia that is blocked by the anxiolytic effects of DOP. In support of this hypothesis, pretreatment with the DOP antagonist, naltrindole (10mg/kg), unmasked etorphine (3mg/kg) antinociception in MOP KO mice. Further, in wildtype (WT) mice, KOP-mediated antinociception by systemic U50,488H (10mg/kg) was blocked by pretreatment with the DOP agonist SNC80 (5mg/kg) and diazepam(1mg/kg). The authors conclude that systemic DOP agonists block systemic KOP antinociception, and these results identify DOP agonists as potential therapeutics for reversing stress-driven addictive and depressive behaviors mediated through KOP activation.

**Altered Cerebellar and Prefrontal Cortex Function In Rhesus Monkeys That Previously Self-Administered Cocaine**

Porter JN, Minhas D, Lopresti BJ, Price JC, Bradberry CW. Psychopharmacology (Berl). 2014 Apr 15. [Epub ahead of print].

Differences in brain function in cocaine users can occur even when frank deficits are not apparent, indicating neuroadaptive consequences of use. Using monkeys to investigate altered metabolic activity following chronic cocaine self-administration allows an assessment of altered function due to cocaine use, without confounding pre-existing differences or polysubstance use often present in clinical studies. The objectives of this study were to evaluate alterations in metabolic function during a working memory task in the prefrontal cortex and the cerebellum following 1 year of chronic cocaine self-administration followed by a 20 month drug-free period. Fluorodeoxyglucose ((18)F) PET imaging was used to evaluate changes in relative regional metabolic activity associated with a delayed match to sample working memory task. Chronic cocaine animals were compared to a control group, and region of interest analyses focused on the dorsolateral prefrontal cortex (DLPFC) and cerebellum. Despite no differences in task performance, in the cocaine group, the cerebellum showed greater metabolic activity during the working memory task (relative to the control task) compared to the control group. There was also a trend toward a significant difference between the groups in DLPFC activity ( $p = 0.054$ ), with the cocaine group exhibiting lower DLPFC metabolic activity during the delay task (relative to the control task) than the control group. The results support clinical indications of increased cerebellar activity associated with chronic cocaine exposure. Consistent with evidence of functional interactions between cerebellum and prefrontal cortex, these changes may serve to compensate for potential impairments in functionality of DLPFC.

**Structural and Molecular Remodeling Of Dendritic Spine Substructures During Long-Term Potentiation** Bosch M, Castro J, Saneyoshi T, Matsuno H, Sur M, Hayashi Y. *Neuron*. 2014 Apr 16; 82(2): 444-59. doi: 10.1016/j.neuron.2014.03.021.

Synapses store information by long-lasting modifications of their structure and molecular composition, but the precise chronology of these changes has not been studied at single-synapse resolution in real time. Here the authors describe the spatiotemporal reorganization of postsynaptic substructures during long-term potentiation (LTP) at individual dendritic spines. Proteins translocated to the spine in four distinct patterns through three sequential phases. In the initial phase, the actin cytoskeleton was rapidly remodeled while active cofilin was massively transported to the spine. In the stabilization phase, cofilin formed a stable complex with F-actin, was persistently retained at the spine, and consolidated spine expansion. In contrast, the postsynaptic density (PSD) was independently remodeled, as PSD scaffolding proteins did not change their amount and localization until a late protein synthesis-dependent third phase. These findings show how and when spine substructures are remodeled during LTP and explain why synaptic plasticity rules change over time.

**Development of a High-Performance Liquid Chromatography-Tandem Mass Spectrometry Method for the Identification and Quantification of CP-47,497, CP-47,497-C8 and JWH-250 in Mouse Brain** Samano KL, Poklis JL, Lichtman AH, Poklis A. *J Anal Toxicol*. 2014 Jul; 38(6): 307-14. doi: 10.1093/jat/bku043. Epub 2014 May 9.

While marijuana continues to be the most widely used illicit drug, abuse of synthetic cannabinoid (SCB) compounds in 'Spice' or 'K2' herbal incense products has emerged as a significant public health concern in many European countries and in the USA. Several of these SCBs have been declared Schedule I controlled substances but detection and quantification in biological samples remain a challenge. Therefore, the authors present a liquid chromatography-tandem mass spectrometry method after liquid-liquid extraction for the quantitation of CP-47,497, CP-47,497-C8 and JWH-250 in mouse brain. They report data for linearity, limit of quantification, accuracy/bias, precision, recovery, selectivity, carryover, matrix effects and stability experiments which were developed and fully validated based on Scientific Working Group for Forensic Toxicology guidelines for forensic toxicology method validation. Acceptable coefficients of variation for accuracy/bias, within- and between-run precision and selectivity were determined, with all values within  $\pm 15\%$  of the target concentration. Validation experiments revealed degradation of CP-47,497 and CP-47,497-C8 at different temperatures, and significant ion suppression was produced in brain for all compounds tested. The method was successfully applied to detect and quantify CP-47,497 in brains from mice demonstrating significant cannabimimetic behavioral effects as assessed by the classical tetrad paradigm.

**Sparse, Decorrelated Odor Coding In the Mushroom Body Enhances Learned Odor Discrimination** Lin AC, Bygrave AM, de Calignon A, Lee T, Miesenböck G. *Nat Neurosci*. 2014 Apr; 17(4): 559-68. doi: 10.1038/nn.3660. Epub 2014 Feb 23.

Sparse coding may be a general strategy of neural systems for augmenting memory capacity. In *Drosophila melanogaster*, sparse odor coding by the Kenyon cells of the mushroom body is thought to generate a large number of precisely addressable locations for the storage of odor-specific memories. However, it remains untested how sparse coding relates to behavioral performance. Here the authors demonstrate that sparseness is controlled by a negative feedback circuit between Kenyon cells and the GABAergic anterior paired lateral (APL) neuron. Systematic activation and blockade of each leg of this feedback circuit showed that Kenyon cells activated APL and APL inhibited Kenyon cells. Disrupting the Kenyon cell-APL feedback loop decreased the sparseness of

Kenyon cell odor responses, increased inter-odor correlations and prevented flies from learning to discriminate similar, but not dissimilar, odors. These results suggest that feedback inhibition suppresses Kenyon cell activity to maintain sparse, decorrelated odor coding and thus the odor specificity of memories.

**Parvalbumin Cell Ablation Of NMDA-R1 Causes Increased Resting Network Excitability With Associated Social and Self-Care Deficits**

Billingslea EN, Tatard-Leitman VM, Anguiano J, Jutzeler CR, Suh J, Saunders JA, Morita S, Featherstone RE, Ortinski PI, Gandal MJ, Lin R, Liang Y, Gur RE, Carlson GC, Hahn CG, Siegel SJ. *Neuropsychopharmacology*. 2014 Jun; 39(7): 1603-13. doi: 10.1038/npp.2014.7. Epub 2014 Feb 14.

NMDA-receptor (NMDAR) hypofunction is strongly implicated in the pathophysiology of schizophrenia. Several convergent lines of evidence suggest that net excitation propagated by impaired NMDAR signaling on GABAergic interneurons may be of particular interest in mediating several aspects of schizophrenia. However, it is unclear which behavioral domains are governed by a net increase of excitation and whether modulating downstream GABAergic signaling can reverse neural and thus behavioral deficits. The current study determines the selective contributions of NMDAR dysfunction on PV-containing interneurons to electrophysiological, cognitive, and negative-symptom-related behavioral phenotypes of schizophrenia using mice with a PVcre-NR1flox-driven ablation of NR1 on PV-containing interneurons. In addition, the authors assessed the efficacy of one agent that directly modulates GABAergic signaling (baclofen) and one agent that indirectly modifies NMDAR-mediated signaling through antagonism of mGluR5 receptors (2-methyl-6-(phenylethynyl) pyridine (MPEP)). The data indicate that loss of NMDAR function on PV interneurons impairs self-care and sociability while increasing N1 latency and baseline gamma power, and reducing induction and maintenance of long-term potentiation. Baclofen normalized baseline gamma power without corresponding effects on behavior. MPEP further increased N1 latency and reduced social behavior in PVcre/NR1+/+ mice. These two indices were negatively correlated before and following MPEP such that as N1 latency increases, sociability decreases. This finding suggests a predictive role for N1 latency with respect to social function. Although previous data suggest that MPEP may be beneficial for core features of autism spectrum disorders, current data suggest that such effects require intact function of NMDAR on PV interneurons.

**Bioretrosynthetic Construction Of A Didanosine Biosynthetic Pathway** Birmingham WR, Starbird CA, Panosian TD, Nannemann DP, Iverson TM, Bachmann BO. *Nat Chem Biol*. 2014 May;10(5):392-9. doi: 10.1038/nchembio.1494. Epub 2014 Mar 23.

Concatenation of engineered biocatalysts into multistep pathways markedly increases their utility, but the development of generalizable assembly methods remains a major challenge. Herein the authors evaluate 'bioretrosynthesis', which is an application of the retrograde evolution hypothesis, for biosynthetic pathway construction. To test bioretrosynthesis, they engineered a pathway for synthesis of the antiretroviral nucleoside analog didanosine (2',3'-dideoxyinosine). Applying both directed evolution- and structure-based approaches, they began pathway construction with a retro-extension from an engineered purine nucleoside phosphorylase and evolved 1,5-phosphopentomutase to accept the substrate 2,3-dideoxyribose 5-phosphate with a 700-fold change in substrate selectivity and threefold increased turnover in cell lysate. A subsequent retrograde pathway extension, via ribokinase engineering, resulted in a didanosine pathway with a 9,500-fold change in nucleoside production selectivity and 50-fold increase in didanosine production. Unexpectedly, the result of this bioretrosynthetic step was not a retro-extension from phosphopentomutase but rather the discovery of a fortuitous pathway-shortening bypass via the engineered ribokinase.

**Phenotypic Differences in hiPSC NPCs Derived From Patients With Schizophrenia** Brennand K, Savas JN, Kim Y, Tran N, Simone A, Hashimoto-Torii K, Beaumont KG, Kim HJ, Topol A, Ladran I, Abdelrahim M, Matikainen-Ankney B, Chao SH, Mrksich M, Rakic P, Fang G, Zhang B, Yates JR 3rd, Gage FH. *Mol Psychiatry*. 2014 Apr 1. doi: 10.1038/mp.2014.22. [Epub ahead of print].

Consistent with recent reports indicating that neurons differentiated in vitro from human-induced pluripotent stem cells (hiPSCs) are immature relative to those in the human brain, gene expression comparisons of the authors' hiPSC-derived neurons to the Allen BrainSpan Atlas indicate that they most resemble fetal brain tissue. This finding suggests that, rather than modeling the late features of schizophrenia (SZ), hiPSC-based models may be better suited for the study of disease predisposition. The authors now report that a significant fraction of the gene signature of SZ hiPSC-derived neurons is conserved in SZ hiPSC neural progenitor cells (NPCs). They used two independent discovery-based approaches—microarray gene expression and stable isotope labeling by amino acids in cell culture (SILAC) quantitative proteomic mass spectrometry analyses—to identify cellular phenotypes in SZ hiPSC NPCs from four SZ patients. From their findings that SZ hiPSC NPCs show abnormal gene expression and protein levels related to cytoskeletal remodeling and oxidative stress, the authors predicted, and subsequently observed, aberrant migration and increased oxidative stress in SZ hiPSC NPCs. These reproducible NPC phenotypes were identified through scalable assays that can be applied to expanded cohorts of SZ patients, making them a potentially valuable tool with which to study the developmental mechanisms contributing to SZ.

**Dietary Triglycerides Act On Mesolimbic Structures To Regulate the Rewarding and Motivational Aspects Of Feeding** Cansell C, Castel J, Denis RG, Rouch C, Delbes AS, Martinez S, Mestivier D, Finan B, Maldonado-Aviles JG, Rijnsburger M, Tschöp MH, Dileone RJ, Eckel RH, la Fleur SE, Magnan C, Hnasko TS, Luquet S. *Mol Psychiatry*. 2014 Apr 15. doi: 10.1038/mp.2014.31. [Epub ahead of print].

Circulating triglycerides (TGs) normally increase after a meal but are altered in pathophysiological conditions, such as obesity. Although TG metabolism in the brain remains poorly understood, several brain structures express enzymes that process TG-enriched particles, including mesolimbic structures. For this reason, and because consumption of high-fat diet alters dopamine signaling, the authors tested the hypothesis that TG might directly target mesolimbic reward circuits to control reward-seeking behaviors. They found that the delivery of small amounts of TG to the brain through the carotid artery rapidly reduced both spontaneous and amphetamine-induced locomotion, abolished preference for palatable food and reduced the motivation to engage in food-seeking behavior. Conversely, targeted disruption of the TG-hydrolyzing enzyme lipoprotein lipase specifically in the nucleus accumbens increased palatable food preference and food-seeking behavior. Finally, prolonged TG perfusion resulted in a return to normal palatable food preference despite continued locomotor suppression, suggesting that adaptive mechanisms occur. These findings reveal new mechanisms by which dietary fat may alter mesolimbic circuit function and reward seeking. *Molecular Psychiatry* advance online publication, 15 April 2014; doi:10.1038/mp.2014.31.

**Methylphenidate Exerts Dose-Dependent Effects on Glutamate Receptors and Behaviors**

Cheng J, Xiong Z, Duffney LJ, Wei J, Liu A, Liu S, Chen GJ, Yan Z. *Biol Psychiatry*. 2014 Apr 12. pii: S0006-3223(14)00243-1. doi: 10.1016/j.biopsych.2014.04.003. [Epub ahead of print].

Methylphenidate (MPH), a psychostimulant drug used to treat attention-deficit/hyperactivity disorder, produces the effects of increasing alertness and improving attention. However, misuse of MPH has been associated with an increased risk of aggression and psychosis. The authors sought to

determine the molecular mechanism underlying the complex actions of MPH. Adolescent (4-week-old) rats were given one injection of MPH at different doses. The impact of MPH on glutamatergic signaling in pyramidal neurons of prefrontal cortex was measured. Behavioral changes induced by MPH were also examined in parallel. Administration of low-dose (.5 mg/kg) MPH selectively potentiated N-methyl-D-aspartate receptor (NMDAR)-mediated excitatory postsynaptic currents (EPSCs) via adrenergic receptor activation, whereas high-dose (10 mg/kg) MPH suppressed both NMDAR-mediated and alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor-mediated EPSCs. The dual effects of MPH on EPSCs were associated with bidirectional changes in the surface level of glutamate receptor subunits. Behavioral tests also indicated that low-dose MPH facilitated prefrontal cortex-mediated temporal order recognition memory and attention. Animals injected with high-dose MPH exhibited significantly elevated locomotive activity. Inhibiting the function of synaptosomal-associated protein 25, a key SNARE protein involved in NMDAR exocytosis, blocked the increase of NMDAR-mediated EPSCs by low-dose MPH. In animals exposed to repeated stress, administration of low-dose MPH effectively restored NMDAR function and temporal order recognition memory via a mechanism dependent on synaptosomal-associated protein 25. These results provide a potential mechanism underlying the cognitive-enhancing effects of low-dose MPH as well as the psychosis-inducing effects of high-dose MPH.

### **Selective Deletion of GRK2 Alters Psychostimulant-Induced Behaviors and Dopamine**

**Neurotransmission** Daigle TL, Ferris MJ, Gainetdinov RR, Sotnikova TD, Urs NM, Jones SR, Caron MG. *Neuropsychopharmacology*. 2014 Apr 29. doi: 10.1038/npp.2014.97. [Epub ahead of print].

GRK2 is a G protein-coupled receptor kinase (GRK) that is broadly expressed and is known to regulate diverse types of receptors. GRK2 null animals exhibit embryonic lethality due to a severe developmental heart defect, which has precluded the study of this kinase in the adult brain. To elucidate the specific role of GRK2 in the brain dopamine (DA) system, the authors used a conditional gene knockout approach to selectively delete GRK2 in DA D1 receptor (D1R)-, DA D2 receptor (D2R)-, adenosine 2A receptor (A2AR)-, or DA transporter (DAT)-expressing neurons. Here they show that select GRK2-deficient mice display hyperactivity, hyposensitivity, or hypersensitivity to the psychomotor effects of cocaine, altered striatal signaling, and DA release and uptake. Mice with GRK2 deficiency in D2R-expressing neurons also exhibited increased D2 autoreceptor activity. These findings reveal a cell-type-specific role for GRK2 in the regulation of normal motor behavior, sensitivity to psychostimulants, dopamine neurotransmission, and D2 autoreceptor function.

### **Kappa Opioid Receptor Activation Potentiates the Cocaine-Induced Increase in Evoked Dopamine Release Recorded in vivo in the Mouse Nucleus Accumbens**

Ehrich JM, Phillips PE, Chavkin C. *Neuropsychopharmacology*. 2014 Jun 27. doi: 10.1038/npp.2014.157. [Epub ahead of print].

Behavioral stressors increase addiction risk in humans and increase the rewarding valence of drugs of abuse including cocaine, nicotine and ethanol in animal models. Prior studies have established that this potentiation of drug reward was mediated by stress-induced release of the endogenous dynorphin opioids and subsequent kappa opioid receptor (KOR) activation. In this study, the authors used in vivo fast scan cyclic voltammetry to test the hypothesis that KOR activation prior to cocaine administration might potentiate the evoked release of dopamine from ventral tegmental (VTA) synaptic inputs to the nucleus accumbens (NAc) and thereby increase the rewarding valence of cocaine. The KOR agonist U50,488 inhibited dopamine release evoked by either medial forebrain bundle (MFB) or pedunculo-pontine tegmental nucleus (PPTg) activation of VTA inputs to

the shell or core of the mouse NAc. Cocaine administration increased the dopamine response recorded in either the shell or core evoked by either MFB or PPTg stimulation. Administration of U50,488 fifteen min prior to cocaine blocked the conditioned place preference (CPP) to cocaine, but only significantly reduced the effect of cocaine on the dopamine response evoked by PPTg stimulation to NAc core. In contrast, administration of U50,488 sixty min prior to cocaine significantly potentiated cocaine CPP and significantly increased the effects of cocaine on the dopamine response evoked by either MFB or PPTg stimulation, recorded in either NAc shell or core. Results of this study support the concept that stress-induced activation of KOR by endogenous dynorphin opioids may enhance the rewarding valence of drugs of abuse by potentiating the evoked dopamine response.

**Neural Basis of Benzodiazepine Reward: Requirement for  $\alpha 2$  Containing GABAA Receptors in the Nucleus Accumbens** Engin E, Bakhurin KI, Smith KS, Hines RM, Reynolds LM, Tang W, Sprengel R, Moss SJ, Rudolph U. *Neuropsychopharmacology*. 2014 Jul; 39(8): 1805-15. doi: 10.1038/npp.2014.41. Epub 2014 Feb 19.

Despite long-standing concerns regarding the abuse liability of benzodiazepines, the mechanisms underlying properties of benzodiazepines that may be relevant to abuse are still poorly understood. Earlier studies showed that compounds selective for  $\alpha 1$ -containing GABAA receptors ( $\alpha 1$ GABAARs) are abused by humans and self-administered by animals, and that these receptors may underlie a preference for benzodiazepines as well as neuroplastic changes observed in the ventral tegmental area following benzodiazepine administration. There is some evidence, however, that even L-838, 417, a compound with antagonistic properties at  $\alpha 1$ GABAARs and agonistic properties at the other three benzodiazepine-sensitive GABAA receptor subtypes, is self-administered, and that the  $\alpha 2$ GABAARs may have a role in benzodiazepine-induced reward enhancement. Using a two-bottle choice drinking paradigm to evaluate midazolam preference and an intracranial self-stimulation (ICSS) paradigm to evaluate the impact of midazolam on reward enhancement, the authors demonstrated that mice carrying a histidine-to-arginine point mutation in the  $\alpha 2$  subunit which renders it insensitive to benzodiazepines ( $\alpha 2$ (H101R) mice) did not prefer midazolam and did not show midazolam-induced reward enhancement in ICSS, in contrast to wild-type controls, suggesting that  $\alpha 2$ GABAARs are necessary for the reward enhancing effects and preference for oral benzodiazepines. Through a viral-mediated knockdown of  $\alpha 2$ GABAARs in the nucleus accumbens (NAc), the authors demonstrated that  $\alpha 2$  in the NAc is necessary for the preference for midazolam. Findings imply that  $\alpha 2$ GABAARs in the NAc are involved in at least some reward-related properties of benzodiazepines, which might partially underlie repeated drug-taking behavior.

**Targeting Cells With Single Vectors Using Multiple-Feature Boolean Logic** Fenno LE, Mattis J, Ramakrishnan C, Hyun M, Lee SY, He M, Tucciarone J, Selimbeyoglu A, Berndt A, Grosenick L, Zalocusky KA, Bernstein H, Swanson H, Perry C, Diester I, Boyce FM, Bass CE, Neve R, Huang ZJ, Deisseroth K. *Nat Methods*. 2014 Jul; 11(7): 763-72. doi: 10.1038/nmeth.2996. Epub 2014 Jun 8.

Precisely defining the roles of specific cell types is an intriguing frontier in the study of intact biological systems and has stimulated the rapid development of genetically encoded tools for observation and control. However, targeting these tools with adequate specificity remains challenging: most cell types are best defined by the intersection of two or more features such as active promoter elements, location and connectivity. Here the authors have combined engineered introns with specific recombinases to achieve expression of genetically encoded tools that is conditional upon multiple cell-type features, using Boolean logical operations all governed by a

single versatile vector. They used this approach to target intersectionally specified populations of inhibitory interneurons in mammalian hippocampus and neurons of the ventral tegmental area defined by both genetic and wiring properties. This flexible and modular approach may expand the application of genetically encoded interventional and observational tools for intact-systems biology.

**Cell-Type-Based Model Explaining Coexpression Patterns Of Genes In the Brain** Grange P, Bohland JW, Okaty BW, Sugino K, Bokil H, Nelson SB, Ng L, Hawrylycz M, Mitra PP. Proc Natl Acad Sci U S A. 2014 Apr 8; 111(14): 5397-402. doi: 10.1073/pnas.1312098111. Epub 2014 Mar 25.

Spatial patterns of gene expression in the vertebrate brain are not independent, as pairs of genes can exhibit complex patterns of coexpression. Two genes may be similarly expressed in one region, but differentially expressed in other regions. These correlations have been studied quantitatively, particularly for the Allen Atlas of the adult mouse brain, but their biological meaning remains obscure. The authors propose a simple model of the coexpression patterns in terms of spatial distributions of underlying cell types and establish its plausibility using independently measured cell-type-specific transcriptomes. The model allows us to predict the spatial distribution of cell types in the mouse brain.

**Genetic Variation Associated With Euphorigenic Effects Of D-Amphetamine Is Associated With Diminished Risk For Schizophrenia and Attention Deficit Hyperactivity Disorder** Hart AB, Gamazon ER, Engelhardt BE, Sklar P, Kähler AK, Hultman CM, Sullivan PF, Neale BM, Faraone SV; Psychiatric Genomics Consortium: ADHD Subgroup, de Wit H, Cox NJ, Palmer AA. 30. Proc Natl Acad Sci U S A. 2014 Apr 22; 111(16):5968-73. doi: 10.1073/pnas.1318810111. Epub 2014 Apr 7.

Here, the authors extended their findings from a genome-wide association study of the euphoric response to d-amphetamine in healthy human volunteers by identifying enrichment between SNPs associated with response to d-amphetamine and SNPs associated with psychiatric disorders. They found that SNPs nominally associated ( $P \leq 0.05$  and  $P \leq 0.01$ ) with schizophrenia and attention deficit hyperactivity disorder were also nominally associated with d-amphetamine response. Furthermore, they found that the source of this enrichment was an excess of alleles that increased sensitivity to the euphoric effects of d-amphetamine and decreased susceptibility to schizophrenia and attention deficit hyperactivity disorder. In contrast, three negative control phenotypes (height, inflammatory bowel disease, and Parkinson disease) did not show this enrichment. Taken together, these results suggest that alleles identified using an acute challenge with a dopaminergic drug in healthy individuals can be used to identify alleles that confer risk for psychiatric disorders commonly treated with dopaminergic agonists and antagonists. More importantly, these results show the use of the enrichment approach as an alternative to stringent standards for genome-wide significance and suggest a relatively novel approach to the analysis of small cohorts in which intermediate phenotypes have been measured.

**Two-Photon Neuronal and Astrocytic Stimulation With Azobenzene-Based Photoswitches** Izquierdo-Serra M, Gascón-Moya M, Hirtz JJ, Pittolo S, Poskanzer KE, Ferrer E, Alibés R, Busqué F, Yuste R, Hernando J, Gorostiza P. J Am Chem Soc. 2014 Jun 18; 136(24): 8693-701. doi: 10.1021/ja5026326. Epub 2014 Jun 5.

Synthetic photochromic compounds can be designed to control a variety of proteins and their biochemical functions in living cells, but the high spatiotemporal precision and tissue penetration of two-photon stimulation have never been investigated in these molecules. Here the authors demonstrate two-photon excitation of azobenzene-based protein switches and versatile strategies to

enhance their photochemical responses. This enables new applications to control the activation of neurons and astrocytes with cellular and subcellular resolution.

### **CNTNAP4 Differentially Contributes to GABAergic and Dopaminergic Synaptic**

**Transmission** Karayannis T, Au E, Patel C, Kruglikov I, Markx S, Delorme R, Héron D, Salomon D, Glessner J, Restituito S, Gordon A, Rodriguez-Murillo L, Roy NC, Gogos JA, Rudy B, Rice ME, Karayiorgou M, Hakonarson H, Keren B, Huguet G, Bourgeron T, Hoeffler C, Tsien RW, Peles E, Fishell G. *Nature*. 2014 Jul 10; 511(7508): 236-40.

Although considerable evidence suggests that the chemical synapse is a lynchpin underlying affective disorders, how molecular insults differentially affect specific synaptic connections remains poorly understood. For instance, Neurexin 1a and 2 (NRXN1 and NRXN2) and CNTNAP2 (also known as CASPR2), all members of the neurexin superfamily of transmembrane molecules, have been implicated in neuropsychiatric disorders. However, their loss leads to deficits that have been best characterized with regard to their effect on excitatory cells. Notably, other disease-associated genes such as BDNF and ERBB4 implicate specific interneuron synapses in psychiatric disorders. Consistent with this, cortical interneuron dysfunction has been linked to epilepsy, schizophrenia and autism. Using a microarray screen that focused upon synapse-associated molecules, the authors identified Cntnap4 (contactin associated protein-like 4, also known as Caspr4) as highly enriched in developing murine interneurons. In this study they show that Cntnap4 is localized presynaptically and its loss leads to a reduction in the output of cortical parvalbumin (PV)-positive GABAergic ( $\gamma$ -aminobutyric acid producing) basket cells. Paradoxically, the loss of Cntnap4 augments midbrain dopaminergic release in the nucleus accumbens. In Cntnap4 mutant mice, synaptic defects in these disease-relevant neuronal populations are mirrored by sensory-motor gating and grooming endophenotypes; these symptoms could be pharmacologically reversed, providing promise for therapeutic intervention in psychiatric disorders.

**Conformational Dynamics Of Ligand-Dependent Alternating Access in LeuT** Kazmier K, Sharma S, Quick M, Islam SM, Roux B, Weinstein H, Javitch JA, McHaourab HS. *Nat Struct Mol Biol*. 2014 May; 21(5): 472-9. doi: 10.1038/nsmb.2816. Epub 2014 Apr 20.

The leucine transporter (LeuT) from *Aquifex aeolicus* is a bacterial homolog of neurotransmitter/sodium symporters (NSSs) that catalyze reuptake of neurotransmitters at the synapse. Crystal structures of wild-type and mutants of LeuT have been interpreted as conformational states in the coupled transport cycle. However, the mechanistic identities inferred from these structures have not been validated, and the ligand-dependent conformational equilibrium of LeuT has not been defined. Here, the authors used distance measurements between spin-label pairs to elucidate Na(+)- and leucine-dependent conformational changes on the intracellular and extracellular sides of the transporter. The results identify structural motifs that underlie the isomerization of LeuT between outward-facing, inward-facing and occluded states. The conformational changes reported here present a dynamic picture of the alternating-access mechanism of LeuT and NSSs that is different from the inferences reached from currently available structural models.

### **Acid-Sensing Ion Channels Contribute To Synaptic Transmission and Inhibit Cocaine-Evoked Plasticity**

Kreple CJ, Lu Y, Taugher RJ, Schwager-Gutman AL, Du J, Stump M, Wang Y, Ghobbeh A, Fan R, Cosme CV, Sowers LP, Welsh MJ, Radley JJ, LaLumiere RT, Wemmie JA. *Nat Neurosci*. 2014 Jun 22. doi: 10.1038/nn.3750. [Epub ahead of print].

Acid-sensing ion channel 1A (ASIC1A) is abundant in the nucleus accumbens (NAc), a region known for its role in addiction. Because ASIC1A has been suggested to promote associative

learning, the authors hypothesized that disrupting ASIC1A in the NAc would reduce drug-associated learning and memory. However, contrary to this hypothesis, they found that disrupting ASIC1A in the mouse NAc increased cocaine-conditioned place preference, suggesting an unexpected role for ASIC1A in addiction-related behavior. Moreover, overexpressing ASIC1A in rat NAc reduced cocaine self-administration. Investigating the underlying mechanisms, the authors identified a previously unknown postsynaptic current during neurotransmission that was mediated by ASIC1A and ASIC2 and thus well positioned to regulate synapse structure and function. Consistent with this possibility, disrupting ASIC1A altered dendritic spine density and glutamate receptor function, and increased cocaine-evoked plasticity, which resemble changes previously associated with cocaine-induced behavior. Together, these data suggest that ASIC1A inhibits the plasticity underlying addiction-related behavior and raise the possibility of developing therapies for drug addiction by targeting ASIC-dependent neurotransmission.

**Executive Control Processes Underlying Multi-Item Working Memory** Lara AH, Wallis JD. *Nat Neurosci.* 2014 Jun; 17(6): 876-83. doi: 10.1038/nn.3702. Epub 2014 Apr 20.

A dominant view of prefrontal cortex (PFC) function is that it stores task-relevant information in working memory. To examine this and determine how it applies when multiple pieces of information must be stored, the authors trained two subjects to perform a multi-item color change detection task and recorded activity of neurons in PFC. Few neurons encoded the color of the items. Instead, the predominant encoding was spatial: a static signal reflecting the item's position and a dynamic signal reflecting the subject's covert attention. These findings challenge the notion that PFC stores task-relevant information. Instead, the authors suggest that the contribution of PFC is in controlling the allocation of resources to support working memory. In support of this, they found that increased power in the alpha and theta bands of PFC local field potentials, which are thought to reflect long-range communication with other brain areas, was correlated with more precise color representations.

**Cyclin D1-Cdk4 Controls Glucose Metabolism Independently Of Cell Cycle Progression** Lee Y, Dominy JE, Choi YJ, Jurczak M, Tolliday N, Camporez JP, Chim H, Lim JH, Ruan HB, Yang X, Vazquez F, Sicinski P, Shulman GI, Puigserver P. *Nature.* 2014 Jun 26; 510(7506): 547-51. doi: 10.1038/nature13267. Epub 2014 May 25.

Insulin constitutes a principal evolutionarily conserved hormonal axis for maintaining glucose homeostasis; dysregulation of this axis causes diabetes. PGC-1 $\alpha$  (peroxisome-proliferator-activated receptor- $\gamma$  coactivator-1 $\alpha$ ) links insulin signalling to the expression of glucose and lipid metabolic genes. The histone acetyltransferase GCN5 (general control non-repressed protein 5) acetylates PGC-1 $\alpha$  and suppresses its transcriptional activity, whereas sirtuin 1 deacetylates and activates PGC-1 $\alpha$ . Although insulin is a mitogenic signal in proliferative cells, whether components of the cell cycle machinery contribute to its metabolic action is poorly understood. Here the authors report that in mice insulin activates cyclin D1-cyclin-dependent kinase 4 (Cdk4), which, in turn, increases GCN5 acetyltransferase activity and suppresses hepatic glucose production independently of cell cycle progression. Through a cell-based high-throughput chemical screen, the authors identify a Cdk4 inhibitor that potently decreases PGC-1 $\alpha$  acetylation. Insulin/GSK-3 $\beta$  (glycogen synthase kinase 3-beta) signalling induces cyclin D1 protein stability by sequestering cyclin D1 in the nucleus. In parallel, dietary amino acids increase hepatic cyclin D1 messenger RNA transcripts. Activated cyclin D1-Cdk4 kinase phosphorylates and activates GCN5, which then acetylates and inhibits PGC-1 $\alpha$  activity on gluconeogenic genes. Loss of hepatic cyclin D1 results in increased gluconeogenesis and hyperglycaemia. In diabetic models, cyclin D1-Cdk4 is chronically elevated and refractory to fasting/feeding transitions; nevertheless further activation of this kinase normalizes

glycaemia. These findings show that insulin uses components of the cell cycle machinery in post-mitotic cells to control glucose homeostasis independently of cell division.

**Discovery of Amphipathic Dynorphin A Analogues To Inhibit the Neuroexcitatory Effects Of Dynorphin A Through Bradykinin Receptors In the Spinal Cord**

Lee YS, Muthu D, Hall SM, Ramos-Colon C, Rankin D, Hu J, Sandweiss AJ, De Felice M, Xie JY, Vanderah TW, Porreca F, Lai J, Hruby VJ. *J Am Chem Soc.* 2014 May 7; 136(18): 6608-16. doi: 10.1021/ja501677q. Epub 2014 Apr 29.

The authors hypothesized that under chronic pain conditions, up-regulated dynorphin A (Dyn A) interacts with bradykinin receptors (BRs) in the spinal cord to promote hyperalgesia through an excitatory effect, which is opposite to the well-known inhibitory effect of opioid receptors. Considering the structural dissimilarity between Dyn A and endogenous BR ligands, bradykinin (BK) and kallidin (KD), this interaction could not be predicted, but it allowed the authors to discover a potential neuroexcitatory target. Well-known BR ligands, BK, [des-Arg(10), Leu(9)]-kallidin (DALKD), and HOE140 showed different binding profiles at rat brain BRs than that previously reported. These results suggest that neuronal BRs in the rat central nervous system (CNS) may be pharmacologically distinct from those previously defined in non-neuronal tissues. Systematic structure-activity relationship (SAR) study at the rat brain BRs was performed, and as a result, a new key structural feature of Dyn A for BR recognition was identified: amphipathicity. NMR studies of two lead ligands, Dyn A-(4-11) 7 and [des-Arg(7)]-Dyn A-(4-11) 14, which showed the same high binding affinity, confirmed that the Arg residue in position 7, which is known to be crucial for Dyn A's biological activity, is not necessary, and that a type I  $\beta$ -turn structure at the C-terminal part of both ligands plays an important role in retaining good binding affinities at the BRs. The authors' lead ligand 14 blocked Dyn A-(2-13) 10-induced hyperalgesic effects and motor impairment in in vivo assays using naïve rats. In a model of peripheral neuropathy, intrathecal (i.th.) administration of ligand 14 reversed thermal hyperalgesia and mechanical hypersensitivity in a dose-dependent manner in nerve-injured rats. Thus, ligand 14 may inhibit abnormal pain states by blocking the neuroexcitatory effects of enhanced levels of Dyn A, which are likely to be mediated by BRs in the spinal cord.

**Symbol Addition By Monkeys Provides Evidence For Normalized Quantity Coding**

Livingstone MS, Pettine WW, Srihasam K, Moore B, Morocz IA, Lee D. *Proc Natl Acad Sci U S A.* 2014 May 6; 111(18): 6822-7. doi: 10.1073/pnas.1404208111. Epub 2014 Apr 21.

Weber's law can be explained either by a compressive scaling of sensory response with stimulus magnitude or by a proportional scaling of response variability. These two mechanisms can be distinguished by asking how quantities are added or subtracted. The authors trained Rhesus monkeys to associate 26 distinct symbols with 0-25 drops of reward, and then tested how they combine, or add, symbolically represented reward magnitude. They found that they could combine symbolically represented magnitudes, and they transferred this ability to a novel symbol set, indicating that they were performing a calculation, not just memorizing the value of each combination. The way they combined pairs of symbols indicated neither a linear nor a compressed scale, but rather a dynamically shifting, relative scaling.

**Impaired Fear Memory Specificity Associated With Deficient Endocannabinoid-Dependent Long-Term Plasticity** Lovelace JW(1), Vieira PA(1), Corches A(2), Mackie K(3), Korzus E(4). 51. *Neuropsychopharmacology*. 2014 Jun; 39(7): 1685-93. doi: 10.1038/npp.2014.15. Epub 2014 Jan 24.

In addition to its central role in learning and memory, N-methyl D-aspartate receptor (NMDAR)-dependent signaling regulates central glutamatergic synapse maturation and has been implicated in schizophrenia. The authors have transiently induced NMDAR hypofunction in infant mice during postnatal days 7-11, followed by testing fear memory specificity and presynaptic plasticity in the prefrontal cortex (PFC) in adult mice. They show that transient NMDAR hypofunction during early brain development, coinciding with the maturation of cortical plasticity results in a loss of an endocannabinoid (eCB)-mediated form of long-term depression (eCB-LTD) at adult central glutamatergic synapses, while another form of presynaptic long-term depression mediated by the metabotropic glutamate receptor 2/3 (mGluR2/3-LTD) remains intact. Mice with this selective impairment of presynaptic plasticity also showed deficits in fear memory specificity. The observed deficit in cortical presynaptic plasticity may represent a neural maladaptation contributing to network instability and abnormal cognitive functioning.

**Calcineurin Downregulation In the Amygdala Is Sufficient To Induce Anxiety-Like and Depression-Like Behaviors in C57BL/6J Male Mice**

Mineur YS, Taylor SR, Picciotto MR. *Biol Psychiatry*. 2014 Jun 15; 75(12): 991-8. doi: 10.1016/j.biopsych.2014.03.009. Epub 2014 Mar 14. The calcium-dependent phosphatase calcineurin is highly expressed in the amygdala, a brain area important for behaviors related to mood disorders and anxiety. Organ transplant patients are administered the calcineurin inhibitor cyclosporine A (CsA) chronically and demonstrate an increased incidence of anxiety and mood disorders. It is therefore important to determine whether chronic blockade of calcineurin may contribute to symptoms of anxiety and depression in these patients. Pharmacological (CSA) and viral-mediated gene transfer (adeno-associated viral expression of short hairpin RNA [shRNA]) approaches were used to inhibit calcineurin activity systemically or selectively in the amygdala of the mouse brain to determine the role of calcineurin in behaviors related to anxiety and depression. Systemic inhibition of calcineurin activity with CsA or local downregulation of calcineurin levels in the amygdala using adeno-associated viral-delivered shRNAs targeting calcineurin B increased measures of anxiety-like behavior in the elevated plus maze, the light/dark box, and the open field test. A decrease in locomotor activity was also observed in mice treated systemically with CsA. In the forced swim model of depression-like behavior, both systemic CsA treatment and shRNA-mediated calcineurin blockade in the amygdala significantly increased immobility. Taken together, these data demonstrate that decreasing calcineurin activity in the amygdala increases anxiety-like behaviors and to some extent depression-like behaviors. These studies suggest that chronic administration of CsA to organ transplant patients could have significant effects on anxiety and mood and this should be recognized as a potential clinical consequence of treatment to prevent transplant rejection.

**The Ctenophore Genome and the Evolutionary Origins Of Neural Systems**

Moroz LL, Kocot KM, Citarella MR, Dosung S, Norekian TP, Povolotskaya IS, Grigorenko AP, Dailey C, Berezikov E, Buckley KM, Ptitsyn A, Reshetov D, Mukherjee K, Moroz TP, Bobkova Y, Yu F, Kapitonov VV, Jurka J, Bobkov YV, Swore JJ, Girardo DO, Fodor A, Gusev F, Sanford R, Bruders R, Kittler E, Mills CE, Rast JP, Derelle R, Solovyev VV, Kondrashov FA, Swalla BJ, Sweedler JV, Rogaev EI, Halanych KM, Kohn AB. *Nature*. 2014 Jun 5; 510(7503): 109-14. doi: 10.1038/nature13400. Epub 2014 May 21.

The origins of neural systems remain unresolved. In contrast to other basal metazoans, ctenophores (comb jellies) have both complex nervous and mesoderm-derived muscular systems. These holoplanktonic predators also have sophisticated ciliated locomotion, behaviour and distinct development. Here the authors present the draft genome of *Pleurobrachia bachei*, Pacific sea gooseberry, together with ten other ctenophore transcriptomes, and show that they are remarkably distinct from other animal genomes in their content of neurogenic, immune and developmental genes. The authors' integrative analyses place Ctenophora as the earliest lineage within Metazoa. This hypothesis is supported by comparative analysis of multiple gene families, including the apparent absence of HOX genes, canonical microRNA machinery, and reduced immune complement in ctenophores. Although two distinct nervous systems are well recognized in ctenophores, many bilaterian neuron-specific genes and genes of 'classical' neurotransmitter pathways either are absent or, if present, are not expressed in neurons. The authors' metabolomic and physiological data are consistent with the hypothesis that ctenophore neural systems, and possibly muscle specification, evolved independently from those in other animals.

### **Sorting Nexin 27 Regulation Of G Protein-Gated Inwardly Rectifying K<sup>+</sup> Channels**

**Attenuates In Vivo Cocaine Response** Munoz MB, Slesinger PA. *Neuron*. 2014 May 7; 82(3): 659-69. doi: 10.1016/j.neuron.2014.03.011.

The subcellular pathways that regulate G protein-gated inwardly rectifying potassium (GIRK or Kir3) channels are important for controlling the excitability of neurons. Sorting nexin 27 (SNX27) is a PDZ-containing protein known to bind GIRK2c/GIRK3 channels, but its function in vivo is poorly understood. Here, the authors investigated the role of SNX27 in regulating GIRK currents in dopamine (DA) neurons of the ventral tegmental area (VTA). Mice lacking SNX27 in DA neurons exhibited reduced GABABR-activated GIRK currents but had normal I<sub>h</sub> currents and DA D2R-activated GIRK currents. Expression of GIRK2a, an SNX27-insensitive splice variant, restored GABABR-activated GIRK currents in SNX27-deficient DA neurons. Remarkably, mice with significantly reduced GABABR-activated GIRK currents in only DA neurons were hypersensitive to cocaine and could be restored to a normal locomotor response with GIRK2a expression. These results identify a pathway for regulating excitability of VTA DA neurons, highlighting SNX27 as a promising target for treating addiction.

### **Hypocretin (Orexin) Facilitates Reward By Attenuating the Antireward Effects Of Its**

**Cotransmitter Dynorphin In Ventral Tegmental Area** Muschamp JW, Hollander JA, Thompson JL, Voren G, Hassinger LC, Onvani S, Kamenecka TM, Borgland SL, Kenny PJ, Carlezon WA Jr. 60. *Proc Natl Acad Sci U S A*. 2014 Apr 22; 111(16): E1648-55. doi: 10.1073/pnas.1315542111. Epub 2014 Mar 24.

Hypocretin (orexin) and dynorphin are neuropeptides with opposing actions on motivated behavior. Orexin is implicated in states of arousal and reward, whereas dynorphin is implicated in depressive-like states. The authors show that, despite their opposing actions, these peptides are packaged in the same synaptic vesicles within the hypothalamus. Disruption of orexin function blunts the rewarding effects of lateral hypothalamic (LH) stimulation, eliminates cocaine-induced impulsivity, and reduces cocaine self-administration. Concomitant disruption of dynorphin function reverses these behavioral changes. The authors also show that orexin and dynorphin have opposing actions on excitability of ventral tegmental area (VTA) dopamine neurons, a prominent target of orexin-containing neurons, and that intra-VTA orexin antagonism causes decreases in cocaine self-administration and LH self-stimulation that are reversed by dynorphin antagonism. These findings identify a unique cellular process by which orexin can occlude the reward threshold-elevating effects of coreleased dynorphin and thereby act in a permissive fashion to facilitate reward.

**Dopamine Transporter Deficiency Syndrome: Phenotypic Spectrum From Infancy To Adulthood** Ng J, Zhen J, Meyer E, Erreger K, Li Y, Kakar N, Ahmad J, Thiele H, Kubisch C, Rider NL, Morton DH, Strauss KA, Puffenberger EG, D'Agnano D, Anikster Y, Carducci C, Hyland K, Rotstein M, Leuzzi V, Borck G, Reith ME, Kurian MA. *Brain*. 2014 Apr; 137(Pt 4): 1107-19. doi: 10.1093/brain/awu022. Epub 2014 Mar 10.

Dopamine transporter deficiency syndrome due to SLC6A3 mutations is the first inherited dopamine 'transportopathy' to be described, with a classical presentation of early infantile-onset progressive parkinsonism dystonia. In this study the authors have identified a new cohort of patients with dopamine transporter deficiency syndrome, including, most significantly, atypical presentation later in childhood with a milder disease course. They report the detailed clinical features, molecular genetic findings and in vitro functional investigations undertaken for adult and paediatric cases. Patients presenting with parkinsonism dystonia or a neurotransmitter profile characteristic of dopamine transporter deficiency syndrome were recruited for study. SLC6A3 mutational analysis was undertaken in all patients. The functional consequences of missense variants on the dopamine transporter were evaluated by determining the effect of mutant dopamine transporter on dopamine uptake, protein expression and amphetamine-mediated dopamine efflux using an in vitro cellular heterologous expression system. The authors identified eight new patients from five unrelated families with dopamine transporter deficiency syndrome. The median age at diagnosis was 13 years (range 1.5-34 years). Most significantly, the case series included three adolescent males with atypical dopamine transporter deficiency syndrome of juvenile onset (outside infancy) and progressive parkinsonism dystonia. The other five patients in the cohort presented with classical infantile-onset parkinsonism dystonia, with one surviving into adulthood (currently aged 34 years) and labelled as having 'juvenile parkinsonism'. All eight patients harboured homozygous or compound heterozygous mutations in SLC6A3, of which the majority are previously unreported variants. In vitro studies of mutant dopamine transporter demonstrated multifaceted loss of dopamine transporter function. Impaired dopamine uptake was universally present, and more severely impacted in dopamine transporter mutants causing infantile-onset rather than juvenile-onset disease. Dopamine transporter mutants also showed diminished dopamine binding affinity, reduced cell surface transporter, loss of post-translational dopamine transporter glycosylation and failure of amphetamine-mediated dopamine efflux. The authors' data series expands the clinical phenotypic continuum of dopamine transporter deficiency syndrome and indicates that there is a phenotypic spectrum from infancy (early onset, rapidly progressive disease) to childhood/adolescence and adulthood (later onset, slower disease progression). Genotype-phenotype analysis in this cohort suggests that higher residual dopamine transporter activity is likely to contribute to postponing disease presentation in these later-onset adult cases. Dopamine transporter deficiency syndrome remains under-recognized and these data highlights that dopamine transporter deficiency syndrome should be considered as a differential diagnosis for both infantile- and juvenile-onset movement disorders, including cerebral palsy and juvenile parkinsonism.

**Cannabinoid Receptor Activation Shifts Temporally Engendered Patterns Of Dopamine Release** Oleson EB, Cachope R, Fitoussi A, Tsutsui K, Wu S, Gallegos JA, Cheer JF. *Neuropsychopharmacology*. 2014 May; 39(6): 1441-52. doi: 10.1038/npp.2013.340. Epub 2013 Dec 18.

The ability to discern temporally pertinent environmental events is essential for the generation of adaptive behavior in conventional tasks, and our overall survival. Cannabinoids are thought to disrupt temporally controlled behaviors by interfering with dedicated brain timing networks. Cannabinoids also increase dopamine release within the mesolimbic system, a neural pathway generally implicated in timing behavior. Timing can be assessed using fixed-interval (FI) schedules,

which reinforce behavior on the basis of time. To date, it remains unknown how cannabinoids modulate dopamine release when responding under FI conditions, and for that matter, how subsecond dopamine release is related to time in these tasks. In the present study, the authors hypothesized that cannabinoids would accelerate timing behavior in an FI task while concurrently augmenting a temporally relevant pattern of dopamine release. To assess this possibility, they measured subsecond dopamine concentrations in the nucleus accumbens while mice responded for food under the influence of the cannabinoid agonist WIN 55,212-2 in an FI task. Their data reveal that accumbal dopamine concentrations decrease proportionally to interval duration--suggesting that dopamine encodes time in FI tasks. The authors further demonstrate that WIN 55,212-2 dose-dependently increases dopamine release and accelerates a temporal behavioral response pattern in a CB1 receptor-dependent manner--suggesting that cannabinoid receptor activation modifies timing behavior, in part, by augmenting time-engendered patterns of dopamine release. Additional investigation uncovered a specific role for endogenous cannabinoid tone in timing behavior, as elevations in 2-arachidonoylglycerol, but not anandamide, significantly accelerated the temporal response pattern in a manner akin to WIN 55,212-2.

**Differential Effects Of Systemic Cholinergic Receptor Blockade On Pavlovian Incentive Motivation and Goal-Directed Action Selection**

Ostlund SB, Koshelev AR, Maidment NT. *Neuropsychopharmacology*. 2014 May; 39(6): 1490-7. doi: 10.1038/npp.2013.348. Epub 2013 Dec 27.

Reward-seeking actions can be guided by external cues that signal reward availability. For instance, when confronted with a stimulus that signals sugar, rats will prefer an action that produces sugar over a second action that produces grain pellets. Action selection is also sensitive to changes in the incentive value of potential rewards. Thus, rats that have been prefed a large meal of sucrose will prefer a grain-seeking action to a sucrose-seeking action. The current study investigated the dependence of these different aspects of action selection on cholinergic transmission. Hungry rats were given differential training with two unique stimulus-outcome (S1-O1 and S2-O2) and action-outcome (A1-O1 and A2-O2) contingencies during separate training phases. Rats were then given a series of Pavlovian-to-instrumental transfer tests, an assay of cue-triggered responding. Before each test, rats were injected with scopolamine (0, 0.03, or 0.1 mg/kg, intraperitoneally), a muscarinic receptor antagonist, or mecamylamine (0, 0.75, or 2.25 mg/kg, intraperitoneally), a nicotinic receptor antagonist. Although the reward-paired cues were capable of biasing action selection when rats were tested off-drug, both anticholinergic treatments were effective in disrupting this effect. During a subsequent round of outcome devaluation testing--used to assess the sensitivity of action selection to a change in reward value--we found no effect of either scopolamine or mecamylamine. These results reveal that cholinergic signaling at both muscarinic and nicotinic receptors mediates action selection based on Pavlovian reward expectations, but is not critical for flexibly selecting actions using current reward values.

**Insulin Excites Anorexigenic Proopiomelanocortin Neurons Via Activation Of Canonical Transient Receptor Potential Channels**

Qiu J, Zhang C, Borgquist A, Nestor CC, Smith AW, Bosch MA, Ku S, Wagner EJ, Rønnekleiv OK, Kelly MJ. *Cell Metab*. 2014 Apr 1; 19(4): 682-93. doi: 10.1016/j.cmet.2014.03.004.

Proopiomelanocortin (POMC) neurons within the hypothalamic arcuate nucleus are vital anorexigenic neurons. Although both the leptin and insulin receptors are coupled to the activation of phosphatidylinositol 3 kinase (PI3K) in POMC neurons, they are thought to have disparate actions on POMC excitability. Using whole-cell recording and selective pharmacological tools, the authors have found that, similar to leptin, purified insulin depolarized POMC and adjacent kisspeptin

neurons via activation of TRPC5 channels, which are highly expressed in these neurons. In contrast, insulin hyperpolarized and inhibited NPY/AgRP neurons via activation of KATP channels. Moreover, Zn(2+), which is found in insulin formulations at nanomolar concentrations, inhibited POMC neurons via activation of KATP channels. Finally, as predicted, insulin given intracerebroventrically robustly inhibited food intake and activated c-fos expression in arcuate POMC neurons. These results show that purified insulin excites POMC neurons in the arcuate nucleus, which the authors propose is a major mechanism by which insulin regulates energy homeostasis.

**Unanchored K48-Linked Polyubiquitin Synthesized by the E3-Ubiquitin Ligase TRIM6 Stimulates the Interferon-IKK $\epsilon$  Kinase-Mediated Antiviral Response** Rajsbaum R, Versteeg GA, Schmid S, Maestre AM, Belicha-Villanueva A, Martínez-Romero C, Patel JR, Morrison J, Pisanelli G, Miorin L, Laurent-Rolle M, Moulton HM, Stein DA, Fernandez-Sesma A, tenOever BR, García-Sastre A. 67. *Immunity*. 2014 Jun 19; 40(6): 880-95. doi: 10.1016/j.immuni.2014.04.018. Epub 2014 May 29.

Type I interferons (IFN-I) are essential antiviral cytokines produced upon microbial infection. IFN-I elicits this activity through the upregulation of hundreds of IFN-I-stimulated genes (ISGs). The full breadth of ISG induction demands activation of a number of cellular factors including the I $\kappa$ B kinase epsilon (IKK $\epsilon$ ). However, the mechanism of IKK $\epsilon$  activation upon IFN receptor signaling has remained elusive. Here the authors show that TRIM6, a member of the E3-ubiquitin ligase tripartite motif (TRIM) family of proteins, interacted with IKK $\epsilon$  and promoted induction of IKK $\epsilon$ -dependent ISGs. TRIM6 and the E2-ubiquitin conjugase Ube2K cooperated in the synthesis of unanchored K48-linked polyubiquitin chains, which activated IKK $\epsilon$  for subsequent STAT1 phosphorylation. The authors' work attributes a previously unrecognized activating role of K48-linked unanchored polyubiquitin chains in kinase activation and identifies the Ube2K-TRIM6-ubiquitin axis as critical for IFN signaling and antiviral response.

**Fluoxetine Epigenetically Alters the Camkii $\alpha$  Promoter In Nucleus Accumbens To Regulate Afosb Binding and Antidepressant Effects** Robison AJ, Vialou V, Sun HS, Labonte B, A Golden S, Dias C, Turecki G, Tamminga C, Russo S, Mazei-Robison M, Nestler EJ. *Neuropsychopharmacology*. 2014 Apr; 39(5): 1178-86. doi: 10.1038/npp.2013.319. Epub 2013 Nov 15.

Chronic social defeat stress in mice produces a susceptible phenotype characterized by several behavioral abnormalities consistent with human depression that are reversed by chronic but not acute exposure to antidepressant medications. Recent work in addiction models demonstrates that the transcription factor  $\Delta$ FosB and protein kinase calmodulin-dependent protein kinase II (CaMKII) are co-regulated in nucleus accumbens (NAc), a brain reward region implicated in both addiction and depression models including social defeat. Previous work has also demonstrated that  $\Delta$ FosB is induced in NAc after chronic social defeat stress or after chronic antidepressant treatment, wherein it mediates a pro-resilience or antidepressant-like phenotype. Here, using chromatin immunoprecipitation assays, the authors found that  $\Delta$ FosB binds the CaMKII $\alpha$  gene promoter in NAc and that this binding increases after mice are exposed to chronic social defeat stress. Paradoxically, chronic exposure to the antidepressant fluoxetine reduces binding of  $\Delta$ FosB to the CaMKII $\alpha$  promoter and reduces CaMKII expression in NAc, despite the fact that  $\Delta$ FosB is induced under these conditions. These data suggest a novel epigenetic mechanism of antidepressant action, whereby fluoxetine induces some chromatin change at the CaMKII $\alpha$  promoter, which blocks the  $\Delta$ FosB binding. Indeed, chronic fluoxetine reduces acetylation and increases lysine-9 dimethylation of histone H3 at the CaMKII $\alpha$  promoter in NAc, effects also seen in depressed humans exposed to

antidepressants. Overexpression of CaMKII in NAc blocks fluoxetine's antidepressant effects in the chronic social defeat paradigm, whereas inhibition of CaMKII activity in NAc mimics fluoxetine exposure. These findings suggest that epigenetic suppression of CaMKII $\alpha$  expression in NAc is behaviorally relevant and offer a novel pathway for possible therapeutic intervention in depression and related syndromes.

**Kinome-Wide Functional Analysis Highlights the Role Of Cytoskeletal Remodeling In Somatic Cell Reprogramming**

Sakurai K, Talukdar I, Patil VS, Dang J, Li Z, Chang KY, Lu CC, Delorme-Walker V, Dermardirossian C, Anderson K, Hanein D, Yang CS, Wu D, Liu Y, Rana TM. *Cell Stem Cell*. 2014 Apr 3; 14(4): 523-34. doi: 10.1016/j.stem.2014.03.001.

The creation of induced pluripotent stem cells (iPSCs) from somatic cells by ectopic expression of transcription factors has galvanized the fields of regenerative medicine and developmental biology. Here, the authors report a kinome-wide RNAi-based analysis to identify kinases that regulate somatic cell reprogramming to iPSCs. They prepared 3,686 small hairpin RNA (shRNA) lentiviruses targeting 734 kinase genes covering the entire mouse kinome and individually examined their effects on iPSC generation. They identified 59 kinases as barriers to iPSC generation and characterized seven of them further. They found that shRNA-mediated knockdown of the serine/threonine kinases TESK1 or LIMK2 promoted mesenchymal-to-epithelial transition, decreased COFILIN phosphorylation, and disrupted Actin filament structures during reprogramming of mouse embryonic fibroblasts. Similarly, knockdown of TESK1 in human fibroblasts also promoted reprogramming to iPSCs. This study reveals the breadth of kinase networks regulating pluripotency and identifies a role for cytoskeletal remodeling in modulating the somatic cell reprogramming process.

**Clozapine Acts as an Agonist at Serotonin 2A Receptors to Counter MK-801-Induced Behaviors through a  $\beta$ Arrestin2-Independent Activation of Akt**

Schmid CL, Streicher JM, Meltzer HY, Bohn LM. *Neuropsychopharmacology*. 2014 Jul; 39(8): 1902-13. doi: 10.1038/npp.2014.38. Epub 2014 Feb 17.

The G protein-coupled serotonin 2A receptor (5-HT<sub>2A</sub>R) is a prominent target for atypical antipsychotic drugs, such as clozapine. Although clozapine is known to inhibit 5-HT<sub>2A</sub>R signaling through G protein-dependent mechanisms, it differs from classic GPCR antagonists, in that it also induces 5-HT<sub>2A</sub>R internalization and activates Akt signaling via a 5-HT<sub>2A</sub>R-mediated event. In this regard, clozapine may also be considered a functionally selective agonist. The cognate neurotransmitter at the 5-HT<sub>2A</sub>R, serotonin, also induces 5-HT<sub>2A</sub>R internalization and Akt phosphorylation. Serotonin promotes interactions with the scaffolding and regulatory protein,  $\beta$ arrestin2, which results in the recruitment and activation of Akt. These interactions prove to be critical for serotonin-induced, 5-HT<sub>2A</sub>R-mediated behavioral responses in mice. Herein, the authors sought to determine whether clozapine also utilizes  $\beta$ arrestin2-mediated mechanisms to induce 5-HT<sub>2A</sub>R signaling, and whether this interaction contributes to its behavioral effects in mice. They demonstrate that unlike serotonin, clozapine-mediated 5-HT<sub>2A</sub>R internalization and Akt phosphorylation is independent of receptor interactions with  $\beta$ arrestin2. Moreover, clozapine-mediated suppression of MK-801 and phencyclidine (PCP)-induced hyperlocomotion is  $\beta$ arrestin2 independent, although it is dependent upon Akt. These results demonstrate that pharmacologically oppositional ligands, serotonin and clozapine, utilize differential mechanisms to achieve the same 5-HT<sub>2A</sub>R-mediated downstream events: Akt phosphorylation and receptor internalization. Although  $\beta$ arrestin2 has no effect on clozapine's actions in vivo, Akt phosphorylation is required for clozapine's efficacy in blocking MK-801- and PCP-induced models of schizophrenic behaviors in mice.

**Prelimbic Cortex and Ventral Tegmental Area Modulate Synaptic Plasticity Differentially In Nucleus Accumbens During Cocaine-Reinstated Drug Seeking** Shen HW, Gipson CD, Huits M, Kalivas PW. *Neuropsychopharmacology*. 2014 Apr; 39(5): 1169-77. doi: 10.1038/npp.2013.318. Epub 2013 Nov 15.

Addictive drug use causes long-lasting changes in synaptic strength and dendritic spine morphology in the nucleus accumbens that might underlie the vulnerability to relapse. Although activity in mesocorticolimbic circuitry is required for reinstating cocaine seeking, its role in reinstatement-associated synaptic plasticity is not well characterized. Using rats extinguished from cocaine self-administration, the authors found potentiated synaptic strength (assessed as the AMPA/NMDA current amplitude ratio) and increased spine head diameter in medium spiny neurons in the accumbens core (NAcore). The basal changes in synaptic strength and morphology in cocaine-extinguished animals were further augmented during cocaine-induced reinstatement. Two NAcore afferents contributing to cocaine reinstatement are glutamatergic inputs from the prefrontal cortex (PL) and dopamine from the ventral tegmental area (VTA). Pharmacological inhibition of either PL or VTA prevented cocaine-primed reinstatement. However, inhibiting the PL further potentiated AMPA/NMDA and spine head diameter, while inactivating the VTA or the combined systemic administration of dopamine D1 and D2 antagonists prevented the increase in AMPA/NMDA and spine diameter induced by cocaine priming. These data indicate that neuronal activity in the VTA and associated dopamine receptor stimulation is necessary for the synaptic potentiation in the NAcore during cocaine-induced reinstatement. Although activity in the PL was necessary for reinstatement, it inhibited synaptic potentiation initiated by an acute cocaine injection. Thus, although the PL and VTA differentially regulate the direction of synaptic plasticity induced by a cocaine-priming injection, coordinated synaptic potentiation by both NAcore afferents is necessary for cocaine-induced relapse.

**Reward Value Comparison via Mutual Inhibition in Ventromedial Prefrontal Cortex** Strait CE, Blanchard TC, Hayden BY. *Neuron*. 2014 Jun 18; 82(6): 1357-66. doi: 10.1016/j.neuron.2014.04.032. Epub 2014 May 29.

Recent theories suggest that reward-based choice reflects competition between value signals in the ventromedial prefrontal cortex (vmPFC). The authors tested this idea by recording vmPFC neurons while macaques performed a gambling task with asynchronous offer presentation. They found that neuronal activity shows four patterns consistent with selection via mutual inhibition: (1) correlated tuning for probability and reward size, suggesting that vmPFC carries an integrated value signal; (2) anti-correlated tuning curves for the two options, suggesting mutual inhibition; (3) neurons rapidly come to signal the value of the chosen offer, suggesting the circuit serves to produce a choice; and (4) after regressing out the effects of option values, firing rates still could predict choice—a choice probability signal. In addition, neurons signaled gamble outcomes, suggesting that vmPFC contributes to both monitoring and choice processes. These data suggest a possible mechanism for reward-based choice and endorse the centrality of vmPFC in that process.

**Parental THC Exposure Leads To Compulsive Heroin-Seeking and Altered Striatal Synaptic Plasticity In the Subsequent Generation** Szutorisz H, DiNieri JA, Sweet E, Egervari G, Michaelides M, Carter JM, Ren Y, Miller ML, Blitzer RD, Hurd YL. *Neuropsychopharmacology*. 2014 May; 39(6): 1315-23. doi: 10.1038/npp.2013.352. Epub 2014 Jan 2.

Recent attention has been focused on the long-term impact of cannabis exposure, for which experimental animal studies have validated causal relationships between neurobiological and behavioral alterations during the individual's lifetime. Here, the authors show that adolescent exposure to  $\Delta(9)$ -tetrahydrocannabinol (THC), the main psychoactive component of cannabis,

results in behavioral and neurobiological abnormalities in the subsequent generation of rats as a consequence of parental germline exposure to the drug. Adult F1 offspring that were themselves unexposed to THC displayed increased work effort to self-administer heroin, with enhanced stereotyped behaviors during the period of acute heroin withdrawal. On the molecular level, parental THC exposure was associated with changes in the mRNA expression of cannabinoid, dopamine, and glutamatergic receptor genes in the striatum, a key component of the neuronal circuitry mediating compulsive behaviors and reward sensitivity. Specifically, decreased mRNA and protein levels, as well as NMDA receptor binding were observed in the dorsal striatum of adult offspring as a consequence of germline THC exposure. Electrophysiologically, plasticity was altered at excitatory synapses of the striatal circuitry that is known to mediate compulsive and goal-directed behaviors. These findings demonstrate that parental history of germline THC exposure affects the molecular characteristics of the striatum, can impact offspring phenotype, and could possibly confer enhanced risk for psychiatric disorders in the subsequent generation.

### **Effects of the Trace Amine-Associated Receptor 1 Agonist RO5263397 on Abuse-Related**

**Effects of Cocaine in Rats** Thorn DA, Jing L, Qiu Y, Gancarz-Kausch AM, Galuska CM, Dietz DM, Zhang Y, Li JX. *Neuropsychopharmacology*. 2014 Apr 18. doi: 10.1038/npp.2014.91. [Epub ahead of print]

Animal knockout studies suggest that trace amine-associated receptor (TAAR) 1 is involved in behavioral effects of psychostimulants such as cocaine. Recently, several highly selective TAAR 1 agonists have been discovered. However, little is known of the impact of TAAR 1 agonists on abuse-related effects of cocaine. Here, the authors report the effects of a TAAR 1 agonist RO5263397 on several abuse-related behavioral effects of cocaine in rats. RO5263397 was evaluated for its effects on cocaine-induced behavioral sensitization, conditioned place preference (CPP), cue- and cocaine prime-induced reinstatement of cocaine-seeking behavior, and cocaine self-administration using behavioral economic analysis. RO5263397 reduced the expression of cocaine behavioral sensitization, cue- and cocaine prime-induced reinstatement of cocaine seeking, and expression but not development of cocaine CPP. Behavioral economic analysis showed that RO5263397 increased the elasticity of the cocaine demand curve, but did not change cocaine consumption at minimal prices. Taken together, this is the first systematic assessment of a TAAR 1 agonist on a range of behavioral effects of cocaine, showing that RO5263397 was efficacious in reducing cocaine-mediated behaviors. Collectively, these data uncover essential neuromodulatory roles of TAAR 1 on cocaine abuse, and suggest that TAAR 1 may represent a novel drug target for the treatment of cocaine addiction.

### **Comprehensive Analysis Of RNA-Protein Interactions By High-Throughput Sequencing-RNA**

**Affinity Profiling** Tome JM, Ozer A, Pagano JM, Gheba D, Schroth GP, Lis JT. *Nat Methods*. 2014 Jun; 11(6): 683-8. doi: 10.1038/nmeth.2970. Epub 2014 May 8.

RNA-protein interactions play critical roles in gene regulation, but methods to quantitatively analyze these interactions at a large scale are lacking. The authors have developed a high-throughput sequencing-RNA affinity profiling (HiTS-RAP) assay by adapting a high-throughput DNA sequencer to quantify the binding of fluorescently labeled protein to millions of RNAs anchored to sequenced cDNA templates. Using HiTS-RAP, they measured the affinity of mutagenized libraries of GFP-binding and NELF-E-binding aptamers to their respective targets and identified critical regions of interaction. Mutations additively affected the affinity of the NELF-E-binding aptamer, whose interaction depended mainly on a single-stranded RNA motif, but not that of the GFP aptamer, whose interaction depended primarily on secondary structure.

**Spatiotemporally Different Origins Of Ng2 Progenitors Produce Cortical Interneurons Versus Glia In the Mammalian Forebrain**

Tsoa RW, Coskun V, Ho CK, de Vellis J, Sun YE. Proc Natl Acad Sci U S A. 2014 May 20; 111(20): 7444-9. doi: 10.1073/pnas.1400422111. Epub 2014 May 5.

The studies on the exact lineage composition of NG2 expressing progenitors in the forebrain have been controversial. A number of studies have revealed the heterogeneous nature of postnatal NG2 cells. However, NG2 cells found in embryonic dates are far less understood. This study indicates that early NG2 progenitors from a ventral origin (i.e., before embryonic day 16.5) tangentially migrate out of the medial ganglionic eminence and give rise to interneurons in deep layers of the dorsal cerebral cortex. The majority of myelinating oligodendrocytes found in both cortical gray and white matters are, in contrast, derived from NG2 progenitors with a neonatal subventricular zone origin. The authors' lineage tracing data reflect the heterogeneous nature of NG2 progenitor populations and define the relationship between lineage divergence and spatiotemporal origins. Beyond the typical lineage tracing studies of NG2(+) cells, by costaining with lineage-specific markers, our study addresses the origins of heterogeneity and its implications in the differentiation potentials of NG2(+) progenitors.

**Repeated  $\Delta$ 9-Tetrahydrocannabinol Exposure In Adolescent Monkeys: Persistent Effects Selective For Spatial Working Memory**

Verrico CD, Gu H, Peterson ML, Sampson AR, Lewis DA. 90. Am J Psychiatry. 2014 Apr 1; 171(4): 416-25. doi: 10.1176/appi.ajp.2013.13030335.

Epidemiological findings suggest that, relative to adults, adolescents are more vulnerable to the adverse persistent effects of cannabis on working memory. However, the potential confounds inherent in human studies preclude direct determination of a cause-and-effect relationship between adolescent cannabis use and heightened susceptibility to persistent working memory impairments. Consequently, the authors examined the effects of repeated exposure to  $\Delta$ 9-tetrahydrocannabinol (THC) on performance of spatial and object working memory tasks in adolescent monkeys. Seven pairs of male adolescent rhesus monkeys, matched for baseline cognitive performance, received vehicle or THC intravenously 5 days/week for 6 months. Performance on spatial and object memory tasks was assessed 23 or 71 hours after drug administration throughout the study. In addition, acute effects on working memory were also assessed at the beginning and end of the 6-month period. Relative to the vehicle-exposed control animals, those with repeated THC exposure had a blunted trajectory of accuracy improvements on the spatial working memory task in a delay-dependent manner. Accuracy improvements on the object working memory task did not differ between groups. Relative to the acute effects of THC on working memory at the beginning of the study, neither sensitivity nor tolerance was evident after 6 months of THC exposure. Because maturation of performance is later for spatial than for object working memory, these findings suggest that persistent effects of THC on cognitive abilities are more evident when exposure coincides with the developmental stage during which the underlying neural circuits are actively maturing.

**The P7C3 Class Of Neuroprotective Compounds Exerts Antidepressant Efficacy In Mice By Increasing Hippocampal Neurogenesis**

Walker AK, Rivera PD, Wang Q, Chuang JC, Tran S, Osborne-Lawrence S, Estill SJ, Starwalt R, Huntington P, Morlock L, Naidoo J, Williams NS, Ready JM, Eisch AJ, Pieper AA, Zigman JM. Mol Psychiatry. 2014 Apr 22. doi: 10.1038/mp.2014.34. [Epub ahead of print].

Augmenting hippocampal neurogenesis represents a potential new strategy for treating depression. Here the authors test this possibility by comparing hippocampal neurogenesis in depression-prone ghrelin receptor (Ghsr)-null mice to that in wild-type littermates and by determining the antidepressant efficacy of the P7C3 class of neuroprotective compounds. Exposure of Ghsr-null mice to chronic social defeat stress (CSDS) elicits more severe depressive-like behavior than in CSDS-

exposed wild-type littermates, and exposure of Ghsr-null mice to 60% caloric restriction fails to elicit antidepressant-like behavior. CSDS resulted in more severely reduced cell proliferation and survival in the ventral dentate gyrus (DG) subgranular zone of Ghsr-null mice than in that of wild-type littermates. Also, caloric restriction increased apoptosis of DG subgranular zone cells in Ghsr-null mice, although it had the opposite effect in wild-type littermates. Systemic treatment with P7C3 during CSDS increased survival of proliferating DG cells, which ultimately developed into mature (NeuN+) neurons. Notably, P7C3 exerted a potent antidepressant-like effect in Ghsr-null mice exposed to either CSDS or caloric restriction, while the more highly active analog P7C3-A20 also exerted an antidepressant-like effect in wild-type littermates. Focal ablation of hippocampal stem cells with radiation eliminated this antidepressant effect, further attributing the P7C3 class antidepressant effect to its neuroprotective properties and resultant augmentation of hippocampal neurogenesis. Finally, P7C3-A20 demonstrated greater proneurogenic efficacy than a wide spectrum of currently marketed antidepressant drugs. Taken together, these data confirm the role of aberrant hippocampal neurogenesis in the etiology of depression and suggest that the neuroprotective P7C3-compounds represent a novel strategy for treating patients with this disease.

**Monoacylglycerol Lipase Inhibition Blocks Chronic Stress-Induced Depressive-Like Behaviors Via Activation of mTOR Signaling** Zhong P, Wang W, Pan B, Liu X, Zhang Z, Long JZ, Zhang HT, Cravatt BF, Liu QS. *Neuropsychopharmacology*. 2014 Jun; 39(7): 1763-76. doi: 10.1038/npp.2014.24. Epub 2014 Jan 30.

The endocannabinoid (eCB) system regulates mood, emotion, and stress coping, and dysregulation of the eCB system is critically involved in pathophysiology of depression. The eCB ligand 2-arachidonoylglycerol (2-AG) is inactivated by monoacylglycerol lipase (MAGL). Using chronic unpredictable mild stress (CUS) as a mouse model of depression, the authors examined how 2-AG signaling in the hippocampus was altered in depressive-like states and how this alteration contributed to depressive-like behavior. They report that CUS led to impairment of depolarization-induced suppression of inhibition (DSI) in mouse hippocampal CA1 pyramidal neurons, and this deficiency in 2-AG-mediated retrograde synaptic depression was rescued by MAGL inhibitor JZL184. CUS induced depressive-like behaviors and decreased mammalian target of rapamycin (mTOR) activation in the hippocampus, and these biochemical and behavioral abnormalities were ameliorated by chronic JZL184 treatments. The effects of JZL184 were mediated by cannabinoid CB1 receptors. Genetic deletion of mTOR with adeno-associated viral (AAV) vector carrying the Cre recombinase in the hippocampus of mTORf/f mice recapitulated depressive-like behaviors induced by CUS and abrogated the antidepressant-like effects of chronic JZL184 treatments. These results suggest that CUS decreases eCB-mTOR signaling in the hippocampus, leading to depressive-like behaviors, whereas MAGL inhibitor JZL184 produces antidepressant-like effects through enhancement of eCB-mTOR signaling.

**Prenatal Cocaine Exposure and Adolescent Neural Responses to Appetitive and Stressful Stimuli** Yip SW, Potenza EB, Balodis IM, Lacadie CM, Sinha R, Mayes LC, Potenza MN.

*Neuropsychopharmacology*. 2014 Jun 6. doi: 10.1038/npp.2014.133. [Epub ahead of print]. Preclinical research has demonstrated the effects of prenatal cocaine exposure (PCE) on brain regions involved in emotional regulation, motivational control, and addiction vulnerability-eg, the ventral striatum (VS), anterior cingulate (ACC), and prefrontal cortex (PFC). However, little is known about the function of these regions in human adolescents with PCE. Twenty-two adolescents with PCE and 22 age-, gender-, and IQ-matched non-cocaine exposed (NCE) adolescents underwent functional magnetic resonance imaging (fMRI) during exposure to individually personalized neutral/relaxing, stressful, and favorite-food cues. fMRI data were compared using

group-level two-tailed t-tests in the BioImage Suite. In comparison with NCE adolescents, PCE adolescents had reduced activity within cortical and subcortical brain regions, including the VS, ACC, and medial and dorsolateral PFC during exposure to favorite-food cues but did not differ in neural responses to stress cues. Subjective food craving was inversely related to dorsolateral PFC activation among PCE adolescents. Among PCE adolescents, subjective anxiety ratings correlated inversely with activations in the orbitofrontal cortex and brainstem during the stress condition and with ACC, dorsolateral PFC, and hippocampus activity during the neutral-relaxing condition. Thus adolescents with PCE display hypoactivation of brain regions involved in appetitive processing, with subjective intensities of craving and anxiety correlating inversely with extent of activation. These findings suggest possible mechanisms by which PCE might predispose to the development of addictions and related disorders, eg, substance-use disorders and binge-eating.

**The Timing Of Dopamine- and Noradrenaline-Mediated Transmission Reflects Underlying Differences In the Extent Of Spillover and Pooling** Courtney NA, Ford CP. J Neurosci. 2014 May 28; 34(22): 7645-56. doi: 10.1523/JNEUROSCI.0166-14.2014.

Metabotropic transmission typically occurs through the spillover activation of extrasynaptic receptors. This study examined the mechanisms underlying somatodendritic dopamine and noradrenaline transmission and found that the extent of spillover and pooling varied dramatically between these two transmitters. In the mouse ventral tegmental area, the time course of D2-receptor-mediated IPSCs (D2-IPSCs) was consistent between cells and was unaffected by altering stimulation intensity, probability of release, or the extent of diffusion. Blocking dopamine reuptake with cocaine extended the time course of D2-IPSCs and suggested that transporters strongly limited spillover. As a result, individual release sites contributed independently to the duration of D2-IPSCs. In contrast, increasing the release of noradrenaline in the rat locus ceruleus prolonged the duration of  $\alpha$ 2-receptor-mediated IPSCs even when reuptake was intact. Spillover and subsequent pooling of noradrenaline activated distal  $\alpha$ 2-receptors, which prolonged the duration of  $\alpha$ 2-IPSCs when multiple release sites were activated synchronously. By using the rapid application of agonists onto large macropatches, the authors determined the concentration profile of agonists underlying the two IPSCs. Incorporating the results into a model simulating extracellular diffusion predicted that the functional range of noradrenaline diffusion was nearly fivefold greater in the locus ceruleus than dopamine in the midbrain. This study demonstrates that catecholamine synapses differentially regulate the extent of spillover and pooling to control the timing of local inhibition and suggests diversity in the roles of uptake and diffusion in governing metabotropic transmission.

**Glucagon-Like Peptide-1 Receptor Activation in the Nucleus Accumbens Core Suppresses Feeding by Increasing Glutamatergic AMPA/Kainate Signaling** Mietlicki-Baase EG, Ortinski PI, Reiner DJ, Sinon CG, McCutcheon JE, Pierce RC, Roitman MF, Hayes MR. J Neurosci. 2014 May 14; 34(20): 6985-92. doi: 10.1523/JNEUROSCI.0115-14.2014.

Glucagon-like peptide-1 receptor (GLP-1R) activation in the nucleus accumbens (NAc) core is pharmacologically and physiologically relevant for regulating palatable food intake. Here, the authors assess whether GLP-1R signaling in the NAc core of rats modulates GABAergic medium spiny neurons (MSNs) through presynaptic-glutamatergic and/or presynaptic-dopaminergic signaling to control feeding. First, ex vivo fast-scan cyclic voltammetry showed that the GLP-1R agonist exendin-4 (Ex-4) does not alter dopamine release in the NAc core. Instead, support for a glutamatergic mechanism was provided by ex vivo electrophysiological analyses showing that Ex-4 activates presynaptic GLP-1Rs in the NAc core to increase the activity of MSNs via a glutamatergic, AMPA/kainate receptor-mediated mechanism, indicated by increased mEPSC frequency and decreased paired pulse ratio in core MSNs. Only a small, direct excitatory effect on

MSNs by Ex-4 was observed, suggesting that the contribution of postsynaptic GLP-1R to MSN activity is minimal. The behavioral relevance of the electrophysiological data was confirmed by the finding that intracore injection of the AMPA/kainate receptor antagonist CNQX attenuated the ability of NAc core GLP-1R activation by Ex-4 microinjection to suppress food intake and body weight gain; in contrast, intracore NMDA receptor blockade by AP-5 did not inhibit the energy balance effects of NAc core Ex-4. Together, these data provide evidence for a novel glutamatergic, but not dopaminergic, mechanism by which NAc core GLP-1Rs promote negative energy balance.

**Cyclic AMP and Afferent Activity Govern Bidirectional Synaptic Plasticity In Striatopallidal Neurons** Augustin SM, Beeler JA, McGehee DS, Zhuang X. *J Neurosci.* 2014 May 7; 34(19): 6692-9. doi: 10.1523/JNEUROSCI.3906-13.2014.

Recent experimental evidence suggests that the low dopamine conditions in Parkinson's disease (PD) cause motor impairment through aberrant motor learning. Those data, along with computational models, suggest that this aberrant learning results from maladaptive corticostriatal plasticity and learned motor inhibition. Dopaminergic modulation of both corticostriatal long-term depression (LTD) and long-term potentiation (LTP) is proposed to be critical for these processes; however, the regulatory mechanisms underlying bidirectional corticostriatal plasticity are not fully understood. Previously, the authors demonstrated a key role for cAMP signaling in corticostriatal LTD. In this study, mouse brain slices were used to perform a parametric experiment that tested the impact of varying both intracellular cAMP levels and the strength of excitatory inputs on corticostriatal plasticity. Using slice electrophysiology in the dorsolateral striatum, the authors demonstrate that both LTP and LTD can be sequentially induced in the same D2-expressing neuron and that LTP was strongest with high intracellular cAMP and LFS, whereas LTD required low intracellular cAMP and high-frequency stimulation. These results provide a molecular and cellular basis for regulating bidirectional corticostriatal synaptic plasticity and may help to identify novel therapeutic targets for blocking or reversing the aberrant synaptic plasticity that likely contributes to motor deficits in PD.

**Cyclin-Dependent Kinase 5 In the Ventral Tegmental Area Regulates Depression-Related Behaviors** Zhong P(1), Liu X, Zhang Z, Hu Y, Liu SJ, Lezama-Ruiz M, Joksimovic M, Liu QS. *J Neurosci.* 2014 Apr 30; 34(18): 6352-66. doi: 10.1523/JNEUROSCI.3673-13.2014.

Dopamine neurons in the ventral tegmental area (VTA) govern reward and motivation and dysregulated dopaminergic transmission may account for anhedonia and other symptoms of depression. Cyclin-dependent kinase 5 (Cdk5) is a proline-directed serine/threonine kinase that regulates a broad range of brain functions through phosphorylation of a myriad of substrates, including tyrosine hydroxylase (TH), the rate-limiting enzyme for dopamine synthesis. The authors investigated whether and how Cdk5 activity in VTA dopamine neurons regulated depression-related behaviors in mice. Using the Cre/LoxP system to selectively delete Cdk5 in the VTA or in midbrain dopamine neurons in Cdk5(loxP/loxP) mice, they showed that Cdk5 loss of function in the VTA induced anxiety- and depressive-like behaviors that were associated with decreases in TH phosphorylation at Ser31 and Ser40 in the VTA and dopamine release in its target region, the nucleus accumbens. The decreased phosphorylation of TH at Ser31 was a direct effect of Cdk5 deletion, whereas decreased phosphorylation of TH at Ser40 was likely caused by impaired cAMP/protein kinase A (PKA) signaling, because Cdk5 deletion decreased cAMP and phosphorylated cAMP response element-binding protein (p-CREB) levels in the VTA. Using Designer Receptors Exclusively Activated by Designer Drugs (DREADD) technology, the authors showed that selectively increasing cAMP levels in VTA dopamine neurons increased phosphorylation of TH at Ser40 and CREB at Ser133 and reversed behavioral deficits induced by

Cdk5 deletion. The results suggest that Cdk5 in the VTA regulates cAMP/PKA signaling, dopaminergic neurotransmission, and depression-related behaviors.

**High Trait Impulsivity Predicts Food Addiction-Like Behavior in the Rat** Velázquez-Sánchez C, Ferragud A, Moore CF, Everitt BJ, Sabino V, Cottone P. *Neuropsychopharmacology*. 2014 Apr 29. doi: 10.1038/npp.2014.98. [Epub ahead of print].

Impulsivity is a behavioral trait frequently seen not only in drug-addicted individuals but also in individuals who pathologically overeat. However, whether impulsivity predates the development of uncontrollable feeding is unknown. In this study, the authors hypothesized that a high impulsivity trait precedes and confers vulnerability for food addiction-like behavior. For this purpose, they trained ad libitum-fed male Wistar rats in a differential reinforcement of low rates of responding (DRL) task to select Low- and High-impulsive rats. Then, they allowed Low- and High-impulsive rats to self-administer a highly palatable diet (Palatable group) or a regular chow diet (Chow group) in 1-h daily sessions, under fixed ratio (FR) 1, FR3, FR5, and under a progressive ratio (PR) schedules of reinforcement. In addition, they tested the compulsiveness for food in Low- and High-impulsive rats by measuring the food eaten in the aversive, open compartment of a light/dark conflict test. Finally, they measured the expression of the transcription factor  $\Delta$ FosB in the shell and the core of the nucleus accumbens, which is a marker for neuroadaptive changes following addictive drug exposure. The data the authors obtained demonstrate that impulsivity is a trait that predicts the development of food addiction-like behaviors, including: (i) excessive intake, (ii) heightened motivation for food, and (iii) compulsive-like eating, when rats are given access to highly palatable food. In addition, they show that the food addiction phenotype in high impulsive subjects is characterized by an increased expression of the transcription factor  $\Delta$ FosB in the nucleus accumbens shell. These results reveal that impulsivity confers an increased propensity to develop uncontrollable overeating of palatable food.

**Infralimbic BDNF/TrkB Enhancement of GluN2B Currents Facilitates Extinction of a Cocaine-Conditioned Place Preference** Otis JM, Fitzgerald MK, Mueller D. *J Neurosci*. 2014 Apr 23; 34(17): 6057-64. doi: 10.1523/JNEUROSCI.4980-13.2014.

Brain-derived neurotrophic factor (BDNF) regulates synaptic activity and behavioral flexibility, and reduction of BDNF strongly predicts psychiatric disorders and cognitive dysfunction. Restoration of BDNF-dependent activity could alleviate these impairments, but BDNF has limited clinical utility due to its pharmacokinetics. Here the authors demonstrate that activation of a primary BDNF target, the tropomyosin-related kinase B (TrkB) receptor, enhances the amplitude and prolongs the decay kinetics of N-methyl-d-aspartate receptor (NMDAR) currents in male rat infralimbic prefrontal pyramidal neurons. Moreover, these effects were prevented and reversed by blockade of NMDARs containing the GluN2B subunit. These results show that this signaling cascade bidirectionally regulates extinction of a cocaine-induced conditioned place preference (CPP), a task that requires behavioral flexibility. Blockade of infralimbic TrkB receptors or GluN2B-containing NMDARs disrupted consolidation of extinction of the CPP. In contrast, extinction was strengthened by potentiation of TrkB receptor activity with infralimbic infusions of BDNF or systemic injections of 7,8 dihydroxyflavone (7,8DHF), the newly synthesized TrkB receptor agonist. The 7,8DHF-induced enhancement of extinction was prevented by infralimbic infusions of a GluN2B-specific receptor antagonist, demonstrating that TrkB receptor activation enhances extinction of cocaine-CPP via GluN2B-containing NMDARs. Together, infralimbic TrkB receptor activation strengthens GluN2B-containing NMDAR currents to support extinction learning. TrkB receptor agonists would therefore be useful as pharmacological adjuncts for extinction-based therapies for treatment of psychiatric disorders associated with reduced BDNF activity.

### **The Role of Arp2/3 in Growth Cone Actin Dynamics and Guidance Is Substrate Dependent**

San Miguel-Ruiz JE, Letourneau PC. J Neurosci. 2014 Apr 23; 34(17): 5895-908. doi: 10.1523/JNEUROSCI.0672-14.2014.

During development extrinsic guidance cues modulate the peripheral actin network in growth cones to direct axons to their targets. The authors wanted to understand the role of the actin nucleator Arp2/3 in growth cone actin dynamics and guidance. Since growth cones migrate in association with diverse adhesive substrates during development, they probed the hypothesis that the functional significance of Arp2/3 is substrate dependent. They report that Arp2/3 inhibition led to a reduction in the number of filopodia and growth cone F-actin content on laminin and L1. However, they found substrate-dependent differences in growth cone motility, actin retrograde flow, and guidance after Arp2/3 inhibition, suggesting that its role, and perhaps that of other actin binding proteins, in growth cone motility is substrate dependent.

### **Synaptic Glutamate Spillover Due To Impaired Glutamate Uptake Mediates Heroin Relapse**

Shen HW(1), Scofield MD, Boger H, Hensley M, Kalivas PW. 9. J Neurosci. 2014 Apr 16; 34(16): 5649-57. doi: 10.1523/JNEUROSCI.4564-13.2014.

Reducing the enduring vulnerability to relapse is a therapeutic goal in treating drug addiction. Studies with animal models of drug addiction show a marked increase in extrasynaptic glutamate in the core subcompartment of the nucleus accumbens (NAcore) during reinstated drug seeking. However, the synaptic mechanisms linking drug-induced changes in extrasynaptic glutamate to relapse are poorly understood. Here, the authors discovered impaired glutamate elimination in rats extinguished from heroin self-administration that leads to spillover of synaptically released glutamate into the nonsynaptic extracellular space in NAcore and investigated whether restoration of glutamate transport prevented reinstated heroin seeking. Through multiple functional assays of glutamate uptake and analyzing NMDA receptor-mediated currents, the authors show that heroin self-administration produced long-lasting downregulation of glutamate uptake and surface expression of the transporter GLT-1. This downregulation was associated with spillover of synaptic glutamate to extrasynaptic NMDA receptors within the NAcore. Ceftriaxone restored glutamate uptake and prevented synaptic glutamate spillover and cue-induced heroin seeking. Ceftriaxone-induced inhibition of reinstated heroin seeking was blocked by morpholino-antisense targeting GLT-1 synthesis. These data reveal that the synaptic glutamate spillover in the NAcore results from reduced glutamate transport and is a critical pathophysiological mechanism underlying reinstated drug seeking in rats extinguished from heroin self-administration.

### **Biphasic Mechanisms Of Amphetamine Action At the Dopamine Terminal**

Siciliano CA, Calipari ES, Ferris MJ, Jones SR. J Neurosci. 2014 Apr 16; 34(16): 5575-82. doi: 10.1523/JNEUROSCI.4050-13.2014.

In light of recent studies suggesting that amphetamine (AMPH) increases electrically evoked dopamine release ([DA]<sub>o</sub>), the authors examined discrepancies between these findings and literature that has demonstrated AMPH-induced decreases in [DA]<sub>o</sub>. The current study has expanded the inventory of AMPH actions by defining two separate mechanisms of AMPH effects on [DA]<sub>o</sub> at high and low doses, one dopamine transporter (DAT) independent and one DAT dependent, respectively. AMPH concentrations were measured via microdialysis in rat nucleus accumbens after intraperitoneal injections of 1 and 10 mg/kg and yielded values of ~10 and 200 nM, respectively. Subsequently, voltammetry in brain slices was used to examine the effects of low (10 nM), moderate (100 nM), and high (10 μM) concentrations of AMPH across a range of frequency stimulations (one pulse; five pulses, 20 Hz; 24 pulses, 60 Hz). The authors discovered biphasic, concentration-dependent effects in WT mice, in which AMPH increased [DA]<sub>o</sub> at low

concentrations and decreased [DA]<sub>o</sub> at high concentrations across all stimulation types. However, in slices from DAT-KO mice, [DA]<sub>o</sub> was decreased by all concentrations of AMPH, demonstrating that AMPH-induced increases in [DA]<sub>o</sub> are DAT dependent, whereas the decreases at high concentrations are DAT independent. The authors propose that low AMPH concentrations are insufficient to disrupt vesicular sequestration, and therefore AMPH acts solely as a DAT inhibitor to increase [DA]<sub>o</sub>. When AMPH concentrations are high, the added mechanism of vesicular depletion leads to reduced [DA]<sub>o</sub>. The biphasic mechanisms observed here confirm and extend the traditional actions of AMPH, but do not support mechanisms involving increased exocytotic release.

**Association of CHRNA5-A3-B4 SNP rs2036527 With Smoking Cessation Therapy Response in African-American Smokers** Zhu AZ, Zhou Q, Cox LS, David SP, Ahluwalia JS, Benowitz NL, Tyndale RF(6). Clin Pharmacol Ther. 2014 Aug; 96(2): 256-65. doi: 10.1038/clpt.2014.88. Epub 2014 Apr 14.

Associations between CHRNA5-A3-B4 variants and smoking behaviors exist; however, the association with smoking abstinence is less understood, particularly that among African Americans. In 1,295 African Americans enrolled in two clinical trials, the authors investigated the association between CHRNA5-A3-B4 and smoking abstinence. The rs2056527(A) allele was associated with lower abstinence with active pharmacotherapy (during treatment: odds ratio (OR)=0.42, P< 0.001; end of treatment (EOT): OR=0.55, P=0.004), or with nicotine gum alone (during treatment: OR=0.31, P< 0.001; EOT: OR=0.51, P=0.02), but not significantly with bupropion, although similar directions and magnitudes were observed (during treatment: OR=0.54, P=0.05; EOT: OR=0.59, P=0.08). In addition, the rs588765(T) allele was associated with abstinence with gum during treatment (OR=2.31, P< 0.01). The SNP rs16969968 occurred at a low frequency and was not consistently associated with abstinence. CHRNA5-A3-B4 variants were not associated with tobacco consumption, and adjustments for smoking behaviors did not alter the associations with smoking abstinence. Together, these data suggest that among African Americans, CHRNA5-A3-B4 variants are not associated with baseline smoking but can influence smoking abstinence during active pharmacotherapy.

**Firing Modes Of Dopamine Neurons Drive Bidirectional GIRK Channel Plasticity** Lalive AL, Munoz MB, Bellone C, Slesinger PA, Lüscher C, Tan KR. J Neurosci. 2014 Apr 9; 34(15): 5107-14. doi: 10.1523/JNEUROSCI.5203-13.2014.

G-protein-coupled inwardly rectifying potassium (GIRK) channels contribute to the resting membrane potential of many neurons, including dopamine (DA) neurons in the ventral tegmental area (VTA). VTA DA neurons are bistable, firing in two modes: one characterized by bursts of action potentials, the other by tonic firing at a lower frequency. Here the authors provide evidence that these firing modes drive bidirectional plasticity of GIRK channel-mediated currents. In acute midbrain slices of mice, they observed that in vitro burst activation of VTA DA neurons potentiated GIRK currents whereas tonic firing depressed these currents. This plasticity was not specific to the metabotropic receptor activating the GIRK channels, as direct activation of GIRK channels by nonhydrolyzable GTP also potentiated the currents. The plasticity of GIRK currents required NMDA receptor and CaMKII activation, and involved protein trafficking through specific PDZ domains of GIRK2c and GIRK3 subunit isoforms. Prolonged tonic firing may thus enhance the probability to switch into burst-firing mode, which then potentiates GIRK currents and favors the return to baseline. In conclusion, activity-dependent GIRK channel plasticity may represent a slow destabilization process favoring the switch between the two firing modes of VTA DA neurons.

**Many Parameter Sets In A Multicompartment Model Oscillator Are Robust To Temperature Perturbations** Caplan JS, Williams AH, Marder E. J Neurosci. 2014 Apr 2; 34(14): 4963-75. doi: 10.1523/JNEUROSCI.0280-14.2014.

Neurons in cold-blooded animals remarkably maintain their function over a wide range of temperatures, even though the rates of many cellular processes increase twofold, threefold, or many-fold for each 10°C increase in temperature. Moreover, the kinetics of ion channels, maximal conductances, and Ca(2+) buffering each have independent temperature sensitivities, suggesting that the balance of biological parameters can be disturbed by even modest temperature changes. In stomatogastric ganglia of the crab *Cancer borealis*, the duty cycle of the bursting pacemaker kernel is highly robust between 7 and 23°C (Rinberg et al., 2013). The authors examined how this might be achieved in a detailed conductance-based model in which exponential temperature sensitivities were given by Q10 parameters. They assessed the temperature robustness of this model across 125,000 random sets of Q10 parameters. To examine how robustness might be achieved across a variable population of animals, the authors repeated this analysis across six sets of maximal conductance parameters that produced similar activity at 11°C. Many permissible combinations of maximal conductance and Q10 parameters were found over broad regions of parameter space and relatively few correlations among Q10s were observed across successful parameter sets. A significant portion of Q10 sets worked for at least 3 of the 6 maximal conductance sets (~11.1%). Nonetheless, no Q10 set produced robust function across all six maximal conductance sets, suggesting that maximal conductance parameters critically contribute to temperature robustness. Overall, these results provide insight into principles of temperature robustness in neuronal oscillators.

**Ghrelin Acts As An Interface Between Physiological State and Phasic Dopamine Signaling** Cone JJ, McCutcheon JE, Roitman MF. J Neurosci. 2014 Apr 2; 34(14): 4905-13. doi: 10.1523/JNEUROSCI.4404-13.2014.

Brief, high-concentration (phasic) spikes in nucleus accumbens dopamine critically participate in aspects of food reward. Although physiological state (e.g., hunger, satiety) and associated hormones are known to affect dopamine tone in general, whether they modulate food-evoked, phasic dopamine specifically is unknown. Here, the authors used fast-scan cyclic voltammetry in awake, behaving rats to record dopamine spikes evoked by delivery of sugar pellets while pharmacologically manipulating central receptors for the gut "hunger" hormone ghrelin. Lateral ventricular (LV) ghrelin increased, while LV ghrelin receptor antagonism suppressed the magnitude of dopamine spikes evoked by food. Ghrelin was effective when infused directly into the lateral hypothalamus (LH), but not the ventral tegmental area (VTA). LH infusions were made in close proximity to orexin neurons, which are regulated by ghrelin and project to the VTA. Thus, we also investigated and found potentiation of food-evoked dopamine spikes by intra-VTA orexin-A. Importantly, intra-VTA blockade of orexin receptors attenuated food intake induced by LV ghrelin, thus establishing a behaviorally relevant connection between central ghrelin and VTA orexin. Further analysis revealed that food restriction increased the magnitude of dopamine spikes evoked by food independent of any pharmacological manipulations. The results support the regulation of food-evoked dopamine spikes by physiological state with endogenous fluctuations in ghrelin as a key contributor. These data highlight a novel mechanism by which signals relating physiological state could influence food reinforcement and food-directed behavior.

**Child Abuse, Depression, and Methylation In Genes Involved With Stress, Neural Plasticity, and Brain Circuitry** Weder N, Zhang H, Jensen K, Yang BZ, Simen A, Jackowski A, Lipschitz D, Douglas-Palumberi H, Ge M, Perepletchikova F, O'Loughlin K, Hudziak JJ, Gelernter J, Kaufman J. *J Am Acad Child Adolesc Psychiatry*. 2014 Apr; 53(4): 417-24.e5. doi: 10.1016/j.jaac.2013.12.025. Epub 2014 Jan 27.

The objective of this study was to determine whether epigenetic markers predict dimensional ratings of depression in maltreated children. A genome-wide methylation study was completed using the Illumina 450K BeadChip array in 94 maltreated and 96 healthy nontraumatized children with saliva-derived DNA. The 450K BeadChip does not include any methylation sites in the exact location as sites in candidate genes previously examined in the literature, so a test for replication of prior research findings was not feasible. Methylation in 3 genes emerged as genome-wide-significant predictors of depression: DNA-Binding Protein Inhibitor ID-3 (ID3); Glutamate Receptor, Ionotropic N-methyl-D-aspartate (NMDA) 1 (GRIN1); and Tubulin Polymerization Promoting Protein (TPPP) ( $p < 5.0 \times 10^{-7}$ , all analyses). These genes are all biologically relevant with ID3 involved in the stress response, GRIN1 involved in neural plasticity, and TPPP involved in neural circuitry development. Methylation in CpG sites in candidate genes were not predictors of depression at significance levels corrected for whole genome testing, but maltreated and control children did have significantly different  $\beta$  values after Bonferroni correction at multiple methylation sites in these candidate genes (e.g., BDNF, NR3C1, FKBP5). This study suggests that epigenetic changes in ID3, GRIN1, and TPPP genes, in combination with experiences of maltreatment, may confer risk for depression in children. The study adds to a growing body of literature supporting a role for epigenetic mechanisms in the pathophysiology of stress-related psychiatric disorders. Although epigenetic changes are frequently long lasting, they are not necessarily permanent. Consequently, interventions to reverse the negative biological and behavioral sequelae associated with child maltreatment are briefly discussed.

## **BEHAVIORAL AND BRAIN DEVELOPMENT RESEARCH**

### **Prevalence of and Risk Factors for Substance Use among Perinatally Human Immunodeficiency Virus-infected and Perinatally Exposed but Uninfected Youth**

Alperen J, Brummel S, Tassiopoulos K, Mellins CA, Kacanek D, Smith R, Seage GR 3rd, Moscicki AB. *J Adolesc Health*. 2014 Mar; 54(3): 341-9.

This study examined risk factors associated with recent substance use (SU) among perinatally human immunodeficiency virus (HIV)-infected (PHIV+) and perinatally exposed, uninfected (PHEU) youth and compared SU lifetime prevalence with the general population of United States (U.S.) adolescents. The authors conducted cross-sectional and longitudinal analyses of 511 PHIV+ and PHEU youth (mean age at study entry, 13.2 years; 51% female; 69% PHIV+; and 72% African-American) enrolled in a U.S. multisite prospective cohort study between 2007 and 2009. Substance use data were collected by audio computer-assisted self-interview. Youth Risk Behavior Surveillance System and Monitoring the Future data were used to compare SU lifetime prevalence with U.S. samples. Perinatal HIV infection was not a statistically significant risk factor for alcohol or marijuana use. Risk factors for alcohol use among PHIV+ youth included higher severity of emotional and conduct problems and alcohol and marijuana use in the home by the caregiver or others. Risk factors for marijuana use among PHIV+ youth included marijuana use in the home, higher severity of conduct problems, and stressful life events. Similar SU risk factors among PHEU youth included SU in the home and higher severity of conduct and emotional problems. Overall, lifetime prevalence of SU by age was similar to that in national surveys. Although SU lifetime prevalence and risk factors for PHIV+ and PHEU adolescents were similar to national norms, the negative consequences are potentially greater for PHIV+ youth. Prevention efforts should begin before SU initiation and address the family and social environment and youth mental health status.

### **Prevalence, Incidence, and Persistence of Psychiatric and Substance Use Disorders among Mothers Living with HIV**

Malee KM, Mellins CA, Huo Y, Tassiopoulos K, Smith R, Sirois PA, Allison SM, Kacanek D, Kapetanovic S, Williams PL, Grant ML, Marullo D, Aidala AA; Pediatric HIV/AIDS Cohort Study (PHACS). *J Acquir Immune Defic Syndr*. 2014 Apr 15; 65(5): 526-34.

The objectives of this study were to evaluate prevalence, incidence, remission, and persistence of psychiatric and substance use disorders among HIV-infected mothers and identify biopsychosocial correlates. HIV-infected mothers (n = 1223) of HIV-exposed uninfected children enrolled in a prospective cohort study; HIV-uninfected mothers (n = 128) served as a comparison group. Mothers provided sociodemographic and health information and completed the Client Diagnostic Questionnaire (CDQ). Prevalence of any psychiatric or substance use disorder at initial evaluation was compared between the 2 groups. Incident, remitting, and persisting disorders were identified for 689 mothers with HIV who completed follow-up CDQs. The authors used logistic regression to evaluate adjusted associations of biopsychosocial characteristics with presence, incidence, remission, and persistence of disorders. Thirty-five percent of mothers screened positive for any psychiatric or substance use disorder at initial evaluation, with no difference by maternal HIV status (P = 1.00). Among HIV-infected mothers, presence of any disorder was associated with younger age [adjusted odds ratio (aOR): 1.39; 95% CI: 1.09 to 1.75], single parenthood (aOR: 1.35; 95% CI: 1.08 to 1.68), and functional limitations (aOR: 2.29; 95% CI: 1.81 to 2.90). Incident disorders were associated with functional limitations (aOR: 1.92; 95% CI: 1.10 to 3.30). Among HIV-infected mothers with a disorder at initial evaluation (n = 238), 61% had persistent disorders. Persistent disorders were associated with lower income (aOR: 2.44; 95% CI: 1.33 to 4.76) and functional limitations (aOR: 3.19; 95% CI: 1.87 to 5.48). Receipt of treatment for any disorder was limited: 4.5% at study entry, 7% at follow-up, 5.5% at both entry and follow-up. Psychiatric and substance

use disorders remain significant comorbid conditions among HIV-infected mothers and require accessible evidence-informed treatment.

**The Use of Cell Phone Support for Non-adherent HIV-infected Youth and Young Adults: An Initial Randomized and Controlled Intervention Trial**

Belzer ME, Naar-King S, Olson J, Sarr M, Thornton S, Kahana SY, Gaur AH, Clark LF; Adolescent Medicine Trials Network for HIV/AIDS Interventions. *AIDS Behav.* 2014 Apr; 18(4): 686-96.

This randomized behavioral trial examined whether youth living with HIV (YLH) receiving cell-phone support with study funded phone plans, demonstrated improved adherence and viral control during the 24 week intervention and 24 weeks post-intervention compared to controls. Monday through Friday phone calls confirmed medications were taken, provided problem-solving support, and referred to services to address adherence barriers. Of 37 participants (ages 15-24), 62 % were male and 70 % were African American. Self-reported adherence was significantly higher in the intervention group compared to the control at 24 and 48 weeks for the past month ( $P = 0.007$ ) and log<sub>10</sub> HIV VL was significantly lower at both 24 weeks (2.82 versus 4.52  $P = 0.002$ ) and 48 weeks (3.23 versus 4.23  $P = 0.043$ ). Adherence and viral load showed medium to large effect sizes across the 48 week study. This is the first study to demonstrate sustained clinically significant reductions in HIV VL using youth friendly technology.

**The Influence of Community Context on How Coalitions Achieve HIV-preventive Structural Change**

Reed SJ, Miller RL, Francisco VT; Adolescent Medical Trials Network for HIV/AIDS Interventions. *Health Educ Behav.* 2014 Feb; 41(1): 100-7.

Community coalition action theory (CCAT) depicts the processes and factors that affect coalition formation, maintenance, institutionalization, actions, and outcomes. CCAT proposes that community context affects coalitions at every phase of development and operation. The authors analyzed data from 12 Connect to Protect coalitions using inductive content analysis to examine how contextual factors (e.g., economics, collaboration, history, norms, and politics) enhance or impede coalitions' success in achieving outcomes. Consistent with CCAT, context affected the objectives that coalitions developed and those they completed. Results suggest that local prevention history and political support have particular impact on coalitions' success in creating structural changes. These data underscore the heuristic value of CCAT, yet also imply that the contextual constructs that affect outcomes are issue specific.

**Substance Abuse Treatment for HIV Infected Young People: An Open Pilot Trial**

Esposito-Smythers C, Brown LK, Wolff J, Xu J, Thornton S, Tidey J; Adolescent Medicine Trials Network for HIV/AIDS Interventions (ATN 069). *J Subst Abuse Treat.* 2014 Feb; 46(2): 244-50.

The purpose of this study was to test an integrated cognitive behavioral and contingency management (CBT/CM) intervention for young people living with HIV (YPLH) with an alcohol and/or cannabis use disorder in an open pilot trial. Seventeen participants (ages 18-24) were recruited from three HIV community clinics. Assessments were completed at pre-and post-treatment as well as 3 month follow-up. Eighty percent of participants were retained in the study. Results suggest that the CBT/CM intervention was acceptable, feasible, and could be delivered with fidelity. Further, participants reported significant reductions in alcohol use, withdrawal symptoms, dependence symptoms and related problems, as well as co-occurring depressive symptoms and delinquent behavior across assessment periods. A trend was evident for reductions in marijuana use and related problems. Overall, these preliminary results suggest that a substance abuse CBT/CM intervention tailored to YPLH is acceptable, feasible, and holds promise for symptomatic improvement. Further testing of this type of protocol is warranted.

**Relations among Prospective Memory, Cognitive Abilities, and Brain Structure in Adolescents who Vary in Prenatal Drug Exposure**

Robey A, Buckingham-Howes S, Salmeron BJ, Black MM, Riggins T. *J Exp Child Psychol*. 2014 Mar 12. [Epub ahead of print].

This investigation examined how prospective memory (PM) relates to cognitive abilities (i.e., executive function, attention, working memory, and retrospective memory) and brain structure in adolescents who vary in prenatal drug exposure (PDE). The sample consisted of 105 (55 female and 50 male) urban, primarily African American adolescents (mean age=15.5years) from low socioeconomic status (SES) families. Approximately 56% (n=59) were prenatally exposed to drugs (heroin and/or cocaine) and 44% (n=46) were not prenatally exposed, but the adolescents were similar in age, gender, race, and SES. Executive functioning, attentional control, working memory, retrospective memory, and overall cognitive ability were assessed by validated performance measures. Executive functioning was also measured by caregiver report. A subset of 52 adolescents completed MRI (magnetic resonance imaging) scans, which provided measures of subcortical gray matter volumes and thickness of prefrontal, parietal, and temporal cortices. Results revealed no differences in PM performance by PDE status, even after adjusting for age and IQ. Executive function, retrospective memory, cortical thickness in frontal and parietal regions, and volume of subcortical regions (i.e., putamen and hippocampus) were related to PM performance in the sample overall, even after adjusting for age, IQ, and total gray matter volume. Findings suggest that variations in PM ability during adolescence are robustly related to individual differences in cognitive abilities, in particular executive function and retrospective memory, and brain structure, but do not vary by PDE status.

**Inhibition during Early Adolescence Predicts Alcohol and Marijuana Use by Late**

**Adolescence** Squeglia LM, Jacobus J, Nguyen-Louie TT, Tapert SF. *Neuropsychology*. 2014 Apr 21. [Epub ahead of print].

Adolescent substance use has been associated with poorer neuropsychological functioning, but it is unclear if deficits predate or follow the onset of use. The goal of this prospective study was to understand how neuropsychological functioning during early adolescence could predict substance use by late adolescence. At baseline, participants were 175 substance-use-naïve healthy 12- to 14-year-olds (41% female) recruited from local schools. Participants completed extensive interviews and neuropsychological tests. Each year, participants' substance use was assessed. By late adolescence (ages 17 to 18), 105 participants transitioned into substance use and 75 remained substance-naïve. Hierarchical linear regressions examined how baseline cognitive performance predicted subsequent substance use, controlling for common substance use risk factors (i.e., family history, externalizing behaviors, gender, pubertal development, and age). Poorer baseline performance on tests of cognitive inhibition-interference predicted higher follow-up peak drinks on an occasion ( $\beta = -.15$ ;  $p < .001$ ), more days of drinking ( $\beta = -.15$ ;  $p < .001$ ), and more marijuana use days ( $\beta = -.17$ ;  $p < .001$ ) by ages 17 to 18, above and beyond covariates. Performances on short-term memory, sustained attention, verbal learning and memory, visuospatial functioning and spatial planning did not predict subsequent substance involvement ( $ps > .05$ ). Compromised inhibitory functioning during early adolescence prior to the onset of substance use was related to more frequent and intense alcohol and marijuana use by late adolescence. Inhibition performance could help identify teens at risk for initiating heavy substance use during adolescence, and potentially could be modified to improve outcome.

**Neural Correlates of Cognitive and Affective Processing in Maltreated Youth with Posttraumatic Stress Symptoms: Does Gender Matter?** Crozier JC, Wang L, Huettel SA, De Bellis MD. *Dev Psychopathol.* 2014 May; 26(2): 491-513.

The authors investigated the relationship of gender to cognitive and affective processing in maltreated youth with posttraumatic stress disorder symptoms using functional magnetic resonance imaging. Maltreated (N = 29, 13 females, 16 males) and nonmaltreated participants (N = 45, 26 females, 19 males) performed an emotional oddball task that involved detection of targets with fear or scrambled face distractors. Results were moderated by gender. During the executive component of this task, left precuneus/posterior middle cingulate hypoactivation to fear versus calm or scrambled face targets were seen in maltreated versus control males and may represent dysfunction and less resilience in attentional networks. Maltreated males also showed decreased activation in the inferior frontal gyrus compared to control males. No differences were found in females. Posterior cingulate activations positively correlated with posttraumatic stress disorder symptoms. While viewing fear faces, maltreated females exhibited decreased activity in the dorsomedial prefrontal cortex and cerebellum I-VI, whereas maltreated males exhibited increased activity in the left hippocampus, fusiform cortex, right cerebellar crus I, and visual cortex compared to their same-gender controls. Gender by maltreatment effects were not attributable to demographic, clinical, or maltreatment parameters. Maltreated girls and boys exhibited distinct patterns of neural activations during executive and affective processing, a new finding in the maltreatment literature.

**Intellectual, Neurocognitive, and Academic Achievement in Abstinent Adolescents with Cannabis Use Disorder** Hooper SR, Woolley D, De Bellis MD. *Psychopharmacology (Berl).* 2014 Apr; 231(8): 1467-77.

The active component of cannabis, delta-9 tetrahydrocannabinol (THC), has a long half-life and widespread neurocognitive effects. There are inconsistent reports of neurocognitive deficits in adults and adolescents with cannabis use disorders (CUD), particularly after a period of abstinence. This study aims to examine neurocognitive measures (IQ, academic achievement, attention, memory, executive functions) in abstinent adolescents with CUD, while controlling for demographic, psychopathology, and poly-substance confounders. The authors investigated neurocognitive performance in three groups: adolescents with CUD after successful first treatment and in full remission (n=33); controls with psychiatric disorders without substance use disorder history (n=37); and healthy adolescents (n=43). Adolescents with psychiatric disorders, regardless of CUD status, performed significantly worse than the healthy adolescents in academic achievement. No group differences were seen in IQ, attention, memory, or executive functions. Lower academic achievement was positively associated with younger age of CUD onset, regular cannabis use, and maximum daily use. In the CUD group, lifetime nicotine use episodes were negatively associated with IQ. Lower overall neurocognitive function was associated with younger age of onset of regular cannabis use and relapse within the 1 year follow-up. Verifiably, abstinent adolescents with CUD history did not differ from the two comparison groups, suggesting that previously reported neurocognitive deficits may be related to other factors, including residual drug effects, preexisting cognitive deficits, concurrent use of other substances (e.g., nicotine), or psychopathology. Adolescents with CUD may not be vulnerable to THC neuropsychological deficits once they achieve remission from all drugs for at least 30 days.

**Indirect Effect of Corticotropin-releasing Hormone Receptor 1 Gene Variation on Negative Emotionality and Alcohol Use via Right Ventrolateral Prefrontal Cortex**

Glaser YG, Zubieta JK, Hsu DT, Villafuerte S, Mickey BJ, Trucco EM, Burmeister M, Zucker RA, Heitzeg MM. *J Neurosci.* 2014 Mar 12; 34(11): 4099-107.

Variations in the corticotropin-releasing hormone receptor 1 (CRHR1) gene have been found to interact with stress in modulating excessive alcohol consumption. However, the neural mechanisms through which CRHR1 influences this risk in humans is largely unknown. This study examined the influence of an intronic CRHR1 gene variant, rs110402, on brain responses to negative emotional words, negative emotional traits, and alcohol use in adolescents and young adults at high risk for alcoholism. Childhood stress was investigated as a potential moderator. Using functional magnetic resonance imaging, the authors found that a region in the right ventrolateral prefrontal cortex (rVLPFC) was more engaged during negative emotional word processing in G homozygotes than in A allele carriers ( $p(\text{FWE corrected}) < 0.01$ ,  $N = 77$ ). Moreover, an indirect effect of genotype on negative emotionality via rVLPFC activation ( $p < 0.05$ ,  $N = 69$ ) was observed, which was further moderated by childhood stress ( $p < 0.05$ ,  $N = 63$ ). Specifically, with low childhood stress, G homozygotes exhibited lower levels of negative emotionality associated with greater rVLPFC activation, suggesting that the rVLPFC is involved in reappraisal that neutralizes negative emotional responses. In addition, the authors found that genotype indirectly modulated excessive alcohol consumption ( $p < 0.05$ ,  $N = 69$ ). Specifically, G homozygotes showed greater rVLPFC activation and had lower levels of negative emotionality, which were associated with fewer binge-drinking days and fewer alcohol related problems. This work provides support for a model in which CRHR1 gene variation modulates the risk of problem drinking via an internalizing/negative affect pathway involving rVLPFC and reappraisal of negative emotion.

**Smoking Patterns and their Relationship to Drinking among First-year College Students**

Hoepfner BB, Bidwell LC, Colby SM, Barnett NP. *Nicotine Tob Res.* 2014 Jun; 16(6): 743-52.

Unlike older smokers, young adult smokers frequently engage in light and intermittent smoking. It remains unclear how stable such smoking patterns are over time, as substantial variability exists between these smokers. This study identified subgroups of college student smokers based on the trajectory of their smoking frequency during the first year of college, thereby examining stability versus instability over time. The authors then tested if the interplay between drinking and smoking differed in the identified groups to determine the relative role drinking may play in intermittent versus more regular smoking. Incoming college students at 3 institutions completed online biweekly surveys of their daily substance use throughout the first year of college. Students who reported smoking at least 1 cigarette during this year ( $n = 266$ ) were included in analyses (70% female, 74% White). Group-based trajectory modeling identified 5 groups of smokers, 3 of which maintained their smoking frequency throughout the year (77%), and 2 groups of infrequent smokers showed significant trends (11% increasing, 12% decreasing). Notably, nondaily smoking was maintained at different specific frequencies (e.g., 1 vs. 3 days per week). Identified groups differed in the relationship between drinking and smoking, where co-occurrence was particularly strong among infrequent smokers, and trends in smoking quantity differed between groups. While there was a diversity of smoking patterns in the sample, patterns of intermittent smoking remain relatively stable for a majority of students throughout the year. Intervention messages targeting drinking and smoking should be tailored on the basis of smoking frequency.

**Gamma-aminobutyric Acid System Genes - No Evidence for a Role in Alcohol Use and Abuse in a Community-based Sample**

Irons DE, Iacono WG, Oetting WS, Kirkpatrick RM, Vrieze SI, Miller MB, McGue M. *Alcohol Clin Exp Res*. 2014 Apr; 38(4): 938-47.

While twin and adoption studies point to substantial genetic influence upon alcohol use, dependence, and other alcohol-related phenotypes, few of the genes underlying variation in these phenotypes have been identified. Markers in genes related to GABAergic activities—a system integral to many of alcohol’s biological effects—have been implicated in alcohol use and alcohol-related psychopathology in linkage and association studies. Using multiple methods, the authors conducted a comprehensive examination of the effects of markers in  $\gamma$ -aminobutyric acid (GABA) system genes in a community-based sample of 7,224 individuals assessed in early and middle adulthood. In addition to testing the effect of individual single nucleotide polymorphism (SNP) markers on alcohol-related phenotypes, the authors computed a polygenic score reflecting the aggregated effects of multiple GABA system SNPs. They also estimated the variance in alcohol-related phenotypes attributable to all GABA system markers considered simultaneously and conducted gene-based association tests. No method produced results indicative of an effect of GABA system variants on measures of alcohol use or misuse. These results reflect alcohol-related behaviors in a population-representative sample, many of whom are still in adolescence, and in which the incidence of heavy drinking and alcohol-related symptomatology are relatively low. Contrasted with existing studies of the association between alcohol use and GABA system genes, our results suggest that the relationship may be limited to particular contexts, such as when accompanied by polysubstance abuse or a familial history of alcoholism.

**Associations of Attention-deficit Hyperactivity Disorder Symptom Dimensions with Smoking Deprivation Effects in Adult Smokers**

Bidwell LC, Ameringer KJ, Leventhal AM. *Psychol Addict Behav*. 2014 Mar; 28(1): 182-92.

Identifying relations of attention deficit hyperactivity disorder (ADHD) symptom dimensions to individual facets of the tobacco withdrawal syndrome could elucidate the mechanisms linking ADHD and regular smoking. This study examined the unique relations of inattention (IN) and hyperactivity-impulsivity (HI) symptom dimensions of ADHD to a variety of tobacco withdrawal symptoms. One hundred thirty-two community-dwelling adult smokers recruited without regard to ADHD status completed a self-report measure of ADHD symptoms experienced over the past 6 months at a baseline visit. At two subsequent experimental sessions (one following overnight tobacco deprivation and one nondeprived; order counterbalanced), participants completed measures of tobacco withdrawal symptoms, mood, and desire to smoke. Preliminary analyses showed that higher levels of IN and HI symptoms were both associated with higher levels of negative affect and concentration difficulties during nondeprived ("baseline") states ( $ps < .01$ ). Over and above nondeprived ratings, higher levels of HI symptoms were associated with larger deprivation-induced increases in negative affect, concentration problems, and desire to smoke, particularly for negative affect relief, during deprived states ( $ps < .01$ ). ADHD symptoms, particularly HI symptoms, are associated with more severe exacerbations in abstinence-induced withdrawal symptoms, which could be an important mechanism of ADHD-smoking comorbidity. These findings suggest the need for clinical studies examining the role of these unique and potentially more severe withdrawal profiles experienced by smokers with high-levels of ADHD symptoms in smoking reinstatement and cessation outcomes.

**Childhood and Current ADHD Symptom Dimensions are Associated with More Severe Cannabis Outcomes in College Students**

Bidwell LC, Henry EA, Willcutt EG, Kinnear MK, Ito TA. *Drug Alcohol Depend.* 2014 Feb 1; 135: 88-94.

Numerous studies have shown that attention deficit/hyperactivity disorder (ADHD) is associated with a higher risk of cannabis use disorders (CUD). However, these studies are limited in that most did not: (a) differentiate the role of hyperactivity-impulsivity (HI) and inattention (IN); (b) control for associated psychopathology; and (c) consider more fine-grained CUD-related measures. The authors' aim was to clarify the unique and interactive contributions of inattention and hyperactivity symptoms to age of cannabis initiation and DSM-IV cannabis dependence, craving, and severity of problems related to cannabis use while statistically controlling for symptoms of comorbid psychopathology in a non-clinical sample of young adults. Cannabis variables, current use of cigarettes and alcohol, current and childhood ADHD, and comorbid internalizing and externalizing psychopathology were assessed in 376 male and female undergraduates. Results indicate that current and childhood IN were independently associated with more severe cannabis use, craving, and problem use-related outcomes in young adulthood ( $p's < .01$ ) and that childhood HI symptoms were associated with earlier initiation of cannabis ( $p < .01$ ). Further, current IN symptoms moderated the relationships between level of use and more severe outcomes ( $p's < .01$ ), such that higher IN strengthened positive associations among use and problem cannabis use. Associations with ADHD symptom dimensions and current use of alcohol and cigarettes were also present. Thus, current and childhood inattention symptoms as well as childhood hyperactive-impulsive symptoms emerged as significant factors in cannabis-related outcomes in young adults, even after statistically controlling for important confounding variables.

**Determining the Impact of Prenatal Tobacco Exposure on Self-regulation at 6 Months** Wiebe SA, Fang H, Johnson C, James KE, Espy KA. *Dev Psychol.* 2014 Jun; 50(6): 1746-56.

The authors' goal in the present study was to examine the effects of maternal smoking during pregnancy on infant self-regulation, exploring birth weight as a mediator and sex as a moderator of risk. A prospective sample of 218 infants was assessed at 6 months of age. Infants completed a battery of tasks assessing working memory/inhibition, attention, and emotional reactivity and regulation. Propensity scores were used to statistically control for confounding risk factors associated with maternal smoking during pregnancy. After prenatal and postnatal confounds were controlled, prenatal tobacco exposure was related to reactivity to frustration and control of attention during stimulus encoding. Birth weight did not mediate the effect of prenatal exposure but was independently related to reactivity and working memory/inhibition. The effect of tobacco exposure was not moderated by sex.

**Emotion Regulation Mediates the Association between ADHD and Depressive Symptoms in a Community Sample of Youth**

Seymour KE, Chronis-Tuscano A, Iwamoto DK, Kurdziel G, Macpherson L. *J Abnorm Child Psychol.* 2014 May; 42(4): 611-21.

The purpose of this study was to examine the longitudinal relationship between attention-deficit/hyperactivity disorder (ADHD) symptoms, emotion regulation (ER) ability, and depressive symptoms within a diverse community sample of 277 youth, ages 9-12 (56 % male). Participants were drawn from a larger study examining adolescent risk behaviors, and completed annual assessments over 3 years. Youth ADHD symptoms were assessed at Time 1 (T1) using the parent-reported Disruptive Behavior Disorders Rating Scale, ER was assessed with the parent-reported Emotion Regulation Checklist at Time 2 (T2), and youth depressive symptoms were assessed using the self-reported Revised Child Anxiety and Depression Scales at Time 3 (T3). Analyses examined T2 ER as a mediator between T1 ADHD symptoms (including the unique contributions of

inattentive [IA] versus hyperactive/impulsive [HI] symptoms) and T3 depressive symptoms. Structural equation modeling (SEM) indicated the path model specified provided an excellent fit to the data. Tests of indirect effects suggested that T2 ER appears to be a significant mechanism that underlies the relationship between T1 ADHD and T3 depression, even when accounting for T1 oppositional defiant and depressive symptoms. Furthermore, while both T1 IA and HI symptoms had significant indirect effects on T3 depression through the mechanism T2 ER, HI proved a more robust predictor of T2 ER than IA. Results of this prospective study support cross-sectional findings pointing to ER as a potential mechanism linking ADHD and depressive symptoms in youth. Clinical implications and future directions are discussed.

**Impulsivity, Sensation-seeking, and Part-time Job Status in Relation to Substance Use and Gambling in Adolescents** Leeman RF, Hoff RA, Krishnan-Sarin S, Patock-Peckham JA, Potenza MN. *J Adolesc Health*. 2014 Apr; 54(4): 460-6.

Although impulsivity, sensation-seeking, and part-time employment have each been linked to risky behaviors in adolescents, their inter-relationships are less well-understood. The authors examined data from adolescents to assess the following predictions: (1) sensation-seeking would relate closely to substance use and gambling; (2) impulsivity would relate closely to alcohol, drug, and gambling problems; and (3) these relationships would be particularly strong among those holding part-time jobs. High-school students (N = 3,106) were surveyed to provide data on impulsivity, sensation-seeking, and part-time job status. Bivariate and logistic regression analyses were conducted to examine relationships with gambling, substance use (i.e., alcohol, cigarettes, and marijuana) and related problems. Both impulsivity and sensation-seeking related significantly to substance use and impulsivity to gambling. Impulsivity had stronger associations with drug and gambling problems than sensation-seeking did. Students with paid part-time jobs were more likely to drink alcohol, binge drink, and use marijuana. Sensation-seeking had a particularly strong relationship to heavy cigarette smoking among students with part-time jobs. Conversely, there was little relationship between part-time job status and smoking among low sensation-seekers. These findings further support the relevance of sensation-seeking, impulsivity, and part-time job status to risky behaviors among adolescents. Sensation-seeking and impulsivity had unique relationships to risky behaviors, in accordance with theory and prior evidence. Impulsive adolescents may be in particular need for interventions to reduce drug use and gambling. Although part-time jobs can be beneficial, parents and caregivers should be mindful of potential negative ramifications of paid work outside the home.

**Effects of Prenatal Methamphetamine Exposure on Behavioral and Cognitive Findings at 7.5 Years of Age** Diaz SD, Smith LM, LaGasse LL, Derauf C, Newman E, Shah R, Arria A, Huestis MA, Della Grotta S, Dansereau LM, Neal C, Lester BM. *J Pediatr*. 2014 Jun; 164(6): 1333-8.

The purpose of this study was to examine child behavioral and cognitive outcomes after prenatal exposure to methamphetamine. The authors enrolled 412 mother-infant pairs (204 methamphetamine-exposed and 208 unexposed matched comparisons) in the Infant Development, Environment, and Lifestyle study. The 151 children exposed to methamphetamine and 147 comparisons who attended the 7.5-year visit were included. Exposure was determined by maternal self-report and/or positive meconium toxicology. Maternal interviews assessed behavioral and cognitive outcomes using the Conners' Parent Rating Scale-Revised: Short Form. After adjusting for covariates, children exposed to methamphetamine had significantly higher cognitive problems subscale scores than comparisons and were 2.8 times more likely to have cognitive problems scores that were above average on the Conners' Parent Rating Scale-Revised: Short Form. No association between prenatal methamphetamine exposure and behavioral problems, measured by the oppositional, hyperactivity, and attention-deficit/hyperactivity disorder index subscales, were found. Prenatal methamphetamine

exposure was associated with increased cognitive problems, which may affect academic achievement and lead to increased negative behavioral outcomes.

**Automated Assessment of the Quality of Diffusion Tensor Imaging Data Using Color Cast of Color-encoded Fractional Anisotropy Images** He X, Liu W, Li X, Li Q, Liu F, Rauh VA, Yin D, Bansal R, Duan Y, Kangarlu A, Peterson BS, Xu D. *Magn Reson Imaging*. 2014 Jun; 32(5): 446-56.

Diffusion tensor imaging (DTI) data often suffer from artifacts caused by motion. These artifacts are especially severe in DTI data from infants, and implementing tight quality controls is therefore imperative for DTI studies of infants. Currently, routine procedures for quality assurance of DTI data involve the slice-wise visual inspection of color-encoded, fractional anisotropy (CFA) images. Such procedures often yield inconsistent results across different data sets, across different operators who are examining those data sets, and sometimes even across time when the same operator inspects the same data set on two different occasions. The authors propose a more consistent, reliable, and effective method to evaluate the quality of CFA images automatically using their color cast, which is calculated on the distribution statistics of the 2D histogram in the color space as defined by the International Commission on Illumination (CIE) on lightness and a and b (LAB) for the color-opponent dimensions (also known as the CIELAB color space) of the images. Experimental results using DTI data acquired from neonates verified that this proposed method is rapid and accurate. The method thus provides a new tool for real-time quality assurance for DTI data.

**Mothers' Unresolved Trauma Blunts Amygdala Response to Infant Distress** Kim S, Fonagy P, Allen J, Strathearn L. *Soc Neurosci*. 2014; 9(4): 352-63.

While the neurobiology of post-traumatic stress disorder has been extensively researched, much less attention has been paid to the neural mechanisms underlying more covert but pervasive types of trauma (e.g., those involving disrupted relationships and insecure attachment). Here, the authors report on a neurobiological study documenting that mothers' attachment-related trauma, when unresolved, undermines her optimal brain response to her infant's distress. The authors examined the amygdala blood oxygenation level-dependent response in 42 first-time mothers as they underwent functional magnetic resonance imaging scanning, viewing happy- and sad-face images of their own infant, along with those of a matched unknown infant. Whereas mothers with no trauma demonstrated greater amygdala responses to the sad faces of their own infant as compared to their happy faces, mothers who were classified as having unresolved trauma in the Adult Attachment Interview (Dynamic Maturational Model) displayed blunted amygdala responses when cued by their own infants' sadness as compared to happiness. Unknown infant faces did not elicit differential amygdala responses between the mother groups. The blunting of the amygdala response in traumatized mothers is discussed as a neural indication of mothers' possible disengagement from infant distress, which may be part of a process linking maternal unresolved trauma and disrupted maternal caregiving.

**Alcohol and Tobacco Use among Maltreated and Non-maltreated Adolescents in a Birth Cohort** Mills R, Alati R, Strathearn L, Najman JM. *Addiction*. 2014 Apr; 109(4): 672-80.

This study examines whether child maltreatment experience predicts adolescent tobacco and alcohol use. The subjects were participants in the Mater-University Study of Pregnancy (MUSP), a birth cohort of 7223, of whom 5158 (71.4%) were available for analysis at the 14-year follow-up. Child protection history was obtained from the state's child protection agency and confidentially linked. Exposure to reported child maltreatment was the primary predictor variable. The outcome variables were self-reported smoking and alcohol use. Associations were adjusted for potential confounders.

Reported child maltreatment was associated with early adolescent smoking [odds ratio (OR) 1.76, 95% confidence interval (CI)=1.32-2.34] after adjustment for socio-demographic variables and coexisting alcohol use. Both neglect/emotional abuse (OR 2.03, 95% CI=1.20-3.42) and neglect/emotional abuse that included physical abuse (OR 1.85, 95% CI=1.19-2.88) were associated with smoking after full adjustment, including for coexisting alcohol use. After full adjustment, including coexisting smoking, only child neglect/emotional abuse predicted early adolescent alcohol use (OR 1.78, 95% CI=1.06-2.97), but not the other types of maltreatment. Reported child maltreatment predicts early adolescent smoking after adjusting for alcohol use, but does not predict alcohol use after adjustment for smoking. Both smoking and alcohol use are predicted by reported child neglect. Early adolescent smoking is also predicted by multi-type maltreatment that includes physical abuse.

### **Race as a Moderator of the Relationship between Distress Tolerance and Cigarette Smoking**

Dahne J, Stratton KJ, Brown R, Amstadter AB, Lejuez CW, MacPherson L. *Subst Use Misuse*. 2014 May; 49(6): 708-14.

The present study examined the role of distress tolerance (DT) and race in relation to cigarette smoking. For this study, between 2008 and 2010, 153 women (62.1% White, 37.9% African American) from the Washington, DC metropolitan area completed a computerized behavioral DT task and self-reported smoking history. Results suggest that low DT (OR = .23,  $p = .03$ ) and the interaction between DT and race (OR = 4.58,  $p = .05$ ) were significantly related to greater odds of being a smoker, such that African American women, but not White women, with low DT were at increased risk for being a lifetime smoker.

### **Adoptive Parent Hostility and Children's Peer Behavior Problems: Examining the Role of Genetically Informed Child Attributes on Adoptive Parent Behavior**

Elam KK, Harold GT, Neiderhiser JM, Reiss D, Shaw DS, Natsuaki MN, Gaysina D, Barrett D, Leve LD. *Dev Psychol*. 2014 May; 50(5): 1543-52.

Socially disruptive behavior during peer interactions in early childhood is detrimental to children's social, emotional, and academic development. Few studies have investigated the developmental underpinnings of children's socially disruptive behavior using genetically sensitive research designs that allow examination of parent-on-child and child-on-parent (evocative genotype-environment correlation [rGE]) effects when examining family process and child outcome associations. Using an adoption-at-birth design, the present study controlled for passive genotype-environment correlation and directly examined evocative rGE while examining the associations between family processes and children's peer behavior. Specifically, the present study examined the evocative effect of genetic influences underlying toddler low social motivation on mother-child and father-child hostility and the subsequent influence of parent hostility on disruptive peer behavior during the preschool period. Participants were 316 linked triads of birth mothers, adoptive parents, and adopted children. Path analysis showed that birth mother low behavioral motivation predicted toddler low social motivation, which predicted both adoptive mother-child and father-child hostility, suggesting the presence of an evocative genotype-environment association. In addition, both mother-child and father-child hostility predicted children's later disruptive peer behavior. Results highlight the importance of considering genetically influenced child attributes on parental hostility that in turn links to later child social behavior. Implications for intervention programs focusing on early family processes and the precursors of disrupted child social development are discussed.

**Birth and Adoptive Parent Anxiety Symptoms Moderate the Link Between Infant Attention Control and Internalizing Problems in Toddlerhood**

Brooker RJ, Neiderhiser JM, Ganiban JM, Leve LD, Shaw DS, Reiss D. Dev Psychopathol. 2014 May; 26(2): 347-59.

Attention control plays an important role in the development of internalizing symptoms in children. The authors explored the degree to which infants' genetic and environmentally based risk moderated the link between attention control and internalizing problems during toddlerhood. These associations were examined within a prospective adoption design, enabling the disentanglement of genetic and environmental risk for internalizing problems. Attention control in adopted infants was observed during periods of distress at age 9 months. Birth parents' anxiety symptoms were used as an index of genetic risk, while adoptive parents' anxiety symptoms were used as an index of environmental risk. Adoptive mothers and fathers reported on children's internalizing problems when children were 18 and 27 months old. Greater attention control in infancy appeared to mitigate genetically based risk for internalizing problems during toddlerhood when children were raised by adoptive parents who were low in anxiety. Findings suggest that for genetically susceptible children who are raised in low-risk environments, attention control may provide a protective factor against developing internalizing problems across early life.

**The Relationship between Maternal-fetal Attachment and Cigarette Smoking over Pregnancy**

Magee SR, Bublitz MH, Orazine C, Brush B, Salisbury A, Niaura R, Stroud LR. Matern Child Health J. 2014 May; 18(4): 1017-22.

Cigarette smoking during pregnancy is one of the most preventable causes of infant morbidity and mortality, yet 80% of women who smoked prior to pregnancy continue to smoke during pregnancy. Past studies have found that lower maternal-fetal attachment predicts smoking status in pregnancy, yet past research has not examined whether maternal-fetal attachment predicts patterns or quantity of smoking among pregnant smokers. The aim of this study was to examine the relationship between maternal-fetal attachment and patterns of maternal smoking among pregnant smokers. The authors used self-reported and biochemical markers of cigarette smoking in order to better understand how maternal-fetal attachment relates to the degree of fetal exposure to nicotine. Fifty-eight pregnant smokers participated in the current study. Women completed the Maternal-Fetal Attachment Scale, reported weekly smoking behaviors throughout pregnancy using the Timeline Follow Back interview, and provided a saliva sample at 30 and 35 weeks gestation and 1 day postpartum to measure salivary cotinine concentrations. Lower maternal-fetal attachment scores were associated with higher salivary cotinine at 30 weeks gestation and 1 day postpartum. As well, women who reported lower fetal attachment reported smoking a greater maximum number of cigarettes per day, on average, over pregnancy. Lower maternal-fetal attachment is associated with greater smoking in pregnancy. Future research might explore whether successful smoking cessation programs improve maternal assessments of attachment to their infants.

**Maternal History of Adoption or Foster Care Placement in Childhood: A Risk Factor for Preterm Birth**

Bublitz MH, Rodriguez D, Polly Gobin A, Waldemore M, Magee S, Stroud LR. Am J Obstet Gynecol. 2014 Apr 5. [Epub ahead of print].

The objective of the study was to assess the impact of maternal history of adoption or foster care placement in childhood on the risk for preterm birth (PTB), controlling for other known risk factors for PTB. Participants were 302 pregnant women from a low-income, diverse sample drawn from 2 intensive prospective studies of maternal mood and behavior and fetal and infant development. Gestational age was determined by best obstetric estimate. Maternal history of adoption or foster care placement prior to age 18 years was determined by maternal report. Other maternal characteristics, including maternal medical conditions, psychosocial characteristics, and health

behaviors, were measured during the second and third trimesters of pregnancy. The odds of delivering preterm (gestational age <37 weeks) were approximately 4 times greater among women with a history of childhood adoption or foster care placement compared with women who were never placed out of the home during childhood. This association remained significant after adjusting for other known risk factors for PTB including maternal medical conditions, psychosocial characteristics, and negative health behaviors in pregnancy. Findings suggest that a history of adoption/foster care placement is an important risk factor for PTB and may be comparable with other established risk factors for PTB including prior history of PTB, body mass index, African-American race, and advanced maternal age. More studies are needed to understand why women with placement history.

**Mapping the Trajectory of Socioeconomic Disparity in Working Memory: Parental and Neighborhood Factors**

Hackman DA, Betancourt LM, Gallop R, Romer D, Brodsky NL, Hurt H, Farah MJ. Child Dev. 2014 Apr 29. [Epub ahead of print].

Working memory (WM) is positively correlated with socioeconomic status (SES). It is not clear, however, if SES predicts the rate of WM development over time or whether SES effects are specific to family rather than neighborhood SES. A community sample of children (n = 316) enrolled between ages 10 and 13 completed four annual assessments of WM. Lower parental education, but not neighborhood disadvantage, was associated with worse WM performance. Neither measure of SES was associated with the rate of developmental change. Consequently, the SES disparity in WM is not a developmental lag that narrows or an accumulating effect that becomes more pronounced. Rather, the relation between family SES and WM originates earlier in childhood and is stable through adolescence.

**Left Middle Frontal Gyrus Response to Inhibitory Errors in Children Prospectively Predicts Early Problem Substance Use**

Heitzeg MM, Nigg JT, Hardee JE, Soules M, Steinberg D, Zubieta J, Zucker RA. Drug Alcohol Depend. 2014 Aug 1; 141: 51-7.

A core vulnerability trait for substance use disorder (SUD) is behavioral disinhibition. Error processing is a central aspect of inhibitory control that determines adaptive adjustment of performance; yet it is a largely overlooked aspect of disinhibition as it relates to risk for SUD. The authors investigated whether differences in brain activation during both successful and failed inhibition predicts early problem substance use. Forty-five 9-12 year olds underwent a functional MRI scan during a go/no-go task. They were then followed over approximately 4 years, completing assessments of substance use. Externalizing behavior was measured at ages 3-8, 9-12 and 11-13. Participants with drug use or problem alcohol use by ages 13-16 (n=13; problem-user group) were individually matched by gender, age, and family history of alcoholism with non-substance-using children (n=13; non-user group). The remaining 19 participants provided an independent sample from which to generate unbiased regions-of-interest for hypothesis testing in the problem-user and non-user groups. No differences were observed between groups in activation during correct inhibition compared with baseline. A significant difference arose in left middle frontal gyrus (LMFG) activation during failed inhibition compared with correct inhibition, with the problem-user group demonstrating blunted activation. The problem-user group also had more externalizing problems at ages 11-13. Logistic regression found that activation of LMFG significantly predicted group membership over and above externalizing problems. Blunted LMFG activation during performance errors may underlie problems adapting behavior appropriately, leading to undercontrolled behavior, early problem substance use and increased risk for SUD.

**Exciting Fear in Adolescence: Does Pubertal Development Alter Threat Processing?** Spielberg JM, Olino TM, Forbes EE, Dahl RE. *Dev Cogn Neurosci*. 2014 Apr; 8: 86-95.

Adolescent development encompasses an ostensible paradox in threat processing. Risk taking increases dramatically after the onset of puberty, contributing to a 200% increase in mortality. Yet, pubertal maturation is associated with increased reactivity in threat-avoidance systems. In the first part of this paper the authors propose a heuristic model of adolescent affective development that may help to reconcile aspects of this paradox, which focuses on hypothesized pubertal increases in the capacity to experience (some) fear-evoking experiences as an exciting thrill. In the second part of this paper, the authors test key features of this model by examining brain activation to threat cues in a longitudinal study that disentangled pubertal and age effects. Pubertal increases in testosterone predicted increased activation to threat cues, not only in regions associated with threat avoidance (i.e., amygdala), but also regions associated with reward pursuit (i.e., nucleus accumbens). These findings are consistent with the authors' hypothesis that puberty is associated with a maturational shift toward more complex processing of threat cues--which may contribute to adolescent tendencies to explore and enjoy some types of risky experiences.

**Prenatal Cocaine Exposure: The Role of Cumulative Environmental Risk and Maternal Harshness in the Development of Child Internalizing Behavior Problems in Kindergarten**

Eiden RD, Godleski S, Colder CR, Schuetze P. *Neurotoxicol Teratol*. 2014 May 4; 44C: 1-10.

This study examined the associations between prenatal exposure to cocaine and other substances and child. The authors investigated whether maternal harshness or cumulative environmental risk mediated or moderated this association. Participants consisted of 216 (116 cocaine exposed, 100 non-cocaine exposed) mother-infant dyads participating in an ongoing longitudinal study of prenatal cocaine exposure. Results indicated that, as hypothesized, maternal harshness moderated the association between prenatal cocaine exposure to child internalizing in kindergarten such that prenatal cocaine exposure increased risk for internalizing problems at high levels of maternal harshness from 7 to 36 months and decreased risk at low levels of harshness. Contrary to hypothesis, the association between prenatal cocaine exposure and child internalizing in kindergarten was not mediated by maternal harshness or cumulative environmental risk. However, cumulative environmental risk (from 1 month of child age to kindergarten) was predictive of child internalizing behavior problems at kindergarten. Results have implications for parenting interventions that may be targeted toward reducing maternal harshness in high risk samples characterized by maternal substance use in pregnancy.

## **CLINICAL NEUROSCIENCE RESEARCH**

### **Neural Correlates of Attentional Bias for Smoking Cues: Modulation by Variance in the Dopamine Transporter Gene**

Wetherill RR, Jagannathan K, Lohoff FW, Ehrman R, O'Brien CP, Childress AR, Franklin TR. *Addict Biol.* 2014 Mar; 19(2): 294–304.

Cigarette-dependent smokers automatically and involuntarily orient attention toward smoking cues (SCs). This attentional bias is clinically significant, as it may contribute to relapse. Thus, identifying neural and genetic correlates of attentional bias is critical for improving interventions. The authors' previous studies show that the dopamine transporter (DAT) *SLC6A3* genotype exerts profound effects on limbic responses to SCs. One potential mechanism underlying these effects is greater attentional bias for SCs. Here, they explored associations between attentional bias for SCs and neural responses to SCs among 'sated' smokers genotyped for the *SLC6A3* polymorphism. Pseudo-continuous arterial spin-labeled perfusion functional magnetic resonance imaging images were acquired during SC exposure in 35 smokers genotyped for the *SLC6A3* variable number of tandem repeats polymorphism ( $n=16$ , 9-repeats;  $n=19$ , 10/10-repeats). Participants completed a visual dot-probe attentional bias task, which contained pictures of smoking and non-smoking pictures, to examine whether genetic variation in DAT influences attentional bias and to investigate relationships between attentional bias and neural responses to SCs. Although attentional bias to smoking pictures was not significantly different between 9-repeats and 10/10-repeats, 9-repeats showed a positive correlation between attentional bias and increased SC-induced brain activity in the amygdala, whereas 10/10-repeats showed an inverse correlation in the medial orbitofrontal cortex (mOFC). In group comparisons, 9-repeats exhibited positive correlations between attentional bias and SCs in the mOFC and amygdala, relative to 10/10-repeats. Findings suggest that genetic variation in the DAT gene influences brain responses associated with attentional bias; thus, providing additional support for a SC-vulnerable endophenotype.

### **Worth the Wait: Effects of Age of Onset of Marijuana Use on White Matter and Impulsivity**

Gruber SA, Dahlgren MK, Sagar KA, Gönenç A, Lukas SE. *Psychopharmacology.* 2014; 231(8):1455–1465.

Marijuana (MJ) use continues to rise, and as the perceived risk of using MJ approaches an all-time historic low, initiation of MJ use is occurring at even younger ages. As adolescence is a critical period of neuromaturation, teens and emerging adults are at greater risk for experiencing the negative effects of MJ on the brain. In particular, MJ use has been shown to be associated with alterations in frontal white matter microstructure, which may be related to reports of increased levels of impulsivity in this population. The aim of this study was to examine the relationship between age of onset of MJ use, white matter microstructure, and reported impulsivity in chronic, heavy MJ smokers. Twenty-five MJ smokers and 18 healthy controls underwent diffusion tensor imaging and completed the Barratt Impulsiveness Scale. MJ smokers were also divided into early onset (regular use prior to age 16) and late onset (age 16 or later) groups in order to clarify the impact of age of onset of MJ use on these variables. MJ smokers exhibited significantly reduced fractional anisotropy (FA) relative to controls, as well as higher levels of impulsivity. Earlier MJ onset was also associated with lower levels of FA. Interestingly, within the early onset group, higher impulsivity scores were correlated with lower FA, a relationship that was not observed in the late onset smokers. MJ use is associated with white matter development and reported impulsivity, particularly in early onset smokers.

**Effects of APOE  $\epsilon$ 4, Age, and HIV on Glial Metabolites and Cognitive Deficits** Chang L, Jiang C, Cunningham E, Buchthal S, Douet V, Andres M, Ernst T. *Neurology*. 2014 Jun 17; 82(24): 2213-2222.

The authors aimed to evaluate the combined effects of HIV and APOE  $\epsilon$ 4 allele(s) on glial metabolite levels, and on known cognitive deficits associated with either condition, across the ages. One hundred seventy-seven participants, primarily of white and mixed race (97 seronegative subjects: aged  $44.7 \pm 1.3$  years, 85 [87.6%] men, 28 [28.9%] APOE  $\epsilon$ 4+; 80 HIV+ subjects: aged  $47.3 \pm 1.1$  years, 73 [91.3%] men, 23 [28.8%] APOE  $\epsilon$ 4+), were assessed cross-sectionally for metabolite concentrations using proton magnetic resonance spectroscopy in 4 brain regions and for neuropsychological performance. Frontal white matter myo-inositol was elevated in subjects with HIV across the age span but showed age-dependent increase in seronegative subjects, especially in APOE  $\epsilon$ 4+ carriers. In contrast, only seronegative APOE  $\epsilon$ 4+ subjects showed elevated myo-inositol in parietal cortex. All APOE  $\epsilon$ 4+ subjects had lower total creatine in basal ganglia. While all HIV subjects showed greater cognitive deficits, HIV+ APOE  $\epsilon$ 4+ subjects had the poorest executive function, fluency memory, and attention/working memory. Higher myo-inositol levels were associated with poorer fine motor function across all subjects, slower speed of information processing in APOE  $\epsilon$ 4+ subjects, and worse fluency in HIV+ APOE  $\epsilon$ 4+ subjects. In frontal white matter of subjects with HIV, the persistent elevation and lack of normal age-dependent increase in myo-inositol suggest that persistent glial activation attenuated the typical antagonistic pleiotropic effects of APOE  $\epsilon$ 4 on neuroinflammation. APOE  $\epsilon$ 4 negatively affects energy metabolism in brain regions rich in dopaminergic synapses. The combined effects of HIV infection and APOE  $\epsilon$ 4 may lead to greater cognitive deficits, especially in those with greater neuroinflammation. APOE  $\epsilon$ 4 allele(s) may be a useful genetic marker to identify white and mixed-race HIV subjects at risk for cognitive decline.

**Abstinence-related Changes in Sleep During Treatment for Cocaine Dependence** Angarita GA, Canavan SV, Forselius E, Bessette A, Pittman B, Morgan PT. *Drug Alc Depend*. 2014 Jan 1; 134: 343-347.

Former sleep studies among non-treatment seeking chronic cocaine users had captured polysomnographic changes for as long as three weeks of abstinence. 20 cocaine dependent participants, randomized to placebo in an ongoing clinical trial, received 12 days of inpatient substance abuse treatment followed by 6 weeks of outpatient cognitive behavioral therapy. Polysomnographic recording was performed on consecutive nights during the 1st and 2nd inpatient and 3rd and 6th outpatient weeks. Number of days abstinent was determined from thrice weekly urine toxicology and self-report. Polysomnographic sleep was compared between study week 1 and 2, using paired *t*-tests. Trajectory of total sleep time (TST) was modeled both as a linear and a quadratic function of days abstinent. Despite reporting an improvement in overall sleep quality, polysomnographic sleep worsened from week 1 to 2. Among all participants, TST and stage 2 sleep time decreased, while REM sleep latency increased. Among participants who began the study with a positive urine test, there was also a decrease in REM and a trend for decreased slow wave sleep. TST compared to number of days abstinent (up to 54 days) was best fit with a quadratic model ( $p = 0.002$ ), suggesting the possibility of an improvement in total sleep time with extended abstinence. This is the first polysomnographic characterization of sleep in a large sample of cocaine users in treatment. Present findings confirm earlier results of poor and deteriorating sleep early in abstinence, and raise the possibility of improvement after an extended abstinence.

**Differential Reward Network Functional Connectivity in Cannabis Dependent and Non-dependent Users**

Filbey FM, Dunlop J. *Drug Alc Depend.* 2014 Jul 1; 140: 101-111. Emergent studies show that similar to other substances of abuse, cue-reactivity to cannabis is also associated with neural response in the brain's reward pathway. However, the inter-relatedness of brain regions during cue-reactivity in cannabis users remains unknown. In this study, the authors conducted a series of investigations to determine functional connectivity during cue-reactivity in 71 cannabis users. First, they used psychophysiological interaction (PPI) analysis to examine coherent neural response to cannabis cues. Second, they evaluated whether these patterns of network functional connectivity differentiated dependent and non-dependent users. Finally, as an exploratory analysis, they determined the directionality of these connections via Granger connectivity analyses. PPI analyses showed reward network functional connectivity with the nucleus accumbens (NAc) seed region during cue exposure. Between-group contrasts found differential effects of dependence status. Dependent users (N = 31) had greater functional connectivity with amygdala and anterior cingulate gyrus (ACG) seeds while the non-dependent users (N = 24) had greater functional connectivity with the NAc, orbitofrontal cortex (OFC) and hippocampus seeds. Granger analyses showed that hippocampal and ACG activation preceded neural response in reward areas. Both PPI and Granger analyses demonstrated strong functional coherence in reward regions during exposure to cannabis cues in current cannabis users. Functional connectivity (but not regional activation) in the reward network differentiated dependent from non-dependent cannabis users. These findings suggest that repeated cannabis exposure causes observable changes in functional connectivity in the reward network and should be considered in intervention strategies.

**Neural Responses to Subliminally Presented Cannabis and Other Emotionally Evocative Cues in Cannabis-dependent Individuals**

Wetherill RR, Childress AR, Jagannathan K, Bender J, Young KA, Suh JJ, O'Brien CP, Franklin TR. *Psychopharm.* 2014 Apr; 231(7): 1397-1407. Addiction theories posit that drug-related cues maintain and contribute to drug use and relapse. Indeed, the authors' recent study in cocaine-dependent patients demonstrated that subliminally presented cocaine-related stimuli activate reward neurocircuitry without being consciously perceived. Activation of reward neurocircuitry may provoke craving and perhaps prime an individual for subsequent drug-seeking behaviors. Using an equivalent paradigm, the authors tested whether cannabis cues activate reward neurocircuitry in treatment-seeking, cannabis-dependent individuals and whether activation was associated with relevant behavioral anchors: Baseline cannabis craving (drug-seeking behavior) and duration of use (degree of conditioning). Twenty treatment-seeking, cannabis-dependent individuals (12 males) underwent event-related blood oxygen level-dependent functional magnetic resonance imaging during exposure to 33-ms cannabis, sexual, and aversive cues presented in a backward-masking paradigm. Drug use history and cannabis craving were assessed prior to imaging. Participants showed increased activity to backward-masked cannabis cues in regions supporting reward detection and interoception, including the left anterior insula, left ventral striatum/amygdala, and right ventral striatum. Cannabis cue-related activity in the bilateral insula and perigenual anterior cingulate cortex was positively associated with baseline cannabis craving, and cannabis cue-related activity in the medial orbitofrontal cortex was positively correlated with years of cannabis use. Neural responses to backward-masked sexual cues were similar to those observed during cannabis cue exposure, while activation to aversive cues was observed only in the left anterior insula and perigenual anterior cingulate cortex. These data highlight the sensitivity of the brain to subliminal reward signals and support hypotheses promoting a common pathway of appetitive motivation.

**Nicotine and Non-Nicotine Smoking Factors Differentially Modulate Craving, Withdrawal and Cerebral Blood Flow as Measured with Arterial Spin Labeling.** Addicott MA, Froeliger B, Kozink RV, Van Wert DM, Westman EC, Rose JE, McClernon FJ. *Neuropsychopharm.* 2014 May 13. [Epub ahead of print].

Smoking cessation results in withdrawal symptoms such as craving and negative mood that may contribute to lapse and relapse. Little is known regarding whether these symptoms are associated with the nicotine or non-nicotine components of cigarette smoke. Using arterial spin labeling, the authors measured resting-state cerebral blood flow in twenty-nine adult smokers across four conditions: (1) nicotine patch+denicotinized cigarette smoking, (2) nicotine patch+abstinence from smoking, (3) placebo patch+denicotinized cigarette smoking, and (4) placebo patch+abstinence from smoking. The authors found that changes in self-reported craving positively correlated with changes in cerebral blood flow from the denicotinized cigarette smoking conditions to the abstinent conditions. These correlations were found in several regions throughout the brain. Self-reported craving also increased from the nicotine to the placebo conditions, but had a minimal relationship with changes in cerebral blood flow. The results of this study suggest that the non-nicotine components of cigarette smoke significantly impacts withdrawal symptoms and associated brain areas, independently of the effects of nicotine. As such, the effects of non-nicotine factors are important to consider in the design and development of smoking cessation interventions and tobacco regulation.

**Risky Decision Making, Prefrontal Cortex, and Mesocorticolimbic Functional Connectivity in Methamphetamine Dependence** Kohno M, Morales AM, Ghahremani DG, Helleman G, London ED. *JAMA Psychiatry.* 2014 Jul 1; 71(7): 812-820.

Various neuropsychiatric disorders, especially addictions, feature impairments in risky decision making; clarifying the neural mechanisms underlying this problem can inform treatment. The objective of this study was to determine how methamphetamine-dependent and control participants differ in brain activation during a risky decision-making task, resting-state functional connectivity within mesolimbic and executive control circuits, and the relationships between these measures. This was a case-control, functional magnetic resonance imaging study of methamphetamine-dependent and healthy comparison participants at rest and when performing the Balloon Analogue Risk Task, which involves the choice to pump a balloon or to cash out in the context of uncertain risk. The study was conducted at a clinical research center at an academic institution, and involved 25 methamphetamine-dependent and 27 control participants. Parametric modulation of activation in the striatum and right dorsolateral prefrontal cortex (rDLPFC; ie, the degree to which activation changed as a linear function of risk and potential reward), both indexed by pump number, and resting-state functional connectivity, were measured in the whole brain with seeds in the midbrain and rDLPFC. Relationships between these outcomes were also tested. Parametric modulation of cortical and striatal activation by pump number during risk taking differed with group. It was stronger in the ventral striatum but weaker in the rDLPFC in methamphetamine-dependent participants than control individuals. Methamphetamine-dependent participants also exhibited greater resting-state functional connectivity of the midbrain with the putamen, amygdala, and hippocampus ( $P < .05$ , whole brain, cluster corrected). This connectivity was negatively related to modulation of rDLPFC activation by risk level during risky decision making. In control participants, parametric modulation of rDLPFC activation by risk during decision making was positively related to resting-state functional connectivity of the rDLPFC with the striatum. Maladaptive decision making by methamphetamine users may reflect circuit-level dysfunction, underlying deficits in task-based activation. Heightened resting-state connectivity within the mesocorticolimbic system, coupled with reduced prefrontal cortical connectivity, may create a bias

toward reward-driven behavior over cognitive control in methamphetamine users. Interventions to improve this balance may enhance treatments for stimulant dependence and other disorders that involve maladaptive decision making.

### **Memory for Drug-Related Visual Stimuli in Young Adult, Cocaine-Dependent Polydrug Users**

Ray S, Pandina R, Bates ME. Am J Drug Alcohol Abuse. 2014 Mar; 40(2): 170-175.

Implicit (unconscious) and explicit (conscious) memory associations with drugs have been examined primarily using verbal cues. However, drug seeking, drug use behaviors, and relapse in chronic cocaine and other drug users are frequently triggered by viewing substance-related visual cues in the environment. The authors thus examined implicit and explicit memory for drug picture cues to understand the relative extent to which conscious and unconscious memory facilitation of visual drug cues occurs during cocaine dependence. Memory for drug-related and neutral picture cues was assessed in 14 inpatient cocaine-dependent polydrug users and a comparison group of 21 young adults with limited drug experience (n=35). Participants completed picture cue exposure, free recall and recognition tasks to assess explicit memory, and a repetition priming task to assess implicit memory. Drug cues, compared to neutral cues, were better explicitly recalled and implicitly primed, and especially so in the cocaine group. In contrast, neutral cues were better explicitly recognized, and especially in the control group. Certain forms of explicit and implicit memory for drug cues were enhanced in cocaine users compared to controls when memory was tested a short time following cue exposure. Enhanced unconscious memory processing of drug cues in chronic cocaine users may be a behavioral manifestation of heightened drug cue salience that supports drug seeking and taking. There may be value in expanding intervention techniques to utilize cocaine users' implicit memory system.

### **Cognitive Performance in Methadone Maintenance Patients: Effects of Time Relative to Dosing and Maintenance Dose Level**

Rass O, Kleykamp BA, Vandrey RG, Bigelow GE, Leoutsakos JM, Stitzer ML, Strain EC, Copersino ML, Mintzer MZ. Exp Clin Psychopharmacol. 2014 Jun; 22(3): 248-256.

Given the long-term nature of methadone maintenance treatment, it is important to assess the extent of cognitive side effects. This study investigated cognitive and psychomotor performance in 51 methadone maintenance patients (MMP) as a function of time since last methadone dose and maintenance dose level. MMP maintained on doses ranging from 40 to 200 mg (mean = 97 mg) completed a battery of psychomotor and cognitive measures across 2 sessions, during peak and trough states, in a double-blind crossover design. Peak sessions were associated with worse performance on measures of sensory processing, psychomotor speed, divided attention, and working memory, compared with trough sessions. The effects of maintenance dose were mixed, with higher dose resulting in worse performance on aspects of attention and working memory, improved performance on executive function, and no effects on several measures. Longer treatment duration was associated with better performance on some measures, but was also associated with increased sensitivity to time since last dose (i.e., worse performance at peak vs. trough) on some measures. The results suggest that cognitive functioning can fluctuate as a function of time since last dose even in MMP who have been maintained on stable doses for an extended time (mean duration in treatment = 4 years), but worsened performance at peak is limited to a subset of functions and may not be clinically significant at these modest levels of behavioral effect. For patients on stable methadone maintenance doses, maintenance at higher doses may not significantly increase the risk of performance impairment.

**Monoamine Polygenic Liability in Health and Cocaine Dependence: Imaging Genetics Study of Aversive Processing and Associations with Depression Symptomatology** Moeller SJ, Parvaz MA, Shumay E, Wu S, Beebe-Wang N, Konova AB, Misyrilis M, Alia-Klein N, Goldstein RZ. *Drug Alcohol Depend.* 2014 Jul 1; 140: 17-24.

Gene polymorphisms that affect serotonin signaling modulate reactivity to salient stimuli and risk for emotional disturbances. Here, the authors hypothesized that these serotonin genes, which have been primarily explored in depressive disorders, could also have important implications for drug addiction, with the potential to reveal important insights into drug symptomatology, severity, and/or possible sequelae such as dysphoria. Using an imaging genetics approach, the current study tested in 62 cocaine abusers and 57 healthy controls the separate and combined effects of variations in the serotonin transporter (5-HTTLPR) and monoamine oxidase A (MAOA) genes on processing of aversive information. Reactivity to standardized unpleasant images was indexed by a psychophysiological marker of stimulus salience (i.e., the late positive potential (LPP) component of the event-related potential) during passive picture viewing. Depressive symptomatology was assessed with the Beck Depression Inventory (BDI). Results showed that, independent of diagnosis, the highest unpleasant LPPs emerged in individuals with MAOA-Low and at least one 'Short' allele of 5-HTTLPR. Uniquely in the cocaine participants with these two risk variants, higher unpleasant LPPs correlated with higher BDI scores. Taken together, these results suggest that a multilocus genetic composite of monoamine signaling relates to depression symptomatology through brain function associated with the experience of negative emotions. This research lays the groundwork for future studies that can investigate clinical outcomes and/or pharmacogenetic therapies in drug addiction and potentially other psychopathologies of emotion dysregulation.

**The Dynamics of Pain: Evidence for Simultaneous Site-Specific Habituation and Site-Nonspecific Sensitization in Thermal Pain** Jepma M, Jones M, Wager TD. *J Pain.* 2014 Jul; 15(7): 734-746.

Repeated exposure to noxious stimuli changes their painfulness, due to multiple adaptive processes in the peripheral and central nervous systems. Somewhat paradoxically, repeated stimulation can produce an increase (sensitization) or a decrease (habituation) in pain. Adaptation processes may also be body-site-specific or operate across body sites, and considering this distinction may help explain the conditions under which habituation versus sensitization occurs. To dissociate the effects of site-specific and site-nonspecific adaptation processes, the authors examined reported pain in 100 participants during counterbalanced sequences of noxious thermal stimulation on multiple skin sites. Analysis of pain ratings revealed 2 opposing sequential effects: Repeated stimulations of the same skin site produced temperature-dependent habituation, whereas repeated stimulations across different sites produced sensitization. Stimulation trials were separated by ~20 seconds, and sensitization was unrelated to the distance between successively stimulated sites, suggesting that neither temporal nor spatial summation occurred. To explain these effects, the authors propose a dynamic model with 2 adaptation processes, one site-specific and the other site-nonspecific. The model explains 93% of the variance in the group-mean pain ratings after controlling for current stimulation temperature, with its estimated parameters showing evidence for habituation for the site-specific process and sensitization for the site-nonspecific process. The 2 pain adaptation processes revealed in this study, and the ability to disentangle them, may hold keys to understanding multiple pain-regulatory mechanisms and their disturbance in chronic pain syndromes. This article presents novel evidence for simultaneous site-specific habituation and site-nonspecific sensitization in thermal pain, which can be disentangled (and the direction and strength of each process estimated) by a dynamic model. The dissociation of site-specific and site-nonspecific adaptation processes may

hold keys to understanding multiple pain-regulatory mechanisms in both healthy and patient populations.

**Asymptomatic HIV-Associated Neurocognitive Impairment Increases Risk for Symptomatic Decline** Grant I, Franklin DR Jr, Deutsch R, Woods SP, Vaida F, Ellis RJ, Letendre SL, Marcotte TD, Atkinson JH, Collier AC, Marra CM, Clifford DB, Gelman BB, McArthur JC, Morgello S, Simpson DM, McCutchan JA, Abramson I, Gamst A, Fennema-Notestine C, Smith DM, Heaton RK. *Neurology*. 2014 Jun 10; 82(23): 2055-2062.

While HIV-associated neurocognitive disorders (HAND) remain prevalent despite combination antiretroviral therapy (CART), the clinical relevance of asymptomatic neurocognitive impairment (ANI), the most common HAND diagnosis, remains unclear. The authors investigated whether HIV-infected persons with ANI were more likely than those who were neurocognitively normal (NCN) to experience a decline in everyday functioning (symptomatic decline). A total of 347 human participants from the CNS HIV Anti-Retroviral Therapy Effects Research (CHARTER) cohort were NCN (n = 226) or had ANI (n = 121) at baseline. Neurocognitive assessments occurred approximately every 6 months, with median (interquartile range) follow-up of 45.2 (28.7-63.7) months. Symptomatic decline was based on self-report (SR) or objective, performance-based (PB) problems in everyday functioning. Proportional hazards modeling was used to generate risk ratios for progression to symptomatic HAND after adjusting for baseline and time-dependent covariates, including CD4+ T-lymphocyte count (CD4), virologic suppression, CART, and mood. The ANI group had a shorter time to symptomatic HAND than the NCN after adjusting for baseline predictors: adjusted risk ratios for symptomatic HAND were 2.0 (confidence interval [CI] 1.1-3.6; p = 0.02) for SR, 5.8 (CI 3.2-10.7; p < 0.0001) for PB, and 3.2 (CI 2.0-5.0; p < 0.0001) for either SR or PB. Current CD4 and depression were significant time-dependent covariates, but antiretroviral regimen, virologic suppression, and substance abuse or dependence were not. This longitudinal study demonstrates that ANI conveys a 2-fold to 6-fold increase in risk for earlier development of symptomatic HAND, supporting the prognostic value of the ANI diagnosis in clinical settings. Identifying those at highest risk for symptomatic decline may offer an opportunity to modify treatment to delay progression.

**HIV Protease Inhibitor Exposure Predicts Cerebral Small Vessel Disease** Soontornniyomkij V, Umlauf A, Chung SA, Cochran ML, Soontornniyomkij B, Gouaux B, Toperoff W, Moore DJ, Masliah E, Ellis RJ, Grant I, Achim CL. *AIDS*. 2014 Jun 1; 28(9): 1297-1306.

HIV-associated neurocognitive disorders (HANDs) remain prevalent in patients who receive HAART and may be associated with cumulative exposure to antiretroviral medications and other factors. The authors proposed that chronic toxic effects of antiretroviral drugs could contribute to cerebral small vessel disease (CSVD), which might be one of the key underpinnings of HAND. Clinicopathological cross-sectional study of HIV-infected adults in the California NeuroAIDS Tissue Network. The authors employed multivariable logistic regression methods to determine associations between HAART exposure (protease inhibitor-based, nonprotease inhibitor-based, or no HAART) and CSVD occurrence (standard histopathology: moderate/severe, mild, or absent). They also associated HAND (relative to normal cognition) with CSVD, HIV-related neuropathologic changes, older age at death ( $\geq 50$  years), sex, or hepatitis C virus infection. The authors found that both mild and moderate/severe CSVD were associated with protease inhibitor-based HAART exposure after adjusting for diabetes mellitus [odds ratio (OR) 2.8 (95% confidence interval, CI 1.03-7.9) and 2.6 (95% CI 1.03-6.7), respectively, n=134]. Moderate/severe CSVD was associated with diabetes after adjusting for HAART exposure [OR 7.4 (95% CI 1.6-70.7), n=134]. Notably, HAND was associated with mild CSVD [OR 4.8 (95% CI 1.1-21.2), n=63], which

remained statistically significant after adjusting for vessel mineralization, HIV encephalitis, microglial nodular lesions, white matter lesions, or older age. Protease inhibitor-based HAART exposure may increase the risk of CSVD and thereby neurocognitive impairment in HIV-infected adults. Apart from the possible direct toxicity to cerebral small vessels, protease inhibitor-based HAART may contribute indirectly to CSVD by inducing metabolic abnormalities.

### **Accelerated White Matter Aging in Schizophrenia: Role of White Matter Blood Perfusion**

Wright SN, Kochunov P, Chiappelli J, McMahon RP, Muellerklein F, Wijtenburg SA, White MG, Rowland LM, Hong LE. *Neurobiol Aging*. 2014 Oct; 35(10): 2411-2418.

Elevated rate of age-related decline in white matter integrity, indexed by fractional anisotropy (FA) from diffusion tensor imaging, was reported in patients with schizophrenia. Its etiology is unknown. The authors hypothesized that a decline of blood perfusion to the white matter may underlie the accelerated age-related reduction in FA in schizophrenia. Resting white matter perfusion and FA were collected using pseudo-continuous arterial spin labeling and high-angular-resolution diffusion tensor imaging, respectively, in 50 schizophrenia patients and 70 controls (age = 18-63 years). Main outcome measures were the diagnosis-by-age interaction on whole-brain white matter perfusion, and FA. Significant age-related decline in brain white matter perfusion and FA were present in both groups. Age-by-diagnosis interaction was significant for FA ( $p < 0.001$ ) but not white matter perfusion. Age-by-diagnosis interaction for FA values remained significant even after accounting for age-related decline in perfusion. Therefore, the authors replicated the finding of an increased rate of age-related white matter FA decline in schizophrenia and observed a significant age-related decline in white matter blood perfusion, although the latter did not contribute to the accelerated age-related decline in FA. The results suggest that factors other than reduced perfusion account for the accelerated age-related decline in white matter integrity in schizophrenia.

### **Substance Abuse Risk in Emerging Adults Associated with Smaller Frontal Gray Matter Volumes and Higher Externalizing Behaviors**

Weiland BJ, Korycinski ST, Soules M, Zubieta JK, Zucker RA, Heitzeg MM. *Drug Alcohol Depend*. 2014 Apr 1; 137: 68-75.

During emerging adulthood, alcohol and substance use peak. Previous research has suggested that prefrontal and subcortical brain volumes may relate to risk for development of substance abuse. Epidemiological studies indicate that early initiation of alcohol or drug use significantly increases the likelihood of later substance use disorder diagnoses. The authors hypothesized that frontal regions would be smaller in young adults with early substance use and related problems (early-risk, ER), compared with a control group without early use/problems (C). The authors further hypothesized that these volumes would be associated with more externalizing behaviors, an additional robust predictor of substance abuse. One hundred and six subjects, ages 18-23, underwent high-resolution anatomical magnetic resonance image scanning. Individuals were categorized as C ( $n=64$ ) or ER ( $n=42$ ) using a composite-score of early alcohol/drug use and problems based on prospectively collected assessments; externalizing behaviors were also previously assessed during adolescence. Neuroanatomical volumes were compared between groups and correlated with behavioral measures. ER subjects exhibited more externalizing behaviors than their control counterparts. Total left frontal cortex and left superior frontal cortex volumes were significantly smaller in the ER group, controlling for family history of alcoholism and current substance use. Total gray matter volumes were negatively associated with substance risk score. Further, externalizing behavior score was negatively correlated with both left superior cortical and left total cortical volumes. These findings suggest that smaller frontal cortical volumes, specifically the left superior frontal cortex, represent an underlying risk factor for substance abuse in emerging adults.

**Interactions Between Disordered Sleep Post-traumatic Stress Disorder, and Substance Use Disorders** Vandrey R, Babson KA, Herrmann ES, Bonn-Miller MO. *Int Rev Psychiatry*. 2014 Apr; 26(2): 237-247.

Disordered sleep is associated with a number of adverse health consequences and is an integral component of many psychiatric disorders. Rates of substance use disorders (SUDs) are markedly higher among individuals with post-traumatic stress disorder (PTSD), and this relationship may be partly mediated by disturbed sleep. Sleep disturbances (e.g. insomnia, daytime sleepiness, vivid nightmares) are hallmark features of PTSD and there is evidence that individuals with PTSD engage in substance use as a means of coping with these symptoms. However, prolonged substance use can lead to more severe sleep disturbances due to the development of tolerance and withdrawal. Behavioural or pharmacological treatment of disordered sleep is associated with improved daytime symptoms and psychosocial functioning among individuals who have developed PTSD. Initial research also suggests that improving sleep could be similarly beneficial in reducing coping oriented substance use and preventing relapse among those seeking treatment for SUDs. Together, these findings suggest that ameliorating sleep disturbance among at-risk individuals would be a viable target for the prevention and treatment of PTSD and associated SUDs, but prospective research is needed to examine this hypothesis. Enhanced understanding of the interrelation between sleep, PTSD, and SUDs may yield novel prevention and intervention approaches for these costly, prevalent and frequently co-occurring disorders.

**Relationship Between Impulsivity, Prefrontal Anticipatory Activation, and Striatal Dopamine Release During Rewarded Task Performance** Weiland BJ, Heitzeg MM, Zald D, Cummiford C, Love T, Zucker RA, Zubieta JK. *Psychiatry Res*. 2014 Jun 5. [Epub ahead of print].

Impulsivity, and in particular the negative urgency aspect of this trait, is associated with poor inhibitory control when experiencing negative emotion. Individual differences in aspects of impulsivity have been correlated with striatal dopamine D2/D3 receptor availability and function. This multi-modal pilot study used both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) to evaluate dopaminergic and neural activity, respectively, using modified versions of the monetary incentive delay task. Twelve healthy female subjects underwent both scans and completed the NEO Personality Inventory Revised to assess Impulsiveness (IMP). The authors examined the relationship between nucleus accumbens (NAcc) dopaminergic incentive/reward release, measured as a change in D2/D3 binding potential between neutral and incentive/reward conditions with [<sup>11</sup>C]raclopride PET, and blood oxygen level-dependent (BOLD) activation elicited during the anticipation of rewards, measured with fMRI. Left NAcc incentive/reward dopaminergic release correlated with anticipatory reward activation within the medial prefrontal cortex (mPFC), left angular gyrus, mammillary bodies, and left superior frontal cortex. Activation in the mPFC negatively correlated with IMP and mediated the relationship between IMP and incentive/reward dopaminergic release in left NAcc. The mPFC, with a regulatory role in learning and valuation, may influence dopamine incentive/reward release.

**Assessment of Safety, Cardiovascular and Subjective Effects after Intravenous Cocaine and Lofexidine** De La Garza R 2nd, Galloway GP, Newton TF, Mendelson J, Haile CN, Dib E, Hawkins RY, Chen CY, Mahoney JJ 3rd, Mojsiak J, Lao G, Anderson A, Kahn R. *Prog Neuropsychopharmacol Biol Psychiatry*. 2014 Apr 3; 50: 44-52.

The primary objective of this study was to determine the safety of lofexidine, an  $\alpha_2$  receptor agonist, alone and concurrent with cocaine in non-treatment seeking cocaine-dependent or cocaine-abusing participants. After screening, eligible participants received double-blind, randomized infusions of saline and 20mg of cocaine on Day 1, and saline and 40mg of cocaine on Day 2.

Subjects were randomized and started receiving daily administration of placebo (N=4) or lofexidine on Day 3 and continued on this schedule until Day 7. Two dosing regimens for lofexidine were investigated: 0.8 QID (N=3) and 0.2mg QID (N=11). On Days 6 and 7, subjects received double-blind infusions of saline and 20mg of cocaine on Day 6, and saline and 40mg of cocaine on Day 7. The data reveal a notable incidence of hemodynamic-related AEs over the course of the study. Two of the three participants at the 0.8mg dose level discontinued, and five of 11 participants at the 0.2mg dose level were withdrawn (or voluntarily discontinued) after hemodynamic AEs. Subjective effects and cardiovascular data were derived from all participants who were eligible to receive infusions (i.e., did not meet stopping criteria) on Days 6 and 7 (6 received lofexidine 0.2mg, QID and 4 received placebo, QID). As expected, cocaine significantly increased heart rate and blood pressure, as well as several positive subjective effects. There was a trend for lofexidine to decrease cocaine-induced cardiovascular changes and cocaine-induced ratings for "any drug effect", "good effects", and "desire cocaine", but sample size issues limit the conclusions that can be drawn. Despite the trends to reduce cocaine-induced subjective effects, cardiovascular AEs may limit future utility of lofexidine as a treatment for this population.

**MDMA Alters Emotional Processing and Facilitates Positive Social Interaction** Wardle MC, de Wit H. *Psychopharmacology* (Berl). 2014 Apr 12. [Epub ahead of print].

±3,4-Methylenedioxymethamphetamine (MDMA, "ecstasy") produces "prosocial" effects, such as feelings of empathy and closeness, thought to be important to its abuse and its value in psychotherapy. However, it is not fully understood how MDMA alters basic emotional processes to produce these effects, or whether it produces corresponding changes in actual social behavior. Here, the authors examined how MDMA affects perceptions of and responses to emotional expressions, and tested its effects on behavior during a social interaction. They also examined whether MDMA's prosocial effects related to a measure of abuse liability. Over three sessions, 36 healthy volunteers with previous ecstasy use received MDMA (0.75, 1.5 mg/kg) and placebo under double-blind conditions. The authors measured (i) mood and cardiovascular effects, (ii) perception of and psychophysiological responses to emotional expressions, (iii) use of positive and negative words in a social interaction, and (iv) perceptions of an interaction partner. They then tested whether these effects predicted desire to take the drug again. MDMA slowed perception of angry expressions, increased psychophysiological responses to happy expressions, and increased positive word use and perceptions of partner empathy and regard in a social interaction. These effects were not strongly related to desire to take the drug again. MDMA alters basic emotional processes by slowing identification of negative emotions and increasing responses to positive emotions in others. Further, it positively affects behavior and perceptions during actual social interaction. These effects may contribute to the efficacy of MDMA in psychotherapy, but appear less closely related to its abuse potential.

**MDMA Decreases the Effects of Simulated Social Rejection** Frye CG, Wardle MC, Norman GJ, de Wit H. *Pharmacol Biochem Behav.* 2014 Feb; 117: 1-6.

3-4-Methylenedioxymethamphetamine (MDMA) increases self-reported positive social feelings and decreases the ability to detect social threat in faces, but its effects on experiences of social acceptance and rejection have not been determined. The authors examined how an acute dose of MDMA affects subjective and autonomic responses to simulated social acceptance and rejection. They predicted that MDMA would decrease subjective responses to rejection. On an exploratory basis, the authors also examined the effect of MDMA on respiratory sinus arrhythmia (RSA), a measure of parasympathetic cardiac control often thought to index social engagement and emotional regulation. Over three sessions, healthy adult volunteers with previous MDMA experience (N=36)

received capsules containing placebo, 0.75 or 1.5 mg/kg of MDMA under counter-balanced double-blind conditions. During expected peak drug effect, participants played two rounds of a virtual social simulation task called "Cyberball" during which they experienced acceptance in one round and rejection in the other. During the task the authors also obtained electrocardiograms (ECGs), from which we calculated RSA. After each round, participants answered questionnaires about their mood and self-esteem. As predicted, MDMA decreased the effect of simulated social rejection on self-reported mood and self-esteem and decreased perceived intensity of rejection, measured as the percent of ball tosses participants reported receiving. Consistent with its sympathomimetic properties, MDMA decreased RSA as compared to placebo. The authors' finding that MDMA decreases perceptions of rejection in simulated social situations extends previous results indicating that MDMA reduces perception of social threat in faces. Together these findings suggest a cognitive mechanism by which MDMA might produce pro-social behavior and feelings and how the drug might function as an adjunct to psychotherapy. These phenomena merit further study in non-simulated social environments.

**'Ecstasy' as a Social Drug: MDMA Preferentially Affects Responses to Emotional Stimuli with Social Content** Wardle MC, Kirkpatrick MG, de Wit H. Soc Cogn Affect Neurosci. 2014 Mar 27. [Epub ahead of print].

3,4-Methylenedioxymethamphetamine (MDMA, 'ecstasy') is used recreationally to improve mood and sociability, and has generated clinical interest as a possible adjunct to psychotherapy. One way that MDMA may produce positive 'prosocial' effects is by changing responses to emotional stimuli, especially stimuli with social content. Here, the authors examined for the first time how MDMA affects subjective responses to positive, negative and neutral emotional pictures with and without social content. The authors hypothesized that MDMA would dose-dependently increase reactivity to positive emotional stimuli and dampen reactivity to negative stimuli, and that these effects would be most pronounced for pictures with people in them. The data were obtained from two studies using similar designs with healthy occasional MDMA users (total N = 101). During each session, participants received MDMA (0, 0.75 and 1.5 mg/kg oral), and then rated their positive and negative responses to standardized positive, negative and neutral pictures with and without social content. MDMA increased positive ratings of positive social pictures, but reduced positive ratings of non-social positive pictures. The authors speculate this 'socially selective' effect contributes to the prosocial effects of MDMA by increasing the comparative value of social contact and closeness with others. This effect may also contribute to its attractiveness to recreational users.

**A Window into the Intoxicated Mind? Speech as an Index of Psychoactive Drug Effects** Bedi G, Cecchi GA, Slezak DF, Carrillo F, Sigman M, de Wit H. Neuropsychopharmacology. 2014 April. [Epub ahead of print].

Abused drugs can profoundly alter mental states in ways that may motivate drug use. These effects are usually assessed with self-report, an approach that is vulnerable to biases. Analyzing speech during intoxication may present a more direct, objective measure, offering a unique 'window' into the mind. Here, the authors employed computational analyses of speech semantic and topological structure after  $\pm$ 3,4-methylenedioxymethamphetamine (MDMA; 'ecstasy') and methamphetamine in 13 ecstasy users. In 4 sessions, participants completed a 10-min speech task after MDMA (0.75 and 1.5mg/kg), methamphetamine (20 mg), or placebo. Latent Semantic Analyses identified the semantic proximity between speech content and concepts relevant to drug effects. Graph-based analyses identified topological speech characteristics. Group-level drug effects on semantic distances and topology were assessed. Machine-learning analyses (with leave-one-out cross-validation) assessed whether speech characteristics could predict drug condition in the individual

subject. Speech after MDMA (1.5mg/kg) had greater semantic proximity than placebo to the concepts friend, support, intimacy, and rapport. Speech on MDMA (0.75mg/kg) had greater proximity to empathy than placebo. Conversely, speech on methamphetamine was further from compassion than placebo. Classifiers discriminated between MDMA (1.5mg/kg) and placebo with 88% accuracy, and MDMA (1.5mg/kg) and methamphetamine with 84% accuracy. For the two MDMA doses, the classifier performed at chance. These data suggest that automated semantic speech analyses can capture subtle alterations in mental state, accurately discriminating between drugs. The findings also illustrate the potential for automated speech-based approaches to characterize clinically relevant alterations to mental state, including those occurring in psychiatric illness.

**Amphetamine Fails to Alter Cued Recollection of Emotional Images: Study of Encoding, Retrieval, and State-Dependency** Weafer J, Gallo DA, de Wit H. PLoS One. 2014 Feb 27; 9(2): e90423.

Stimulant drugs facilitate both encoding and retrieval of salient information in laboratory animals, but less is known about their effects on memory for emotionally salient visual images in humans. The current study investigated dextroamphetamine (AMP) effects on memory for emotional pictures in healthy humans, by administering the drug only at encoding, only at retrieval, or at both encoding and retrieval. During the encoding session, all participants viewed standardized positive, neutral, and negative pictures from the International Affective Picture System (IAPS). 48 hours later they attended a retrieval session testing their cued recollection of these stimuli. Participants were randomly assigned to one of four conditions (N=20 each): condition AP (20 mg AMP at encoding and placebo (PL) at retrieval); condition PA (PL at encoding and AMP at retrieval); condition AA (AMP at encoding and retrieval); or condition PP (PL at encoding and retrieval). Amphetamine produced its expected effects on physiological and subjective measures, and negative pictures were recollected more frequently than neutral pictures. However, contrary to hypotheses, AMP did not affect recollection for positive, negative, or neutral stimuli, whether it was administered at encoding, retrieval, or at both encoding and retrieval. Moreover, recollection accuracy was not state-dependent. Considered in light of other recent drug studies in humans, this study highlights the sensitivity of drug effects to memory testing conditions and suggests future strategies for translating preclinical findings to human behavioral laboratories.

**Regular Exercise is Associated with Emotional Resilience to Acute Stress in Healthy Adults** Childs E, de Wit H. Front Physiol. 2014 May 1. [Epub ahead of print].

Physical activity has long been considered beneficial to health and regular exercise is purported to relieve stress. However empirical evidence demonstrating these effects is limited. In this study, the authors compared psychophysiological responses to an acute psychosocial stressor between individuals who did, or did not, report regular physical exercise. Healthy men and women (N = 111) participated in two experimental sessions, one with the Trier Social Stress Test (TSST) and one with a non-stressful control task. The authors measured heart rate, blood pressure, cortisol, and self-reported mood before and at repeated times after the tasks. Individuals who reported physical exercise at least once per week exhibited lower heart rate at rest than non-exercisers, but the groups did not differ in their cardiovascular responses to the TSST. Level of habitual exercise did not influence self-reported mood before the tasks, but non-exercisers reported a greater decline in positive affect after the TSST in comparison to exercisers. These findings provide modest support for claims that regular exercise protects against the negative emotional consequences of stress, and suggest that exercise has beneficial effects in healthy individuals. These findings are limited by their

correlational nature, and future prospective controlled studies on the effects of regular exercise on response to acute stress are needed.

**Voxelwise lp-ntPET for Detecting Localized, Transient Dopamine Release of Unknown Timing: Sensitivity Analysis and Application to Cigarette Smoking in the PET Scanner** Kim

SJ, Sullivan JM, Wang S, Cosgrove KP, Morris ED. Human Brain Mapping. 2014 April [Epub ahead of print].

The “linear parametric neurotransmitter PET” (lp-ntPET) model estimates time variation in endogenous neurotransmitter levels from dynamic PET data. The pattern of dopamine (DA) change over time may be an important element of the brain’s response to addictive substances such as cigarettes or alcohol. The authors have extended the lp-ntPET model from the original region of interest (ROI) - based implementation to be able to apply the model at the voxel level. The resulting endpoint is a dynamic image, or movie, of transient neurotransmitter changes. Simulations were performed to select threshold values to reduce the false positive rate when applied to real (11) C-raclopride PET data. The authors tested the new voxelwise method on simulated data, and finally, they applied it to (11) C-raclopride PET data of subjects smoking cigarettes in the PET scanner. In simulation, the temporal precision of neurotransmitter response was shown to be similar to that of ROI-based lp-ntPET (standard deviation ~ 3 min). False positive rates for the voxelwise method were well controlled by combining a statistical threshold (the F-test) with a new spatial (cluster-size) thresholding operation. Sensitivity of detection for the new algorithm was greater than 80% for the case of short-lived DA changes that occur in subregions of the striatum as might be the case with cigarette smoking. Finally, in (11) C-raclopride PET data, DA movies reveal for the first time that different temporal patterns of the DA response to smoking may exist in different subregions of the striatum. These spatiotemporal patterns of neurotransmitter change created by voxelwise lp-ntPET may serve as novel biomarkers for addiction and/or treatment efficacy.

**Cocaine Dependent Individuals with Attenuated Striatal Activation during Reinforcement Learning Are More Susceptible to Relapse** Stewart JL, Connolly CG, May AC, Tapert SF,

Wittmann M, Paulus MP. Psychiatry Research. 2014; 223(2): 129–139.

Cocaine-dependent individuals show altered brain activation during decision making. It is unclear, however, whether these activation differences are related to relapse vulnerability. This study tested the hypothesis that brain-activation patterns during reinforcement learning are linked to relapse 1 year later in individuals entering treatment for cocaine dependence. Subjects performed a Paper-Scissors-Rock task during functional magnetic resonance imaging (fMRI). A year later, the authors examined whether subjects had remained abstinent (n=15) or relapsed (n=15). Although the groups did not differ on demographic characteristics, behavioral performance, or lifetime substance use, abstinent patients reported greater motivation to win than relapsed patients. The fMRI results indicated that compared with abstinent individuals, relapsed users exhibited lower activation in (1) bilateral inferior frontal gyrus and striatum during decision making more generally; and (2) bilateral middle frontal gyrus and anterior insula during reward contingency learning in particular.

Moreover, whereas abstinent patients exhibited greater left middle frontal and striatal activation to wins than losses, relapsed users did not demonstrate modulation in these regions as a function of outcome valence. Thus, individuals at high risk for relapse relative to those who are able to abstain allocate fewer neural resources to action-outcome contingency formation and decision making, as well as having less motivation to win on a laboratory-based task.

### **Cannabis Cue Reactivity and Craving among Never, Infrequent and Heavy Cannabis Users**

Henry EA, Kaye JT, Bryan AD, Hutchison KE, Ito TA. *Neuropsychopharmacology*. 2014 Apr; 39(5): 1214-21.

Substance cue reactivity is theorized as having a significant role in addiction processes, promoting compulsive patterns of drug-seeking and drug-taking behavior. However, research extending this phenomenon to cannabis has been limited. To that end, the goal of the current work was to examine the relationship between cannabis cue reactivity and craving in a sample of 353 participants varying in self-reported cannabis use. Participants completed a visual oddball task whereby neutral, exercise, and cannabis cue images were presented, and a neutral auditory oddball task while event-related brain potentials (ERPs) were recorded. Consistent with past research, greater cannabis use was associated with greater reactivity to cannabis images, as reflected in the P300 component of the ERP, but not to neutral auditory oddball cues. The latter indicates the specificity of cue reactivity differences as a function of substance-related cues and not generalized cue reactivity. Additionally, cannabis cue reactivity was significantly related to self-reported cannabis craving as well as problems associated with cannabis use. Implications for cannabis use and addiction more generally are discussed.

### **$\Delta(9)$ -Tetrahydrocannabinol Treatment during Human Monocyte Differentiation Reduces Macrophage Susceptibility to HIV-1 Infection**

Williams JC, Appelberg S, Goldberger BA, Klein TW, Sleasman JW, Goodenow MM. *J Neuroimmune Pharmacol*. 2014 Jun; 9(3):369-79.

The major psychoactive component of marijuana,  $\Delta(9)$ -tetrahydrocannabinol (THC), also acts to suppress inflammatory responses. Receptors for THC, CB1, CB2, and GPR55, are differentially expressed on multiple cell types including monocytes and macrophages, which are important modulators of inflammation in vivo and target cells for HIV-1 infection. Use of recreational and medicinal marijuana is increasing, but the consequences of marijuana exposure on HIV-1 infection are unclear. Ex vivo studies were designed to investigate effects on HIV-1 infection in macrophages exposed to THC during or following differentiation. THC treatment of primary human monocytes during differentiation reduced HIV-1 infection of subsequent macrophages by replication competent or single cycle CCR5 using viruses. In contrast, treatment of macrophages with THC immediately prior to or continuously following HIV-1 exposure failed to alter infection. Specific receptor agonists indicated that the THC effect during monocyte differentiation was mediated primarily through CB2. THC reduced the number of p24 positive cells with little to no effect on virus production per infected cell, while quantitation of intracellular viral gag pinpointed the THC effect to an early event in the viral life cycle. Cells treated during differentiation with THC displayed reduced expression of CD14, CD16, and CD163 and donor dependent increases in mRNA expression of selected viral restriction factors, suggesting a fundamental alteration in phenotype. Ultimately, the mechanism of THC suppression of HIV-1 infection was traced to a reduction in cell surface HIV receptor (CD4, CCR5 and CXCR4) expression that diminished entry efficiency.

### **Multi-atlas Segmentation of Subcortical Brain Structures via the AutoSeg Software Pipeline**

Wang J, Vachet C, Rumple A, Gouttard S, Ouziel C, Perrot E, Du G, Huang X, Gerig G, Styner M. *Front Neuroinform*. 2014 Feb 6; 8:7.

Automated segmenting and labeling of individual brain anatomical regions, in MRI are challenging, due to the issue of individual structural variability. Although atlas-based segmentation has shown its potential for both tissue and structure segmentation, due to the inherent natural variability as well as disease-related changes in MR appearance, a single atlas image is often inappropriate to represent the full population of datasets processed in a given neuroimaging study. As an alternative for the case of single atlas segmentation, the use of multiple atlases alongside label fusion techniques has

been introduced using a set of individual "atlases" that encompasses the expected variability in the studied population. In this study, the authors proposed a multi-atlas segmentation scheme with a novel graph-based atlas selection technique. They first paired and co-registered all atlases and the subject MR scans. A directed graph with edge weights based on intensity and shape similarity between all MR scans is then computed. The set of neighboring templates is selected via clustering of the graph. Finally, weighted majority voting is employed to create the final segmentation over the selected atlases. This multi-atlas segmentation scheme is used to extend a single-atlas-based segmentation toolkit entitled AutoSeg, which is an open-source, extensible C++ based software pipeline employing BatchMake for its pipeline scripting, developed at the Neuro Image Research and Analysis Laboratories of the University of North Carolina at Chapel Hill. AutoSeg performs N4 intensity inhomogeneity correction, rigid registration to a common template space, automated brain tissue classification based skull-stripping, and the multi-atlas segmentation. The multi-atlas-based AutoSeg has been evaluated on subcortical structure segmentation with a testing dataset of 20 adult brain MRI scans and 15 atlas MRI scans. The AutoSeg achieved mean Dice coefficients of 81.73% for the subcortical structures.

**Simultaneous Multi-Slice fMRI using Spiral Trajectories** Zahneisen B, Poser BA, Ernst T, Stenger AV. *J Neuroimage*. 2014 May 15; 92: 8-18.

Parallel imaging methods using multi-coil receiver arrays have been shown to be effective for increasing MRI acquisition speed. However parallel imaging methods for fMRI with 2D sequences show only limited improvements in temporal resolution because of the long echo times needed for BOLD contrast. Recently, Simultaneous Multi-Slice (SMS) imaging techniques have been shown to increase fMRI temporal resolution by factors of four and higher. In SMS fMRI multiple slices can be acquired simultaneously using Echo Planar Imaging (EPI) and the overlapping slices are unaliased using a parallel imaging reconstruction with multiple receivers. The slice separation can be further improved using the "blipped-CAIPI" EPI sequence that provides a more efficient sampling of the SMS 3D k-space. In this paper a blipped-spiral SMS sequence for ultra-fast fMRI is presented. The blipped-spiral sequence combines the sampling efficiency of spiral trajectories with the SMS encoding concept used in blipped-CAIPI EPI. The authors show that blipped spiral acquisition can achieve almost whole brain coverage at 3mm isotropic resolution in 168 ms. They also demonstrate that the high temporal resolution allows for dynamic BOLD lag time measurement using visual/motor and retinotopic mapping paradigms. The local BOLD lag time within the visual cortex following the retinotopic mapping stimulation of expanding flickering rings is directly measured and easily translated into an eccentricity map of the cortex.

**Tracking the Dynamics of the Social Brain: ERP Approaches for Social Cognitive and Affective Neuroscience** Amodio DM, Bartholow BD, Ito TA. *Soc Cogn Affect Neurosci*. 2014 Mar; 9(3): 385-93.

Event-related potential (ERP) approaches to social cognitive and affective neuroscience (SCAN) are not as widely used as other neuroimaging techniques, yet they offer several unique advantages. In particular, the high temporal resolution of ERP measures of neural activity make them ideally suited for studying the dynamic interplay of rapidly unfolding cognitive and affective processes. In this article, the authors highlight the utility of ERP methods for scientists investigating questions of SCAN. They begin with a brief description of the physiological basis of ERPs and discussion of methodological practices. They then discuss how ERPs may be used to address a range of questions concerning social perception, social cognition, attitudes, affect and self-regulation, with examples of research that has used the ERP approach to contribute important theoretical advances in these areas.

Whether used alone or in combination with other techniques, the ERP is an indispensable part of the social and affective neuroscientist's methodological toolkit.

**Group-Wise fMRI Activation Detection on DICCCOL Landmarks** Lv J, Guo L, Zhu D, Zhang T, Hu X, Han J, Liu T. Neuroinformatics. 2014 Apr 29. [Epub ahead of print].

Group-wise activation detection in task-based fMRI has been widely used because of its robustness to noises and its capacity to deal with variability of individual brains. However, current group-wise fMRI activation detection methods typically rely on the co-registration of individual brains' fMRI images, which has difficulty in dealing with the remarkable anatomic variation of different brains. As a consequence, the resulted misalignments could significantly degrade the required inter-subject correspondences, thus substantially reducing the sensitivity and specificity of group-wise fMRI activation detection. To deal with these challenges, this paper presents a novel approach to detecting group-wise fMRI activation on our recently developed and validated Dense Individualized and Common Connectivity-based Cortical Landmarks (DICCCOL). The basic idea here is that the first-level general linear model (GLM) analysis is first performed on the fMRI signal of each corresponding DICCCOL landmark in individual brain's own space, and then the estimated effect sizes of the same landmark from a group of subjects are statistically assessed with the mixed-effect model at the group level. Finally, the consistently activated DICCCOL landmarks are determined and declared in a group-wise fashion in response to external block-based stimuli. These experimental results have demonstrated that the proposed approach can detect meaningful activations.

**Characterization of U-shape Streamline Fibers: Methods and Applications** Zhang T, Chen H, Guo L, Li K, Li L, Zhang S, Shen D, Hu X, Liu T. Med Image Anal. 2014 Jul; 18(5): 795-807.

Diffusion tensor imaging (DTI), high angular resolution diffusion imaging (HARDI), and diffusion spectrum imaging (DSI) have been widely used in the neuroimaging field to examine the macro-scale fiber connection patterns in the cerebral cortex. However, the topographic and geometric relationships between diffusion imaging derived streamline fiber connection patterns and cortical folding patterns remain largely unknown. This paper specifically identifies and characterizes the U-shapes of diffusion imaging derived streamline fibers via a novel fiber clustering framework and examines their co-localization patterns with cortical sulci based on DTI, HARDI, and DSI datasets of human, chimpanzee and macaque brains. The authors verified the presence of these U-shaped streamline fibers that connect neighboring gyri by coursing around cortical sulci such as the central sulcus, pre-central sulcus, post-central sulcus, superior temporal sulcus, inferior frontal sulcus, and intra-parietal sulcus. This study also verified the existence of U-shape fibers across data modalities (DTI/HARDI/DSI) and primate species (macaque, chimpanzee and human), and suggests that the common pattern of U-shape fibers coursing around sulci is evolutionarily-preserved in cortical architectures.

## **EPIDEMIOLOGY RESEARCH**

**Rates Of Substance Use Of American Indian Students In 8th, 10th, And 12th Grades Living On Or Near Reservations: Update, 2009-2012** Stanley LR, Harness SD, Swaim RC, Beauvais F. Public Health Rep. 2014 Mar-Apr; 129(2): 156-63.

Understanding the similarities and differences between substance use rates for American Indian (AI) young people and young people nationally can better inform prevention and treatment efforts. The authors compared substance use rates for a large sample of AI students living on or near reservations for the years 2009–2012 with national prevalence rates from Monitoring the Future (MTF). They identified and sampled schools on or near AI reservations by region; 1,399 students in sampled schools were administered the American Drug and Alcohol Survey. They computed lifetime, annual, and last-month prevalence measures by grade and compared them with MTF results for the same time period. Prevalence rates for AI students were significantly higher than national rates for nearly all substances, especially for 8th graders. Rates of marijuana use were very high, with lifetime use higher than 50% for all grade groups. Other findings of interest included higher binge drinking rates and OxyContin® use for AI students. The results from this study demonstrate that adolescent substance use is still a major problem among reservation-based AI adolescent students, especially 8th graders, where prevalence rates were sometimes dramatically higher than MTF rates. Given the high rates of substance userelated problems on reservations, such as academic failure, delinquency, violent criminal behavior, suicidality, and alcohol-related mortality, the costs to members of this population and to society will continue to be much too high until a comprehensive understanding of the root causes of substance use are established.

**Alcohol and Marijuana Use Patterns Associated With Unsafe Driving Among U.S. High School Seniors: High Use Frequency, Concurrent Use, and Simultaneous Use** Terry-McElrath YM, O'Malley PM, Johnston LD. Journal of Studies on Alcohol and Drugs, 75(3), 378–389.

This article examines noncausal associations between high school seniors' alcohol and marijuana use status and rates of self-reported unsafe driving in the past 12 months. Analyses used data from 72,053 students collected through annual surveys of nationally representative cross-sectional samples of U.S. 12th-grade students from 1976 to 2011. Two aspects of past-12-month alcohol and marijuana use were examined: (a) use frequency and (b) status as a nonuser, single substance user, concurrent user, or simultaneous user. Measures of past-12-month unsafe driving included any tickets/warnings or accidents, as well as tickets/warnings or accidents following alcohol or marijuana use. Analyses explored whether an individual's substance use frequency and simultaneous use status had differential associations with their rate of unsafe driving. Higher substance use frequency (primarily alcohol use frequency) was significantly and positively associated with unsafe driving. The rate of engaging in any unsafe driving was also significantly and positively associated with simultaneous use status, with the highest rate associated with simultaneous use, followed by concurrent use, followed by use of alcohol alone. Individuals who reported simultaneous use most or every time they used marijuana had the highest likelihood of reporting unsafe driving following either alcohol or marijuana use. This article expands the knowledge on individual risk factors associated with unsafe driving among teens. Efforts to educate U.S. high school students (especially substance users), parents, and individuals involved in prevention programming and driver's education about the increased risks associated with various forms of drug use status may be useful.

**Early Life Conditions Of Overall and Cause-specific Mortality Among Inner-city African Americans**

Juon H-S, Evans-Polce RJ, Ensminger M. Am J Public Health. 2014; 104(3): 548-54.

The authors examined how early life conditions influence midlife overall and cause-specific mortality in a community cohort of disadvantaged African Americans. Using a prospective design, they assessed first-grade children and their teachers and families when children were 6 years old, with follow-up at ages 16, 32, and 42 years. The authors obtained information on death from family members, neighbors, and the National Death Index (NDI). They conducted a survival analysis and competing risk analysis to examine early life predictors of mortality. Of 1242 participants, 87 (7%) had died by 2004. In multivariate Cox proportional hazards regression, males who lived in foster care and females with lower math grades in first grade were more likely to die by age 42 years. In multivariate competing risks analysis, hospitalization by the time of first grade was related to mortality from acute and chronic illness. Male gender, being in foster care, and aggressive behavior in first grade were related to mortality from drug use, violence, or suicide. Early classroom, environmental, and family-level interventions are potentially beneficial in reducing later overall and cause-specific mortality.

**Incidence and Prevalence Of Intrasubtype HIV-1 Dual Infection In At-risk Men In The United States**

Wagner GA, Pacold ME, Kosakovsky Pond SL, Caballero G, Chaillon A, Rudolph A, Morris SR, Little SJ, Richman DD, Smith D. J Infect Dis. 2014; 209(7): 1032-8.

Human immunodeficiency virus type 1 (HIV-1) dual infection (DI) has been associated with decreased CD4 T-cell counts and increased viral loads; however, the frequency of intrasubtype DI is poorly understood. The authors used ultra-deep sequencing (UDS) to estimate the frequency of DI in a primary infection cohort of predominantly men who have sex with men (MSM). HIV-1 genomes from longitudinal blood samples of recently infected, therapy-naïve participants were interrogated with UDS. DI was confirmed when maximum sequence divergence was excessive and supported by phylogenetic analysis. Coinfection was defined as DI at baseline; superinfection was monoinfection at baseline and DI at a later time point. Of 118 participants, 7 were coinfecting and 10 acquired superinfection. Superinfection incidence rate was 4.96 per 100 person-years (95% confidence interval [CI], 2.67-9.22); 6 occurred in the first year and 4 in the second. Overall cumulative prevalence of intrasubtype B DI was 14.4% (95% CI, 8.6%-22.1%). Primary HIV-1 incidence was 4.37 per 100 person-years (95% CI, 3.56-5.36). Intrasubtype DI was frequent and comparable to primary infection rates among MSM in San Diego; however, superinfection rates declined over time. DI is likely an important component of the HIV epidemic dynamics and development of stronger immune responses to the initial infection may protect from superinfection.

**"Every 'never' I Ever Said Came True": Transitions From Opioid Pills To Heroin Injecting**

Mars SG, Bourgois P, Karandinos G, Montero F, Ciccarone D. Int J Drug Policy. 2014; 25(2): 257-66.

This qualitative study documents the pathways to injecting heroin by users in Philadelphia and San Francisco before and during a pharmaceutical opioid pill epidemic. Data was collected through in-depth, semi-structured interviews (conducted between 2010 and 2012) that were, conducted against a background of longer-term participant-observation, ethnographic studies of street-based drug users and dealers in Philadelphia (2007-12) and San Francisco (1994-2007, 2012). Philadelphia and San Francisco were selected for their contrasting political economies, immigration patterns and source type of heroin. In Philadelphia, the ethnographers found heroin injectors, usually white users, who had started their opiate using careers with prescription opioids rather than transitioning from other drugs. In both Philadelphia and San Francisco, most of the young heroin injectors interviewed began, their drug-use trajectories with opioid pills--usually Percocet (oxycodone and

acetaminophen), generic short acting oxycodone or, OxyContin (long-acting oxycodone)--before transitioning to heroin, usually by nasal inhalation (sniffing) or smoking at first, followed by injecting. While most of the Philadelphia users were born in the city or its suburbs and had started using both opioid pills and heroin there, many of the San Francisco users had initiated their pill and sometimes heroin use elsewhere and had migrated to the city from around the country. Nevertheless, patterns of transition of younger injectors were similar in both cities suggesting an evolving national pattern. In contrast, older users in both Philadelphia and San Francisco were more likely to have graduated to heroin injection from non-opiate drugs such as cannabis, methamphetamine and cocaine. Pharmaceutical opioid initiates typically reported switching to heroin for reasons of cost and ease-of-access to supply after becoming physically and emotionally dependent on opioid pills. Many expressed surprise and dismay at their progression to sniffing and subsequently to injecting heroin. Historically and structurally these users found themselves caught at the intersection of two major developments in the opiate supply: (1) an over 500% increase in opiate pill prescription from 1997 to 2005 resulting in easy access to diverted supplies of less stigmatized opiates than heroin and (2) a heroin supply glut, following the US entry of Colombian-sourced, heroin in the early 1990s, that decreased cost and increased purity at the retail level. A nationwide up-cycle of heroin use may be occurring among young inner city, suburban and rural youth fueled by widespread prescription opioid pill use.

**Incarceration Among Street-involved Youth In A Canadian Study: Implications For Health and Policy Interventions** Omura JD, Wood E, Nguyen P, Kerr T, DeBeck K. *Int J Drug Policy*. 2014; 25(2): 291-6.

Risk factors for incarceration have been well described among adult drug using populations; however, less is known about incarceration among at-risk youth. This study examines the prevalence and correlates of incarceration among street-involved youth in a Canadian setting. From September 2005 to May 2012, data were collected from the At-Risk Youth Study, a prospective cohort of street-involved youth aged 14-26 who use illicit drugs. Generalized estimating equation (GEE) logistic regression was used to identify factors associated with recent incarceration defined as incarceration in the previous six months. Among 1019 participants, 362 (36%) reported having been recently incarcerated during the study period. In multivariate GEE analysis, homelessness (adjusted odds ratio [AOR] =1.60), daily crystal methamphetamine use (AOR=1.56), public injecting (AOR=1.33), drug dealing (AOR=1.48) and being a victim of violence (AOR=1.68) were independently associated with incarceration (all  $p < 0.05$ ). Conversely, female gender (AOR=0.48), lesbian, gay, bisexual, transgender or two-spirited (LGBT) identification (AOR=0.47) and increasing age of first hard drug use (AOR=0.96) were negatively associated with incarceration (all  $p < 0.05$ ). Incarceration was common among our study sample. Youth who were homeless, used crystal methamphetamine, and engaged in risky behaviors including public injection and drug dealing were significantly more likely to have been recently incarcerated. Structural interventions including expanding addiction treatment and supportive housing for at-risk youth may help reduce criminal justice involvement among this population and associated health, social and fiscal costs.

**Health Correlates Of Co-occurring Substance Use For Women With HIV In Cocaine Use Recovery** McCabe BE, Feaster DJ, Mitrani VB. *Addict Behav*. 2014; 39(3): 725-8.

The goal of this study was to examine clinical correlates of alcohol, opioid, cannabis, sedative, or other co-occurring substance use disorders in a sample of 124 HIV+ women in recovery from cocaine use disorders. Data was collected from a baseline assessment for a randomized trial comparing a family therapy intervention to a health promotion group intervention. Substance use disorders were assessed with a computer-administered structured diagnostic interview.

Psychological distress was measured with the Brief Symptom Inventory. Sleep problems were measured with the Short Sleep Index from the Hamilton Anxiety and Depression Rating Scales. Pain was assessed with items from the Medical Outcomes Study-HIV scale. HIV health was assessed with blood tests for T-cell count and HIV Viral Load Suppression, as well as a nurse-administered symptom assessment. Women with a co-occurring opioid use disorder were significantly more likely to have psychological distress and sleep problems, but less likely to have severe pain. Even though there was no difference in T-cell count or Viral Load, women with opioid use disorder were significantly more likely to have high HIV symptoms. Women in recovery with HIV who have co-occurring cocaine use and opioid use disorders were more likely to have several indicators of worse mental and physical health. Interventions may need to be tailored to meet the needs of this subgroup of women. Future research should examine whether these co-occurring conditions are associated with greater likelihood of relapse or poor treatment response, and whether this higher-risk profile exists in other groups.

**Initial Reactions To Tobacco and Cannabis Smoking: A Twin Study** Agrawal A, Madden PAF, Bucholz KK, Heath AC, Lynskey MT. *Addiction*. 2014; 109(4): 663-71.

Initial subjective reactions to cannabis and tobacco, broadly classified as positive or negative; have previously been explored for their associations with onset and maintenance of subsequent abuse/dependence. The authors examine (i) the factorial architecture of self-reported initial reactions to cannabis and tobacco; (ii) whether these factors associate with concurrently reported age at onset of DSM-IV diagnosis of nicotine dependence and cannabis abuse/dependence; and (iii) estimate heritable variation in and co-variation between the factors. Factorial and exploratory structural equation modeling was conducted to examine the factor structure of initial reactions. Cox proportional hazards modeling was employed to examine their association with time to onset of diagnosis of DSM-IV nicotine dependence and cannabis abuse/dependence. Classical twin modeling, using univariate and multivariate models, was used to parse variance in each factor (and the covariance between factors) to their additive genetic, shared environmental and non-shared environmental sources. General population sample of Caucasian female twins aged 18-32 years, with a life-time history of tobacco [n=2393] and cannabis [n=1445] use. Self-report of initial subjective reactions to tobacco (cigarettes) and cannabis the first time they were used and time to onset of life-time history of DSM-IV diagnosis of abuse (cannabis) and dependence (cannabis or nicotine). Factors representing putatively positive and negative reactions to cannabis and tobacco emerged. Initial reactions to tobacco were associated with onset of DSM-IV diagnosis of nicotine dependence and cannabis abuse/dependence while initial reactions to cannabis were associated with onset of DSM-IV diagnosis of cannabis abuse/dependence alone. Genetic factors played a moderate role in each factor (heritability of 27-35%,  $P < 0.05$ ), with the remaining variance attributed to individual-specific environment. Co-variation across the factors indexing positive and negative initial reactions was attributable to genetic sources (0.18-0.58,  $P < 0.05$ ) and to overlapping individual-specific environmental factors (-0.16 to 0.36,  $P < 0.05$ ). Initial subjective reactions to tobacco are associated with onset of DSM-IV diagnosis of nicotine dependence and cannabis abuse/dependence while initial subjective reactions to cannabis are only associated with onset of diagnosis of DSM-IV cannabis abuse/dependence. Genetic and environmental factors underpin the overlap across the factors representing initial reactions, both positive and negative.

**Influence Of Conduct Problems and Depressive Symptomatology On Adolescent Substance Use: Developmentally Proximal Versus Distal Effects**

Maslowsky J, Schulenberg JE, Zucker RA.

Dev Psychol. 2014; 50(4): 1179-89.

The identification of developmentally specific windows at which key predictors of adolescent substance use are most influential is a crucial task for informing the design of appropriately targeted substance use prevention and intervention programs. The current study examined effects of conduct problems and depressive symptomatology on changes in alcohol, cigarette, and marijuana from 8th through 12th grade. The authors examined the effects of relatively developmentally distal versus proximal mental health problems on adolescent substance use and tested for gender differences. With a national, longitudinal sample from the Monitoring the Future study (N = 3,014), structural equation modeling was used to test the effects of 8th and 10th grade conduct problems and depressive symptomatology on subsequent changes in alcohol, cigarette, and marijuana use from 8th through 12th grade. Results indicated that relatively distal (8th grade) mental health problems were stronger predictors of increases in alcohol, cigarette, and marijuana use than were relatively more proximal (10th grade) mental health problems. Eighth grade conduct problems had the strongest effects on alcohol and marijuana use, and 8th grade depressive symptomatology had the strongest effects on cigarette use. Few gender differences were observed. These results suggest that intervening in earlier appearing conduct problems and depressive symptomatology may lead to a reduction in adolescent substance use in 10th and 12th grades and beyond.

**The Predictive Value Of Smoking Expectancy and the Heritability Of Its Accuracy**

Treur JL, Boomsma DI, Lubke GH, Bartels M, Vink JM. Nicotine Tob Res. 2014; 16(3): 359-68.

Among smokers, former smokers, and never-smokers, this study aimed to (a) determine the predictive value of smoking expectancy on future smoking status, and (b) test the relative contribution of genes and environment to a person's ability to accurately predict future smoking status. For smokers, smoking expectancy reflects the intention to continue smoking; for former smokers, it reflects the intention to take up smoking again; and for never-smokers, it reflects the intention to initiate smoking. A longitudinal design was employed in which participants of the Netherlands Twin Register completed 2 consecutive surveys 2 years apart between 1993 and 2011 (3,591 adolescents aged 14-18 years), or between 1993 and 2004 (11,568 adults, aged 18+ years). Smoking expectancy was measured by asking, "Do you think you'll smoke in a year's time?" with answer categories ranging from "certainly not" to "absolutely yes" on a 5-point scale. To determine the predictive value of smoking expectancy, analyses were performed in smokers, former smokers, and never-smokers separately. Data of 2,987 adolescents and 4,911 adult twins were analyzed to estimate heritability. A dichotomous variable reflected the ability to predict future smoking status (correct/incorrect). Smoking expectancy significantly predicted future smoking status among former smokers and never-smokers. The ability to accurately predict future smoking status was explained by additive genetic factors for 59% of adolescents and 27% of adults, with the remainder being explained by unique environmental factors. A single question on smoking expectancy helps predict future smoking status. Variation in how well subjects predict their future smoking behavior is influenced by genetic factors, especially during adolescence.

**Risks For Early Substance Involvement Associated With Parental Alcoholism and Parental Separation In An Adolescent Female Cohort**

Waldron M, Vaughan EL, Bucholz KK, Lynskey MT, Sartor CE, Duncan AE, Madden PAF, Heath AC. Drug Alcohol Depend. 2014; 138: 130-6.

The authors examined timing of substance involvement as a joint function of parental history of alcoholism and parental separation during childhood. Data were drawn from a large cohort of female like-sex twins [n=613 African Ancestry (AA), n=3550 European or other ancestry (EA)].

Cox proportional hazards regression was conducted predicting age at first use of alcohol, first alcohol intoxication, first use and regular use of cigarettes, and first use of cannabis and other illicit drugs from dummy variables coding for parental alcoholism and parental separation. Propensity score analysis was also conducted comparing intact and separated families by predicted probability of parental separation. In EA families, increased risk of substance involvement was found in both alcoholic and separated families, particularly through ages 10 or 14 years, with risk to offspring from alcoholic separated families further increased. In AA families, associations with parental alcoholism and parental separation were weak and with few exceptions statistically nonsignificant. While propensity score findings confirmed unique risks observed in EA families, intact and separated AA families were poorly matched on risk-factors presumed to predate parental separation, especially parental alcoholism, requiring cautious interpretation of AA survival-analytic findings. For offspring of European ancestry, parental separation predicts early substance involvement that is not explained by parental alcoholism nor associated family background characteristics. Additional research is needed to better characterize risks associated with parental separation in African American families.

**Accuracy Of Reports Of Lifetime Mental and Physical Disorders: Results From the Baltimore Epidemiological Catchment Area Study** Takayanagi Y, Spira AP, Roth KB, Gallo JJ, Eaton WW, Mojtabai R. JAMA Psychiatry. 2014; 71(3): 273-80.

Our understanding of how mental and physical disorders are associated and contribute to health outcomes in populations depends on accurate ascertainment of the history of these disorders. Recent studies have identified substantial discrepancies in the prevalence of mental disorders among adolescents and young adults depending on whether the estimates are based on retrospective reports or multiple assessments over time. It is unknown whether such discrepancies are also seen in midlife to late life. Furthermore, no previous studies have compared lifetime prevalence estimates of common physical disorders such as diabetes mellitus and hypertension ascertained by prospective cumulative estimates vs retrospective estimates. The objective of this study was to examine the lifetime prevalence estimates of mental and physical disorders during midlife to late life using both retrospective and cumulative evaluations. Prospective population-based survey (Baltimore Epidemiologic Catchment Area Survey) with 4 waves of interviews of 1071 community residents in Baltimore, Maryland, between 1981 and 2005. Lifetime prevalence of selected mental and physical disorders at wave 4 (2004-2005), according to both retrospective data and cumulative evaluations based on 4 interviews from wave 1 to wave 4. Retrospective evaluations substantially underestimated the lifetime prevalence of mental disorders as compared with cumulative evaluations. The respective lifetime prevalence estimates ascertained by retrospective and cumulative evaluations were 4.5% vs. 13.1% for major depressive disorder, 0.6% vs. 7.1% for obsessive-compulsive disorder, 2.5% vs. 6.7% for panic disorder, 12.6% vs. 25.3% for social phobia, 9.1% vs. 25.9% for alcohol abuse or dependence, and 6.7% vs. 17.6% for drug abuse or dependence. In contrast, retrospective lifetime prevalence estimates of physical disorders ascertained at wave 4 were much closer to those based on cumulative data from all 4 waves. The respective prevalence estimates ascertained by the 2 methods were 18.2% vs. 20.2% for diabetes, 48.4% vs. 55.4% for hypertension, 45.8% vs. 54.0% for arthritis, 5.5% vs. 7.2% for stroke, and 8.4% vs. 10.5% for cancer. One-time, cross-sectional population surveys may consistently underestimate the lifetime prevalence of mental disorders. The population burden of mental disorders may therefore be substantially higher than previously appreciated.

**Heavy Alcohol Use In Early Adulthood As A Function Of Childhood ADHD: Developmentally Specific Mediation By Social Impairment and Delinquency**

Molina BSG, Walther CAP, Cheong J, Pedersen SL, Gnagy EM, Pelham WE. *Exp Clin Psychopharmacol.* 2014; 22(2): 110-21.

Frequent heavy drinking in early adulthood, particularly prior to age 21, is associated with multiple health and legal consequences including continued problems with drinking later into adulthood. Children with attention-deficit/hyperactivity disorder (ADHD) are at risk of alcohol use disorder in adulthood, but little is known about their frequency of underage drinking as young adults or about mediational pathways that might contribute to this risky outcome. The current study used data from the Pittsburgh ADHD Longitudinal Study to test social impairment and delinquency pathways from childhood ADHD to heavy drinking in early adulthood for individuals with ( $n = 148$ ) and without ( $n = 117$ ) childhood ADHD. Although ADHD did not predict heavy drinking, indirect mediating effects in opposing directions were found. A delinquency pathway from childhood ADHD to increased heavy drinking included adolescent and subsequently adult delinquent behavior. A social impairment pathway from childhood ADHD to decreased heavy drinking included adolescent, but not adult, social impairment. These findings help explain the heterogeneity of results for alcohol use among individuals with ADHD and suggest that common ADHD-related impairments may operate differently from each other and distinctly across developmental periods.

**Early Adolescent Alcohol Use In Context: How Neighborhoods, Parents, and Peers Impact**

**Youth** Trucco EM, Colder CR, Wieczorek WF, Lengua LJ, Hawk Jr., LW. *Dev Psychopathol.* 2014; 26(2): 425-36.

Developmental-ecological models are useful for integrating risk factors across multiple contexts and conceptualizing mediational pathways for adolescent alcohol use, yet these comprehensive models are rarely tested. This study used a developmental-ecological framework to investigate the influence of neighborhood, family, and peer contexts on alcohol use in early adolescence ( $N = 387$ ). Results from a multi-informant longitudinal cross-lagged mediation path model suggested that high levels of neighborhood disadvantage were associated with high levels of alcohol use 2 years later via an indirect pathway that included exposure to delinquent peers and adolescent delinquency. Results also indicated that adolescent involvement with delinquent peers and alcohol use led to decrements in parenting, rather than being consequences of poor parenting. Overall, the study supported hypothesized relationships among key microsystems thought to influence adolescent alcohol use, and thus findings underscore the utility of developmental-ecological models of alcohol use.

**Testing For Measured Gene-environment Interaction: Problems With the Use Of Cross-product Terms and a Regression Model Reparameterization Solution**

Aliev F, Latendresse SJ, Bacanu S-A, Neale MC, Dick DM. *Behav Genet.* 2014; 44(2): 165-81.

The study of gene-environment interaction (GE) has garnered widespread attention. The most common way to assess interaction effects is in a regression model with a GE interaction term that is a product of the values specified for the genotypic (G) and environmental (E) variables. In this paper the authors discuss the circumstances under which interaction can be modeled as a product term and cases in which use of a product term is inappropriate and may lead to erroneous conclusions about the presence and nature of interaction effects. In the case of a binary coded genetic variant (as used in dominant and recessive models, or where the minor allele occurs so infrequently that it is not observed in the homozygous state), the regression coefficient corresponding to a significant interaction term reflects a slope difference between the two genotype categories and appropriately characterizes the statistical interaction between the genetic and environmental variables. However, when using a three-category polymorphic genotype, as is commonly done when modeling an additive effect, both false positive and false negative results can

occur, and the nature of the interaction can be misrepresented. The authors present a reparameterized regression equation that accurately captures interaction effects without the constraints imposed by modeling interactions using a single cross-product term. In addition, they provide a series of recommendations for making conclusions about the presence of meaningful GE interactions, which take into account the nature of the observed interactions and whether they map onto sensible genotypic models.

**Effects Of Language Of Assessment On the Measurement Of Acculturation: Measurement Equivalence and Cultural Frame Switching** Schwartz SJ, Benet-Martinez V, Knight GP, Unger JB, Zamboanga BL, Des Rosiers SE, Stephens DP, Huang S, Szapocznik J. *Psychol Assess.* 2014; 26(1): 100-14.

The present study used a randomized design, with fully bilingual Hispanic participants from the Miami area, to investigate 2 sets of research questions. First, the authors sought to ascertain the extent to which measures of acculturation (Hispanic and U.S. practices, values, and identifications) satisfied criteria for linguistic measurement equivalence. Second, they sought to examine whether cultural frame switching would emerge--that is, whether latent acculturation mean scores for U.S. acculturation would be higher among participants randomized to complete measures in English and whether latent acculturation mean scores for Hispanic acculturation would be higher among participants randomized to complete measures in Spanish. A sample of 722 Hispanic students from a Hispanic-serving university participated in the study. Participants were first asked to complete translation tasks to verify that they were fully bilingual. Based on ratings from 2 independent coders, 574 participants (79.5% of the sample) qualified as fully bilingual and were randomized to complete the acculturation measures in either English or Spanish. Theoretically relevant criterion measures--self-esteem, depressive symptoms, and personal identity--were also administered in the randomized language. Measurement equivalence analyses indicated that all of the acculturation measures--Hispanic and U.S. practices, values, and identifications--met criteria for configural, weak/metric, strong/scalar, and convergent validity equivalence. These findings indicate that data generated using acculturation measures can, at least under some conditions, be combined or compared across languages of administration. Few latent mean differences emerged. These results are discussed in terms of the measurement of acculturation in linguistically diverse populations.

**Relationship Between Hunger, Adherence To Antiretroviral Therapy and Plasma HIV RNA Suppression Among HIV-positive Illicit Drug Users In A Canadian Setting** Anema A, Kerr T, Milloy M-J, Feng C, Montaner JSG, Wood E. *AIDS Care.* 2014; 26(4): 459-65.

Food insecurity may be a barrier to achieving optimal HIV treatment-related outcomes among illicit drug users. This study therefore, aimed to assess the impact of severe food insecurity, or hunger, on plasma HIV RNA suppression among illicit drug users receiving antiretroviral therapy (ART). A cross-sectional Multivariate logistic regression model was used to assess the potential relationship between hunger and plasma HIV RNA suppression. A sample of  $n = 406$  adults was derived from a community-recruited open prospective cohort of HIV-positive illicit drug users, in Vancouver, British Columbia (BC), Canada. A total of 235 (63.7%) reported "being hungry and unable to afford enough food," and 241 (59.4%) had plasma HIV RNA  $< 50$  copies/ml. In unadjusted analyses, self-reported hunger was associated with lower odds of plasma HIV RNA suppression (Odds Ratio = 0.59, 95% confidence interval [CI]: 0.39-0.90,  $p = 0.015$ ). In multivariate analyses, this association was no longer significant after controlling for socio-demographic, behavioral, and clinical characteristics, including 95% adherence (Adjusted Odds Ratio [AOR] = 0.65, 95% CI: 0.37-1.10,  $p = 0.105$ ). Multivariate models stratified by 95% adherence found that the direction and magnitude of this association was not significantly altered by the adherence level. Hunger was common among

illicit drug users in this setting. Although, there was an association between hunger and lower likelihood of plasma HIV RNA suppression, this did not persist in adjusted analyses. Further research is warranted to understand the social-structural, policy, and physical factors shaping the HIV outcomes of illicit drug users.

**Trajectories Of Posttraumatic Stress Among Urban Residents** Lowe SR, Galea S, Uddin M, Koenen KC. *Am J Community Psychol.* 2014; 53(1-2): 159-72.

Urban residents experience a wide range of traumatic events and are at increased risk of assaultive violence. Although previous research has examined trajectories of posttraumatic stress (PTS) through latent class growth analysis (LCGA) among persons exposed to the same index events (e.g., a natural disaster), PTS trajectories have not been documented among urban residents. The aims of this study were to conduct LGCA with a sample of trauma survivors from Detroit, Michigan (N = 981), and to explore predictors of trajectory membership. Participants completed three annual telephone surveys, each of which included the posttraumatic stress disorder (PTSD) Checklist-Civilian Version. Four PTS trajectories were detected. Although the majority evidenced a trajectory of consistently few symptoms (Low: 72.5%), 4.6% were in a trajectory of chronic severe PTSD (High), and the remainder were in trajectories of consistently elevated, but generally subclinical, levels of PTS (Decreasing: 12.3%; Increasing: 10.6%). Socioeconomic disadvantage (e.g., lower income), more extensive trauma history (e.g., childhood abuse), and fewer social resources (e.g., lower social support) were associated with membership in higher PTS trajectories, relative to the Low trajectory. The results suggest that efforts to reduce PTS in urban areas need to attend to socioeconomic vulnerabilities in addition to trauma history and risk for ongoing trauma exposure.

**Comparing Factor, Class, and Mixture Models Of Cannabis Initiation and DSM Cannabis Use Disorder Criteria, Including Craving, In the Brisbane Longitudinal Twin Study**

Kubarych TS, Kendler KS, Aggen SH, Estabrook R, Edwards AC, Clark SL, Martin NG, Hickie IB, Neale MC, Gillespie NA. *Twin Res Hum Genet.* 2014; 17(2): 89-98.

Accumulating evidence suggests that the Diagnostic and Statistical Manual of Mental Disorders (DSM) diagnostic criteria for cannabis abuse and dependence are best represented by a single underlying factor. However, it remains possible that models with additional factors, or latent class models or hybrid models, may better explain the data. Using structured interviews, 626 adult male and female twins provided complete data on symptoms of cannabis abuse and dependence, plus a craving criterion. The authors compared latent factor analysis, latent class analysis, and factor mixture modeling using normal theory marginal maximum likelihood for ordinal data. Their aim was to derive a parsimonious, best-fitting cannabis use disorder (CUD) phenotype based on DSM-IV criteria and determine whether DSM-5 craving loads onto a general factor. When compared with latent class and mixture models, factor models provided a better fit to the data. When conditioned on initiation and cannabis use, the association between criteria for abuse, dependence, withdrawal, and craving were best explained by two correlated latent factors for males and females: a general risk factor to CUD and a factor capturing the symptoms of social and occupational impairment as a consequence of frequent use. Secondary analyses revealed a modest increase in the prevalence of DSM-5 CUD compared with DSM-IV cannabis abuse or dependence. It is concluded that, in addition to a general factor with loadings on cannabis use and symptoms of abuse, dependence, withdrawal, and craving, a second clinically relevant factor defined by features of social and occupational impairment was also found for frequent cannabis use.

**Predictors Of Substance Abuse Treatment Participation Among Homeless Adults** Ibabe I, Stein JA, Nyamathi A, Bentler PM. J Subst Abuse Treat. 2014; 46(3): 374-81.

The current study focuses on the relationships among a trauma history, a substance use history, chronic homelessness, and the mediating role of recent emotional distress in predicting drug treatment participation among adult homeless people. The authors explored the predictors of participation in substance abuse treatment because enrolling and retaining clients in substance abuse treatment programs is always a challenge particularly among homeless people. Participants were 853 homeless adults from Los Angeles, California. Using structural equation models, findings indicated that trauma history, substance use history and chronicity of homelessness were associated, and were significant predictors of greater recent emotional distress. The most notable result was that recent emotional distress predicted less participation in current substance abuse treatment (both formal and self-help) whereas a substance use history alone predicted significantly more participation in treatment. Implications concerning treatment engagement and difficulties in obtaining appropriate dual-diagnosis services for homeless mentally distressed individuals are discussed.

**Racial Susceptibility For QT Prolongation In Acute Drug Overdoses** Manini AF, Stimmel B, Vlahov D. J Electrocardiol. 2014; 47(2): 244-50.

QT prolongation independently predicts adverse cardiovascular events in suspected poisoning. The authors aimed to evaluate the association between race and drug-induced QT prolongation for patients with acute overdose. This was a cross-sectional observational study at two urban teaching hospitals. Consecutive adult ED patients with acute drug overdose were prospectively enrolled over a two year period. The primary outcome, long-QT, was defined using standard criteria: QTc>470 ms in females and>460 ms in males. The association between race and drug-induced QT prolongation was tested, considering several confounding variables. In 472 patients analyzed (46% female, mean age 42.3), QT prolongation occurred in 12.7%. Blacks had two-fold increased odds of drug-induced QT prolongation (OR 2.01, CI 1.03-3.91) and Hispanics had 48% decreased odds of drug-induced QT prolongation (OR 0.52, CI 0.29-0.94). The authors found significant racial susceptibility to drug-induced QT prolongation in this large urban study of acute overdoses.

**Hospitals As A 'risk Environment': An Ethno-epidemiological Study Of Voluntary and Involuntary Discharge From Hospital Against Medical Advice Among People Who Inject Drugs** McNeil R, Small W, Wood E, Kerr T. Soc Sci Med. 2014; 105: 59-66.

People who inject drugs (PWID) experience high levels of HIV/AIDS and hepatitis C (HCV) infection that, together with injection-related complications such as non-fatal overdose and injection-related infections, lead to frequent hospitalizations. However, injection drug-using populations are among those most likely to be discharged from hospital against medical advice, which significantly increases their likelihood of hospital readmission, longer overall hospital stays, and death. In spite of this, little research has been undertaken examining how social-structural forces operating within hospital settings shape the experiences of PWID in receiving care in hospitals and contribute to discharges against medical advice. This ethno-epidemiological study was undertaken in Vancouver, Canada to explore how the social-structural dynamics within hospitals function to produce discharges against medical advice among PWID. In-depth interviews were conducted with thirty PWID recruited from among participants in ongoing observational cohort studies of people who inject drugs who reported that they had been discharged from hospital against medical advice within the previous two years. Data were analyzed thematically, and by drawing on the risk environment & framework and concepts of social violence. These findings illustrate how intersecting social and structural factors led to inadequate pain and withdrawal management, which

led to continued drug use in hospital settings. In turn, diverse forms of social control operating to regulate and prevent drug use in hospital settings amplified drug-related risks and increased the likelihood of discharge against medical advice. Given the significant morbidity and health care costs associated with discharge against medical advice among drug-using populations, there is an urgent need to reshape the social-structural contexts of hospital care for PWID by shifting emphasis toward evidence-based pain and drug treatment augmented by harm reduction supports, including supervised drug consumption services.

### **Do Metropolitan HIV Epidemic Histories and Programs For People Who Inject Drugs and Men Who Have Sex With Men Predict AIDS Incidence and Mortality Among Heterosexuals?**

Friedman SR, West BS, Tempalski B, Morton CM, Cleland CM, Des Jarlais DC, Hall HI, Cooper HLF. *Ann Epidemiol.* 2014; 24(4): 304-11.

The authors focus on a little-researched issue-how human immunodeficiency virus (HIV) epidemics and programs in key populations in metropolitan areas affect epidemics in other key populations. They consider (1) How are earlier epidemics among people who inject drugs (PWID) and men who have sex with men (MSM) related to later AIDS incidence and mortality among heterosexuals?; (2) Were prevention programs targeting PWID or MSM associated with lower AIDS incidence and mortality among heterosexuals?; and (3) Was the size of the potential bridge population of noninjecting drug users (NIDUs) in a metropolitan area associated with later AIDS incidence and mortality among heterosexuals? Using data for 96 large U.S. metropolitan areas, Poisson regression assessed associations of population prevalence's of HIV-infected PWID and MSM (1992); NIDU population prevalence (1992-1994); drug use treatment coverage for PWID (1993); HIV counseling and testing coverage for MSM and for PWID (1992); and syringe exchange presence (2000) with CDC data on AIDS incidence and mortality among heterosexuals in 2006-2008, with appropriate socioeconomic controls. Population density of HIV+ PWID and of NIDUs was positively related, and prevention programs for PWID negatively related to later AIDS incidence among heterosexuals and later mortality among heterosexuals living with AIDS. HIV+ MSM population density and prevention programs for MSM were not associated with these outcomes. Efforts to reduce HIV transmission among PWID and NIDUs may reduce AIDS and AIDS-related mortality among heterosexuals. More research is needed at metropolitan area, network, and individual levels into HIV bridging across key populations and how interventions in one key population affect HIV epidemics in other key populations.

### **Institutional Ethical Review and Ethnographic Research Involving Injection Drug Users: A Case Study**

Small W, Maher L, Kerr T. *Soc Sci Med.* 2014; 104(): 157-62.

Ethnographic research among people who inject drugs (PWID) involves complex ethical issues. While ethical review frameworks have been critiqued by social scientists, there is a lack of social science research examining institutional ethical review processes, particularly in relation to ethnographic work. This case study describes the institutional ethical review of an ethnographic research project using observational fieldwork and in-depth interviews to examine injection drug use. The review process and the salient concerns of the review committee are recounted, and the investigators & responses to the committees concerns and requests are described to illustrate how key issues were resolved. The review committee expressed concerns regarding researcher safety when conducting fieldwork, and the investigators were asked to liaise with the police regarding the proposed research. An ongoing dialogue with the institutional review committee regarding researcher safety and autonomy from police involvement, as well as formal consultation with a local drug user group and solicitation of opinions from external experts, helped to resolve these issues. This case study suggests that ethical review processes can be particularly challenging for

ethnographic projects focused on illegal behaviors, and that while some challenges could be mediated by modifying existing ethical review procedures, there is a need for legislation that provides legal protection of research data and participant confidentiality.

**Social Network Structure and HIV Infection Among Injecting Drug Users In Lithuania: Gatekeepers As Bridges Of Infection** Gyarmathy VA, Caplinskiene I, Caplinskas S, Latkin CA.

AIDS Behav. 2014; 18(3): 505-10.

The aim of the study was to assess-while controlling for individual risk characteristics-how certain social network structural characteristics (degree, eigenvector, and betweenness centrality) are related to HIV infections. Injecting drug users (N = 299) in Vilnius, Lithuania were recruited using incentivized chain referral sampling for a cross-sectional study. Sociometric social links were established between participants, and UCINET was used to calculate network measures. HIV prevalence was 10 %, and all except two knew they were infected. Of the five variables that remained significant in the final multivariate model, one showed temporal cumulative infection risk (more years since first drug injecting), three reflected informed altruism (always using condoms, less distributive syringe sharing and having not more than one sex partner), and one pointed to the importance of social network structure (between centrality, indicating bridge populations). Loess regression indicates that between may have the highest impact on HIV prevalence (about 60 vs. 20 % estimated HIV prevalence for the highest betweenness centrality values vs. highest age values). This analysis contributes to existing evidence showing both potential informed altruism (or maybe social desirability bias) in connection with HIV infection, and a link between HIV infection risk and the role of bridges within the social network of injecting drug user populations. These findings suggest the importance of harm reduction activities, including confidential testing and counseling, and of social network interventions.

**Health and Social Harms Associated With Crystal Methamphetamine Use Among Street-involved Youth In A Canadian Setting** Uhlmann S, Debeck K, Simo A, Kerr T, Montaner JSG, Wood E. Am J Addict. 2014.

Despite recent increases in crystal methamphetamine use among high-risk populations such as street-involved youth, few prospective studies have examined the health and social outcomes associated with active crystal methamphetamine use. The authors enrolled 1,019 street-involved youth in Vancouver, Canada, in a prospective cohort known as the at-risk youth study (ARYS). Participants were assessed semi-annually and a generalized estimating equation (GEE) logistic regression was used to identify factors independently associated with active crystal methamphetamine use. Among 1,019 participants recruited into ARYS between 2005 and 2012 the median follow up duration was 17 months, 320 (31.4%) participants were female and 454 (44.6%) had previously used crystal methamphetamine at baseline. In adjusted GEE analyses, active crystal methamphetamine use was independently associated with Caucasian ethnicity (adjusted odds ratio [AOR] =1.37; 95% confidence interval [CI]: 1.04-1.81), homelessness (AOR=1.34; 95% CI: 1.15-1.56), injection drug use (AOR=3.40; 95% CI: 2.76-4.19), non-fatal overdose (AOR=1.46; 95%CI: 1.07-2.00), being a victim of violence (AOR=1.19; 95% CI: 1.02-1.38), involvement in sex work (AOR=1.39; 95% CI: 1.03-1.86), and drug dealing (AOR=1.60; 95% CI: 1.35-1.90).Prevalence of crystal methamphetamine use was high in this setting and active use was independently associated with a range of serious health and social harms. Evidence-based strategies to prevent and treat crystal methamphetamine use are urgently needed.

**HIV Infection Among Female Sex Workers In Concentrated and High Prevalence Epidemics: Why A Structural Determinants Framework Is Needed** Shannon K, Goldenberg SM, Deering KN, Strathdee SA. *Curr Opin HIV AIDS*. 2014; 9(2): 174-82.

This article reviews the current state of the epidemiological literature on female sex work and HIV from the past 18 months. The authors offer a conceptual framework for structural HIV determinants and sex work that unpacks intersecting structural, interpersonal, and individual biological and behavioral factors. Their review suggests that despite the heavy HIV burden among female sex workers (FSWs) globally, data on the structural determinants shaping HIV transmission dynamics have only begun to emerge. Emerging research suggests that factors operating at macro structural (e.g., migration, stigma, criminalized laws), community organization (e.g., empowerment) and work environment levels (e.g., violence, policing, access to condoms HIV testing, HAART) act dynamically with interpersonal (e.g., dyad factors, sexual networks) and individual biological and behavioral factors to confer risks or protections for HIV transmission in female sex work. Future research should be guided by a Structural HIV Determinants Framework to better elucidate the complex and iterative effects of structural determinants with interpersonal and individual biological and behavioral factors on HIV transmission pathways among FSWs, and meet critical gaps in optimal access to HIV prevention, treatment, and care for FSWs globally.

**Parental History Of Substance Use Disorders (SUD) and SUD In Offspring: A Controlled Family Study Of Bipolar Disorder** Wilens TE, Yule A, Martelon M, Zulauf C, Faraone SV. *Am J Addict*. 2014; 1-7

Adolescents with bipolar disorder (BPD) have been previously shown to be at very high risk for substance use disorders (SUD). The authors now examine the influence of a parental history of substance use disorders on SUD risk in offspring with and without BPD. They studied 190 parents ascertained through 104 adolescent BPD probands and 189 parents ascertained through 98 control probands using structured interviews. They compared the prevalence of SUD using logistic regression. While adjusting for BPD in their combined sample, probands with a parental history of SUD were more likely to have an alcohol use disorder compared to probands without a parental history. Probands with a parental history of SUD were not more likely to have a drug use disorder or overall SUD compared to probands without a parental history. BPD in the offspring did not pose any additional risk between parental history of SUD and offspring SUD. Alcohol use disorders were more common in the offspring of parents with a SUD history compared to parents without SUD and the risk was not influenced by offspring BPD. Clarifying the mechanisms linking parental SUD to offspring SUD, particularly in children and adolescents with BPD, would help clinicians to educate and monitor high-risk families, which would facilitate strategies to mitigate risks associated with parental substance abuse.

**Relationship Between Psychiatric Disorders and Sexually Transmitted Diseases In A Nationally Representative Sample** Magidson JF, Blashill AJ, Wall MM, Balan IC, Wang S, Lejuez CW, Blanco C. *J Psychosom Res*. 2014; 76(4): 322-8.

Sexually transmitted diseases (STDs) are a significant public health concern. Numerous internalizing and externalizing psychiatric disorders have been found to be related to STD risk. However, to date, no studies have examined several psychiatric disorders simultaneously to account for STD risk. Given that psychiatric disorders often co-occur and can be explained by a limited number of latent dimensions of psychopathology, it is important to examine whether the relationship between STDs and psychiatric disorders is best explained by broad dimensions of psychopathology. The current study examined the associations between a range of Axis I and II psychiatric disorders at baseline and rates of STDs at a three-year follow-up in a large, nationally

representative sample of adults in the United States (n=34,434). A confirmatory factor analysis (CFA) was conducted to fit three factors, two internalizing and one externalizing. Structural equation modeling (SEM) was used to assess the relationships between and among the factors and STD status and to test for mediation. In bivariate analyses, most Axis I and Axis II disorders were associated with STD diagnosis at Wave 2, whereas the results of the structural model showed that only the externalizing factor was significantly associated with STD diagnosis at Wave 2. Further, the externalizing factor mediated the relationship between one of the internalizing factors and STD diagnosis. Findings suggest the unique contribution of externalizing psychopathology to STD risk and the importance of examining latent dimensions of disorders when understanding this relationship between psychiatric disorders and STDs.

**Associations Between DSM-IV Mental Disorders and Subsequent Self-reported Diagnosis Of Cancer** O'Neill S, Posada-Villa J, Medina-Mora ME, Al-Hamzawi AO, Piazza M, Tachimori H, Hu C, Lim C, Bruffaerts R, Lepine J-P, Matschinger H, de Girolamo G, de Jonge P, Alonso J, Caldas-de-Almeida JM, Florescu S, Kiejna A, Levinson D, Kessler RC, Scott KM. *J Psychosom Res.* 2014; 76(3): 207-12.

The associations between mental disorders and cancer remain unclear. It is also unknown whether any associations vary according to life stage or gender. This paper examines these research questions using data from the World Mental Health Survey Initiative. The World Health Organization Composite International Diagnostic Interview retrospectively assessed the lifetime prevalence of 16 DSM-IV mental disorders in face-to-face household population surveys in nineteen countries (n = 52,095). Cancer was indicated by self-report of diagnosis. Smoking was assessed in questions about current and past tobacco use. Survival analyses estimated associations between first onset of mental disorders and subsequently reported cancer. After adjustment for comorbidity, panic disorder, specific phobia and alcohol abuse were associated with a subsequently self-reported diagnosis of cancer. There was an association between number of mental disorders and the likelihood of reporting a cancer diagnosis following the onset of the mental disorder. This suggests that the associations between mental disorders and cancer risk may be generalized, rather than specific to a particular disorder. Depression is more strongly associated with self-reported cancers diagnosed early in life and in women. PTSD is also associated with cancers diagnosed early in life. This study reports the magnitude of the associations between mental disorders and a self-reported diagnosis of cancer and provides information about the relevance of comorbidity, gender and the impact at different stages of life. The findings point to a link between the two conditions and lend support to arguments for early identification and treatment of mental disorders.

**DSM-5 Latent Classes Of Alcohol Users In A Population-based Sample: Results From the Sao Paulo Megacity Mental Health Survey, Brazil** Castaldelli-Maia JM, Silveira CM, Siu ER, Wang Y-P, Milhoranca IA, Alexandrino-Silva C, Borges G, Viana MC, Andrade AG, Andrade LH, Martins SS. *Drug Alcohol Depend.* 2014; 136: 92-9.

The authors aimed to identify different categorical phenotypes based upon the DSM-V criteria of alcohol use disorders (AUD) among alcohol users who had at least one drink per week in the past year (n=948). Data are from the Sao Paulo Megacity Mental Health Survey collected in 2005-2007, as part of the World Mental Health Survey Initiative. A latent class analysis of the 11 DSM-5-AUD criteria was performed using Mplus, taking into account complex survey design features. Weighted logistic regression models were used to examine demographic correlates of the DSM-5-AUD latent classes. The best latent-class model was a three-class model. The authors found a "non-symptomatic class" (69.7%), a "use in larger amounts class" (23.2%), defined by high probability (>70%) of the "use in larger amounts" criterion only, and a "high-moderate symptomatic class" (7.1%), defined by

high-moderate probability of all the 11 AUD criteria. Compared to those in the non-symptomatic class, individuals in the "high-moderate symptomatic class" were more likely to have been married, have lower educational attainment and to be unemployed or in non-regular/informal employment. Those on the "use in larger amounts class" were more likely to have been married or never married. The two symptomatic classes clearly represented the dimensionality of the new proposed AUD criteria, and could be more specifically targeted by different prevention or treatment strategies. DSM-5-AUD has the advantage of shedding light on risky drinkers included in the "use in larger amounts class", allowing for preventive interventions, which will reach a large number of individuals.

**Use Of Hospital-based Services Among Young Adults With Behavioral Health Diagnoses Before and After Health Insurance Expansions** Meara E, Golberstein E, Zaha R, Greenfield SF, Beardslee WR, Busch SH. *JAMA Psychiatry*. 2014; 71(4): 404-11.

Young adults have high levels of behavioral health needs but often lack health insurance. Recent health reforms have increased coverage, but it is unclear how use of hospital-based care changed after expanding insurance. The objective of this study was to evaluate the association between health insurance coverage expansions and use of hospital-based care among young adults with behavioral health diagnoses. Quasi-experimental analyses of community hospital inpatient and emergency department use from 2003-2009 based on hospital discharge data, comparing differential changes in service use among young adults with behavioral health diagnoses in Massachusetts vs other states before and after Massachusetts 2006 health reform. This population-based sample included inpatient admissions (n = 2,533,307, representing 12,821,746 weighted admissions across 7 years) nationwide and emergency department visits (n = 6,817,855 across 7 years) from Maryland and Massachusetts for 12- to 25-year-old patients. Inpatient admission rates per 1000 population for primary diagnosis of any behavioral health disorder by diagnosis; emergency department visit rates per 1000 population by behavioral health diagnosis; and insurance coverage for hospital discharges. After 2006, uninsurance among 19- to 25-year-old individuals in Massachusetts decreased from 26% to 10% (16 percentage points; 95% CI, 13-20). Young adults experienced relative declines in inpatient admission rates of 2.0 per 1000 for primary diagnoses of any behavioral health disorder (95% CI, 0.95-3.2), 0.38 for depression (95% CI, 0.18-0.58), and 1.3 for substance use disorder (95% CI, 0.68-1.8). The increase in emergency department visits with any behavioral health diagnosis after 2006 was lower among young adults in Massachusetts compared with Maryland (16.5 per 1000; 95% CI, 11.4-21.6). Among young adults in Massachusetts, the percentage of behavioral health discharges that were uninsured decreased by 5.0 (95% CI, 3.0-7.2) percentage points in inpatient settings and 5.0 (95% CI, 1.7-7.8) percentage points in emergency departments relative to other states. Expanded health insurance coverage for young adults was not associated with large increases in hospital-based care for behavioral health, but it increased financial protection for young adults with behavioral health diagnoses and for the hospitals that care for them.

**The Impact Of Childhood Emotional Abuse On Violence Among People Who Inject Drugs**

Lake S, Wood E, Dong H, Dobrer S, Montaner J, Kerr T. *Drug Alcohol Rev*. 2014

Childhood emotional abuse is a known risk factor for various poor social and health outcomes. While people who inject drugs (IDU) report high levels of violence, in addition to high rates of childhood maltreatment, the relationship between childhood emotional abuse and later life violence within this population has not been examined. Cross-sectional data were derived from an open prospective cohort of IDU in Vancouver, Canada. Childhood emotional abuse was measured using the Childhood Trauma Questionnaire. The authors used multivariate logistic regression to examine

potential associations between childhood emotional abuse and being a recent victim or perpetrator of violence. Between December 2005 and May 2013, 1437 IDU were eligible for inclusion in this analysis, including 465 (32.4%) women. In total, 689 (48.0%) reported moderate to severe history of childhood emotional abuse, whereas 333 (23.2%) reported being a recent victim of violence and 173 (12.0%) reported being a recent perpetrator of violence. In multivariate analysis, being a victim of violence (adjusted odds ratio=1.49, 95% confidence interval 1.15-1.94) and being a perpetrator of violence (adjusted odds ratio=1.58, 95% confidence interval 1.12-2.24) remained independently associated with childhood emotional abuse. The authors found high rates of childhood emotional abuse and subsequent adult violence among this sample of IDU. Emotional abuse was associated with both victimization and perpetration of violence. These findings highlight the need for policies and programmers that address both child abuse and historical emotional abuse among adult IDU.

**Proximal and Time-varying Effects Of Cigarette, Alcohol, Marijuana and Other Hard Drug Use On Adolescent Dating Aggression** McNaughton Reyes HL, Foshee VA, Bauer DJ, Ennett ST. *J Adolesc.* 2014; 37(3): 281-9.

Although numerous studies have established a link between substance use and adult partner violence, little research has examined the relationship during adolescence and most extant research has not examined multiple substance use types. The current study used hierarchical growth modeling to simultaneously examine proximal (between-person) and time-varying (within-person) relations between cigarette, alcohol, marijuana and hard drug use and physical dating aggression across grades 8 through 12 while controlling for demographic covariates and shared risk factors. Proximal effects of marijuana use on dating aggression were found for girls and proximal effects of hard drug use on dating aggression were found for boys. Time-varying effects were found for alcohol for both boys and girls and for hard drug use for boys only. Overall, findings suggest that alcohol, marijuana and hard drug use predict whether and when adolescents engage in dating aggression and should be targeted by prevention interventions.

**Conceptual and Data-based Investigation Of Genetic Influences and Brain Asymmetry: A Twin Study Of Multiple Structural Phenotypes** Eyer LT, Vuoksimaa E, Panizzon MS, Fennema-Notestine C, Neale MC, Chen C-H, Jak A, Franz CE, Lyons MJ, Thompson WK, Spoon KM, Fischl BD, Anders M, Kremen WS. *J Cogn Neurosci.* 2014; 26(5): 1100-17.

Right-left regional cerebral differences are a feature of the human brain linked to functional abilities, aging, and neurodevelopmental and mental disorders. The role of genetic factors in structural asymmetry has been incompletely studied. The authors analyzed data from 515 individuals (130 monozygotic twin pairs, 97 dizygotic pairs, and 61 unpaired twins) from the Vietnam Era Twin Study of Aging to answer three questions about genetic determinants of brain structural asymmetry: First, does the magnitude of heritability differ for homologous regions in each hemisphere? Despite adequate power to detect regional differences, heritability estimates were not significantly larger in one hemisphere versus the other, except left > right inferior lateral ventricle heritability. Second, do different genetic factors influence left and right hemisphere size in homologous regions? Interhemispheric genetic correlations were high and significant; in only two subcortical regions (pallidum and accumbens) did the estimate statistically differ from 1.0. Thus, there was little evidence for different genetic influences on left and right hemisphere regions. Third, to what extent do genetic factors influence variability in left-right size differences? There was no evidence that variation in asymmetry (i.e., the size difference) of left and right homologous regions was genetically determined, except in pallidum and accumbens. The findings suggest that genetic factors do not play a significant role in determining individual variation in the degree of regional cortical size asymmetries measured with MRI, although they may do so for volume of some

subcortical structures. Despite varying interpretations of existing data, the authors view the present results as consistent with previous findings.

**Associations Between DSM-IV Mental Disorders and Diabetes Mellitus: A Role For Impulse Control Disorders and Depression**

de Jonge P, Alonso J, Stein DJ, Kiejna A, Aguilar-Gaxiola S, Viana MC, Liu Z, O'Neill S, Bruffaerts R, Caldas-de-Almeida JM, Lepine J-P, Matschinger H, Levinson D, de Girolamo G, Fukao A, Bunting B, Haro JM, Posada-Villa JA, Al-Hamzawi AO, Medina-Mora ME, Piazza M, Hu C, Sasu C, Lim CCW, Kessler RC, Scott KM. *Diabetologia*. 2014; 57(4): 699-709.

No studies have evaluated whether the frequently observed associations between depression and diabetes could reflect the presence of comorbid psychiatric conditions and their associations with diabetes. The authors therefore examined the associations between a wide range of pre-existing Diagnostic Statistical Manual, 4th edition (DSM-IV) mental disorders with self-reported diagnosis of diabetes. They performed a series of cross-sectional face-to-face household surveys of community-dwelling adults (n = 52,095) in 19 countries. The World Health Organization Composite International Diagnostic Interview retrospectively assessed lifetime prevalence and age at onset of 16 DSM-IV mental disorders. Diabetes was indicated by self-report of physician's diagnosis together with its timing. The authors analyzed the associations between all mental disorders and diabetes, without and with comorbidity adjustment. They identified 2,580 cases of adult-onset diabetes mellitus (21 years +). Although all 16 DSM-IV disorders were associated with diabetes diagnosis in bivariate models, only depression (OR 1.3; 95% CI 1.1, 1.5), intermittent explosive disorder (OR 1.6; 95% CI 1.1, 2.1), binge eating disorder (OR 2.6; 95% CI 1.7, 4.0) and bulimia nervosa (OR 2.1; 95% CI 1.3, 3.4) remained after comorbidity adjustment. Depression and impulse control disorders (eating disorders in particular) were significantly associated with diabetes diagnosis after comorbidity adjustment. These findings support the focus on depression as having a role in diabetes onset, but suggest that this focus may be extended towards impulse control disorders. Acknowledging the comorbidity of mental disorders is important in determining the associations between mental disorders and subsequent diabetes.

**Effect Of First Episode Axis I Disorders On Quality Of Life** Rubio JM, Olfson M, Perez-Fuentes G, Garcia-Toro M, Wang S, Blanco C. *J Nerv Ment Dis*. 2014; 202(4): 271-4.

Cross-sectional studies indicate that mental disorders are inversely associated with quality of life (QoL) and that the magnitude of the negative correlation varies across disorders. The aims of this study were to examine whether QoL decreases after new onset of psychiatric disorders and to characterize variations across disorders. Data were drawn from a longitudinal study representative of the adult US population. Changes were examined in QoL, as measured by the Short Form-12 version 2, after incidence of Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV), disorders at wave 2 in individuals without the given disorder at wave 1. A sub analysis examined change of QoL after incidence of mental disorders in individuals without a history of any mental disorder. With the exception of alcohol abuse, new incidence of each examined DSM-IV disorder was associated with a decrement in QoL, being the largest for major depressive disorder and generalized anxiety disorder. Incidence of these disorders was associated with a decrease in QoL even in individuals without history or presence of any other mental disorder. Although the incidence of most DSM-IV disorders is associated with a decrement in QoL, mood and anxiety disorders have the largest impact.

**Amygdala Activation and Emotional Processing In Adolescents At Risk For Substance Use Disorders** Thatcher DL, Pajtek S, Tarter R, Long EC, Clark DB. *J Child Adolesc Subst Abuse*. 2014; 23(3): 200-204.

Studies are needed that examine neurobiological characteristics in high risk individuals prior to substance use disorder (SUD) development. In this pilot study, 4 adolescent subjects at high risk (having at least 1 parent with a SUD) for SUD were compared with 4 adolescent reference subjects on a corticolimbic reactivity paradigm, where they were presented with affect-laden faces or geometric shapes. fMRI was used to measure cortical activation in response to these stimuli. High risk subjects, compared to low risk, exhibited greater left amygdala activation ( $t=3.60$ ,  $df=6$ ,  $p=0.01$ ), suggesting they may exhibit hyper-responsivity of the amygdala in response to emotional stimuli.

**The Phenomenon Of Low-frequency Heroin Injection Among Street-based Urban Poor: Drug User Strategies and Contexts Of Use** Wenger LD, Lopez AM, Comfort M, Kral AH. *Int J Drug Policy*. 2014

Dominant public health and medical discourse has relied on a pharmacocentric conception of heroin use—that is, the notion that heroin users inject compulsively to stave off physical and psychological withdrawal. Previous research disputes this claim suggesting that other patterns of heroin use, such as occasional, recreational, or controlled use are possible. In the authors' previous cross-sectional epidemiological research, they identified the phenomenon of low frequency heroin injection (low-FHI), among street-based drug users. The goal of the current study was to qualitatively assess and contextualize this phenomenon over time among a sample of street-based low-FHI. 29 low-FHI and 25 high frequency heroin injectors (high-FHI) were followed for 2 years, during which they participated in a series of in-depth interviews. Qualitative data were coded using an inductive analysis approach. As similarities and differences between participants were discovered, transcripts were queried for supportive quotations as well as negative cases. The authors found the social context among low-FHI and high-FHI to be similar with the exception of their patterns of heroin use. Thus, they focused this analysis on understanding motivations for and management of low-FHI. Two major categories of low-FHI emerged from the data: maintenance and transitioning low-FHI. Maintenance low-FHI sustained low-FHI over time. Some of these heroin users were circumstantial low-FHI, who maintained low-FHI as a result of their social networks or life events, and others maintained low-FHI purposefully. Transitioning low-FHI did not sustain low use throughout the study. We found that heroin use patterns frequently shift over time and these categories help identify factors impacting drug use within particular moments in an individual's life. Given the various patterns of heroin use that were identified in this study, when working with IDUs, one must assess the specifics of heroin use patterns including drug preferences, desire for substance abuse treatment, as well as basic physical and mental health care needs.

**Does Stress Mediate the Development Of Substance Use Disorders Among Youth Transitioning To Young Adulthood?** Cornelius J, Kirisci L, Reynolds M, Tarter R. *Am J Drug Alcohol Abuse*. 2014; 40(3): 225-9.

Stress is a well-documented factor in the development of addiction. However, no longitudinal studies to date have assessed the role of stress in mediating the development of substance use disorders (SUD). The authors' previous results have demonstrated that a measure called Transmissible Liability Index (TLI) assessed during pre-adolescent years serves as a significant predictor of risk for substance use disorder among young adults. However, it remains unclear whether life stress mediates the relationship between TLI and SUD, or whether stress predicts SUD. The authors conducted a longitudinal study involving 191 male subjects to assess whether life stress

mediates the relationship between TLI as assessed at age 10-12 and subsequent development of SUD at age 22, after controlling for other relevant factors. Logistic regression demonstrated that the development of SUD at age 22 was associated with stress at age 19. A path analysis demonstrated that stress at age 19 significantly predicted SUD at age 22. However, stress did not mediate the relationship between the TLI assessed at age 10-12 and SUD in young adulthood. These findings confirm that stress plays a role in the development of SUD, but also shows that stress does not mediate the development of SUD. Further studies are warranted to clarify the role of stress in the etiology of SUD.

**Alcohol Dependence and Reproductive Timing In African and European Ancestry Women: Findings In A Midwestern Twin Cohort** Waldron M, Bucholz KK, Madden PAF, Duncan AE, Sartor CE, Heath AC. *J Stud Alcohol Drugs*. 2014; 75(2): 235-40.

The authors examined associations between reproductive onset and history of alcohol dependence (AD) in 475 African ancestries (AA) and 2,865 European or other ancestry (EA) female twins. Participants were drawn from a U.S. Midwestern birth cohort study of like-sex female twin pairs born between 1975 and 1985, ages 21-32 as of last completed assessment. Cox proportional hazards regression models were estimated predicting age at first childbirth from history of AD, separately by race/ethnicity, without and with adjustment for sociodemographic characteristics, body mass index, and history of other substance involvement, psychopathology, and family and childhood risks. Among EA twins, AD predicted early childbearing through age 17 and delayed childbearing from age 25 onward; in adjusted models, AD was associated with overall delayed childbearing. Among AA twins, reproductive timing and AD were not significantly related in either unadjusted or adjusted models. Findings for twins of European ancestry are consistent with well-documented links between early alcohol mis/use and teenage parenting as well as delays in childbearing associated with drinking-related reproductive and relationship difficulties. Extension of analyses to other racial/ethnic groups of sufficient sample size remains important.

**Comorbidity Between Major Depression and Alcohol Use Disorder From Adolescence To Adulthood** Briere FN, Rohde P, Seeley JR, Klein D, Lewinsohn PM. *Compr Psychiatry*. 2014; 55(3): 526-33.

Limited information exists regarding the long-term development of comorbidity between Major Depressive Disorder (MDD) and Alcohol Use Disorder (AUD; abuse/dependence). Using a representative prospective study, the authors examine multiple aspects pertaining to MDD+AUD comorbidity, with a focus on the relation between disorders across periods (adolescence, early adulthood, adulthood) and cumulative impairments by age 30. 816 participants were diagnostically interviewed at ages 16, 17, 24, and 30. Rates of comorbid MDD+AUD were low in adolescence (2%), but increased in early adulthood (11%) and adulthood (7%). Rates of cumulative comorbidity were elevated (21%). Most individuals with a history of MDD or AUD had the other disorder, except for women with MDD. Prospectively, adolescent AUD predicted early adult MDD, while early adult MDD predicted adult AUD. Compared to pure disorders, MDD+AUD was associated with higher risk of alcohol dependence, suicide attempt, lower global functioning, and life dissatisfaction. Lifetime rates of comorbid MDD+AUD were considerably higher than in cross-sectional studies. Comorbidity was partly explained by bidirectional and developmentally-specific associations and predicted selected rather than generalized impairments. Clinically, these findings emphasize the need to always carefully assess comorbidity in patients with MDD or AUD, taking into account concurrency and developmental timing.

### **ADHD Symptoms, Autistic Traits, and Substance Use and Misuse In Adult Australian Twins**

De Alwis D, Agrawal A, Reiersen AM, Constantino JN, Henders A, Martin NG, Lynskey MT. *J Stud Alcohol Drugs*. 2014; 75(2): 211-21.

Attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder frequently co-occur. Several studies show increased risk of substance use disorders in ADHD, yet there is limited information related to how ADHD symptoms, autistic traits, and their combined effects are associated with nicotine, alcohol, and cannabis use and use disorders in the general population. Cross-sectional interview and self-report questionnaire data from 3,080 young adult Australian twins (mean age 31.9 years) were used to assess ADHD symptoms, autistic traits, substance use, and substance use disorders. Substance use disorders-based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, criteria-were assessed in the full sample as well as in those who reported substance use. Logistic regression analyses were used for comparing the associations between ADHD symptoms, autistic traits, substance use, and substance misuse after conduct disorder, sex, age, and zygosity were controlled for. Greater ADHD symptoms and autistic traits scores were associated with elevated levels of regular smoking; cannabis use; and nicotine, alcohol, and cannabis use disorders, even after conduct disorder was adjusted for. In contrast, for alcohol use, those with high autistic traits scores were less likely to report drinking to intoxication. However, upon initiation, and similar to the findings for nicotine and cannabis, they were at elevated risk for developing alcohol dependence. Increased liability to ADHD and elevated autistic traits scores were associated with substance use and misuse, with the exception of alcohol use. Given the social underpinnings of drinking, persons with autistic traits may be less likely to engage in it; however, upon engagement in drinking, their vulnerability to alcohol dependence is elevated.

### **Moderating the Covariance Between Family Member's Substance Use Behavior** Verhulst B, Eaves LJ, Neale MC. *Behav Genet*. 2014

Twin and family studies implicitly assume that the covariation between family members remains constant across differences in age between the members of the family. However, age-specificity in gene expression for shared environmental factors could generate higher correlations between family members who are more similar in age. Cohort effects (cohort genotype or cohort common environment) could have the same effects, and both potentially reduce effect sizes estimated in genome-wide association studies where the subjects are heterogeneous in age. In this paper the authors describe a model in which the covariance between twins and non-twin siblings is moderated as a function of age difference. They describe the details of the model and simulate data using a variety of different parameter values to demonstrate that model fitting returns unbiased parameter estimates. Power analyses are then conducted to estimate the sample sizes required to detect the effects of moderation in a design of twins and siblings. Finally, the model is applied to data on cigarette smoking. The authors find that (1) the model effectively recovers the simulated parameters; (2) the power is relatively low and therefore requires large sample sizes before small to moderate effect sizes can be found reliably, and (3) the genetic covariance between siblings for smoking behavior decays very rapidly. Result 3 implies that, e.g., genome-wide studies of smoking behavior that use individuals assessed at different ages, or belonging to different birth-year cohorts may have had substantially reduced power to detect effects of genotype on cigarette use. It also implies that significant special twin environmental effects can be explained by age-moderation in some cases. This effect likely contributes to the missing heritability paradox.

### **ADHD, Conduct Disorder, Substance Use Disorder, and Nonprescription Stimulant Use**

Brook JS, Balka EB, Zhang C, Brook DW. *J Atten Disord.* 2014.

The objective of this study was to assess whether the relationship of an ADHD diagnosis by adolescence to nonprescription stimulant use in adulthood is direct or indirect, via Conduct Disorder (CD) and/or Substance Use Disorder (SUD). Data were obtained from multiple waves of interviews and questionnaires completed by 551 community-based participants when they were between the mean ages of 14.1 and 36.6 years. The results of the structural equation model (SEM) supported both a direct association between early ADHD and later nonprescription stimulant use ( $B = .18, z = 2.74$ ) and the relationship from ADHD to later nonprescription stimulant use ( $B = .01, z = 1.72$ ) via CD and SUD. The longitudinal data supporting these paths suggest that efforts to prevent and treat the misuse of nonprescription stimulants may be more effective if attention is paid to those with a history of ADHD, as well as to those who also had CD and SUD.

### **Spatial Analysis Of HIV Positive Injection Drug Users In San Francisco, 1987 To 2005**

Martinez AN, Mobley LR, Lorvick J, Novak SP, Lopez A, Kral AH. *Int J Environ Res Public Health.* 2014; 11(4): 3937-55.

Spatial analyses of HIV/AIDS related outcomes are growing in popularity as a tool to understand geographic changes in the epidemic and inform the effectiveness of community-based prevention and treatment programs. The Urban Health Study was a serial, cross-sectional epidemiological study of injection drug users (IDUs) in San Francisco between 1987 and 2005 ( $N = 29,914$ ). HIV testing was conducted for every participant. Participant residence was geocoded to the level of the United States Census tract for every observation in dataset. Local indicators of spatial autocorrelation (LISA) tests were used to identify univariate and bivariate Census tract clusters of HIV positive IDUs in two time periods. The authors further compared three tract level characteristics (% poverty, % African Americans, and % unemployment) across areas of clustered and non-clustered tracts. They identified significant spatial clustering of high numbers of HIV positive IDUs in the early period (1987-1995) and late period (1996-2005). They found significant bivariate clusters of Census tracts where HIV positive IDUs and tract level poverty were above average compared to the surrounding areas. These data suggest that poverty, rather than race, was an important neighborhood characteristic associated with the spatial distribution of HIV in SF and its spatial diffusion over time.

### **A Longitudinal Study Of Childhood ADHD and Substance Dependence Disorders In Early**

**Adulthood** Breyer JL, Lee S, Winters KC, August GJ, Realmuto GM. *Psychol Addict Behav.* 2014; 28(1): 238-46.

Attention deficit hyperactivity disorder (ADHD) is a childhood disorder that is associated with many behavioral and social problems. These problems may continue when an individual continues to meet criteria for ADHD as an adult. In this study, the authors describe the outcome patterns for three different groups: individuals who had ADHD as children, but no longer meet criteria as adults (Childhood-Limited ADHD,  $n = 71$ ); individuals who met ADHD criteria as children and continue to meet criteria as young adults (Persistent ADHD  $n = 79$ ); and a control group of individuals who did not meet ADHD diagnostic criteria in childhood or adulthood ( $n = 69$ ). Groups were compared with examine differences in change in rates of alcohol, marijuana, and nicotine dependence over 3 time points in young adulthood (mean ages 18, 20, and 22 years). The method used is notable as this longitudinal study followed participants from childhood into young adulthood instead of relying on retrospective self-reports from adult participants. Results indicated that there were no significant group differences in change in rates of substance dependence over time. However, individuals whose ADHD persisted into adulthood were significantly more likely to meet DSM-IV criteria for

alcohol, marijuana, and nicotine dependence across the 3 time points after controlling for age, sex, childhood stimulant medication use, and childhood conduct problems. Implications of these findings, as well as recommendations for future research, are discussed.

**Under-reporting Bipolar Disorder In Large-scale Epidemiologic Studies** Karam EG, Sampson N, Itani L, Andrade LH, Borges G, Chiu WT, Florescu S, Horiguchi I, Zarkov Z, Akiskal H. *J Affect Disord.* 2014; 159: 147-54.

The purpose of this study was to investigate if the prevalence of bipolar disorder in epidemiologic studies is an underestimate, as suggested by clinical studies. The authors analyzed data from 8 countries that participated in the World Mental Health Survey Initiative (n=47,552). They identified 6.8% and 18.9% of the sample who they think were screened out inappropriately (SCI) from the euphoric and irritable bipolar sections respectively. The authors compared them to those who were allowed to continue the section (CONT, 2.6% of the sample for euphoric; 1.0% for irritable) and to the reference group (REF, 69.5% of the sample). The SCI group had consistently higher rates of major depression (29.1% vs. 6.4%), earlier age of onset (24.3y vs. 32.4y), more suicide attempts (13.3% vs. 5.9%), and more episodes (4.2 vs. 2.7) than the REF for the euphoric group. Similar findings exist for the irritable group. Also, comorbidity with anxiety, disruptive behavior disorders and substance use were much higher than the REF. As with all epidemiologic studies, recall bias cannot be ruled out. The findings above suggest that a number of the SCI subjects belong to the bipolar group. A revision of instruments used in epidemiologic research will probably prove what clinical studies have been showing that bipolar disorder is more common than has been reported.

**A New Survey Of Methamphetamine Users In Treatment: Who They Are, Why They Like "meth," and Why They Need Additional Services** Maxwell JC. *Subst Use Misuse.* 2014; 49(6): 639-44.

The quality and quantity of illicit methamphetamine has recently increased due to introduction of a new precursor, 1-phenyl-2-propanone (P2P). This paper updates the problems associated with methamphetamine use. Methamphetamine-using clients (N = 222) entering a Texas program participated in computer-assisted interviews in 2010 and 2011 about routes of administration, other drugs used, severity of dependence, mental and physical health, perceived risks and benefits of use, family history, and abuse and neglect experienced as children and adults. Special needs of this population include therapies for trauma, gender-focused counseling, safe housing, and prevention messages to discourage use of the drug.

**The Longitudinal Age and Birth Cohort Trends Of Smoking In Sweden: A 24-year Follow-up Study** Midlov P, Calling S, Sundquist J, Sundquist K, Johansson SE. *Int J Public Health.* 2014; 59(2): 243-50.

The aim of this study is to analyze longitudinally, the annual effects of age group and birth cohort on smoking in the Swedish population during a 24-year period and to analyze the smoking trends for different levels of education. A random sample of adult, non-institutionalized persons aged 16-71 years was interviewed every 8 years by professional interviewers. In addition to three time-related variables--year of interview, age at the time of the interview, and year of birth—the authors included the following explanatory variables in the analyses: sex, educational level, and urbanization. The authors found significant decreases in smoking prevalence in all studied subgroups. The adjusted odds ratios for age were 0.89 (95 % CI 0.88-0.90) and 0.92 (95 % CI 0.91-0.93) for men and women, respectively. The decreases in smoking over time were significant in all levels of education, except for in women with low educational level. In Sweden, the prevalence of

smoking has decreased in most age groups and cohorts, and in persons in most levels of education, albeit less so in women with low educational level.

**The Association Of Tobacco Use and Gender To Cardiac Rehabilitation Outcomes: A Preliminary Investigation** Weinberger AH, Mazure CM, McKee SA, Caulin-Glaser T. J Subst Use. 2014; 19(1-2): 171-175.

Cardiac rehabilitation (CR) outcomes are measured in terms of cardiovascular disease (CVD) risk factor reductions, and these predict long-term cardiac status. This report examines whether reported tobacco use has differential effects on successful cardiovascular risk factor modification, especially for women who have greater smoking-related CVD consequences than men. A retrospective cohort analysis was conducted on 1138 adults (74% male) with diagnosed CVD who participated in 7 weeks of a comprehensive CR program. Eleven CVD risk factors were assessed at CR entry and completion. Tobacco use was assessed by self-report at CR entry. The primary outcomes were attainment of goal levels for each risk factor. Fewer current and former tobacco users reached the preset goal for Maximal Exercise Capacity. Fewer women than men reached the preset goal for HDL. Women who were current or former tobacco users were less likely to meet the target goals for Triglycerides and more likely to meet target goals for Total Cholesterol and Non-HDL Cholesterol. This preliminary study suggests the importance of identifying the effect of tobacco use and gender on CR outcomes and the need to evaluate modification of key cardiovascular risk factors for subgroups of cardiac patients.

**Evidence For Risk Reduction Among Amphetamine-Injecting Men Who Have Sex With Men; Results From National HIV Behavioral Surveillance Surveys In the Seattle Area 2008-2012**

Burt RD, Thiede H. AIDS Behav. 2014.

In the Seattle area men who have sex with men and also inject amphetamines (amphetamine-injecting MSM/IDU) are disproportionately likely to be infected with HIV. To characterize their distinctive characteristics, the authors combined data from two Seattle-area surveys of men who have sex with men (MSM) and two surveys of injection drug users (IDU). Amphetamine-injecting MSM/IDU was compared with: male IDU, MSM and other MSM/IDU. Amphetamine-injecting MSM/IDU were older than MSM but younger than IDU, more likely to be white than either group, and had an educational level higher than IDU but below MSM. They had the highest HIV prevalence (56 vs. 4-19%). However, reported HIV cases among them fell from 92 in 1990 to 25 in 2012. They were most likely to report ten or more sex partners (49 vs. 4-26%), an STD diagnosis (22 vs. 1-7%) and be tested for HIV (odds ratio 1.00 vs. 0.34-0.52), and least likely to share needles (odds ratio 1.00 vs. 6.80-10.50). While sexual risk remains high, these data suggest measurable and effective risk reduction with respect to sharing injection equipment and HIV testing among Seattle-area amphetamine-injecting MSM/IDU.

**Dopamine Receptor Gene D4 Polymorphisms and Early Sexual Onset: Gender and Environmental Moderation In A Sample Of African-American Youth** Kogan SM, Lei M-K, Beach SRH, Brody GH, Windle M, Lee S, Mackillop J, Chen Y-F. J Adolesc Health. 2014.

Early sexual onset and its consequences disproportionately affect African-American youth, particularly male youth. The dopamine receptor D4 gene (DRD4) has been linked to sexual activity and other forms of appetitive behavior, particularly for male youth and in combination with environmental factors (gene environment [GE] effects). The differential susceptibility perspective suggests that DRD4 may exert this effect by amplifying the effects of both positive and negative environments. The authors hypothesized that DRD4 status would amplify the influence of both positive and negative neighborhood environments on early sexual onset among male, but not

female, African-Americans. Hypotheses were tested with self-report, bio specimen, and census data from five prospective studies of male and female African-American youth in rural Georgia communities, N=1,677. Early sexual onset was defined as intercourse before age 14. No significant GE findings emerged for female youth. Male youth with a DRD4 long allele were more likely than those with two DRD4 short alleles to report early sexual onset in negative community environments and not to report early onset in positive community environments. Dopaminergic regulation of adolescent sexual behaviors may operate differently by gender. DRD4 operated as an environmental amplification rather than a vulnerability factor.

### **Response Inhibition Moderates the Association Between Drug Use and Risky Sexual Behavior**

Nydegger LA, Ames SL, Stacy AW, Grenard JL. *Subst Use Misuse*. 2014.

HIV infection is problematic among all drug users, not only injection drug users. Drug users are at risk for contracting HIV by engaging in risky sexual behaviors. The present study sought to determine whether inhibitory processes moderate the relationship between problematic drug use and HIV-risk behaviors (unprotected sex and multiple sex partners). One hundred ninety-six drug offenders enrolled in drug education programs were administered a battery of computer-based assessments. Measures included a cued go/no-go assessment of inhibitory processes, the Drug Abuse Screening Test (DAST) assessment of problematic drug use, and self-report assessment of condom use and multiple sex partners. Findings revealed that response inhibition assessed by the proportion of false alarms on the cued go/no-go moderated the relationship between problematic drug use and an important measure of HIV risk (condom nonuse) among drug offenders. However, response inhibition did not moderate the relationship between problematic drug use and another measure of HIV risk: multiple sex partners. Among this sample of drug offenders, the authors have found a relationship between problematic drug use and condom nonuse, which is exacerbated by poor control of inhibition. These findings have implications for the development of HIV intervention components among high-risk populations.

### **HIV-associated Obstructive Lung Diseases: Insights and Implications For the Clinician**

Drummond MB, Kirk GD. *Lancet Respir Med*. 2014.

The effectiveness of antiretroviral therapy to control HIV infection has led to the emergence of an older HIV population who are at risk of chronic diseases. Through a comprehensive search of major databases, this Review summarizes information about the associations between chronic obstructive pulmonary disease (COPD), asthma, and HIV infection. Asthma and COPD are more prevalent in HIV-infected populations; 16-20% of individuals with HIV infection has asthma or COPD, and poorly controlled HIV infection worsens spirometric and diffusing capacity measurements, and accelerates lung function decline by about 55-75 mL/year. Up to 21% of HIV-infected individuals have obstructive ventilatory defects and reduced diffusing capacity is seen in more than 50% of HIV-infected populations. Specific pharmacotherapy considerations are needed to care for HIV-infected populations with asthma or COPD—protease inhibitor regimens to treat HIV (such as ritonavir) can result in systemic accumulation of inhaled corticosteroids and might increase pneumonia risk, exacerbating the toxicity of this therapy. Therefore, it is essential for clinicians to have a heightened awareness of the increased risk and manifestations of obstructive lung diseases in HIV-infected patients and specific therapeutic considerations to care for this population. Screening spirometry and tests of diffusing capacity might be beneficial in HIV-infected people with a history of smoking or respiratory symptoms.

## **PREVENTION RESEARCH**

**Can We Build An Efficient Response To The Prescription Drug Abuse Epidemic? Assessing the Cost Effectiveness Of Universal Prevention In The PROSPER Trial** Crowley DM, Jones DE, Coffman DL, Greenberg MT. *Prev Med.* 2014; 62(): 71-7.

Prescription drug abuse has reached epidemic proportions. Nonmedical prescription opioid use carries increasingly high costs. Despite the need to cultivate efforts that are both effective and fiscally responsible, the cost-effectiveness of universal evidence-based-preventive-interventions (EBPIs) is rarely evaluated. This study explores the performance of these programs to reduce nonmedical prescription opioid use. Sixth graders from twenty-eight rural public school districts in Iowa and Pennsylvania were blocked by size and geographic location and then randomly assigned to experimental or control conditions (2002-2010). Within the intervention communities, prevention teams selected a universal family and school program from a menu of EBPIs. All families were offered a family-based program in the 6th grade and received one of three school-based programs in 7th-grade. The effectiveness and cost-effectiveness of each school program by itself and with an additional family-based program were assessed using propensity and marginal structural models. This work demonstrates that universal school-based EBPIs can efficiently reduce nonmedical prescription opioid use. Further, findings illustrate that family-based programs may be used to enhance the cost-effectiveness of school-based programs. Universal EBPIs can effectively and efficiently reduce nonmedical prescription opioid use. These programs should be further considered when developing comprehensive responses to this growing national crisis.

**Callous-Unemotional Behavior and Early-Childhood Onset Of Behavior Problems: The Role Of Parental Harshness and Warmth** Waller R, Gardner F, Shaw DS, Dishion TJ, Wilson MN, Hyde LW. *J Clin Child Adolesc Psychol.* 2014.

Youth with callous-unemotional (CU) behavior are at risk of developing more severe forms of aggressive and antisocial behavior. Previous cross-sectional studies suggest that associations between parenting and conduct problems are less strong when children or adolescents have high levels of CU behavior, implying lower malleability of behavior compared to low-CU children. The current study extends previous findings by examining the moderating role of CU behavior on associations between parenting and behavior problems in a very young sample, both concurrently and longitudinally, and using a variety of measurement methods. Data were collected from a multi-ethnic, high-risk sample at ages 2 to 4 (364; 49% female). Parent-reported CU behavior was assessed at age 3 using a previously validated measure (Hyde et al., 2013). Parental harshness was coded from observations of parent-child interactions and parental warmth was coded from 5-min speech samples. In this large and young sample, CU behavior moderated cross-sectional correlations between parent-reported and observed warmth and child behavior problems. However, in cross-sectional and longitudinal models testing parental harshness, and longitudinal models testing warmth, there was no moderation by CU behavior. The findings are in line with recent literature suggesting parental warmth may be important to child behavior problems at high levels of CU behavior. In general, however, the results of this study contrast with much of the extant literature and suggest that in young children, affective aspects of parenting appear to be related to emerging behavior problems, regardless of the presence of early CU behavior.

**Replication Test Of Early Universal Prevention Effects On Young Adult Substance Misuse** Spoth R, Trudeau L, Redmond C, Shin C. *J Consult Clin Psychol.* 2014.

For many substances, more frequent and problematic use occurs in young adulthood; these types of use are predicted by the timing of initiation during adolescence. The authors replicated and

extended an earlier study examining whether delayed substance initiation during adolescence, resulting from universal preventive interventions implemented in middle school, reduces problematic use in young adulthood. Participants were middle school students from 36 Iowa schools randomly assigned to the Strengthening Families Program: For Parents and Youth 10-14 (Molgaard, Spoth, & Redmond, 2000) plus Life Skills Training (LST; Botvin, 1995, 2000), LST-only, or a control condition. Self-report questionnaires were collected at 11 time points, including 4 during young adulthood. The intercept (average level) and rate of change (slope) in young adult frequency measures (drunkenness, alcohol-related problems, cigarettes, and illicit drugs) across ages 19-22 were modeled as outcomes influenced by growth factors describing substance initiation during adolescence. Analyses entailed testing a 2-step hierarchical latent growth curve model; models included the effects of baseline risk, intervention condition assignment, and their interaction. Analyses showed significant indirect intervention effects on the average levels of all young adult outcomes, through effects on adolescent substance initiation growth factors, along with Intervention Risk interaction effects favoring the higher risk subsample. Additional direct effects on young adult use were observed in some cases. Relative reduction rates were larger for the higher risk subsample at age 22, ranging from 5.8% to 36.4% on outcomes showing significant intervention effects. The authors conclude that universal preventive interventions implemented during early adolescence have the potential to decrease the rates of substance use and associated problems into young adulthood.

### **Coercive Family Process and Early-onset Conduct Problems From Age 2 To School Entry**

Smith JD, Dishion TJ, Shaw DS, Wilson MN, Winter CC, Patterson GR. *Dev Psychopathol.* 2014; 1-16.

The emergence and persistence of conduct problems (CPs) during early childhood is a robust predictor of behavior problems in school and of future maladaptation. In this study the authors examined the reciprocal influences between observed coercive interactions between children and caregivers, oppositional and aggressive behavior, and growth in parent report of early childhood (ages 2-5) and school-age CPs (ages 7.5 and 8.5). Participants were drawn from the Early Steps multisite randomized prevention trial that includes an ethnically diverse sample of male and female children and their families (N = 731). A parallel-process growth model combining latent trajectory and cross-lagged approaches revealed the amplifying effect of observed coercive caregiver-child interactions on children's noncompliance, whereas child oppositional and aggressive behaviors did not consistently predict increased coercion. The slope and initial levels of child oppositional and aggressive behaviors and the stability of caregiver-child coercion were predictive of teacher-reported oppositional behavior at school age. Families assigned to the Family Check-Up condition had significantly steeper declines in child oppositional and aggressive behavior and moderate reductions in oppositional behavior in school and in coercion at age 3. Results were not moderated by child gender, race/ethnicity, or assignment to the intervention condition. The implications of these findings are discussed with respect to understanding the early development of CPs and to designing optimal strategies for reducing problem behavior in early childhood with families most in need.

### **Is Serotonin Transporter Genotype Associated With Epigenetic Susceptibility Or Vulnerability? Examination Of the Impact Of Socioeconomic Status Risk On African American Youth**

Beach SRH, Brody GH, Lei MK, Kim S, Cui J, Philibert RA. *Dev Psychopathol.* 2014; 26(2): 289-304.

The authors hypothesized that presence of the short allele in the promoter region of the serotonin transporter would moderate the effect of early cumulative socioeconomic status (SES) risk on

epigenetic change among African American youth. Contrasting hypotheses regarding the shape of the interaction effect were generated using vulnerability and susceptibility frameworks and applied to data from a sample of 388 African American youth. Early cumulative SES risk assessed at 11-13 years based on parent report interacted with presence of the short allele to predict differential methylation assessed at age 19. Across multiple tests, a differential susceptibility perspective rather than a diathesis-stress framework best fit the data for genes associated with depression, consistently demonstrating greater epigenetic response to early cumulative SES risk among short allele carriers. A pattern consistent with greater impact among short allele carriers also was observed using all cytosine nucleotide-phosphate-guanine nucleotide sites across the genome that was differentially affected by early cumulative SES risk. The authors conclude that the short allele is associated with increased responsiveness to early cumulative SES risk among African American youth, leading to epigenetic divergence for depression-related genes in response to exposure to heightened SES risk among short allele carriers in a "for better" or "for worse" pattern.

### **Understanding the Link Between Early Sexual Initiation and Later Sexually Transmitted Infection: Test and Replication In Two Longitudinal Studies**

Epstein M, Bailey JA, Manhart LE, Hill KG, Hawkins JD, Haggerty KP, Catalano RF. *J Adolesc Health*. 2014; 54(4): 435-441.e2. Age at sexual initiation is strongly associated with sexually transmitted infections (STI); yet, prevention programs aiming to delay sexual initiation have shown mixed results in reducing STI. This study tested three explanatory mechanisms for the relationship between early sexual debut and STI: number of sexual partners, individual characteristics, and environmental antecedents. A test-and-replicate strategy was employed using two longitudinal studies: the Seattle Social Development Project (SSDP) and Raising Healthy Children (RHC). Childhood measures included pubertal age, behavioral disinhibition, and family, school, and peer influences. Alcohol use and age of sexual debut were measured during adolescence. Lifetime number of sexual partners and having sex under the influence were measured during young adulthood. Sexually transmitted infection diagnosis was self-reported at age 24. Early sex was defined as debut at <15 years. Path models were developed in SSDP evaluating relationships between measures, and were then tested in RHC. The relationship between early sex and STI was fully mediated by lifetime sex partners in SSDP, but only partially in RHC, after accounting for co-occurring factors. Behavioral disinhibition predicted early sex, early alcohol use, number of sexual partners, and sex under the influence, but had no direct effect on STI. Family management protected against early sex and early alcohol use, whereas antisocial peers exacerbated the risk. Early sexual initiation, a key mediator of STI, is driven by antecedents that influence multiple risk behaviors. Targeting co-occurring individual and environmental factors may be more effective than discouraging early sexual debut and may concomitantly improve other risk behaviors.

### **Effects Of Mindfulness-Oriented Recovery Enhancement On Reward Responsiveness and Opioid Cue-Reactivity**

Garland EL, Froeliger B, Howard MO. *Psychopharmacology (Berl)*. 2014. Dysregulated reward processing is a hallmark feature of drug addiction; however, scant research has evaluated restructuring reward processing in the context of addiction treatment. The authors examined effects of Mindfulness-Oriented Recovery Enhancement (MORE) on reward responsiveness (RR) and opioid cue-reactivity in a sample of chronic pain patients with opioid use problems. They previously reported that MORE decreased pain, opioid misuse, and craving relative to a social support control group (SG). Here, they examined whether these outcomes were linked to changes in RR in a subset of participants. Participants were chronic pain patients (71 women, age 46.6, 13.9) who received MORE (20) or SG (29). RR was measured before and after 8 weeks of treatment via heart rate (HR) and heart rate variability (HRV) responses during a dot probe task that

included opioid-related, pain-related, and natural reward stimuli, as well as craving ratings. The MORE group, who reported decreased opioid misuse and opioid craving during treatment, evidenced less subjective opioid cue-reactivity, greater HR decelerations, and greater increases in HRV to all cues after treatment compared to the SG; HR and HRV effects were most pronounced for natural reward cues. Within the MORE group, HR deceleration to natural reward cues was correlated with increased subjective arousal to the cues, whereas HR deceleration to opioid cues was correlated with decreased subjective arousal. Effects of MORE on craving were mediated by enhanced RR. Results suggest that during treatment with MORE, cardiac-autonomic responsiveness to non-drug reward increases, while reactivity to opioid reward decreases. Studies are needed to discern whether changes in RR were a result or a determinant of reductions in opioid misuse and craving. RR may play a role in addiction treatment.

**General and Substance-specific Predictors Of Young Adult Nicotine Dependence, Alcohol Use Disorder, and Problem Behavior: Replication In Two Samples** Bailey JA, Samek DR, Keyes MA, Hill KG, Hicks BM, McGue M, Iacono WG, Epstein M, Catalano RF, Haggerty KP, Hawkins JD. *Drug Alcohol Depend.* 2014; 138: 161-8.

This paper presents two replications of a heuristic model for measuring environment in studies of gene-environment interplay in the etiology of young adult problem behaviors. Data were drawn from two longitudinal, U.S. studies of the etiology of substance use and related behaviors: the Raising Healthy Children study (RHC; N=1040, 47% female) and the Minnesota Twin Family Study (MTFS; N=1512, 50% female). RHC included a Pacific Northwest, school-based, community sample. MTFS included twins identified from state birth records in Minnesota. Both studies included commensurate measures of general family environment and family substance-specific environments in adolescence (RHC ages 10-18; MTFS age 18), as well as young adult nicotine dependence, alcohol and illicit drug use disorders, HIV sexual risk behavior, and antisocial behavior (RHC ages 24, 25; MTFS age 25). Results from the two samples were highly consistent and largely supported the heuristic model proposed by Bailey et al. (2011). Adolescent general family environment, family smoking environment, and family drinking environment predicted shared variance in problem behaviors in young adulthood. Family smoking environment predicted unique variance in young adult nicotine dependence. Family drinking environment did not appear to predict unique variance in young adult alcohol use disorder. Organizing environmental predictors and outcomes into general and substance-specific measures provides a useful way forward in modeling complex environments and phenotypes. Results suggest that programs aimed at preventing young adult problem behaviors should target general family environment and family smoking and drinking environments in adolescence.

**Factors That Predict Financial Sustainability Of Community Coalitions: Five Years Of Findings From The PROSPER Partnership Project** Greenberg MT, Feinberg ME, Johnson LE, Perkins DF, Welsh JA, Spoth RL. *Prev Sci.* 2014.

This study is a longitudinal investigation of the Promoting School-community-university Partnerships to Enhance Resilience (PROSPER) partnership model designed to evaluate the level of sustainability funding by community prevention teams, including which factors impact teams; generation of sustainable funding. Community teams were responsible for choosing, implementing with quality, and sustaining evidence-based programs (EBPs) intended to reduce substance misuse and promote positive youth and family development. Fourteen US rural communities and small towns were studied. Data were collected from PROSPER community team members (164) and prevention coordinators (10) over a 5-year period. Global and specific aspects of team functioning were assessed over six waves. Outcome measures were the total funds (cash and in-kind) raised to

implement prevention programs. All 14 community teams were sustained for the first 5 years. However, there was substantial variability in the amount of funds raised, and these differences were predicted by earlier and concurrent team functioning and by team sustainability planning. Given the sufficient infrastructure and ongoing technical assistance provided by the PROSPER partnership model, local sustainability of EBPs is achievable.

**The Family Check-Up and Service Use In High-Risk Families Of Young Children: A Prevention Strategy With A Bridge To Community-Based Treatment** Leijten P, Shaw DS, Gardner F, Wilson MN, Matthys W, Dishion TJ. *Prev Sci.* 2014.

Integration of empirically supported prevention programs into existing community services is a critical step toward effecting sustainable change for the highest-risk members in a community. The authors examined if the Family Check-Up-known to reduce disruptive behavior problems in young children-can provide a bridge to the use of community treatment services among high-risk indigent families. The study's 731 income-eligible families with a 2-year-old child were screened and randomized to the Family Check-Up (FCU) intervention or a control condition. Families were provided yearly FCUs from age 2 through ages 5. Regression analyses on families; service use at child age 7.5 revealed increased service use, compared with that of the control group. Child disruptive behavior and socioeconomic status moderated the effect of the intervention on service use. Families who reported higher levels of disruptive child behavior and lower socioeconomic status showed more service use, suggesting the intervention increased service use among the highest-risk families. Greater use of community services did not mediate the effect of the FCU on reduced oppositional-defiant child behavior. Implications of these findings for the design and ecology of community treatment services in the context of evidence-based practices are discussed.

**Putting Theory To the Test: Examining Family Context, Caregiver Motivation, and Conflict In The Family Check-Up Model** Fosco GM, Van Ryzin M, Stormshak EA, Dishion TJ. *Dev Psychopathol.* 2014; 26(2): 305-18.

This study examined contextual factors (caregiver depression, family resources, ethnicity, and initial levels of youth problem behavior) related to the effectiveness of the Family Check-Up (FCU) and evaluated family processes as a mediator of FCU intervention response and adolescent antisocial behavior. The authors followed a sample of 180 ethnically diverse youths of families who engaged in the FCU intervention. Family data were collected as part of the FCU assessment, and youth data were collected over 4 years, from sixth through ninth grade. Findings indicated that caregiver depression and minority status predicted greater caregiver motivation to change. In turn, caregiver motivation was the only direct predictor of FCU intervention response during a 1-year period. Growth in family conflict from sixth through eighth grade mediated the link between FCU response and ninth-grade antisocial behavior. This study explicitly tested core aspects of the FCU intervention model and demonstrated that caregiver motivation is a central factor that underlies family response to the FCU. The study also provided support for continued examination of family process mechanisms that account for enduring effects of the FCU and other family-centered interventions.

**A Web-based, Health Promotion Program For Adolescent Girls and Their Mothers Who Reside In Public Housing** Schwinn TM, Schinke S, Fang L, Kandasamy S. *Addict Behav.* 2014; 39(4): 757-60.

This study tested a brief web-based, family-involvement health promotion program aimed at drug use, physical activity, and nutrition for adolescent girls, aged 10 to 12 years, who reside in public housing. Separately, girls (n=67) and their mothers (n=67) completed baseline measures online.

Following baseline, 36 randomly assigned mother-daughter dyads jointly completed a 3-session, health promotion program online. Subsequently, all girls and mothers separately completed posttest and 5-month follow-up measures. Attrition at posttest and 5-month follow-up measures was 3% and 9%, respectively. At posttest, intervention-arm girls, relative to control-arm girls, reported greater mother-daughter communication and parental monitoring. Intervention-arm mothers reported greater mother-daughter communication and closeness as well as increased vegetable intake and physical activity. At 5-month follow-up, intervention-arm girls and mothers, relative to those in the control arm, reported greater levels of parental monitoring. Intervention-arm girls also reported greater mother-daughter communication and closeness, reduced stress, greater refusal skills, and increased fruit intake. Findings indicate the potential of a brief, web-based program to improve the health of low-income girls and their mothers.

**Item-based Analysis Of Delayed Reward Discounting Decision Making** Gray JC, Amlung MT, Acker JD, Sweet LH, MacKillop J. *Behav Processes*. 2014; 103: 256-60.

Delayed reward discounting (DRD) is a behavioral economic index of time preference, referring to how much an individual devalues a reward based on its delay in time, and has been linked to a wide array of health behaviors. It is commonly assessed using a task that asks participants to make dichotomous choices between two monetary rewards, one available immediately and the other after a delay. This study sought to shorten an extended iterative DRD assessment to increase its versatility and efficiency. Data were drawn from two young adult samples, an exploratory sample (N=130) and a confirmatory sample (N=247). In the exploratory sample, eight items were identified as predicting the majority of the variance in the full task area under the curve (AUC) ( $R(2)=.821$ ;  $p<.001$ ). In the confirmatory sample, the same eight items similarly predicted the majority of variance in the full task AUC ( $R(2)=.844$ ,  $p<.001$ ). These results provide initial support for the validity of a brief 8-item assessment of DRD. Priorities for further validation and potential applications are discussed.

**Teacher, Parent, and Peer Reports Of Early Aggression As Screening Measures For Long-term Maladaptive Outcomes: Who Provides the Most Useful Information?** Clemans KH,

Musci RJ, Leoutsakos J-MS, Ialongo NS. *J Consult Clin Psychol*. 2014; 82(2): 236-47.

This study compared the ability of teacher, parent, and peer reports of aggressive behavior in early childhood to accurately classify cases of maladaptive outcomes in late adolescence and early adulthood. Weighted kappa analyses determined optimal cut points and relative classification accuracy among teacher, parent, and peer reports of aggression assessed for 691 students (54% male; 84% African American and 13% White) in the fall of first grade. Outcomes included antisocial personality, substance use, incarceration history, risky sexual behavior, and failure to graduate from high school on time. Peer reports were the most accurate classifier of all outcomes in the full sample. For most outcomes, the addition of teacher or parent reports did not improve overall classification accuracy once peer reports were accounted for. Additional gender-specific and adjusted kappa analyses supported the superior classification utility of the peer report measure. The results suggest that peer reports provided the most useful classification information of the 3 aggression measures. Implications for targeted intervention efforts in which screening measures are used to identify at-risk children are discussed.

**Drug Use Trajectories After A Randomized Controlled Trial Of MTFC: Associations With Partner Drug Use** Rhoades KA, Leve LD, Harold GT, Kim H, Chamberlain P. *J Res Adolesc.* 2014; 24(1): 40-54.

Trajectories of drug use were examined in a sample of women with prior juvenile-justice system involvement. One hundred fifty-three young women who participated in a randomized controlled trial of Multidimensional Treatment Foster Care (MTFC) in adolescence were assessed on five occasions over a 24-month period in young adulthood (mean age = 22.29 years at T1). Participants assigned to the MTFC condition during adolescence reported greater decreases in drug use than girls assigned to the treatment as usual (TAU) condition. Partner drug use was significantly associated with women's concurrent drug use, although participants in the MTFC condition were more resilient to partner drug use than in the TAU condition. Implications for drug use prevention and intervention programs during adolescence are discussed.

**Who Uses A Prescription Drug Monitoring Program and How? Insights From A Statewide Survey Of Oregon Clinicians** Irvine JM, Hallvik SE, Hildebran C, Marino M, Beran T, Deyo RA. *J Pain.* 2014.

Prescription drug monitoring programs (PDMP) are relatively new but potentially useful tools to enhance prudent prescribing of controlled substances. However, little is known about the types of clinicians who make most use of PDMPs, how they are incorporated into workflow, or how clinicians and patients respond to the information. The authors therefore surveyed a random sample of Oregon providers, with 1065 respondents. Clinicians in emergency medicine, primary care, and pain and addiction specialties were the largest number of registrants but many frequent prescribers of controlled substances were not registered to use the PDMP. Among users, 95% reported accessing the PDMP when they suspected a patient of abuse or diversion, but fewer than half would check it for every new patient or every time they prescribe a controlled drug. Nearly all PDMP users reported that they discuss worrisome PDMP data with patients; 54% reported making mental health or substance abuse referrals, and 36% reported sometimes discharging patients from the practice. Clinicians reported frequent patient denial or anger, and only occasional requests for help with drug dependence. More research is needed to optimize how clinicians use PDMPs across settings, and how clinicians and patients respond to the data. This study examined differences between PDMP users and non-users and how clinicians in various specialties use PDMPs in practice. A better understanding of effective PDMP use will facilitate access to treatment for patients with pain, while curbing the prescription drug epidemic, and may ultimately reduce abuse, misuse, and overdose death.

**Temporal Trends In Marijuana Attitudes, Availability and Use In Colorado Compared To Non-medical Marijuana States: 2003-11** Schuermeyer J, Salomonsen-Sautel S, Price RK, Balan S, Thurstone C, Min S-J, Sakai JT. *Drug Alcohol Depend.* 2014.

In 2009, policy changes were accompanied by a rapid increase in the number of medical marijuana cardholders in Colorado. Little published epidemiological work has tracked changes in the state around this time. Using the National Survey on Drug Use and Health, the authors tested for temporal changes in marijuana attitudes and marijuana-use-related outcomes in Colorado (2003-11) and differences within-year between Colorado and thirty-four non-medical-marijuana states (NMMS). Using regression analyses, the authors further tested whether patterns seen in Colorado prior to (2006-8) and during (2009-11) marijuana commercialization differed from patterns in NMMS while controlling for demographics. Within Colorado those reporting "great-risk" to using marijuana 1-2 times/week dropped significantly in all age groups studied between 2007-8 and 2010-11 (e.g. from 45% to 31% among those 26 years and older;  $p=0.0006$ ). By 2010-11 past-year

marijuana abuse/dependence had become more prevalent in Colorado for 12-17 year olds (5% in Colorado, 3% in NMMS;  $p=0.03$ ) and 18-25 year olds (9% vs. 5%;  $p=0.02$ ). Regressions demonstrated significantly greater reductions in perceived risk (12-17 year olds,  $p=0.005$ ; those 26 years and older,  $p=0.01$ ), and trend for difference in changes in availability among those 26 years and older and marijuana abuse/dependence among 12-17 year olds in Colorado compared to NMMS in more recent years (2009-11 vs. 2006-8). These results show that commercialization of marijuana in Colorado has been associated with lower risk perception. Evidence is suggestive for marijuana abuse/dependence. Analyses including subsequent years 2012+ once available, will help determine whether such changes represent momentary vs. sustained effects.

### **Mindfulness-Oriented Recovery Enhancement Ameliorates the Impact Of Pain On Self-Reported Psychological and Physical Function Among Opioid-Using Chronic Pain Patients**

Garland EL, Thomas E, Howard MO. *J Pain Symptom Manage*. 2014.

Chronic pain impacts one-third of the U.S. population, and its effects are debilitating for individuals and costly to the medical system. Although opioids are commonly prescribed to address chronic pain, they confer risk for misuse and addiction, and may not fully restore life function - particularly with regard to psychosocial factors. Because of the multiplicity of impacts that chronic pain may have on daily functioning, broad-spectrum behavioral interventions are needed. The purpose of this study was to conduct follow-up analyses from a pilot randomized controlled trial of Mindfulness-Oriented Recovery Enhancement (MORE) to assess specific effects of MORE on various bio psychosocial aspects of pain-related impairment. Chronic pain patients ( $N=115$ ; mean age 48 to 14 years; 68% female) were randomly assigned to either eight weeks of MORE or to a support group (SG). Domains of pain-related functional interference were measured with the Brief Pain Inventory at pre- and post-treatment, and at a three-month follow-up. Treatment effects were analyzed with multivariate intention-to-treat models. MORE participants reported significantly greater reductions in functional interference than SG participants at post-treatment across all domains, including: general activity, mood, walking ability, normal work, relationships, sleep, and enjoyment of life. These effects were largely maintained by the three-month follow-up; however, general activity level and walking ability were no longer significant, indicating differential long-term effects between physiological and psychological functioning. Findings demonstrate preliminary efficacy of MORE as a treatment for pain-related functional impairments, and suggest that effects may be more pronounced and durable for aspects of psychological function.

### **Preventing High-Risk Sexual Behavior In Early Adulthood With Family Interventions In Adolescence: Outcomes and Developmental Processes**

Caruthers AS, Van Ryzin MJ, Dishion TJ. *Prevention Science* 2014; 15 (S1), S59-S69. doi: 10.1007/s11121-013-0383-9.

Adolescent study participants who engaged in a brief, family-centered intervention (the Family Check-Up, FCU) were later assessed for the intervention's effects on high-risk sexual behavior (HRSB) in early adulthood (age 22). Participants ( $N = 998$  adolescents and their families) were randomly assigned to a family-centered intervention in sixth grade and were offered a gated, multilevel intervention that included (a) a school-based family resource center, (b) the FCU, and (c) more intensive, family-based treatment. All services were voluntary, but high-risk families were actively recruited into the FCU. Approximately 23% of the intervention families engaged in the FCU and approximately 18% engaged in more intensive treatment. Using an intent-to-treat design, we found that the direct effect of the FCU on HRSB was not significant; however, an analysis of the developmental processes indicated that intervention families demonstrated improved family relationship quality when compared to control families, which in turn resulted in lower levels of HRSB in early adulthood. Furthermore, the significant effect of family relationship quality on

HRSB was mediated by differences in parental monitoring and early sexual activity, and these effects varied as a function of gender and ethnicity. Indirect effects of the FCU on HRSB were significant via multiple different pathways. The implications of these findings for enhancing the impact of family-centered interventions are discussed.

### **Does Early Intervention Prevent Health-Risking Sexual Behaviors Related To HIV/AIDS?**

Kellam SG, Wang W, Mackenzie AC, Brown CH, Ompad DC, Or F, Ialongo NS, Poduska JM, Windham A. *Prevention Science* 2014; 15 (S1), 1-5. DOI 10.1007/s11121-013-0455-x.

The Good Behavior Game (GBG), a method of teacher classroom behavior management, was tested in first- and second-grade classrooms in 19 Baltimore City Public Schools beginning in the 1985-1986 school year. The intervention was directed at the classroom as a whole to socialize children to the student role and reduce aggressive, disruptive behaviors, confirmed antecedents of a profile of externalizing problem outcomes. This article reports on the GBG impact on the courses and interrelationships among aggressive, disruptive behavior through middle school, risky sexual behaviors, and drug abuse and dependence disorders through ages 19-21. In five poor to lower-middle class, mainly African American urban areas, classrooms within matched schools were assigned randomly to either the GBG intervention or the control condition. Balanced assignment of children to classrooms was made, and teachers were randomly assigned to intervention or control. Analyses involved multilevel growth mixture modeling. By young adulthood, significant GBG impact was found in terms of reduced high-risk sexual behaviors and drug abuse and dependence disorders among males who in first grade and through middle school were more aggressive, disruptive. A replication with the next cohort of first-grade children with the same teachers occurred during the following school year, but with minimal teacher mentoring and monitoring. Findings were not significant but generally in the predicted direction. A universal classroom-based prevention intervention in first- and second-grade classrooms can reduce drug abuse and dependence disorders and risky sexual behaviors.

### **The Onset Of STI Diagnosis Through Age 30: Results From The Seattle Social Development Project Intervention**

Hill KG, Bailey JA, Hawkins JD, Catalano RF, Kosterman R, Oesterle S, Abbott RD. *Prevention Science* 2014; 15 (S1), S19-S32. doi: 10.1007/s11121-013-0382-x.

The objectives of this study were to examine (1) whether the onset of sexually transmitted infections (STI) through age 30 differed for youths who received a social developmental intervention during elementary grades compared to those in the control condition; (2) potential social-developmental mediators of this intervention; and (3) the extent to which these results differed by ethnicity. A nonrandomized controlled trial followed participants to age 30, 18 years after the intervention ended. Three intervention conditions were compared: a full-intervention group, assigned to intervention in grades 1 through 6; a late intervention group, assigned to intervention in grades 5 and 6 only; and a no-treatment control group. Eighteen public elementary schools serving diverse neighborhoods including high-crime neighborhoods of Seattle are the setting of the study. Six hundred eight participants in three intervention conditions were interviewed from age 10 through 30. Interventions include teacher training in classroom instruction and management, child social and emotional skill development, and parent workshops. Outcome is the cumulative onset of participant report of STI diagnosis. Adolescent family environment, bonding to school, antisocial peer affiliation, early sex initiation, alcohol use, cigarette use, and marijuana use were tested as potential intervention mechanisms. Complementary log-log survival analysis found significantly lower odds of STI onset for the full-intervention compared to the control condition. The lowering of STI onset risk was significantly greater for African Americans and Asian Americans compared to European Americans. Family environment, school bonding, and delayed

initiation of sexual behavior mediated the relationship between treatment and STI hazard. A universal intervention for urban elementary school children, focused on classroom management and instruction, children's social competence, and parenting practices may reduce the onset of STI through age 30, especially for African Americans.

**Universal Family-Focused Intervention With Young Adolescents: Effects On Health-Risking Sexual Behaviors and STDs Among Young Adults** Spoth R, Clair S, Trudeau L. *Prevention Science* 2014; 15 (S1), S47-58. doi: 10.1007/s11121-012-0321-2.

Considering the prevalence and consequences of health-risking sexual behaviors (HRSBs) and STDs among young adults, their prevention is a public health priority. Emerging etiological and prevention outcome literatures suggested study of the long-term effects of universal family-focused interventions on young adult HRSBs and STDs. Although earlier studies have demonstrated intervention impact on adolescent substance misuse, no study has examined universal family-focused intervention effects on young adult HRSBs and STDs via reductions in adolescent misuse. Sixth grade students and their families enrolled in 33 rural Midwestern schools were randomly assigned to experimental conditions. Self-report questionnaires provided data at pretest (Ns = 238, 221, and 208 for the Iowa Strengthening Families Program [ISFP], Preparing for the Drug Free Years [PDFY], and control groups, respectively), with seven data points through young adulthood (age 21). In latent growth modeling, three young adult HRSB measures (number of sexual partners, condom use, substance use with sex) and lifetime STDs were specified as distal outcomes mediated by adolescent substance initiation growth factors (average level and rate of change). Results showed that the models fit the data and, except for condom use, there were significant indirect effects, with a higher frequency of significant findings for ISFP. The model additions of direct intervention effects on young adult outcomes generally were not supported, consistent with a model positing that long-term intervention effects on young adult HRSBs and STDs outcomes are indirect. As an indication of the practical significance of long-term effects, analyses revealed relative reduction rates ranging from 6% to 46% for significant outcomes.

**A Longitudinal Analysis Of Cigarette Prices In Military Retail Outlets** Haddock CK, Hyder ML, Poston WSC, Jahnke SA, Williams LN, Lando H. *Am J Public Health*. 2014; 104(4): e82-7. The authors conducted a longitudinal assessment of tobacco pricing in military retail outlets, including trends within each service branch. They determined the price of a single pack of Marlboro Red cigarettes at military retail stores located in the continental United States, Alaska, and Hawaii and at their nearest Walmart's in spring 2011 and 2013 (128 for pairs available at both assessments). The average difference between cigarettes sold in military retail outlets and Walmart's decreased from 24.5% in 2011 to 12.5% in 2013. The decrease was partially attributable to significant price decreases at Walmart's. The largest increases in cigarette prices occurred on naval installations. Potential savings at stores on several installations remained substantial in 2013; the largest approached \$6 per pack. Stores on 17 military installations decreased cigarette prices during the study period. Tobacco can be purchased in military retail stores at substantial savings over civilian stores. If tobacco pricing is to cease to be an incentive for use among personnel, a revised military tobacco pricing policy is needed.

**Patterns Of Drug and Alcohol Use Associated With Lifetime Sexual Re-victimization and Current Posttraumatic Stress Disorder Among Three National Samples Of Adolescent, College, and Household-residing Women**

Walsh K, Resnick HS, Danielson CK, McCauley JL, Saunders BE, Kilpatrick DG. *Addict Behav.* 2014; 39(3): 684-9.

Sexual re-victimization (experiencing 2 or more rapes) is prevalent and associated with increased risk for posttraumatic stress disorder (PTSD) and substance use. However, no national epidemiologic studies have established the prevalence or relative odds of a range of types of substance use as a function of sexual victimization history and PTSD status. Using three national female samples, the current study examined associations between sexual re-victimization, PTSD, and past-year substance use. Participants were 1763 adolescent girls, 2000 college women, and 3001 household-residing women. Rape history, PTSD, and use of alcohol, marijuana, other illicit drugs, and non-medical prescription drugs were assessed via structured telephone interviews of U.S. households and colleges in 2005-2006. Chi-square and logistic regression were used to estimate the prevalence and odds of past-year substance use. Relative to single and non-victims: Re-victimized adolescents and household-residing women reported more other illicit and non-medical prescription drug use; re-victimized college women reported more other illicit drug use. Past 6-month PTSD was associated with increased odds of drug use for adolescents, non-medical prescription drug use for college women, and all substance use for household-residing women. Re-victimization and PTSD were associated with more deviant substance use patterns across samples, which may reflect self-medication with substances. Findings also could be a function of high-risk environment or common underlying mechanisms. Screening and early intervention in pediatric, primary care, and college clinics may prevent subsequent rape, PTSD, and more severe substance use.

**Hazards Of New Media: Youth's Exposure To Tobacco Ads/promotions** Cavazos-Rehg PA, Krauss MJ, Spitznagel EL, Gruzza RA, Bierut LJ. *Nicotine Tob Res.* 2014; 16(4): 437-44.

A gap in knowledge exists about the youth's exposure to pro tobacco campaigns via new electronic media outlets. In response, the authors use national data to delineate the associations between tobacco ads/promotions delivered through new media outlets (i.e., social network sites and text messages) and youth attitudes/beliefs about tobacco and intent to use (among youth who had not yet used tobacco). Data were derived from the 2011 National Youth Tobacco Survey, a nationally representative sample of U.S. youth enrolled in both public and private schools (N = 15,673). Logistic regression models were used to examine associations between demographic characteristics and reported exposure to tobacco ads/promotions via social networking sites and text messages. Logistic regression models were also used to investigate associations between exposure tobacco ads/promotions and attitudes toward tobacco. The authors found that highly susceptible youth (i.e., minorities, very young youth, and youth who have not yet used tobacco) have observed tobacco ads/promotions on social networking sites and text messages. These youth are more likely to have favorable attitudes toward tobacco, including the intention to use tobacco among those who had not yet used tobacco. These findings underscore the need for policy strategies to more effectively monitor and regulate tobacco advertising via new media outlets.

**Early Life Emotional Neglect and HIV Risk Taking Among Men Using The Internet To Find Other Men For Unprotected Sex** Klein H. *Child Abuse Negl.* 2014; 38(3): 434-44.

Using a Syndemics Theory conceptual model, this study examines the relationship between emotional neglect experiences during childhood and/or adolescence and involvement in HIV risk taking in a sample of adult men who actively seek partners for unprotected sex via the Internet. The study was based on a national random sample of 332 MSM who use the Internet to seek men with whom they can engage in unprotected sex. Data collection was conducted via telephone interviews

between January 2008 and May 2009. Structural equation analysis was undertaken to examine the specific nature of the relationships involved in understanding HIV risk practices. Emotional neglect was highly prevalent among the men participating in this study. Emotional neglect experiences were not found to be related directly to involvement in HIV risk taking in adulthood. Emotional neglect was found to be an important variable in the overall structural equation. Its effect on HIV risk taking was indirect, operating principally by having a negative impact upon self-esteem, which in turn had a negative effect on attitudes toward condom use, which in turn were related strongly and directly to risk taking. Childhood experiences with emotional neglect are relevant to understanding HIV risk practices among MSM in adulthood, but the relationship is not as simple as usually conceptualized. Rather, emotional neglect appears to impact risk taking indirectly, through its effects on mental health functioning, which in turn affects risk-related attitudes.

**Trajectories Of Risk For Early Sexual Activity and Early Substance Use In The Fast Track Prevention Program**

Conduct Problems Prevention Research Group. *Prevention Science* 2014; 15 (S1), S31-S46. doi: 10.1007/s11121-012-0328-8.

Children who exhibit early-starting conduct problems are more likely than their peers to initiate sexual activity and substance use at an early age, experience pregnancy, and contract a sexually-transmitted disease [STD], placing them at risk for HIV/AIDS. Hence, understanding the development of multi-problem profiles among youth with early-starting conduct problems may benefit the design of prevention programs. In this study, 1,199 kindergarten children (51% African American; 47% European American; 69% boys) over-sampled for high rates of aggressive-disruptive behavior problems were followed through age 18. Latent class analyses (LCA) were used to define developmental profiles associated with the timing of initiation of sexual activity, tobacco and alcohol/drug use and indicators of risky adolescent sex (e.g. pregnancy and STD). Half of the high-risk children were randomized to a multi-component preventive intervention (Fast Track). The intervention did not significantly reduce membership in the classes characterized by risky sex practices. However, additional analyses examined predictors of poor outcomes, which may inform future prevention efforts.

**Sex Risk Behavior Among Adolescent and Young Adult Children Of Opiate Addicts: Outcomes From The Focus On Families' Prevention Trial and An Examination Of Childhood and Concurrent Predictors Of Sex Risk Behavior**

Skinner ML, Fleming CB, Haggerty KP, Catalano RF. *Prevention Science* 2014; 15 (S1), S70-S77. doi: 10.1007/s11121-012-0327-9.

This study reports on rates and predictors of sex risk behavior among a sample of adolescent and young adult children of parents enrolled in methadone treatment for opiate addiction. Data are from 151 participants (80 males, 71 females) in the Focus on Families (FOF) project, a randomized trial of a family intervention and a study of the development of at-risk children. The study participants are children of parents enrolled in methadone treatment between 1990 and 1993. Participants were interviewed in 2005 when they ranged in age from 15 to 29 years. In the year prior to the follow-up, 79% of the males and 83% of females were sexually active, 26% of males and 10% of females had more than one partner in the prior year, and 34% of males and 24% of females reported having sex outside of a committed relationship. Twenty-four percent of males and 17% of females met criteria for high-risk sexual behavior, reporting casual or multiple partners in the prior year and inconsistent condom use. Participants in the intervention and control conditions did not differ significantly in terms of any measure of sex risk behavior examined. None of the measures of parent behavior and family processes derived from data at baseline of the FOF study predicted whether participants engaged in high-risk sex. Among measures derived from data collected at long-term follow-up, however, having ever met criteria for substance abuse or dependence predicted greater likelihood of

high-risk sexual behavior, and being married or being in a romantic relationship was associated with lower likelihood of high-risk sexual behavior. The findings point to the important role of committed relationships in regulating sex risk behavior among this population, as well as heightened levels of sex risk behavior associated with substance abuse or dependence.

**A Brief Measure Of Peer Affiliation and Social Acceptance (PASA): Validity In An Ethnically Diverse Sample Of Early Adolescents** Dishion TJ, Kim H, Stormshak EA, O'Neill M. *J Clin Child Adolesc Psychol.* 2014.

The purpose of this study was to conduct a multiagent-multimethod analysis of the validity of a brief measure of deviant peer affiliations and social acceptance (PASA) in young adolescents. Peer relationships are critical to child and adolescent social and emotional development, but currently available measures are tedious and time consuming. The PASA consists of a youth, parent, and teacher report that can be collected longitudinally to study development and intervention effectiveness. This longitudinal study included 998 middle school students and their families. The authors collected the PASA and peer sociometrics data in Grade 7 and a multiagent-multimethod construct of deviant peer clustering in Grade 8. Confirmatory factor analyses of the multiagent-multimethod data revealed that the constructs of deviant peer affiliations and social acceptance and rejection were distinguishable as unique but correlated constructs within the PASA. Convergent, discriminant, concurrent, and predictive validity of the PASA was satisfactory, although the acceptance and rejection constructs were highly correlated and showed similar patterns of concurrent validity. Factor invariance was established for mother reports and for father reports. Results suggest that the PASA is a valid and reliable measure of peer affiliation and of social acceptance among peers during the middle school years and provides a comprehensive yet brief assessment of peer affiliations and social acceptance.

**Observational Measures Of Implementer Fidelity For A School-Based Preventive Intervention: Development, Reliability, and Validity** Cross W, West J, Wyman PA, Schmeelk-Cone K, Xia Y, Tu X, Teisl M, Brown CH, Forgatch M. *Prev Sci.* 2014.

Current measures of implementer fidelity often fail to adequately measure core constructs of adherence and competence, and their relationship to outcomes can be mixed. To address these limitations, the authors used observational methods to assess these constructs and their relationships to proximal outcomes in a randomized trial of a school-based preventive intervention (Rochester Resilience Project) designed to strengthen emotion self-regulation skills in first-third graders with elevated aggressive-disruptive behaviors. Within the intervention group (203), a subsample (76) of students was selected to reflect the overall sample. Implementers were 10 paraprofessionals. Videotaped observations of three lessons from year 1 of the intervention (14 lessons) were coded for each implementer-child dyad on adherence (content) and competence (quality). Using multilevel modeling, the authors examined how much of the variance in the fidelity measures was attributed to implementer and to the child within implementer. Both measures had large and significant variance accounted for by implementer (competence, 68%; adherence, 41%); child within implementer did not account for significant variance indicating that ratings reflected stable qualities of the implementer rather than the child. Raw adherence and competence scores shared 46% of variance (68%). Controlling for baseline differences and age, the amount (adherence) and quality (competence) of program delivered predicted children's enhanced response to the intervention on both child and parent reports after 6 months, but not on teacher report of externalizing behavior. These findings support the use of multiple observations for measuring fidelity and that adherence and competence are important components of fidelity which could be assessed by many programs using these methods.

**Developmental Trajectories Of African American Adolescents' Family Conflict: Differences In Mental Health Problems In Young Adulthood** Choe DE, Stoddard SA, Zimmerman MA. *Dev Psychol.* 2014; 50(4): 1226-32.

Family conflict is a salient risk factor for African American adolescents; mental health problems. No study the authors are aware of has estimated trajectories of their family conflict and whether groups differ in internalizing and externalizing problems during the transition to young adulthood, a critical antecedent in adult mental health and psychopathology. As hypothesized, latent class growth analysis approximated 4 developmental trajectories of family conflict during high school for 681 African American adolescents (49% boys). Trajectory classes differed in anxiety, depressive symptoms, and violent behavior at age 20, supporting expectations that adolescents demonstrating elevated levels and atypical trajectories of family conflict in high school would report greater mental health problems as young adults. Family conflict jeopardizes African American adolescents; transition to young adulthood by contributing to mental health problems.

**VA Health Service Utilization For Homeless and Low-income Veterans: A Spotlight On the VA Supportive Housing (VASH) Program In Greater Los Angeles** Gabrielian S, Yuan AH, Andersen RM, Rubenstein LV, Gelberg L. *Med Care.* 2014; 52(5): 454-61.

The US Department of Housing and Urban Development (HUD)-VA Supportive Housing (VASH) program-the VA's Housing First effort-is central to efforts to end Veteran homelessness. Yet, little is known about health care utilization patterns associated with achieving HUD-VASH housing. The authors compare health service utilization at the VA Greater Los Angeles among: (1) formerly homeless Veterans housed through HUD-VASH (HUD-VASH Veterans); (2) currently homeless Veterans; (3) housed, low-income Veterans not in HUD-VASH; and (4) housed, not low-income Veterans. The authors performed a secondary database analysis of Veterans (n=62,459) who received VA Greater Los Angeles care between October 1, 2010 and September 30, 2011. They described medical/surgical and mental health utilization [inpatient, outpatient, and emergency department (ED)]. They controlled for demographics, need, and primary care use in regression analyses of utilization data by housing and income status. HUD-VASH Veterans had more inpatient, outpatient, and ED use than currently homeless Veterans. Adjusting for demographics and need, HUD-VASH Veterans and the low-income housed Veterans had similar likelihoods of medical/surgical inpatient and outpatient utilization, compared with the housed, not low-income group. Adjusting first for demographics and need (model 1), then also for primary care use (model 2), HUD-VASH Veterans had the greatest decrease in incident rates of specialty medical/surgical, mental health, and ED care from models 1 to 2, becoming similar to the currently homeless, compared with the housed, not low-income group. These findings suggest that currently homeless Veterans underuse health care relative to housed Veterans. HUD-VASH may address this disparity by providing housing and linkages to primary care.

**Time-varying Processes Involved In Smoking Lapse In A Randomized Trial Of Smoking Cessation Therapies** Vasilenko SA, Piper ME, Lanza ST, Liu X, Yang J, Li R. *Nicotine Tob Res.* 2014; 16 Suppl 2: S135-43.

Researchers have increasingly begun to gather ecological momentary assessment (EMA) data on smoking, but new statistical methods are necessary to fully unlock information from such data. In this paper, the authors use a new technique, the logistic time-varying effect model (logistic TVEM), to examine the odds of smoking in the 2 weeks after a quit attempt. Data are from a subsample of participants from a randomized, placebo-controlled trial of smoking cessation pharmacotherapies who achieved initial abstinence (N = 1,106, 58% female). Participants completed up to 4 EMA assessments per day during the 2 weeks after their quit day. Predictors include baseline nicotine

dependence, EMA measures of craving and negative affect, and whether an individual was assigned to a placebo, monotherapy, or combination therapy condition. Time-varying effects of these predictors were estimated using logistic TVEM. Cravings were a significant predictor of smoking throughout the entire 2 weeks post quit, whereas the effect of baseline dependence became non-significant by the second week, and the effect of negative affect increased over time. Individuals in the monotherapy and combination therapy conditions had decreased odds of smoking compared with placebo in the first week post quit, but these differences were non-significant in the second week. Findings suggest that pharmacotherapies are more effective compared with placebo earlier in a quit attempt, when the effect of baseline nicotine dependence on smoking is stronger, whereas the effect of craving and negative affect increased over time. Future cessation therapies may be more successful by providing additional support in the second week after quit attempt

### **Multidimensional Examination Of Impulsivity In Relation To Disordered Gambling**

Mackillop J, Miller JD, Fortune E, Maples J, Lance CE, Campbell WK, Goodie AS. *Exp Clin Psychopharmacol.* 2014; 22(2): 176-85.

Impulsivity has been consistently associated with pathological gambling (PG), but the diversity of definitions and measures of impulsivity has led to ambiguity with regard to which indices are independently relevant. Toward clarifying this relationship, the current study examined indices from an array of commonly used impulsivity measures in relation to PG severity in an adult community sample of frequent gamblers (N = 353). These included both survey assessments and behavioral tasks. Using a factor analytic approach, 4 latent factors were identified among 19 indices and were designated reward sensitivity, punishment sensitivity, delay discounting, and cognitive impulsivity. All 4 latent variables were positively and independently related to PG severity, albeit at a trend level for cognitive impulsivity in a combined model. These findings reveal 4 generally independent domains of impulsivity that are related to PG severity, clarify which assessment measures aggregate in each domain, and illustrate the importance of measurement specificity in studying impulsivity in relation to PG and other psychiatric disorders.

### **Proximal and Time-varying Effects Of Cigarette, Alcohol, Marijuana and Other Hard Drug Use On Adolescent Dating Aggression**

McNaughton Reyes HL, Foshee VA, Bauer DJ, Ennett ST. *J Adolesc.* 2014; 37(3): 281-9.

Although numerous studies have established a link between substance use and adult partner violence, little research has examined the relationship during adolescence and most extant research has not examined multiple substance use types. The current study used hierarchical growth modeling to simultaneously examine proximal (between-person) and time-varying (within-person) relations between cigarette, alcohol, marijuana and hard drug use and physical dating aggression across grades 8 through 12 while controlling for demographic covariates and shared risk factors. Proximal effects of marijuana use on dating aggression were found for girls and proximal effects of hard drug use on dating aggression were found for boys. Time-varying effects were found for alcohol for both boys and girls and for hard drug use for boys only. Overall, findings suggest that alcohol, marijuana and hard drug use predict whether and when adolescents engage in dating aggression and should be targeted by prevention interventions.

### **Friendship Group Position and Substance Use**

Osgood DW, Feinberg ME, Wallace LN, Moody J. *Addict Behav.* 2014; 39(5): 923-33.

This paper examines how an adolescent's position relative to cohesive friendship groups in the school-wide social network is associated with alcohol, tobacco, and marijuana use. The authors extend prior research in this area by refining the categories of group positions, using more extensive

friendship information, applying newer analytic methods to identify friendship groups, and making strategic use of control variables to clarify the meaning of differences among group positions. The authors report secondary analyses of 6th through 9th grade data from the PROSPER study, which include approximately 9500 adolescents each year from 27 school districts and 368 school grade cohort friendship networks. They find that core members of friendship groups were more likely to drink than isolates and liaisons, especially in light of their positive social integration in school, family, and religious contexts. Isolates were more likely to use cigarettes than core members, even controlling for all other factors. Finally, liaisons were more likely to use marijuana than core members.

**Longitudinal Associations Between Experienced Racial Discrimination and Depressive Symptoms In African American Adolescents** English D, Lambert SF, Ialongo NS. *Dev Psychol.* 2014; 50(4): 1190-6.

While recent evidence has indicated that experienced racial discrimination is associated with increased depressive symptoms for African American adolescents, most studies rely on cross-sectional and short-term longitudinal research designs. As a result, the direction and persistence of this association across time remains unclear. This article examines longitudinal associations between experienced racial discrimination and depressive symptoms among a community sample of African American adolescents (N = 504) from Grade 7 to Grade 10, while controlling for multiple alternative causal pathways. Sex was tested as a moderator of the link between experienced racial discrimination and later depressive symptoms. Structural equation modeling revealed that experienced racial discrimination was positively associated with depressive symptoms 1 year later across all waves of measurement. The link between experienced racial discrimination at Grade 7 and depressive symptoms at Grade 8 was stronger for females than males. Findings highlight the role of experienced racial discrimination in the etiology of depressive symptoms for African Americans across early adolescence.

**A Continuum Of Approaches Toward Developing Culturally Focused Prevention Interventions: From Adaptation To Grounding** Okamoto SK, Kulis S, Marsiglia FF, Steiker LKH, Dustman P. *J Prim Prev.* 2014; 35(2): 103-12.

The purpose of this article is to describe a conceptual model of methods used to develop culturally focused interventions. The authors describe a continuum of approaches ranging from non-adapted/surface-structure adapted programs to culturally grounded programs, and present recent examples of interventions resulting from the application of each of these approaches. The model has implications for categorizing culturally focused prevention efforts more accurately, and for gauging the time, resources, and level of community engagement necessary to develop programs using each of the different methods. The model also has implications for funding decisions related to the development and evaluation of programs, and for planning of participatory research approaches with community members.

**Dyadic Coregulation and Deviant Talk In Adolescent Friendships: Interaction Patterns Associated With Problematic Substance Use In Early Adulthood** Piehler TF, Dishion TJ. *Dev Psychol.* 2014; 50(4): 1160-9.

In a sample of 711 ethnically diverse adolescents, the observed interpersonal dynamics of dyadic adolescent friendship interactions were coded to predict early adulthood tobacco, alcohol, and marijuana use. Deviant discussion content within the interactions was coded along with dyadic coregulation (i.e., interpersonal coordination, attention synchrony). Structural equation modeling revealed that, as expected, deviant content in adolescent interactions at age 16-17 years was

strongly predictive of problematic use of tobacco, alcohol, and marijuana at ages 22 and 23. Although dyadic coregulation was not directly predictive of early adulthood substance use, it did moderate the impact of deviant talk within the dyad on future alcohol and marijuana use. For these substances, high levels of dyadic coregulation increased the risk associated with high levels of deviant talk for problematic use in early adulthood. Results held when comparing across genders and across ethnic groups. The results suggest that these interpersonal dynamics are associated with developmental trajectories of risk for or resilience to peer influence processes.

**Gambling and Sexual Behaviors In African-American Adolescents** Martins SS, Lee GP, Kim JH, Letourneau EJ, Storr CL. *Addict Behav.* 2014; 39(5): 854-60.

Late adolescence represents a developmental risk period when many youth become involved in multiple forms of high-risk behaviors with adverse consequences. This study assessed the degree to which two such behaviors, adolescent sexual behaviors and gambling, were associated in a community-based sample with a large African-American presence. Data are derived from a cohort study. This study focuses on 427 African-American participants with complete information on gambling and sexual behaviors by age 18 (72% of original cohort). Gambling involvement and related problems were based on responses to the South Oaks Gambling Screen - Revised for Adolescents. Several questions assessed sexual behaviors, including age of initiation. Multivariable logistic regression models adjusted for demographics, intervention status, impulsivity, depressive and anxiety symptoms, and alcohol and illegal drug use. Almost half of the sample (49%, n=211) had gambled at least once before age 18. More gamblers than non-gamblers had initiated sexual intercourse by age 18 (aOR: 2.29 [1.16, 4.52]). Among those who had initiated sexual activity, more gamblers than non-gamblers with high impulsivity levels at age 13 (vs. low impulsivity levels) had become pregnant or had impregnated someone. Among those who had initiated sexual activity by age 18, more male gamblers had impregnated someone by age 18 as compared to female gamblers becoming pregnant. Gambling and sexual behaviors often co-occur among adolescents. Such findings prompt the need for the inclusion of gambling, an often overlooked risky behavior, in behavioral prevention/intervention programs targeting adolescents.

**Prevalence and Co-occurrence Of Addictive Behaviors Among Former Alternative High School Youth** Sussman S, Arpawong TE, Sun P, Tsai J, Rohrbach LA, Spruijt-Metz D. *J Behav Addict.* 2014; 3(1): 33-40.

Recent work has studied multiple addictions using a matrix measure, which taps multiple addictions through single responses for each type. The present study investigated use of a matrix measure approach among former alternative high school youth (average age = 19.8 years) at risk for addictions. Lifetime and last 30-day prevalence of one or more of 11 addictions reviewed in other work (Sussman, Lisha & Griffiths, 2011) was the primary focus (i.e., cigarettes, alcohol, other/hard drugs, eating, gambling, Internet, shopping, love, sex, exercise, and work). Also, the co-occurrence of two or more of these 11 addictive behaviors was investigated. Finally, the latent class structure of these addictions, and their associations with other measures, was examined. The authors found that ever and last 30-day prevalence of one or more of these addictions was 79.2% and 61.5%, respectively. Ever and last 30-day co-occurrence of two or more of these addictions was 61.5% and 37.7%, respectively. Latent Class Analysis suggested two groups: a generally Non-addicted Group (67.2% of the sample) and a "Work Hard, Play Hard"-addicted Group that was particularly invested in addiction to love, sex, exercise, the Internet, and work. Supplementary analyses suggested that the single-response type self-reports may be measuring the addictions they intend to measure. The authors suggest implications of these results for future studies and the development of prevention

and treatment programs, though much more validation research is needed on the use of this type of measure.

**Historical Trauma As Public Narrative: A Conceptual Review Of How History Impacts Present-day Health** Mohatt NV, Thompson AB, Thai ND, Tebes JK. Soc Sci Med. 2014; 106: 128-36.

Theories of historical trauma increasingly appear in the literature on individual and community health, especially in relation to racial and ethnic minority populations and groups that experience significant health disparities. As a consequence of this rapid growth, the literature on historical trauma comprises disparate terminology and research approaches. This critical review integrates this literature in order to specify theoretical mechanisms that explain how historical trauma influences the health of individuals and communities. The authors argue that historical trauma functions as a public narrative for particular groups or communities that connects present-day experiences and circumstances to the trauma so as to influence health. Treating historical trauma as a public narrative shifts the research discourse away from an exclusive search for past causal variables that influence health to identifying how present-day experiences, their corresponding narratives, and their health impacts are connected to public narratives of historical trauma for a particular group or community. The authors discuss how the connection between historical trauma and present-day experiences, related narratives, and health impacts may function as a source of present-day distress as well as resilience.

**Condom Use Self-efficacy and HIV Risk Practices Among Men Who Use The Internet To Find Male Partners For Unprotected Sex** Klein H. Am J Mens Health. 2014; 8(3): 190-204.

This research examines the levels of condom use self-efficacy in a population of men who have sex with men who are at great risk for contracting/transmitting HIV. It focuses on the relationship between condom use self-efficacy and risk involvement, and examines the factors associated with greater/lower levels of condom use self-efficacy. The data come from a national sample of men, randomly chosen, who used any of 16 websites specifically to identify other men with whom they could engage in unprotected sex. Data were collected between January 2008 and May 2009 from 332 men, via telephone interviews. Multivariate analyses and structural equation modeling were used to test a conceptual model based on syndemics theory. Overall levels of condom use self-efficacy were fairly high, and self-efficacy was related inversely to involvement in HIV risk practices. Six factors were found to be indicative of levels of condom use self-efficacy: the number of drug problems experienced, sexual role identity as a "bottom," not caring about the HIV serostatus of potential sex partners, experiencing childhood maltreatment, having confidence in HIV-related information provided in other men's online profiles, and level of HIV knowledge. Condom use self-efficacy plays an integral role in HIV risk practices among high-risk men who have sex with men. This is true despite the fact that, overall, condom use self-efficacy levels were fairly high in this population.

**Correlates Of Incident Trichomonas Vaginalis Infections Among African American Female Adolescents** Swartzendruber A, Sales JM, Brown JL, Diclemente RJ, Rose ES. Sex Transm Dis. 2014; 41(4): 240-5.

*Trichomonas vaginalis* is the most common curable sexually transmitted infection associated with adverse reproductive health and pregnancy outcomes and may amplify HIV transmission. The objective was to identify correlates of incident *T. vaginalis* infections among African American adolescent girls. Data were collected via audio computer-assisted self-interviews at baseline and every 6 months for 18 months from 701 African American girls (14-20 years) in an HIV prevention

trial. At each assessment, self-collected vaginal swabs were assayed for *T. vaginalis*, *Chlamydia trachomatis*, and *Neisseria gonorrhoea*. Generalized estimating equations assessed associations between incident *T. vaginalis* infection and sociodemographic characteristics, substance use, partner-level factors, sexual risk behaviors, douching, and other sexually transmitted infections. Of 605 (86.3%) participants who completed at least 1 follow-up assessment, an incident *T. vaginalis* infection was detected among 20.0% (n = 121). Factors associated with incident infection in adjusted analysis included the following: cigarette smoking (adjusted odds ratio [AOR], 1.66; 95% confidence interval [CI], 1.04-2.64), using alcohol on an increasing number of days in the past 3 months (AOR, 1.02; 95% CI, 1.00-1.04), acquisition of *C. trachomatis* (AOR, 2.27; 95% CI, 1.40-3.69) or *N. gonorrhoea* (AOR, 5.71; 95% CI, 2.97-11.02), and *T. vaginalis* infection at the previous assessment (AOR, 3.16; 95% CI, 1.96-5.07). Incident *T. vaginalis* infections were common. Strategies to reduce infection rates among this population may include improving partner notification and treatment services. The benefits of rescreening, screening adolescents screened for or infected with *C. trachomatis* or *N. gonorrhoea*, and associations between substance use and *T. vaginalis* acquisition warrant further investigation.

**From Counselor Skill To Decreased Marijuana Use: Does Change Talk Matter?** Barnett E, Moyers TB, Sussman S, Smith C, Rohrbach LA, Sun P, Spruijt-Metz D. *J Subst Abuse Treat.* 2014; 46(4): 498-505.

Client language about change, or change talk, is hypothesized to mediate the relationship between counselor fidelity in motivational interviewing (MI) and drug use outcomes. To investigate this causal chain, this study used data from an MI booster delivered to alternative high school students immediately after a universal classroom-based drug abuse prevention program. One hundred and seventy audio-recorded MI sessions about substance use were coded using the motivational interviewing skill code 2.5. Structural equation modeling showed that percentage of change talk on the part of the client mediated three of the four relationships between MI quality indicators and marijuana outcomes, while percentage of reflections of change talk showed a main effect of counselor skill on marijuana outcomes. Findings support change talk as an active ingredient of MI and provide new empirical support for the micro-skills of MI.

**A Social Network-informed Latent Class Analysis Of Patterns Of Substance Use, Sexual Behavior, and Mental Health: Social Network Study III, Winnipeg, Manitoba, Canada**

Hopfer S, Tan X, Wylie JL. *Am J Public Health.* 2014; 104(5): 834-9.

The authors assessed whether a meaningful set of latent risk profiles could be identified in an inner-city population through individual and network characteristics of substance use, sexual behaviors, and mental health status. Data came from 600 participants in Social Network Study III, conducted in 2009 in Winnipeg, Manitoba, Canada. The authors used latent class analysis (LCA) to identify risk profiles and, with covariates, to identify predictors of class. A 4-class model of risk profiles fit the data best: (1) solitary users reported poly drug use at the individual level, but low probabilities of substance use or concurrent sexual partners with network members; (2) social-all-substance users reported poly drug use at the individual and network levels; (3) social-non injection drug users reported less likelihood of injection drug and solvent use; (4) low-risk users reported low probabilities across substances. Unstable housing, preadolescent substance use, age, and hepatitis C status predicted risk profiles. Incorporation of social network variables into LCA can distinguish important subgroups with varying patterns of risk behaviors that can lead to sexually transmitted and blood borne infections.

**Measuring HIV/AIDS-Related Stigma Across South Africa: A Versatile and Multidimensional Scale** Smith EA, Miller JA, Newsome V, Sofolahan YA, Airhihenbuwa CO. Health Educ Behav. 2014.

Reducing HIV/AIDS-related stigma is critical in the fight against HIV/AIDS. Although national campaigns and prevention programs have been implemented across South Africa to address this critical concern, assessing the impact of these initiatives is difficult as it requires that measurement of HIV/AIDS-related stigma is uniform and comparable nationwide. The appropriateness of existing stigma measures for this task is unclear as measurement of HIV/AIDS-related stigma may be qualitatively different across South Africa's diverse population. The current study assesses a theoretically and culturally informed multidimensional, HIV/AIDS-related stigma scale for measurement invariance across a sample drawn from two culturally distinct South African provinces: Limpopo (n = 597) and Western Cape (n = 598). Results suggest measurement invariance across groups for the HIV/AIDS stigma scale, supporting the scale's integrity and appropriateness for use across diverse populations.

**Assessment Of Mobile Device and SMS Use For Diet and Exercise Information Among Rural Mexican-American Adolescents** Collins JL, Champion JD. J Pediatr Nurs. 2014.

This is a pilot study regarding the use of mobile technology and short message service (SMS) for diet and exercise among rural Mexican American adolescents (RMAA). Authors used convenience sampling to recruit RMAA seeking care at a rural healthcare clinic and conducted three focus groups (n=12). Content analysis was used to identify categories and subcategories. Participants applied diet and exercise information in their lives based on an interaction with community and through the use of mobile devices. Culturally sensitive use of mobile devices and SMS may be a tool to provide rural adolescent populations with resources.

**Typology Of Alcohol Users Based On Longitudinal Patterns Of Drinking** Harrington M, Velicer WF, Ramsey S. Addict Behav. 2014; 39(3): 607-21.

Worldwide, alcohol is the most commonly used psychoactive substance. However, heterogeneity among alcohol users has been widely recognized. This paper presents a typology of alcohol users based on an implementation of idiographic methodology to examine longitudinal daily and cyclic (weekly) patterns of alcohol use at the individual level. A secondary data analysis was performed on the pre-intervention data from a large randomized control trial. A time series analysis was performed at the individual level, and a dynamic cluster analysis was employed to identify homogenous longitudinal patterns of drinking behavior at the group level. The analysis employed 180 daily observations of alcohol use in a sample of 177 alcohol users. The first order autocorrelations ranged from  $-.76$  to  $.72$ , and seventh order autocorrelations ranged from  $-.27$  to  $.79$ . Eight distinct profiles of alcohol users were identified, each characterized by a unique configuration of first and seventh autoregressive terms and longitudinal trajectories of alcohol use. External validity of the profiles confirmed the theoretical relevance of different patterns of alcohol use. Significant differences among the eight subtypes were found on gender, marital status, frequency of drug use, lifetime alcohol dependence, family history of alcohol use and the Short Index of Problems. These findings demonstrate that individuals can have very different temporal patterns of drinking behavior. The daily and cyclic patterns of alcohol use may be important for designing tailored interventions for problem drinkers.

**The Role Of Positive Affect In Pain and Its Treatment** Finan PH, Garland EL. Clin J Pain. 2014. This narrative review summarizes and integrates the available literature on PA and pain to: (1) Provide a brief overview of PA and summarize the key findings that have emerged in the study of PA and chronic pain; (2) Provide a theoretical foundation from which to understand how PA operates in the context of chronic pain; and (3) Highlight how the prevailing psychosocial treatments for chronic pain address PA in the therapeutic context, and offer suggestions for how future treatment development research can maximize the benefit of PA for patients with chronic pain. To that end, we review experimental studies that have assessed the association of evoked PA and pain sensitivity, as well as clinical studies that have assessed the association of naturally occurring PA and clinical pain in the context of chronic pain. The evidence suggests PA influences pain, over and above the influence of NA. We offer an "upward spiral" model of positive affect, resilience and pain self-management, which makes specific predictions that PA will buffer maladaptive cognitive and affective responses to pain, and promote active engagement in valued goals that enhance chronic pain self-management.

**Young Adult Follow-up Of Adolescent Girls In Juvenile Justice Using The Columbia Suicide Severity Rating Scale** Kerr DCR, Gibson B, Leve LD, Degarmo DS. Suicide Life Threat Behav. 2014; 44(2): 113-29.

This study focused on the reliability and validity of the Columbia Suicide Severity Scale (C-SSRS). Severely delinquent adolescent girls (166) participated in a treatment trial and repeated assessments over time. Lifetime suicide attempt history was measured using the C-SSRS in early adulthood (144; 7-12 years post baseline). Non clinician raters showed strong interpreter reliability using the C-SSRS. Self-reports, caseworker reports, and caregiver reports of girls; suicide attempt histories collected at baseline correlated with adult participants; recollections of their baseline attempt histories. Suicidal ideation measured prospectively across a 7- to -12-year period was associated with retrospectively reported suicide attempt across the same period.

**Barriers To Drug Use Behavior Change Among Primary Care Patients In Urban United States Community Health Centers** Padwa H, Ni Y-M, Barth-Rogers Y, Arangua L, Andersen R, Gelberg L. Subst Use Misuse. 2014; 49(6): 743-51.

In 2011 and 2012, 147 patients in urban United States Community Health Centers who misused drugs, but did not meet criteria for drug dependence, received a brief intervention as part of a National Institute on Drug Abuse-funded clinical trial of a screening and brief intervention protocol. Potential study participants were identified using the World Health Organization (WHO) Alcohol, Smoking, and Substance Involvement Screening Test. Data gathered during brief interventions were analyzed using grounded theory strategies to identify barriers patients believed inhibited drug use behavior change. Numerous perceived barriers to drug use behavior change were identified. Study implications and limitations are discussed.

## **BEHAVIORAL AND INTEGRATIVE TREATMENT RESEARCH**

**Parallel Demand-withdraw Processes in Family Therapy for Adolescent Drug Abuse** Rynes KN, Rohrbaugh MJ, Lebensohn-Chialvo F, Shoham V. *Psychol Addict Behav.* 2014 Jun; 28(2): 420-30.

Isomorphism, or parallel process, occurs in family therapy when patterns of therapist-client interaction replicate problematic interaction patterns within the family. This study investigated parallel demand-withdraw processes in brief strategic family therapy (BSFT) for adolescent drug abuse, hypothesizing that therapist-demand/adolescent-withdraw interaction (TD/AW) cycles observed early in treatment would predict poor adolescent outcomes at follow-up for families who exhibited entrenched parent-demand/adolescent-withdraw interaction (PD/AW) before treatment began. Participants were 91 families who received at least four sessions of BSFT in a multisite clinical trial on adolescent drug abuse (Robbins et al., 2011). Prior to receiving therapy, families completed videotaped family interaction tasks from which trained observers coded PD/AW. Another team of raters coded TD/AW during two early BSFT sessions. The main dependent variable was the number of drug-use days that adolescents reported in timeline follow-back interviews 7 to 12 months after family therapy began. Zero-inflated Poisson regression analyses supported the main hypothesis, showing that PD/AW and TD/AW interacted to predict adolescent drug use at follow-up. For adolescents in high PD/AW families, higher levels of TD/AW predicted significant increases in drug use at follow-up, whereas for low PD/AW families, TD/AW and follow-up drug use were unrelated. Results suggest that attending to parallel demand-withdraw processes in parent-adolescent and therapist-adolescent dyads may be useful in family therapy for substance-using adolescents.

**Binge Drinking, Stimulant Use and HIV Risk in a Sample of Illicit Drug Using Heterosexual Black Men** Keen L, Dyer TP, Whitehead NE, Latimer W. *Addict Behav.* 2014 Sep; 39(9): 1342-5. Relatively little research has examined the effects of binge drinking and HIV risk in heterosexual Black men. Even less research has explored this relationship in illicit drug using heterosexual Black men who are at an elevated risk of contracting and transmitting HIV through various vectors, including risky sexual behavior, in the Black community. The purpose of the current study is to examine the associations between binge drinking, drug use and HIV status in a community-based sample of 127 self-identified heterosexual Black men. Overall, 17% reported binge drinking in the past month. Both stimulant use (AOR 7.29; 95% CIs, 2.07, 25.70), and binge drinking (AOR=5.28; 95% CIs, 1.34, 20.91) were associated with HIV status. These findings will inform prevention interventions to reduce the HIV risk among Black heterosexual men.

**Injection and Non-injection Drug Use and Infectious Disease in Baltimore City: Differences by Race** Keen L, Khan M, Clifford L, Harrell PT, Latimer WW. *Addict Behav.* 2014 Sep; 39(9): 1325-8.

The current study examines differences in the prevalence of biologically-confirmed hepatitis C virus (HCV), HIV, and coinfection between Black and White adult cocaine/heroin users across three drug use subgroups identified in previous research (Harrell et al., 2012): Non-injection smoking crack/nasal heroin users, heroin injectors, and polydrug injectors. 59% of the 482 participants in the study were male. Significant race differences emerged between drug use subgroup memberships. Non-injection smoking crack/nasal heroin users were predominantly Black (75%), while heroin injectors and polydrug injectors were predominantly White (69% and 72%, respectively). Polydrug injectors accounted for nearly three quarters of the HCV positive diagnoses in Whites. Though HIV disease status, stratified by race, did not differ significantly between drug

use subgroups, the non-injection smoking crack/nasal heroin subgroup contained over half of the HIV positive diagnoses in the sample and was predominantly Black. Despite much lower rates of injection, Blacks (8%) had a higher prevalence of coinfection than Whites (3%;  $X(2) (2)=6.18$ ,  $p=.015$ ). The current findings are consistent with trends in the recent HIV transmission statistics where sexual activity has overtaken injection drug use as a HIV risk factor. The current findings also provide further support to the notion of injection drug use as an exceedingly high-risk behavior for HCV and coinfection, specifically those who are polysubstance injectors.

**Task Importance Affects Event-Based Prospective Memory Performance in Adults with HIV-Associated Neurocognitive Disorders and HIV-Infected Young Adults with Problematic Substance Use**

Woods SP, Doyle KL, Morgan EE, Naar-King S, Outlaw AY, Nichols SL, Loft S. J Int Neuropsychol Soc. 2014 May 16: 1-11. [Epub ahead of print].

Two experiments were conducted to examine the effects of task importance on event-based prospective memory (PM) in separate samples of adults with HIV-associated neurocognitive disorders (HAND) and HIV-infected young adults with substance use disorders (SUD). All participants completed three conditions of an ongoing lexical decision task: (1) without PM task requirements; (2) with PM task requirements that emphasized the importance of the ongoing task; and (3) with PM task requirements that emphasized the importance of the PM task. In both experiments, all HIV+ groups showed the expected increase in response costs to the ongoing task when the PM task's importance was emphasized. In Experiment 1, individuals with HAND showed significantly lower PM accuracy as compared to HIV+ subjects without HAND when the importance of the ongoing task was emphasized, but improved significantly and no longer differed from HIV+ subjects without HAND when the PM task was emphasized. A similar pattern of findings emerged in Experiment 2, whereby HIV+ young adults with SUD (especially cannabis) showed significant improvements in PM accuracy when the PM task was emphasized. Findings suggest that both HAND and SUD may increase the amount of cognitive attentional resources that need to be allocated to support PM performance in persons living with HIV infection.

**Measuring Ethnic Identity in Latino Adolescents with Substance Use Disorders** Burrow-Sanchez JJ. Subst Use Misuse. 2014 Jun; 49(8): 982-6.

The Multigroup Ethnic Identity Measure (MEIM) is a frequently used instrument to assess the level of ethnic identity in adolescents. The factor structure of the MEIM has extensively been studied in diverse nonclinical samples, while research with clinical samples of adolescents is lacking. The purpose of the current study is to identify the factor structure of the MEIM in a clinical sample of Latino adolescents ( $N = 106$ ) with substance use disorders. A confirmatory factor analysis was used to test three competing factor structure models of the MEIM. Results indicated that a six-item two-factor model best fit the data for Latino adolescents in this study. Implications of these results and suggestions for further research are discussed.

**Substance Use Recovery Outcomes among a Cohort of Youth Participating in a Mobile-based Texting Aftercare Pilot Program** Gonzales R, Ang A, Murphy DA, Glik DC, Anglin MD. J Subst Abuse Treat. 2014 Jul; 47(1): 20-6.

Project ESQYIR (Educating & Supporting Inquisitive Youth in Recovery) is a pilot study examining the feasibility of a 12-week mobile-based aftercare intervention for youth (ages 12 to 24) transitioning out of community-based substance abuse treatment programs. From January 2012 through July 2013, a total of 80 youth were recruited from outpatient and residential treatment programs, geographically dispersed throughout Los Angeles County, California. Results revealed that youth who participated in the texting mobile pilot intervention were significantly less likely to

relapse to their primary compared to the aftercare as usual control condition (OR=0.52, p=0.002) over time (from baseline throughout the 12-week aftercare pilot program to a 90-day follow-up). Participants in the texting aftercare pilot program also reported significantly less substance use problem severity ( $\beta=-0.46$ , p=0.03) and were more likely to participate in extracurricular recovery behaviors ( $\beta=1.63$ , p=0.03) compared to participants in the standard aftercare group. Collectively, findings from this pilot aftercare study suggest that mobile texting could provide a feasible way to engage youth in recovery after substance abuse treatment to aid with reducing relapse and promoting lifestyle behavior change.

**HIV-related Sexual Risk Behavior among African American Adolescent Girls** Danielson CK, Walsh K, McCauley J, Ruggiero KJ, Brown JL, Sales JM, Rose E, Wingood GM, Diclemente RJ. *J Womens Health (Larchmt)*. 2014 May; 23(5): 413-9.

Latent class analysis (LCA) is a useful statistical tool that can be used to enhance understanding of how various patterns of combined sexual behavior risk factors may confer differential levels of HIV infection risk and to identify subtypes among African American adolescent girls. Data for this analysis is derived from baseline assessments completed prior to randomization in an HIV prevention trial. Participants were African American girls (n=701) aged 14-20 years presenting to sexual health clinics. Girls completed an audio computer-assisted self-interview, which assessed a range of variables regarding sexual history and current and past sexual behavior. Two latent classes were identified with the probability statistics for the two groups in this model being 0.89 and 0.88, respectively. In the final multivariate model, class 1 (the "higher risk" group; n=331) was distinguished by a higher likelihood of >5 lifetime sexual partners, having sex while high on alcohol/drugs, less frequent condom use, and history of sexually transmitted diseases (STDs), when compared with class 2 (the "lower risk" group; n=370). The derived model correctly classified 85.3% of participants into the two groups and accounted for 71% of the variance in the latent HIV-related sexual behavior risk variable. The higher risk class also had worse scores on all hypothesized correlates (e.g., self-esteem, history of sexual assault or physical abuse) relative to the lower risk class. Sexual health clinics represent a unique point of access for HIV-related sexual risk behavior intervention delivery by capitalizing on contact with adolescent girls when they present for services. Four empirically supported risk factors differentiated higher versus lower HIV risk. Replication of these findings is warranted and may offer an empirical basis for parsimonious screening recommendations for girls presenting for sexual healthcare services.

**Direct and Indirect Associations between Social Anxiety and Nicotine Dependence and Cessation Problems: Multiple Mediator Analyses** Buckner JD, Farris SG, Schmidt NB, Zvolensky MJ. *Nicotine Tob Res*. 2014 Jun; 16(6): 807-14.

Little empirical work has evaluated why socially anxious smokers are especially vulnerable to more severe nicotine dependence and cessation failure. Presumably, these smokers rely on cigarettes to help them manage their chronically elevated negative affect elicited by a wide array of social contexts. The current study examined the direct and indirect effects of social anxiety cross-sectionally in regard to a range of smoking processes among 466 treatment-seeking smokers. Negative affect and negative affect reduction motives were examined as mediators of the relations of social anxiety with nicotine dependence and cessation problems. Social anxiety was directly and robustly associated with perceived barriers to smoking cessation and problems experienced during past quit attempts. Social anxiety was also associated with greater nicotine dependence and smoking inflexibility indirectly through negative affect and negative affect smoking motives. Negative affect and smoking to reduce negative affect mediated these relations. These findings document the

important role of negative affect and negative affect reduction motives in the relationships of social anxiety with nicotine dependence and cessation problems.

**A Preliminary Randomized Controlled Trial of a Behavioral Exercise Intervention for Smoking Cessation** Abrantes AM, Bloom EL, Strong DR, Riebe D, Marcus BH, Desaulniers J, Fokas K, Brown RA. *Nicotine Tob Res.* 2014 May 8. [Epub ahead of print].

Previous exercise intervention studies for smoking cessation have been challenged by a number of methodological limitations that confound the potential efficacy of aerobic exercise for smoking cessation. The preliminary efficacy of a behavioral exercise intervention that incorporated features designed to address prior limitations was tested in a randomized controlled trial (RCT). Sixty-one smokers (65.6% female, mean age = 47.3 years; smoked a mean of 19.7 cigarettes/day) were randomized to receive either a 12-week exercise intervention OR a 12-week health education contact control. Participants in both conditions received an 8-week telephone-delivered, standard smoking cessation protocol (with the transdermal nicotine patch). Follow-ups were conducted at the end of treatment (EOT), 6- and 12-month timepoints. There were no differences between conditions with respect to the number of weekly exercise or health education sessions attended ( $9.3 \pm 2.8$  vs.  $9.3 \pm 3.0$ , respectively). While not statistically significant, participants in the exercise condition demonstrated higher verified abstinence rates (EOT: 40% vs. 22.6%, odds ratio [OR] = 2.28; 6- and 12-month follow-ups: 26.7% vs. 12.9%, OR = 2.46). Irrespective of treatment condition, higher levels of moderate-to-vigorous exercise were associated with lower levels of depressive symptoms during the intervention. The results of this small RCT point toward the benefit of a behavioral exercise intervention, designed to address previous methodological limitations, for smoking cessation. Given the potential public health impact of the demonstrated efficacy of exercise for smoking cessation, the continued development and optimization of exercise interventions for smokers through larger RCTs merits pursuit.

**Examining Two Different Schedules of Financial Incentives for Smoking Cessation among Pregnant Women** Higgins ST, Washio Y, Lopez AA, Heil SH, Solomon LJ, Lynch ME, Hanson JD, Higgins TM, Skelly JM, Redner R, Bernstein IM. *Prev Med.* 2014 Apr 2. pii: S0091-7435(14)00118-2.

The objective of this study was to examine whether an efficacious voucher-based incentives intervention for decreasing smoking during pregnancy and increasing fetal growth could be improved without increasing costs. The strategy was to redistribute the usual incentives so that higher values were available early in the quit attempt. 118 pregnant smokers in greater Burlington, Vermont (studied December, 2006-June, 2012) were randomly assigned to the revised contingent voucher (RCV) or usual contingent voucher (CV) schedule of abstinence-contingent vouchers, or to a non-contingent voucher (NCV) control condition wherein vouchers were provided independent of smoking status. Smoking status was biochemically verified; serial sonographic estimates of fetal growth were obtained at gestational weeks 30-34. RCV and CV conditions increased point-prevalence abstinence above NCV levels at early (RCV: 40%, CV: 46%, NCV: 13%,  $p=.007$ ) and late-pregnancy (RCV: 45%; CV: 36%; NCV, 18%;  $p=.04$ ) assessments, but abstinence levels did not differ between the RCV and CV conditions. The RCV intervention did not increase fetal growth above control levels while the CV condition did so ( $p<.05$ ). This trial further supports the efficacy of CV for increasing antepartum abstinence and fetal growth, but other strategies (e.g., increasing overall incentive values) will be necessary to improve outcomes further.

**A Culturally Adapted Smoking Cessation Intervention for Korean Americans: A Mediating Effect of Perceived Family Norm Toward Quitting** Kim SS, Kim SH, Fang H, Kwon S, Shelley D, Ziedonis D. *J Immigr Minor Health*. 2014 May 31. [Epub ahead of print].

Korean men and women have the highest current smoking rates across all Asian ethnic subgroups in the United States. This is a 2-arm randomized controlled study of a culturally adapted smoking cessation intervention. The experimental condition received eight weekly 40-min individualized counseling sessions that incorporated Korean-specific cultural elements, whereas the control condition received eight weekly 10-min individualized counseling sessions that were not culturally adapted. All participants also received nicotine patches for 8 weeks. One-hundred nine Korean immigrants (91 men and 18 women) participated in the study. The rate of biochemically verified 12-month prolonged abstinence was significantly higher for the experimental condition than the control condition (38.2 vs. 11.1 %,  $\chi^2 = 10.7$ ,  $p < 0.01$ ). Perceived family norm significantly mediated the effect of cessation intervention on abstinence. Smoking cessation intervention for Korean Americans should be culturally adapted and involve family members to produce a long-term treatment effect.

**Young Adult Waterpipe Smokers: Smoking Behaviors and Associated Subjective and Physiological Effects** Shishani K1, Howell D2, McPherson S2, Roll J2. *Addict Behav*. 2014 Jun; 39(6): 1113-9.

The purpose of this pilot study was to investigate smoking behaviors and subjective and physiological effects of nicotine on young adult occasional waterpipe smokers. This study utilized a repeated-measures design that included one repeated factor for condition (nicotine and non-nicotine). For each participant, the sequencing of the repeated factor was assigned using random allocation. The two nicotine conditions were nicotine (0.75 g) and non-nicotine (0 g placebo) tobacco. Over the course of two weeks, twenty-two participants completed subjective (Acute Subjective Effects of Nicotine) and physiological (blood pressure, heart rate, and CO level) measures. Additional measures (QSU and MNWS-R) were used to assess for withdrawal symptoms. **SAMPLE:** The participants ( $n=22$ ) were young adults ( $23 \pm 3.1$  years); 71% smoked waterpipe once a month in the past year and 29% smoked waterpipe 1-2 times per week. In addition, 60% reported sharing their waterpipe with friends while smoking. None of the participants reported using any other forms of tobacco products. Under the nicotine condition, participants tended to smoke longer (i.e. smoking duration,  $p=0.004$ ), take more puffs ( $p=0.03$ ), take shorter puffs ( $p=0.03$ ), and inhale less volume with each puff ( $p=0.02$ ). The repeated measures analysis of the factor headrush revealed an effect of the nicotine condition ( $F=9.69$ ,  $p<0.001$ , partial  $\eta(2)=0.31$ ) and time ( $F=8.17$ ,  $p=0.02$ , partial  $\eta(2)=0.30$ ). Heart rate increased significantly across the nicotine condition ( $F=7.92$ ,  $p=0.01$ , partial  $\eta(2)=0.31$ ) and over time ( $F=12.64$ ,  $p=0.01$ , partial  $\eta(2)=0.41$ ). This study demonstrates how differences between nicotine and non-nicotine waterpipe smoking are associated with changes in smoking behaviors, experiencing a headrush and an increase in heart rate.

**Randomized Trial on Mindfulness Training for Smokers Targeted to a Disadvantaged Population** Davis JM, Goldberg SB, Anderson MC, Manley AR, Smith SS, Baker TB. *Subst Use Misuse*. 2014 Apr; 49(5): 571-85.

The authors report the results of a randomized trial comparing a novel smoking cessation treatment Mindfulness Training for Smokers (MTS) to a usual care therapy (Controls), which included the availability of a tobacco quit line and nicotine patches. Data were collected from 196 low socioeconomic status smokers in 2010-2011 in Madison, Wisconsin. Participants were randomized to either MTS or a telephonic quit line. The primary outcome was 6-month smoking abstinence

measured by carbon monoxide breath testing and Time-Line Follow-Back. Among treatment initiators (randomized participants who participated in the intervention), abstinence rates were significantly different between the MTS (38.7%) and control (20.6%,  $p = .05$ ) groups. Study limitations are also discussed. Results suggest that further study is warranted.

**Finding the Right Match: Mindfulness Training May Potentiate the Therapeutic Effect of Nonjudgment of Inner Experience on Smoking Cessation** Schuman-Olivier Z, Hoepfner BB, Evins AE, Brewer JA. *Subst Use Misuse*. 2014 Apr; 49(5): 586-94.

Mindfulness training (MT) is an emerging therapeutic modality for addictive disorders. Nonjudgment of inner experience, a component of mindfulness, may influence addiction treatment response. To test whether this component influences smoking cessation, tobacco smokers ( $n = 85$ ) in a randomized control trial of MT vs. Freedom from Smoking (FFS), a standard cognitive-behaviorally-oriented treatment, were divided into split-half subgroups based on baseline Five Facet Mindfulness Questionnaire nonjudgment subscale. Smokers who rarely judge inner experience (nonjudgment  $> 30.5$ ) smoked less during follow-up when randomized to MT (3.9 cigs/d) vs. FFS (11.1 cigs/d),  $p < .01$ . Measuring trait nonjudgment may help personalize treatment assignments, improving outcomes.

**Smoking- and Menstrual-related Symptomatology during Short-term Smoking Abstinence by Menstrual Phase and Depressive Symptoms** Allen SS, Allen AM, Tosun N, Lunos S, al'Absi M, Hatsukami D. *Addict Behav*. 2014 May; 39(5): 901-6.

Menstrual phase and depressive symptoms are known to minimize quit attempts in women. Therefore, the influence of these factors on smoking- and menstrual-related symptomatology during acute smoking cessation was investigated in a controlled cross-over lab-study. Participants ( $n=147$ ) completed two six-day testing weeks during their menstrual cycle with testing order randomly assigned (follicular vs. luteal). The testing week consisted of two days of ad libitum smoking followed by four days of biochemically verified smoking abstinence. Daily symptomatology measures were collected. Out of the 11 total symptoms investigated, six were significantly associated with menstrual phase and nine were significantly associated with level of depressive symptoms. Two significant interactions were noted indicating that there may be a stronger association between depressive symptoms with negative affect and premenstrual pain during the follicular phase compared to the luteal phase. Overall, these observations suggest that during acute smoking abstinence in premenopausal smokers, there is an association between depressive symptoms and symptomatology whereas menstrual phase appears to have less of an effect. Further study is needed to determine the effect of these observations on smoking cessation outcomes, as well as to define the mechanism of menstrual phase and depressive symptoms on smoking-related symptomatology.

**Delay Discounting Rates: A Strong Prognostic Indicator of Smoking Relapse** Sheffer CE, Christensen DR, Landes R, Carter LP, Jackson L, Bickel WK. *Addict Behav*. 2014 May 5. pii: S0306-4603(14)00131-2.

Recent evidence suggests that several dimensions of impulsivity and locus of control are likely to be significant prognostic indicators of relapse. One-hundred and thirty-one treatment seeking smokers were enrolled in six weeks of multi-component cognitive-behavioral therapy with eight weeks of nicotine replacement therapy. Cox proportional hazard regressions were used to model days to relapse with each of the following: delay discounting of \$100, delay discounting of \$1000, six subscales of the Barratt Impulsiveness Scale (BIS), Rotter's Locus of Control (RLOC), Fagerstrom's Test for Nicotine Dependence (FTND), and the Perceived Stress Scale (PSS). Hazard ratios for a

one standard deviation increase were estimated with 95% confidence intervals for each explanatory variable. Likelihood ratios were used to examine the level of association with days to relapse for different combinations of the explanatory variables while accounting for nicotine dependence and stress level. These analyses found that the \$100 delay discounting rate had the strongest association with days to relapse. Further, when discounting rates were combined with the FTND and PSS, the associations remained significant. When the other measures were combined with the FTND and PSS, their associations with relapse non-significant. These findings indicate that delay discounting is independently associated with relapse and adds to what is already accounted for by nicotine dependence and stress level. They also signify that delay discounting is a productive new target for enhancing treatment for tobacco dependence. Consequently, adding an intervention designed to decrease discounting rates to a comprehensive treatment for tobacco dependence has the potential to decrease relapse rates.

**Tobacco Cessation Treatment for Alaska Native Adolescents: Group Randomized Pilot Trial**

Patten CA1, Fadahunsi O, Hanza MM, Smith CA, Decker PA, Boyer R, Ellsworth L, Brockman TA, Hughes CA, Bronars CA, Offord KP. *Nicotine Tob Res.* 2014 Jun; 16(6): 836-45.

Tobacco cessation treatments have not been evaluated among Alaska Native (AN) adolescents. This pilot study evaluated the feasibility and the potential efficacy of a targeted cessation intervention for AN youth using a group randomized design. Eight villages in western Alaska were randomly assigned to receive the intervention (n = 4 villages) or a delayed treatment control condition (written materials only; n = 4 villages). Ten adolescents aged 12-17 years were targeted from each village with a planned enrollment of 80. The intervention was held over a weekend, and youth traveled from their villages to quit tobacco use with other teens. The intervention comprised 8 hr of group-based counseling. Talking circles, personal stories from elders, and recreational activities were included to enhance cultural acceptability and participation. Newsletters were mailed weekly for 5-weeks postprogram. Assessments were conducted at baseline, week 6 (end-of-treatment), and 6 months. Self-reported tobacco abstinence was confirmed with salivary cotinine. Recruitment targets were met in the intervention (41 enrolled) but not in control villages (27 enrolled). All intervention participants attended the weekend program. Retention was high; 98% of intervention and 86% of control participants completed 6-month follow-up. The 7-day point-prevalence self-reported tobacco abstinence rates for intervention and control participants were 10% (4/41) and 0% (0/27) at both week 6 and 6 months (p = .15). Only 1 adolescent in the intervention condition was biochemically confirmed abstinent at week 6 and none at 6 months. The intensive individual-focused intervention used in this study was feasible but not effective for tobacco cessation among AN youth. Alternative approaches are warranted.

**Treatment Models for Targeting Tobacco use During Treatment for Cannabis Use Disorder:**

**Case Series** Lee DC, Budney AJ, Brunette MF, Hughes JR, Etter JF, Stanger C. *Addict Behav.* 2014 Aug; 39(8): 1224-30.

Approximately 50% of individuals seeking treatment for cannabis use disorders (CUD) also smoke tobacco, and tobacco smoking is a predictor of poor outcomes for those in treatment for CUD. Quitting tobacco is associated with long-term abstinence from alcohol and illicit drugs, yet there are no established treatments for CUD that also target tobacco smoking. This report highlights issues related to cannabis and tobacco co-use and discusses potential treatment approaches targeting both substances. Data is shared from the first six participants enrolled in an intervention designed to simultaneously target tobacco use in individuals seeking treatment for CUD. The twelve-week program comprised computer-assisted delivery of Motivational Enhancement Therapy, Cognitive Behavioral Therapy, and Contingency Management, i.e., abstinence-based incentives for CUD. In

addition, participants were encouraged to complete an optional tobacco intervention consisting of nicotine-replacement therapy and computer-assisted delivery of a behavioral treatment tailored for tobacco and cannabis users. All participants completed the cannabis intervention and at least a portion of the tobacco intervention: all completed at least one tobacco computer module (mean=2.5 modules) and 50% initiated nicotine replacement therapy. Five of six participants achieved abstinence from cannabis. The number of tobacco quit attempts was lower than expected, however all participants attempted to reduce tobacco use during treatment. Simultaneously targeting tobacco during treatment for CUD did not negatively impact cannabis outcomes. Participation in the tobacco intervention was high, but cessation outcomes were poor suggesting that alternative strategies might be needed to more effectively prompt quit attempts and enhance quit rates.

**Pretreatment Measures of Brain Structure and Reward-Processing Brain Function in Cannabis Dependence: An Exploratory Study of Relationships with Abstinence during Behavioral Treatment**

Yip SW, DeVito EE, Kober H, Worhunsky PD, Carroll KM, Potenza MN. *Drug Alcohol Depend.* 2014 Jul 1; 140: 33-41.

Cannabis is widely abused, and efficacies of therapeutics for cannabis dependence remain suboptimal. Magnetic resonance imaging (MRI) may aid in the identification of biological markers for successful treatment outcomes (i.e., abstinence). Twenty men with cannabis dependence and twenty non-substance-using healthy comparison (HC) men underwent MRI scanning. Cannabis-dependent individuals then participated in a 12-week randomized clinical trial of behavioral treatments (contingency management (CM), cognitive behavioral therapy (CBT) or both). Pretreatment functional and structural data were compared between the cannabis-dependent and HC participants. In addition, individuals with cannabis dependence were subdivided based on the successful achievement of 21 days of consecutive abstinence during treatment to assess whether abstinent versus non-abstinent cannabis-dependent participants displayed different pretreatment functional and structural characteristics when compared to HC participants. In comparison to HC participants, cannabis-dependent participants demonstrated greater ventral striatal activation during the receipt of losing outcomes and smaller putamen volumes. Cannabis-dependent participants who did not subsequently achieve 21 days of consecutive abstinence had increased activity within the striatum during the receipt of losing outcomes, relative to HC participants. Cannabis-dependent participants who did not achieve 21 days of abstinence had decreased bilateral putamen volumes prior to treatment, relative to HC participants. Individual differences in pretreatment striatal function and structure may relate to individual differences in treatment responses for cannabis dependence. While mechanisms underlying these associations require further exploration, the striatum might mediate treatment responses via its role in associative reward-learning (e.g., through skills training in CBT or reinforcement of abstinence in CM).

**Ecological Momentary Assessment of Posttraumatic Stress Disorder Symptoms during a Smoking Quit Attempt**

Dedert EA, Dennis PA, Swinkels CM, Calhoun PS, Dennis MF, Beckham JC. *Nicotine Tob Res.* 2014 Apr 1; 6(4): 430-6.

Smokers with posttraumatic stress disorder (PTSD) tend to lapse more quickly following a quit attempt, which might be explained by changes in PTSD symptoms during a quit attempt. The present study examines changes in PTSD symptoms, negative affect, and craving before and during a quit attempt. Participants in this study were 52 smokers with PTSD who completed random-alarm ecological momentary assessments of PTSD symptoms, negative affect, cigarette craving, and smoking behavior throughout a prequit phase of ad hoc smoking, a phase of abstinence from smoking, and a postlapse phase. Relative to the prequit phase, the abstinent phase was marked by decreases in PTSD reexperiencing, avoidance, and numbing clusters ( $p \leq .01$ ). The odds of PTSD

symptom or negative affect variability from one reading in the ecological momentary assessment (EMA) to the next reading was decreased in PTSD reexperiencing, avoidance, and numbing clusters ( $ps \leq .02$ ). Smoking cravings were also mildly decreased in the abstinent and postlapse phases ( $ps < .01$ ), although some cravings in both phases were rated at the maximum intensity. Increased craving was predicted by the previous EMA reading of PTSD symptoms. Results suggested that smoking abstinence is not associated with exacerbation of PTSD symptoms, but PTSD symptoms during abstinence were related to craving levels during the quit attempt.

**Ecological Momentary Assessment of Antecedents and Consequences of Smoking in Adults with Attention-Deficit/Hyperactivity Disorder**

Mitchell JT1, Dennis MF, English JS, Dennis PA, Brightwood A, Beckham JC, Kollins SH. *Subst Use Misuse*. 2014 May 14. [Epub ahead of print].

The current study assessed antecedents and consequences of ad lib cigarette smoking in smokers diagnosed with attention-deficit/hyperactivity disorder (ADHD) using ecological momentary assessment (EMA). Adult smokers with ADHD ( $n = 17$ ) completed 870 smoking and 622 nonsmoking electronic diary entries over a 7-day observation period of their naturalistic smoking behavior. Data collection occurred from 2011 to 2012. Generalized estimating equations indicated that ADHD smokers were more likely to smoke when urge to smoke, negative affect, boredom, stress, worry, and restlessness were elevated. In addition, participants were more likely to smoke in situations that elicited higher levels of nervousness and frustration. ADHD symptoms, in general, did not differ between smoking and nonsmoking contexts, though hyperactive-impulsive ADHD symptoms were elevated prior to smoking in frustrating situations. Additional situational antecedent variables were associated with smoking, including being in the presence of others smoking, being in a bar or restaurant, while outside, and while consuming caffeinated or alcoholic beverages. Participants also reported a significant improvement in urge to smoke, negative affect, stress, hunger, and ADHD symptoms after smoking a cigarette. Findings suggest certain contextual factors that may maintain ad lib cigarette smoking in smokers with ADHD and identify potential treatment targets in smoking cessation interventions for this at-risk group. Clinical implications and future research directions are discussed.

**The Role of Daily Hassles and Distress Tolerance in Predicting Cigarette Craving during a Quit Attempt**

Volz AR1, Dennis PA, Dennis MF, Calhoun PS, Wilson SM, Beckham JC. *Nicotine Tob Res*. 2014 Jun; 16(6): 872-5.

Ecological momentary assessment (EMA) has shown that smoking behavior is linked to transient variables in the smoker's immediate context. Such research suggests that daily hassles (e.g., losing one's keys) may be more likely to lead to cigarette craving and eventual lapse than infrequent, large-scale stressors (e.g., death of a loved one) among individuals attempting to quit smoking. However, individual differences in distress tolerance (DT) may moderate the relationship between daily hassles and daily cigarette craving during a quit attempt. A sample of 56 veterans and community members drawn from a larger smoking-cessation study completed structured interviews and paper-and-pencil questionnaires during an initial laboratory visit and, directly following a quit attempt, were monitored via EMA. Multilevel modeling was used to examine the relationship between daily hassles and daily cigarette craving and to determine whether DT moderated this relationship. Daily hassles were positively associated with daily cigarette craving, and this association was moderated by individual differences in DT, such that the lower one's DT, the stronger the relationship between daily hassles and daily cigarette craving. This model explained 13% of the intraindividual variability and 8% of the interindividual variability in daily cigarette craving. Smoking-cessation interventions may be strengthened by targeting smokers' individual responses to contextual factors,

such as by helping smokers develop skills to cope more effectively with distress prior to and during the quit phase.

**Do Ethnicity and Gender Moderate the Influence of Posttraumatic Stress Disorder on Time to Smoking Lapse?** Wilson SM, Dedert EA, Dennis PA, Dennis MF, Calhoun PS, Kirby AC, Beckham JC. *Addict Behav.* 2014 Jul; 39(7): 1163-7.

Following a smoking cessation attempt, smokers with posttraumatic stress disorder (PTSD) experience smoking relapse at a higher and faster rate. Black ethnicity and female gender are also associated with lower success rates following smoking cessation. No study to date has prospectively examined how ethnicity and gender may moderate the effect of PTSD on smoking relapse. It was hypothesized that female gender and Black ethnicity would significantly predict early lapse after quitting; further, it was predicted that ethnicity and gender would moderate the effect of PTSD on relapse rate. Smokers with PTSD (n=48) and without PTSD (n=56) completed ecological momentary assessment (EMA) the week after a quit date, and self-initiated EMA entries after smoking lapse. Smoking abstinence was biologically verified. The sample included Black (62%) and White (38%) participants, and was 50% female. Study hypotheses were tested with Cox proportional hazards regression modeling time to first smoking lapse. Study results confirmed the main hypothesis, with a significant PTSD × Ethnicity interaction emerging. The effect of PTSD on smoking relapse was significant for White participants but not for Black participants. No significant gender moderation was found. Taken together, study results support previous research, and suggest that the relationship between smoking and PTSD is stronger for White smokers than for minorities. This study has significant implications for research in smoking and mental disease, as well as for smoking cessation treatments for Black smokers.

**Factors Predicting Development of Opioid Use Disorders among Individuals who Receive an Initial Opioid Prescription: Mathematical Modeling using a Database of Commercially-insured Individuals** Cochran BN, Flentje A, Heck NC, Van Den Bos J, Perlman D, Torres J, Valuck R, Carter J. *Drug Alcohol Depend.* 2014 May 1; 138: 202-8.

Prescription drug abuse in the United States and elsewhere in the world is increasing at an alarming rate with non-medical opioid use, in particular, increasing to epidemic proportions over the past two decades. It is imperative to identify individuals most likely to develop opioid abuse or dependence to inform large-scale, targeted prevention efforts. The present investigation utilized a large commercial insurance claims database to identify demographic, mental health, physical health, and healthcare service utilization variables that differentiate persons who receive an opioid abuse or dependence diagnosis within two years of filling an opioid prescription (OUDs) from those who do not receive such a diagnosis within the same time frame (non-OUDs). When compared to non-OUDs, OUDs were more likely to: (1) be male (59.9% vs. 44.2% for non-OUDs) and younger (M=37.9 vs. 47.7); (2) have a prescription history of more opioids (1.7 vs. 1.2), and more days supply of opioids (M=272.5, vs. M=33.2); (3) have prescriptions filled at more pharmacies (M=3.3 per year vs. M=1.3); (4) have greater rates of psychiatric disorders; (5) utilize more medical and psychiatric services; and (6) be prescribed more concomitant medications. A predictive model incorporating these findings was 79.5% concordant with actual OUDs in the data set. Understanding correlates of OUD development can help to predict risk and inform prevention efforts.

**Cannabis Abstinence during Treatment and One-Year Follow-Up: Relationship to Neural Activity in Men** Kober H1, DeVito EE, DeLeone CM, Carroll KM, Potenza MN.

Neuropsychopharmacology. 2014 Apr 7. [Epub ahead of print].

Cannabis is among the most frequently abused substances in the United States. Cognitive control is a contributory factor in the maintenance of substance-use disorders and may relate to treatment response. Therefore, the authors assessed whether cognitive-control-related neural activity before treatment differs between treatment-seeking cannabis-dependent and healthy individuals and relates to cannabis-abstinence measures during treatment and 1-year follow-up. Cannabis-dependent males (N=20) completed a functional magnetic resonance imaging (fMRI) cognitive-control (Stroop) task before a 12-week randomized controlled trial of cognitive-behavioral therapy and/or contingency management. A healthy-comparison group (N=20) also completed the fMRI task. Cannabis use was assessed by urine toxicology and self-report during treatment, and by self-report across a 1-year follow-up period (N=18). The cannabis-dependent group displayed diminished Stroop-related neural activity relative to the healthy-comparison group in multiple regions, including those strongly implicated in cognitive-control and addiction-related processes (e.g., dorsolateral prefrontal cortex and ventral striatum). The groups did not differ significantly in response times (cannabis-dependent, N=12; healthy-comparison, N=14). Within the cannabis-dependent group, greater Stroop-related activity in regions including the dorsal anterior cingulate cortex was associated with less cannabis use during treatment. Greater activity in regions including the ventral striatum was associated with less cannabis use during 1-year posttreatment follow-up. These data suggest that lower cognitive-control-related neural activity in classic 'control' regions (e.g., dorsolateral prefrontal cortex and dorsal anterior cingulate) and classic 'salience/reward/learning' regions (e.g., ventral striatum) differentiates cannabis-dependent individuals from healthy individuals and relates to less abstinence within-treatment and during long-term follow-up. Clinically, results suggest that treatment development efforts that focus on enhancing cognitive control in addition to abstinence may improve treatment outcomes in cannabis dependence.

**Computerized versus In-person Brief Intervention for Drug Misuse: A Randomized Clinical Trial** Schwartz RP, Gryczynski J, Mitchell SG, Gonzales A, Moseley A, Peterson TR, Ondersma SJ, O'Grady KE. Addiction. 2014 Jan; 109: 1091-1098.

Several studies have found that brief interventions (BIs) for drug misuse have superior effectiveness to no-treatment controls. However, many health centers do not provide BIs for drug use consistently due to insufficient behavioral health staff capacity. Computerized BIs for drug use are a promising approach, but their effectiveness compared with in-person BIs has not been established. This study compared the effectiveness of a computerized brief intervention (CBI) to an in-person brief intervention (IBI) delivered by a behavioral health counselor. This was a two-arm randomized clinical trial, conducted in two health centers in New Mexico, United States. Participants were 360 adult primary care patients with moderate-risk drug scores on the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) who were randomly assigned on a 1: 1 basis to a computerized brief intervention (CBI) or to an in-person brief intervention (IBI) delivered by a behavioral health counselor. Assessments were conducted at baseline and 3-month follow-up, and included the ASSIST and drug testing on hair samples. The IBI and CBI conditions did not differ at 3 months on global ASSIST drug scores [ $b = -1.79$ ; 95% confidence interval (CI) =  $-4.37, 0.80$ ] or drug-positive hair tests [odds ratio (OR) = 0.97; 95% CI = 0.47, 2.02]. There was a statistically significant advantage of CBI over IBI in substance-specific ASSIST scores for marijuana ( $b = -1.73$ ; 95% CI =  $-2.91, -0.55$ ; Cohen's  $d = 0.26$ ;  $P = 0.004$ ) and cocaine ( $b = -4.48$ ; 95% CI =  $-8.26, -0.71$ ; Cohen's  $d = 0.50$ ;  $P = 0.021$ ) at 3 months. Computerized brief intervention can be an

effective alternative to in-person brief intervention for addressing moderate drug use in primary care.

**HIV Testing and Sexual Risk Reduction Counseling in Office-based Buprenorphine/Naloxone Treatment** Edelman EJ, Moore BA, Caffrey S, Sikkema KJ, Jones ES, Schottenfeld RS, Fiellin DA, Fiellin LE. *J Addict Med.* 2013 Nov-Dec; 7(6): 410-6.

The authors assessed the feasibility and preliminary efficacy of human immunodeficiency virus (HIV) testing with sexual risk reduction counseling for opioid-dependent patients initiating office-based buprenorphine/naloxone treatment. They conducted a 14-week randomized, controlled trial with 30 patients (original target of 114) assigned to receive buprenorphine/naloxone induction/stabilization and HIV testing with Brief Sexual Risk Management (BSRM) or Enhanced Sexual Risk Management (ESRM). The authors evaluated process measures and compared outcomes at baseline and during the 3-month follow-up. Similar proportions of patients receiving BSRM and ESRM underwent HIV testing (93% vs 80%;  $P = 0.28$ ) and completed counseling sessions (80% vs 67%;  $P = 0.40$ ). Brief Sexual Risk Management sessions were shorter than ESRM sessions (15.4 vs 23.4 minutes), with comparable manual adherence ( $P = 0.80$ ). Outcomes did not vary by BSRM versus ESRM. Although the recruitment of opioid-dependent patients with sexual risk behaviors is challenging, HIV testing with sexual risk reduction counseling in office-based buprenorphine/naloxone treatment practice is feasible. Interventions to decrease sexual risk behaviors among a segment of this population are necessary.

**Randomized Clinical Trial of Disulfiram for Cocaine Dependence or Abuse During Buprenorphine Treatment** Schottenfeld RS, Chawarski MC, Cubells JF, George TP, Lappalainen J, Kosten TR. *Drug Alcohol Depend.* 2014 Mar 1; 136: 36-42.

Disulfiram may be efficacious for treating cocaine dependence or abuse, possibly through inhibiting dopamine  $\beta$ -hydroxylase (D $\beta$ H). Consequently, this randomized, placebo-controlled clinical trial of disulfiram during buprenorphine maintenance treatment evaluated the study hypothesis that disulfiram is superior to placebo and explored whether disulfiram response is greatest for participants with a single nucleotide polymorphism coding for genetically low D $\beta$ H (T-allele carriers). The authors randomized 177 buprenorphine-treated opioid dependent participants with cocaine dependence or abuse to 12 weeks of double-blind treatment with disulfiram 250mg daily ( $n=91$ ) or placebo ( $n=86$ ). Of 155 participants genotyped, 84 were CC-homozygous, and 71 CT or TT genotypes. Primary outcomes included days per week cocaine use, number of cocaine-negative urine tests, and maximum consecutive weeks of cocaine abstinence. The authors analyzed an intention-to-treat comparison between disulfiram and placebo. They also explored potential pharmacogenetic interactions and examined treatment responses of four participant groups based on medication (disulfiram or placebo) by genotype (CC-homozygous or T-allele carrier) classification. Disulfiram participants reported significantly less frequent cocaine use; the differences in cocaine-negative urine tests or consecutive weeks abstinence were not significant. Frequency of cocaine use was lowest in disulfiram-treated T-allele carriers; differences in cocaine-negative urine tests or consecutive weeks abstinence were not significant among the four medication-genotype groups. The findings provide limited support for the efficacy of disulfiram for reducing cocaine use and suggest that its mechanism of action may involve inhibition of D $\beta$ H. Further studies of its efficacy, mechanism of action, and pharmacogenetics of response are warranted.

## **RESEARCH ON PHARMACOTHERAPIES FOR DRUG ABUSE**

### **William L. Woolverton: A Case History In Unraveling the Behavioral Pharmacology Of**

**Stimulants** Nader MA, Balster RL, Henningfield JE. *Neuropharmacology*. 2014 May 20. Clinical findings suggest that the most promising strategy for cocaine addiction is a combination of indirect-acting monoamine agonists with some form of behavioral intervention. This approach can be traced back to preclinical research, some of which was conducted by William L. Woolverton. The goal of this brief review is to provide readers with an appreciation for the experimental breadth involving both behavior and pharmacology that encompassed Woolverton's amazing career, from the evaluation of abuse liability of drugs to the use of complex behavioral contingencies to better model the human condition. The authors begin with Woolverton's research using simple and complex schedules of reinforcement to evaluate abuse liability and how that has impacted current animal models. They also discuss his use of cocaine vs. food choice schedules of reinforcement as a model to evaluate potential medications for treating cocaine use disorders. Woolverton concluded that drug taking behavior was not "impulsive" and "out of control" as has often been proposed, but rather directly determined by the environmental contingencies and the context of its availability, providing a nuanced understanding of drug-behavior interactions. This article is part of a Special Issue entitled 'CNS Stimulants'

### **The Cannabinoid Agonist HU-210: Pseudo-Irreversible Discriminative Stimulus Effects In**

**Rhesus Monkeys** Hrubá L, McMahon LR. *Eur J Pharmacol*. 2014 Mar 15;727:35-42.

Synthetic cannabinoid abuse and case reports of adverse effects have raised concerns about the pharmacologic mechanisms underlying in vivo effects. Here, a synthetic cannabinoid identified in abused products (HU-210) was compared to the effects of  $\Delta(9)$ -THC and two other synthetic cannabinoid agonists used extensively in pre-clinical studies (CP 55,940 and WIN 55,212-2). One group of monkeys discriminated  $\Delta(9)$ -THC (0.1mg/kg i.v.); a separate group received chronic  $\Delta(9)$ -THC (1mg/kg/12h s.c.) and discriminated rimonabant (1mg/kg i.v.). CP 55,940, HU-210,  $\Delta(9)$ -THC, and WIN 55,212-2 produced  $\Delta(9)$ -THC lever responding. HU-210 had a long duration (i.e., 1-2 days), whereas that of the other cannabinoids was 5h or less. Rimonabant (1mg/kg) produced surmountable antagonism; single dose-apparent affinity estimates determined in the presence of  $\Delta(9)$ -THC, CP 55,940, and WIN 55,212-2 did not differ from each other. In contrast, rimonabant (1mg/kg) produced a smaller rightward shift in the HU-210 dose-effect function. In  $\Delta(9)$ -THC treated monkeys, the relative potency of CP 55,940,  $\Delta(9)$ -THC, and WIN 55,212-2 to attenuate the discriminative stimulus effects of rimonabant was the same as that evidenced in the  $\Delta(9)$ -THC discrimination, whereas HU-210 was unexpectedly more potent in attenuating the effects of rimonabant. In conclusion, the same receptor subtype mediates the discriminative stimulus effects of  $\Delta(9)$ -THC, CP 55,940 and WIN 55,212-2. The limited effectiveness of rimonabant to either prevent or reverse the effects of HU-210 appears to be due to very slow dissociation or pseudo-irreversible binding of HU-210 at cannabinoid receptors.

### **Blood Levels Do Not Predict Behavioral Or Physiological Effects Of $\Delta^9$ -Tetrahydro-**

**cannabinol In Rhesus Monkeys With Different Patterns Of Exposure** Ginsburg BC, Hrubá L, Zaki A, Javors MA, McMahon LR. *Drug Alcohol Depend*. 2014 Jun 1; 139: 1-8.

Recent changes in the legality of cannabis have prompted evaluation of whether blood levels of  $\Delta(9)$ -tetrahydrocannabinol (THC) or its metabolites could be used to substantiate impairment, particularly related to behavioral tasks such as driving. However, because marked tolerance develops to behavioral effects of THC, the applicability of a particular threshold of blood THC as an index of impairment in people with different patterns of use remains unclear. Studies relevant to

this issue are difficult to accomplish in humans, as prior drug exposure is difficult to control. Here, effects of THC to decrease rectal temperature and operant response rate compared to levels of THC and its metabolites were studied in blood in two groups of monkeys: one received intermittent treatment with THC (0.1 mg/kg i.v. every 3-4 days) and another received chronic THC (1 mg/kg/12 h s.c.) for several years. In monkeys with intermittent THC exposure, a single dose of THC (3.2 mg/kg s.c.) decreased rectal temperature and response rate. The same dose did not affect response rate or rectal temperature in chronically exposed monkeys, indicative of greater tolerance. In both groups, blood levels of THC peaked 20-60 min post-injection and had a similar half-life of elimination, indicating no tolerance to the pharmacokinetics of THC. Notably, in both groups, the behavioral effects of THC were not apparent when blood levels were maximal (20-min post-administration). These data indicate that thresholds for blood levels of THC do not provide a consistent index of behavioral impairment across individuals with different patterns of THC exposure.

### **Abuse-Related Effects Of Dual Dopamine/Serotonin Releasers With Varying Potency To**

**Release Norepinephrine In Male Rats and Rhesus Monkeys** Banks ML, Bauer CT, Blough BE, Rothman RB, Partilla JS, Baumann MH, Negus SS. *Exp Clin Psychopharmacol.* 2014 Jun; 22(3): 274-84.

d-Amphetamine selectively promotes release of both dopamine (DA) and norepinephrine (NE) versus serotonin (5HT), and chronic d-amphetamine treatment decreases cocaine-taking behavior in rats, nonhuman primates, and humans. However, abuse liability limits the clinical utility of amphetamine maintenance for treating cocaine abuse. One strategy to improve safety and efficacy of monoamine releasers as candidate anticocaine medications has been to develop dual DA/5HT releasers like 1-naphthyl-2-aminopropane (PAL-287), but the pharmacology of this class of compounds has not been extensively examined. In particular, PAL-287 has similar potencies to release DA, 5HT, and NE, and the role of manipulating NE release potency on abuse-related or anticocaine effects of dual DA/5HT releasers is not known. To address this issue, the present study compared effects of four novel DA/5HT releasers that varied >800-fold in their selectivities to release DA/5HT versus NE: [1-(5-chloro-1H-indol-3-yl)propan-2-amine (PAL-542), 1-(5-fluoro-1H-indol-3-yl)propan-2-amine (PAL-544), 1-(1H-indol-5-yl)propan-2-amine (PAL-571), and (R)-1-(1H-indol-1-yl)propain-2-amine (PAL-569). Abuse-related effects of all four compounds were evaluated in assays of intracranial self-stimulation (ICSS) in rats and cocaine discrimination in rats and monkeys, and none of the compounds reliably facilitated ICSS or substituted for cocaine. Anticocaine effects of the compound with highest selectivity to release DA/5HT versus NE (PAL-542) were tested in an assay of cocaine versus food choice in rhesus monkeys, and PAL-542 failed to reduce cocaine choice. These results suggests that potency to release NE has minimal influence on abuse liability of dual DA/5HT releasers, and reducing relative potency to release NE versus DA/5HT does not improve anticocaine efficacy.

### **Rat Nucleus Accumbens Core Astrocytes Modulate Reward and the Motivation to Self-Administer Ethanol after Abstinence**

Bull C, Freitas KC, Zou S, Poland RS, Syed WA, Urban DJ, Minter SC, Shelton KL, Hauser KF, Negus SS, Knapp PE, Bowers MS. *Neuropsychopharmacology.* 2014 Jun 6.

Our understanding of the active role that astrocytes play in modulating neuronal function and behavior is rapidly expanding, but little is known about the role that astrocytes may play in drug-seeking behavior for commonly abused substances. Given that the nucleus accumbens is critically involved in substance abuse and motivation, the authors sought to determine if nucleus accumbens astrocytes influence the motivation to self-administer ethanol following abstinence. They found that

the packing density of astrocytes that were expressing glial fibrillary acidic protein increased in the nucleus accumbens core during abstinence from EtOH self-administration. No change was observed in the nucleus accumbens shell. This increased nucleus accumbens core astrocyte density positively correlated with the motivation for ethanol. Astrocytes can communicate with one another and influence neuronal activity through gap-junction hemichannels. Because of this, the effect of blocking gap-junction hemichannels on the motivation for ethanol was examined. The motivation to self-administer ethanol after 3 wks abstinence was increased following microinjection of gap-junction hemichannel blockers into the nucleus accumbens core at doses that block both neuronal and astrocytic channels. In contrast, no effect was observed following microinjection of doses that are not thought to block astrocytic channels or following microinjection of either dose into the nucleus accumbens shell. Additionally, the motivation for sucrose after 3 wks abstinence was unaffected by nucleus accumbens core gap-junction hemichannel blockers. Next, Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) were selectively expressed in nucleus accumbens core astrocytes to test the effect of astrocyte stimulation. DREADD activation increased cytosolic calcium in primary astrocytes, facilitated responding for rewarding brain stimulation, and reduced the motivation for ethanol after 3 wks abstinence. This is the first work to modulate drug-seeking behavior with astrocyte-specific DREADDs. Taken together, these findings demonstrate that nucleus accumbens core astrocytes can shape the motivation to self-administer ethanol; suggesting that the development of ligands which selectively stimulate astrocytes may be a successful strategy to abate ethanol-seeking behavior.

**Effects Of the Nicotinic Acetylcholine Receptor Antagonist Mecamylamine On the Discriminative Stimulus Effects Of Cocaine In Male Rhesus Monkeys** Banks ML. *Exp Clin Psychopharmacol.* 2014 Jun; 22(3): 266-7.

Preclinical drug discrimination procedures have been useful in understanding the pharmacological mechanisms of the subjective-like effects of abused drugs. Converging lines of evidence from neurochemical and behavioral studies implicate a potential role of nicotinic acetylcholine (nACh) receptors in the abuse-related effects of cocaine. The aim of the present study was to determine the effects of the nACh receptor antagonist mecamylamine on the discriminative stimulus effects of cocaine in nonhuman primates. The effects of mecamylamine on the cocaine-like discriminative stimulus effects of nicotine were also examined. Male rhesus monkeys ( $n = 5$ ) were trained to discriminate 0.32 mg/kg, IM cocaine from saline in a 2-key, food-reinforced discrimination procedure. Initially, potency and time course of cocaine-like discriminative stimulus effects were determined for nicotine and mecamylamine alone. Test sessions were then conducted examining the effects of mecamylamine on cocaine or the cocaine-like discriminative stimulus effects of nicotine. Curiously, mecamylamine produced partial cocaine-like discriminative stimulus effects. Mecamylamine did not significantly alter the discriminative stimulus effects of cocaine up to doses that significantly decreased rates of operant responding. Mecamylamine and nicotine combinations were not different than saline. These results confirm previous nonhuman primate studies of partial substitution with nicotine and extend these findings with mecamylamine. Furthermore, these results extend previous results in rats suggesting cocaine may have nACh receptor antagonist properties.

**The Effect Of Chronic Amphetamine Treatment On Cocaine-Induced Facilitation Of Intracranial Self-Stimulation In Rats** Bauer CT, Banks ML, Negus SS. *Psychopharmacology (Berl).* 2014 Jun; 231(12): 2461-70.

Chronic amphetamine treatment reduces cocaine self-administration in pre-clinical and clinical settings, and amphetamine has been proposed as a candidate medication for treatment of cocaine abuse. The objective of the present study was to investigate whether chronic amphetamine

treatment can decrease abuse-related cocaine effects in an assay of intracranial self-stimulation (ICSS). Thirteen adult male Sprague-Dawley rats were equipped with intracranial electrodes targeting the medial forebrain bundle and trained to lever press for pulses of brain stimulation in a "frequency-rate" ICSS procedure. Cocaine (10 mg/kg) was administered before (day 0), during (days 7 and 14), and after (posttreatment days 1 and 3) 2 weeks of continuous treatment with either amphetamine (0.32 mg/kg/h, n=7) or saline (n=6) via osmotic pump. Prior to treatment, cocaine facilitated ICSS in all rats. Saline treatment had no effect on baseline ICSS or cocaine-induced facilitation of ICSS at any time. Conversely, amphetamine produced a sustained though submaximal facilitation of baseline ICSS, and cocaine produced little additional facilitation of ICSS during amphetamine treatment. Termination of amphetamine treatment produced a depression of baseline ICSS and recovery of cocaine-induced facilitation of ICSS. These data suggest that chronic amphetamine treatment blunts expression of abuse-related cocaine effects on ICSS in rats.

**Effects Of Chronic Varenicline Treatment On Nicotine, Cocaine, and Concurrent Nicotine+Cocaine Self-Administration** Mello NK, Fivel PA, Kohut SJ, Carroll FI.

Neuropsychopharmacology. 2014 Apr; 39(5): 1222-31.

Nicotine dependence and cocaine abuse are major public health problems, and most cocaine abusers also smoke cigarettes. An ideal treatment medication would reduce both cigarette smoking and cocaine abuse. Varenicline is a clinically available, partial agonist at  $\alpha 4\beta 2^*$  and  $\alpha 6\beta 2^*$  nicotinic acetylcholine receptors (nAChRs) and a full agonist at  $\alpha 7$  nAChRs. Varenicline facilitates smoking cessation in clinical studies and reduced nicotine self-administration, and substituted for the nicotine-discriminative stimulus in preclinical studies. The present study examined the effects of chronic varenicline treatment on self-administration of IV nicotine, IV cocaine, IV nicotine+cocaine combinations, and concurrent food-maintained responding by five cocaine- and nicotine-experienced adult rhesus monkeys (*Macaca mulatta*). Varenicline (0.004-0.04mg/kg/h) was administered intravenously every 20min for 23h each day for 7-10 consecutive days. Each varenicline treatment was followed by saline-control treatment until food- and drug-maintained responding returned to baseline. During control treatment, nicotine+cocaine combinations maintained significantly higher levels of drug self-administration than nicotine or cocaine alone ( $P < 0.05-0.001$ ). Varenicline dose-dependently reduced responding maintained by nicotine alone (0.0032mg/kg/inj) ( $P < 0.05$ ), and in combination with cocaine (0.0032mg/kg/inj) ( $P < 0.05$ ) with no significant effects on food-maintained responding. However, varenicline did not significantly decrease self-administration of a low dose of nicotine (0.001mg/kg), cocaine alone (0.0032 and 0.01mg/kg/inj), or 0.01mg/kg cocaine combined with the same doses of nicotine. The authors conclude that varenicline selectively attenuates the reinforcing effects of nicotine alone but not cocaine alone, and its effects on nicotine+cocaine combinations are dependent on the dose of cocaine.

**Acute and Chronic Effects Of The M1/M4-Preferring Muscarinic Agonist Xanomeline On Cocaine Vs. Food Choice In Rats** Thomsen M, Fulton BS, Caine SB. Psychopharmacology (Berl). 2014 Feb; 231(3): 469-79.

The authors previously showed that the M1/M4-preferring muscarinic agonist xanomeline can acutely attenuate or eliminate cocaine self-administration in mice. Medications used to treat addictions will arguably be administered in (sub)chronic or repeated regimens. Tests of acute effects often fail to predict chronic effects, highlighting the need for chronic testing of candidate medications. Rats were trained to lever press under a concurrent FR5 FR5 schedule of intravenous cocaine and food reinforcement. Once baseline behavior stabilized, the effects of 7 days once-daily injections of xanomeline were evaluated. Xanomeline pretreatment dose-dependently (1.8-

10 mg/kg/day) shifted the dose-effect curve for cocaine rightward (up to 5.6-fold increase in A 50), with reallocation of behavior to the food-reinforced lever. There was no indication of tolerance, rather effects grew over days. The suppression of cocaine choice appeared surmountable at high cocaine doses, and xanomeline treatment did not significantly decrease total-session cocaine or food intake. In terms of xanomeline's potential for promoting abstinence from cocaine in humans, the findings were mixed. Xanomeline did produce reallocation of behavior from cocaine to food with a robust increase in food reinforcers earned at some cocaine/xanomeline dose combinations. However, effects appeared surmountable, and food-maintained behavior was also decreased at some xanomeline/cocaine dose combinations, suggesting clinical usefulness may be limited. These data nevertheless support the notion that chronic muscarinic receptor stimulation can reduce cocaine self-administration. Future studies should show whether ligands with higher selectivity for M1 or M1/M4 subtypes would be less limited by undesired effects and can achieve higher efficacy

### **Locomotor Activating Effects Of Cocaine and Scopolamine Combinations In Rats:**

**Isobolographic Analysis** Thomsen M. Behav Pharmacol. 2014 Apr 24.

Muscarinic cholinergic receptors are currently receiving renewed interest as viable targets for treating various psychiatric disorders. Dopaminergic and muscarinic systems interact in complex ways. The goal of this study was to quantify the interaction between a systemically administered psychomotor stimulant and muscarinic antagonist at the behavioral level. Through isobolographic analysis of locomotor activity data, the authors assessed the effects of three cocaine/scopolamine mixtures in terms of deviation from simple dose addition (additivity), at four effect levels. All three mixtures produced some more-than-additive (synergistic) effects, as lower doses were needed to produce the given effects relative to the calculated effect of additive doses. A mixture with comparable contributions from cocaine and scopolamine produced significantly more-than-additive effects at all but the lowest effect level examined. A mostly-cocaine mixture was more-than-additive only at low effect levels, whereas a mostly-scopolamine mixture produced effects more consistent with additivity, with only the highest effect level barely reaching significant synergism. This study confirms and quantifies previous findings that suggested synergistic effects of stimulants and muscarinic antagonists. The synergism implies that cocaine and scopolamine stimulate locomotor activity through nonidentical pathways, and was most pronounced for a mixture containing cocaine and scopolamine in comparable proportions.

### **Designing Bifunctional NOP Receptor-Mu Opioid Receptor Ligands From NOP-Receptor Selective Scaffolds. Part II** Journigan VB, Polgar WE, Khroyan TV, Zaveri NT. Bioorg Med Chem. 2014 Apr 15; 22(8): 2508-16.

The nociceptin opioid receptor (NOP) and its endogenous peptide ligand nociceptin/orphanin FQ have been shown to modulate the pharmacological effects of the classical opioid receptor system. Suppression of opioid-induced reward associated with mu-opioid receptor (MOP)-mediated analgesia, without decreasing anti-nociceptive efficacy, can potentially be achieved with NOP agonists having bifunctional agonist activity at MOP, to afford 'non-addicting' analgesics. In Part II of this series, the authors describe a continuing structure-activity relationship (SAR) study of the NOP-selective piperidin-4-yl-1,3-dihydroindol-2-one scaffold, to obtain bifunctional activity at MOP, and a suitable ratio of NOP/MOP agonist activity that produces a non-addicting analgesic profile. The SAR reported here is focused on the influence of various piperidine nitrogen aromatic substituents on the ratio of binding affinity and intrinsic activity at both the NOP and MOP receptors.

**The Vesicular Monoamine Transporter-2: An Important Pharmacological Target For the Discovery Of Novel Therapeutics To Treat Methamphetamine Abuse** Nickell JR, Siripurapu KB, Vartak A, Crooks PA, Dwoskin LP. *Adv Pharmacol.* 2014; 69: 71-106.

Methamphetamine abuse escalates, but no approved therapeutics are available to treat addicted individuals. Methamphetamine increases extracellular dopamine in reward-relevant pathways by interacting at vesicular monoamine transporter-2 (VMAT2) to inhibit dopamine uptake and promote dopamine release from synaptic vesicles, increasing cytosolic dopamine available for reverse transport by the dopamine transporter (DAT). VMAT2 is the target of our iterative drug discovery efforts to identify pharmacotherapeutics for methamphetamine addiction. Lobeline, the major alkaloid in *Lobelia inflata*, potently inhibited VMAT2, methamphetamine-evoked striatal dopamine release, and methamphetamine self-administration in rats but exhibited high affinity for nicotinic acetylcholine receptors (nAChRs). Defunctionalized, unsaturated lobeline analog, meso-transdiene (MTD), exhibited lobeline-like in vitro pharmacology, lacked nAChR affinity, but exhibited high affinity for DAT, suggesting potential abuse liability. The 2,4-dichlorophenyl MTD analog, UKMH-106, exhibited selectivity for VMAT2 over DAT, inhibited methamphetamine-evoked dopamine release, but required a difficult synthetic approach. Lobelane, a saturated, defunctionalized lobeline analog, inhibited the neurochemical and behavioral effects of methamphetamine; tolerance developed to the lobelane-induced decrease in methamphetamine self-administration. Improved drug-likeness was afforded by the incorporation of a chiral N-1,2-dihydroxypropyl moiety into lobelane to afford GZ-793A, which inhibited the neurochemical and behavioral effects of methamphetamine, without tolerance. From a series of 2,5-disubstituted pyrrolidine analogs, AV-2-192 emerged as a lead, exhibiting high affinity for VMAT2 and inhibiting methamphetamine-evoked dopamine release. Current results support the hypothesis that potent, selective VMAT2 inhibitors provide the requisite preclinical behavioral profile for evaluation as pharmacotherapeutics for methamphetamine abuse and emphasize selectivity for VMAT2 relative to DAT as a criterion for reducing abuse liability of the therapeutic.

**Environmental Enrichment Reduces Methamphetamine Cue-Induced Reinstatement But Does Not Alter Methamphetamine Reward Or VMAT2 Function** Hofford RS, Darna M, Wilmouth CE, Dwoskin LP, Bardo MT. *Behav Brain Res.* 2014 May 10; 270C: 151-158.

Environmental factors influence a variety of health-related outcomes. In general, being raised in an environment possessing social, sensory, and motor enrichment reduces the rewarding effects of various drugs, thus protecting against abuse vulnerability. However, in the case of methamphetamine (METH), which acts at the vesicular monoamine transporter 2 (VMAT2) to enhance dopamine release from the cytosol, previous evidence suggests that METH reward may not be altered by environmental enrichment. This study examined the influence of an enriched environment on measures of METH reward, METH seeking, and VMAT2 function. Rats were raised from weaning to adulthood in either an enriched environment (presence of social cohorts and novel objects) or an isolated environment (no cohorts or novel objects). Rats in these two conditions were subsequently tested for their acquisition of conditioned place preference (CPP), METH self-administration, maintenance of self-administration at various unit doses of METH (0.001-0.5mg/kg/infusion), and cue-induced reinstatement. VMAT2 function in striatum from these two groups also was assessed. No significant environment effects were found in CPP or METH self-administration, which paralleled a lack of effect in VMAT2 function between groups. However, cue-induced reinstatement was reduced by environmental enrichment. Together, these results suggest that environmental enrichment does not alter VMAT2 function involved in METH reward. However, the enrichment-induced decrease in cue-induced reinstatement indicates that enrichment

may have a beneficial effect against relapse following a period of extinction via a neural mechanism other than striatal VMAT2 function,

**The Relationship Between the Nicotine Metabolite Ratio and Three Self-report Measures Of Nicotine Dependence Across Sex and Race** Schnoll, RA, George TP, Hawk L, Cinciripini P,

Wileyto P, Tyndale RF. *Psychopharmacology (Berl)*. 2014; 231(12): 2515-23.

Variability in the rate of nicotine metabolism, measured by the nicotine metabolite ratio (NMR), is associated with smoking behavior. However, data linking the NMR with nicotine dependence measured by the Fagerstrom test for nicotine dependence (FTND) are mixed. Few past studies have examined alternative measures of nicotine dependence and how this relationship may vary by sex and race. Using data from smokers undergoing eligibility evaluation for a smoking cessation clinical trial (n=833), this study examined variability in the relationship between NMR and nicotine dependence across sex and race and using three measures of nicotine dependence: FTND, time-to-first-cigarette (TTFC), and the heaviness of smoking index (HSI). Controlling for sex and race, nicotine metabolism was associated with nicotine dependence only when using the HSI ( $p<0.05$ ). Male normal metabolizers of nicotine were more likely to have high nicotine dependence based on the FTND and HSI ( $p<0.05$ ), but NMR was not related to measures of nicotine dependence in women. For African Americans, the NMR was associated with nicotine dependence only for the TTFC ( $p<0.05$ ), but NMR was not associated with nicotine dependence among Caucasians. Post hoc analyses indicated that the NMR was associated with cigarettes per day, overall, and among men and Caucasians ( $p<0.05$ ). While there was some variation in the relationship between nicotine metabolism and nicotine dependence across measures and sex and race, the results indicate that this relationship may be more attributable to the association between NMR and cigarettes per day.

**Are Statewide Restaurant and Bar Smoking Bans Associated With Reduced Cigarette Smoking Among Those With Mental Illness?** Smith PH, Young-Wolff KC Hyland A, McKee

SA. *Nicotine Tob Res*. 2014; 16(6): 846-54.

Smoke-free air laws have effectively reduced cigarette consumption at the population level; however, the influence of these policies on smoking among those with mental illness is unclear. The authors examined whether associations between statewide restaurant/bar smoking bans and cigarette smoking varied by psychiatric diagnoses and gender. They analyzed data from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC, Wave 1: 2001-2002; Wave 2: 2004-2005; n = 7,317 smokers). All analyses were stratified by gender. The authors examined whether tobacco cessation was associated with the interaction between ban implementation and Wave 1 psychiatric diagnoses (alcohol use disorder [AUD], anxiety disorder [AD], or mood disorder), adjusting for relevant covariates. Among those who continued to use tobacco at Wave 2, they examined associations between Wave 2 cigarettes per day (CPD) and the diagnoses ban interactions, controlling for Wave 1 CPD and other relevant covariates. Among men with an AUD and women with an AD, ban implementation was associated with 6% and 10% greater probability of tobacco cessation at Wave 2, respectively. Among men in the overall sample, ban implementation was associated with smoking 0.8 fewer CPD at Wave 2. Associations with CPD were nonsignificant among women. Interactions between ban implementation and psychiatric diagnoses were also nonsignificant when examining CPD, suggesting consistent reductions in CPD among men but not among women. This study provided the first evidence that statewide restaurant/bar smoking bans may be associated with reduced smoking among those with select psychiatric conditions.

**Methylnaltrexone: Its Pharmacological Effects Alone and Effects On Morphine In Healthy Volunteers** Zacny JP, Wroblewski K, Coalson DW. Psychopharmacology (Berl). 2014.

Methylnaltrexone bromide (MTNX) is a peripherally acting mu-opioid receptor antagonist, prescribed for the treatment of opioid-induced constipation in patients with advanced illness who are receiving palliative care. Studies have used this drug to determine if other opioid-induced effects besides constipation are altered by MTNX in humans and have suggested, based on their results, that these other effects are altered by peripheral opioid actions. The primary objective of this report is to present results that provide indirect evidence that MTNX has centrally mediated effects, albeit slight, and secondarily to describe the effects of MTNX on psychopharmacological effects of morphine. In a crossover, randomized, placebo-controlled, double-blind study, 29 healthy volunteers received 0.45mg/kg MTNX or saline subcutaneously, followed by saline intravenously. In three other conditions, 0.143mg/kg of morphine sulfate administered intravenously was preceded by subcutaneous administration of 0, 0.225, or 0.45mg/kg MTNX. Before and after drug administration, subjective and physiological measures, including pupil diameter, were assessed. Two separate analyses confirmed that 0.45mg/kg MTNX alone induced a slight degree of miosis, a centrally mediated opioid agonist effect. This dose had minimal subjective effects. MTNX at either or both the 0.225 and 0.45mg/kg dose reduced some subjective effects of morphine without altering miosis. The authors present indirect evidence that MTNX crosses the blood-brain barrier in humans. Therefore, whether the reductions in subjective effects of morphine by MTNX that were observed in past studies and in this study can be attributed to peripheral mechanisms is open to question.

**Optimizing Treatments For Nicotine Dependence By Increasing Cognitive Performance**

**During Withdrawal** Ashare RL, Schmidt HD. Expert Opin Drug Discov. 2014; 9(6): 579-94.

Current FDA-approved smoking cessation pharmacotherapies have limited efficacy and are associated with high rates of relapse. Therefore, there is a clear need to develop novel antismoking medications. Nicotine withdrawal is associated with cognitive impairments that predict smoking relapse. It has been proposed that these cognitive deficits are a hallmark of nicotine withdrawal that could be targeted in order to prevent smoking relapse. Thus, pharmacotherapies that increase cognitive performance during nicotine withdrawal may represent potential smoking cessation agents. The authors review the clinical literature demonstrating that nicotine withdrawal is associated with deficits in working memory, attention and response inhibition. They then briefly summarize different classes of compounds and strategies to increase cognitive performance during nicotine withdrawal. Particular emphasis has been placed on translational research in order to highlight areas for which there is strong rationale for pilot clinical trials of potential smoking cessation medications. There is emerging evidence that supports deficits in cognitive function as a plausible nicotine withdrawal phenotype. The authors furthermore believe that the translational paradigms presented here may represent efficient and valid means for the evaluation of cognitive-enhancing medications as possible treatments for nicotine dependence.

**Differential Effects Of Non-Nicotine Tobacco Constituent Compounds On Nicotine Self-administration In Rats**

Hall BJ, Wells C, Allenby C, Lin MY, Hao I, Marshall L, Rose JE, Levin ED. Pharmacol Biochem Behav. 2014; 120: 103-8.

Tobacco smoking has been shown to be quite addictive in people. However, nicotine itself is a weak reinforcer compared to other commonly abused drugs, leading speculation that other factors contribute to the high prevalence of tobacco addiction in the human population. In addition to nicotine, there are over 5000 chemical compounds that have been identified in tobacco smoke, and more work is needed to ascertain their potential contributions to tobacco's highly addictive properties, or as potential candidates for smoking cessation treatment. In this study, the authors

examined seven non-nicotine tobacco constituent compounds (anabasine, anatabine, nornicotine, myosmine, harmine, norharmine, and tyramine) for their effects on nicotine self-administration behavior in rats. Young adult female Sprague-Dawley rats were allowed to self-administer nicotine (0.03 mg/kg/50 \*1 infusion) under a fixed ratio-1 schedule of reinforcement. Each self-administration session lasted 45 min. Doses of each tobacco constituent compound were administered subcutaneously 10 min prior to the start of each session in a repeated measures, counterbalanced order two times. Anabasine displayed a biphasic dose-effect function. Pretreatment with 0.02 mg/kg anabasine resulted in a 25% increase in nicotine self-administration, while 2.0mg/kg of anabasine reduced nicotine infusions per session by over 50%. Pretreatment with 2.0mg/kg anatabine also significantly reduced nicotine self-administration by nearly half. These results suggest that some non-nicotine tobacco constituents may enhance or reduce nicotine's reinforcing properties. Also, depending upon the appropriate dose, some of these compounds may also serve as potential smoking cessation agents.

### **Nicotine Dependence As A Moderator Of Genetic Influences On Smoking Cessation**

**Treatment Outcome** Leventhal AM, Lee W, Bergen AW, Swan GE, Tyndale RF, Lerman C, Conti DV. *Drug Alcohol Depend.* 2014; 138: 109-17.

Genetic influences on smoking cessation treatment outcome may be affected by pretreatment patient characteristics. Nicotine dependence is arguably the most salient clinical factor in smoking cessation. In this secondary analysis of clinical trial data (N=793), the authors examined nicotine dependence severity as a moderator of the effects of 1198 single nucleotide polymorphisms (SNPs) in 53 biologically-relevant gene regions on smoking cessation outcomes. P-values were adjusted to account for multiple correlated SNPs within a gene region; corrected system-wide significance was  $5 \times 10^{-4}$ . SNP nicotine dependence interactions reached region-wide significance for several SNPs in the Dopamine Beta Hydroxylase (DBH) locus ( $0.0005 < \text{Adjusted-P} < 0.05$ ), including rs1541333, which reached system-wide significance for predicting end of treatment (EOT) abstinence (Adjusted-P=0.0004). A haplotype including 6 DBH SNPs predicted abstinence at EOT (OR=1.7, P=0.001) and 6-month follow-up (OR=1.6, P=0.008) in those with high nicotine dependence (n=526) but not in those with low dependence (n=227). The DBH signal observed here may be distinct from a previously reported genome-wide significant signal for former smoking status and from the principal haplotype associated with plasma dopamine beta-hydroxylase activity. A haplotype within the Chromosome 15 Nicotinic Acetylcholine Receptor gene region predicted abstinence at EOT in those with high (OR=2.0, P=0.0004) but not low (P=0.6) dependence in post hoc analyses. Considering pre-treatment nicotine dependence level may optimize the prediction of genetic influences on cessation outcomes. If replicated, results like these may inform prognosticative genomic screening panels designed to identify smokers at high risk of relapse when coupled with severe nicotine dependence.

### **Combination Treatment With Varenicline and Bupropion in an Adaptive Smoking Cessation Paradigm**

Rose JE, Behm FM. *Am J Psychiatry* June 17 2014.

The authors assessed the efficacy and safety of combination treatment with varenicline and sustained-release bupropion for smokers who, based on an assessment of initial smoking reduction prior to the quit date, were deemed unlikely to achieve abstinence using nicotine patch treatment. In a randomized, double-blind, parallel-group adaptive treatment trial, the authors identified 222 cigarette smokers who failed to show a reduction of more than 50% in smoking after 1 week of nicotine patch treatment. Smokers were randomly assigned to receive 12 weeks of varenicline plus bupropion or varenicline plus placebo. The primary outcome measure was continuous smoking abstinence at weeks 8–11 after the target quit date. Both treatments were well tolerated. Participants

who received the combination treatment had a significantly higher abstinence rate than those who received varenicline plus placebo (39.8% compared with 25.9%; odds ratio=1.89; 95% CI=1.07, 3.35). Combination treatment had a significantly greater effect on abstinence rate in male smokers (odds ratio=4.26; 95% CI=1.73, 10.49) than in female smokers (odds ratio=0.94; 95% CI=0.43, 2.05). It also had a significantly greater effect in highly nicotine-dependent smokers (odds ratio=3.51, 95% CI=1.64, 7.51) than in smokers with lower levels of dependence (odds ratio=0.71, 95% CI=0.28, 1.80). Among smokers who did not show a sufficient initial response to prequit nicotine patch treatment, combination treatment with varenicline and bupropion proved more efficacious than varenicline alone for male smokers and for smokers with a high degree of nicotine dependence.

### **Nipping Cue Reactivity In the Bud: Baclofen Prevents Limbic Activation Elicited By Subliminal Drug Cues**

Young KA, Franklin TR, Roberts DC, Jagannathan K, Suh JJ, Wetherill RR, Wang Z, Kampman KM, O'Brien CP, Childress AR. *J Neurosci.* 2014 Apr; 34(14): 5038-43. Relapse is a widely recognized and difficult to treat feature of the addictions. Substantial evidence implicates cue-triggered activation of the mesolimbic dopamine system as an important contributing factor. Even drug cues presented outside of conscious awareness (i.e., subliminally) produce robust activation within this circuitry, indicating the sensitivity and vulnerability of the brain to potentially problematic reward signals. Because pharmacological agents that prevent these early cue-induced responses could play an important role in relapse prevention, the authors examined whether baclofen—a GABA<sub>B</sub> receptor agonist that reduces mesolimbic dopamine release and conditioned drug responses in laboratory animals—could inhibit mesolimbic activation elicited by subliminal cocaine cues in cocaine-dependent individuals. Twenty cocaine-dependent participants were randomized to receive baclofen (60 mg/d; 20 mg t.i.d.) or placebo. Event-related BOLD fMRI and a backward-masking paradigm were used to examine the effects of baclofen on subliminal cocaine (vs neutral) cues. Sexual and aversive cues were included to examine specificity. The authors observed that baclofen-treated participants displayed significantly less activation in response to subliminal cocaine (vs neutral) cues, but not sexual or aversive (vs neutral) cues, than placebo-treated participants in a large interconnected bilateral cluster spanning the ventral striatum, ventral pallidum, amygdala, midbrain, and orbitofrontal cortex (voxel threshold  $p < 0.005$ ; cluster corrected at  $p < 0.05$ ). These results suggest that baclofen may inhibit the earliest type of drug cue-induced motivational processing—that which occurs outside of awareness—before it evolves into a less manageable state.

### **Naltrexone Treatment For Opioid Dependence: Does Its Effectiveness Depend On Testing The Blockade?**

Sullivan MA, Bisaga A, Mariani JJ, Glass A, Levin FR, Comer SD, Nunes EV. *Drug Alcohol Depend.* 2013 Nov; 133(1): 80-5. FDA approval of long-acting injectable naltrexone (Vivitrol) for opioid dependence highlights the relevance of understanding mechanisms of antagonist treatment. Principles of learning suggest an antagonist works through extinguishing drug-seeking behavior, as episodes of drug use ("testing the blockade") fail to produce reinforcement. The authors hypothesized that opiate use would moderate the effect of naltrexone, specifically, that opiate-positive urines precede dropout in the placebo group, but not in the active-medication groups. An 8-week, double-blind, placebo-controlled trial (N=57), compared the efficacy of low (192 mg) and high (384 mg) doses of a long-acting injectable naltrexone (Depotrex) with placebo (Comer et al., 2006). A Cox proportional hazard model was fit, modeling time-to-dropout as a function of treatment assignment and urine toxicology during treatment. Interaction of opiate urines with treatment group was significant. Opiate-positive urines predicted dropout on placebo and low-dose, but less so on high-dose naltrexone, where positive

urines were more likely followed by sustained abstinence. Among patients with no opiate-positive urines, retention was higher in both low- and high-dose naltrexone conditions, compared to placebo. Findings confirm that injection naltrexone produces extinction of drug-seeking behavior after episodes of opiate use. Adequate dosage appears important, as low-dose naltrexone resembled the placebo group; opiate positive urines were likely to be followed by dropout from treatment. The observation of high treatment retention among naltrexone-treated patients who do not test the blockade, suggests naltrexone may also exert direct effects on opiate-taking behavior that do not depend on extinction, perhaps by attenuating craving or normalizing dysregulated hedonic or neuroendocrine systems.

### **Vaccine For Cocaine Dependence: A Randomized Double-Blind Placebo-Controlled Efficacy Trial**

Kosten TR, Domingo CB, Shorter D, Orson F, Green C, Somoza E, Sekerka R, Levin FR, Mariani JJ, Stitzer M, Tompkins DA, Rotrosen J, Thakkar V, Smoak B, Kampman K. *Drug Alcohol Depend.* 2014 Jul; 140[Epub ahead of print] 42-7.

The authors evaluated the immunogenicity, efficacy, and safety of succinyl-norcocaine conjugated to cholera toxin B protein as a vaccine for cocaine dependence. This 6-site, 24 week Phase III randomized double-blind placebo-controlled trial assessed efficacy during weeks 8 to 16. The authors measured urine cocaine metabolites thrice weekly as the main outcome. The 300 subjects (76% male, 72% African-American, mean age 46 years) had smoked cocaine on average for 13 days monthly at baseline. They hypothesized that retention might be better and positive urines lower for subjects with anti-cocaine IgG levels of  $\geq 42 \mu\text{g/mL}$  (high IgG), which was attained by 67% of the 130 vaccine subjects receiving five vaccinations. Almost 3-times fewer high than low IgG subjects dropped out (7% vs 20%). Although for the full 16 weeks cocaine positive urine rates showed no significant difference between the three groups (placebo, high, low IgG), after week 8, more vaccinated than placebo subjects attained abstinence for at least two weeks of the trial (24% vs 18%), and the high IgG group had the most cocaine-free urines for the last 2 weeks of treatment (OR=3.02), but neither were significant. Injection site reactions of induration and tenderness differed between placebo and active vaccine, and the 29 serious adverse events did not lead to treatment related withdrawals, or deaths. The vaccine was safe, but it only partially replicated the efficacy found in the previous study based on retention and attaining abstinence.

### **C-Ring Cannabinoid Lactones: A Novel Cannabinergic Chemotype** Sharma R, Nikas SP, Guo JJ, Mallipeddi S, Wood JT, Makriyannis A. *ACS Med Chem Lett.* 2014 Apr; 5(4): 400-4.

As a part of their controlled-deactivation ligand development project, the authors recently disclosed a series of (-)- $\Delta(8)$ -tetrahydrocannabinols (THCs) with a metabolically labile ester group at the 2'-position of the side chain. Now, they have replaced the C-ring in the classical THC structure with a hydrolyzable seven-membered lactone. One of the synthesized analogues binds with high affinity to the CB1 receptor ( $K_i = 4.6 \text{ nM}$ ) and exhibits much lower affinities for the mCB2 and the hCB2. Also, in vitro functional characterization found the compound to be an agonist at rCB1. Consistent with our rational design, the lead cannabinergic lactone identified here is susceptible to metabolic inactivation by plasma esterases, while the respective acid metabolite is inactive at CB receptors. These results are highlighted with molecular modeling of the two regiosomeric lactones.

### **Physiologic and Metabolic Safety Of Butyrylcholinesterase Gene Therapy In Mice** Murthy V, Gao Y, Geng L, LeBrasseur NK, White TA, Parks RJ, Brimijoin S. *Vaccine.* 2014 Jul; 32(33): 4155-62.

In continuing efforts to develop gene transfer of human butyrylcholinesterase (BChE) as therapy for cocaine addiction, the authors conducted wide-ranging studies of physiological and metabolic

safety. For that purpose, mice were given injections of adeno-associated virus (AAV) vector or helper-dependent adenoviral (hdAD) vector encoding human or mouse BChE mutated for optimal cocaine hydrolysis. Age-matched controls received saline or AAV-luciferase control vector. At times when transduced BChE was abundant, physiologic and metabolic parameters in conscious animals were evaluated by non-invasive Echo-MRI and an automated "Comprehensive Laboratory Animal Monitoring System" (CLAMS). Despite high vector doses (up to 10(13) particles per mouse) and high levels of transgene protein in the plasma (~1500-fold above baseline), the CLAMS apparatus revealed no adverse physiologic or metabolic effects. Likewise, body composition determined by Echo-MRI, and glucose tolerance remained normal. A CLAMS study of vector-treated mice given 40mg/kg cocaine showed none of the physiologic and metabolic fluctuations exhibited in controls. The authors conclude that neither the tested vectors nor great excesses of circulating BChE affect general physiology directly, while they protect mice from disturbance by cocaine. Hence, viral gene transfer of BChE appears benign and worth exploring as a therapy for cocaine abuse and possibly other disorders as well.

### **Kinetic Characterization Of Human Butyrylcholinesterase Mutants For the Hydrolysis Of Cocaethylene**

Hou S, Zhan M, Zheng X, Zhan CG, Zheng F. *Biochem J.* 2014 Jun; 460(3): 447-57. It is known that the majority of cocaine users also consume alcohol. Alcohol can react with cocaine to produce a significantly more cytotoxic compound, cocaethylene. Hence a truly valuable cocaine-metabolizing enzyme as treatment for cocaine abuse/overdose should be efficient for not only cocaine itself, but also cocaethylene. The catalytic parameters ( $k_{cat}$  and  $K_M$ ) of human BChE (butyrylcholinesterase) and two mutants (known as cocaine hydrolases E14-3 and E12-7) for cocaethylene are characterized in the present study, for the first time, in comparison with those for cocaine. On the basis of the obtained kinetic data, wild-type human BChE has a lower catalytic activity for cocaethylene ( $k_{cat}=3.3 \text{ min}^{-1}$ ,  $K_M=7.5 \text{ }\mu\text{M}$  and  $k_{cat}/K_M=4.40 \times 10^5 \text{ M}^{-1}\cdot\text{min}^{-1}$ ) compared with its catalytic activity for (-)-cocaine. E14-3 and E12-7 have a considerably improved catalytic activity against cocaethylene compared with the wild-type BChE. E12-7 is identified as the most efficient enzyme for hydrolysing cocaethylene in addition to its high activity for (-)-cocaine. E12-7 has an 861-fold improved catalytic efficiency for cocaethylene ( $k_{cat}=3600 \text{ min}^{-1}$ ,  $K_M=9.5 \text{ }\mu\text{M}$  and  $k_{cat}/K_M=3.79 \times 10^8 \text{ M}^{-1}\cdot\text{min}^{-1}$ ). It has been demonstrated that E12-7 as an exogenous enzyme can indeed rapidly metabolize cocaethylene in rats. Further kinetic modelling has suggested that E12-7 with an identical concentration as that of the endogenous BChE in human plasma can effectively eliminate (-)-cocaine, cocaethylene and norcocaine in simplified kinetic models of cocaine abuse and overdose associated with the concurrent use of cocaine and alcohol.

### **Interaction Of Psychoactive Tryptamines With Biogenic Amine Transporters And Serotonin Receptor Subtypes**

Blough BE, Landavazo A, Decker AM, Partilla JS, Baumann MH, Rothman RB. *Psychopharmacology (Berl).* 2014 May; [Epub ahead of print]. Synthetic hallucinogenic tryptamines, especially those originally described by Alexander Shulgin, continue to be abused in the USA. The range of subjective experiences produced by different tryptamines suggests that multiple neurochemical mechanisms are involved in their actions, in addition to the established role of agonist activity at serotonin 2A (5-HT<sub>2A</sub>) receptors. This study evaluated the interaction of a series of synthetic tryptamines with biogenic amine neurotransmitter transporters and with serotonin (5-HT) receptor subtypes implicated in psychedelic effects. Neurotransmitter transporter activity was determined in rat brain synaptosomes. Receptor activity was determined using calcium mobilization and DiscoverX PathHunter® assays in HEK293, Gα16-CHO, and CHOK1 cells transfected with human receptors. Twenty-one tryptamines were analyzed

in transporter uptake and release assays, and 5-HT<sub>2A</sub>, serotonin 1A (5-HT<sub>1A</sub>), and 5-HT<sub>2A</sub>  $\beta$ -arrestin functional assays. Eight of the compounds were found to have 5-HT-releasing activity. Thirteen compounds were found to be 5-HT uptake inhibitors or were inactive. All tryptamines were 5-HT<sub>2A</sub> agonists with a range of potencies and efficacies, but only a few compounds were 5-HT<sub>1A</sub> agonists. Most tryptamines recruited  $\beta$ -arrestin through 5-HT<sub>2A</sub> activation. All psychoactive tryptamines are 5-HT<sub>2A</sub> agonists, but 5-HT transporter (SERT) activity may contribute significantly to the pharmacology of certain compounds. The in vitro transporter data confirm structure-activity trends for releasers and uptake inhibitors whereby releasers tend to be structurally smaller compounds. Interestingly, two tertiary amines were found to be selective substrates at SERT, which dispels the notion that 5-HT-releasing activity is limited only to primary or secondary amines.

**Abuse-Related Effects Of Dual Dopamine/Serotonin Releasers With Varying Potency To Release Norepinephrine In Male Rats and Rhesus Monkeys** Banks ML, Bauer CT, Blough BE, Rothman RB, Partilla JS, Baumann MH, Negus SS. *Exp Clin Psychopharmacol*. 2014 Jun; 22(3): 274-84.

d-Amphetamine selectively promotes release of both dopamine (DA) and norepinephrine (NE) versus serotonin (5HT), and chronic d-amphetamine treatment decreases cocaine-taking behavior in rats, nonhuman primates, and humans. However, abuse liability limits the clinical utility of amphetamine maintenance for treating cocaine abuse. One strategy to improve safety and efficacy of monoamine releasers as candidate anticocaine medications has been to develop dual DA/5HT releasers like 1-naphthyl-2-aminopropane (PAL-287), but the pharmacology of this class of compounds has not been extensively examined. In particular, PAL-287 has similar potencies to release DA, 5HT, and NE, and the role of manipulating NE release potency on abuse-related or anticocaine effects of dual DA/5HT releasers is not known. To address this issue, the present study compared effects of four novel DA/5HT releasers that varied >800-fold in their selectivities to release DA/5HT versus NE: [1-(5-chloro-1H-indol-3-yl)propan-2-amine (PAL-542), 1-(5-fluoro-1H-indol-3-yl)propan-2-amine (PAL-544), 1-(1H-indol-5-yl)propan-2-amine (PAL-571), and (R)-1-(1H-indol-1-yl)propain-2-amine (PAL-569). Abuse-related effects of all four compounds were evaluated in assays of intracranial self-stimulation (ICSS) in rats and cocaine discrimination in rats and monkeys, and none of the compounds reliably facilitated ICSS or substituted for cocaine. Anticocaine effects of the compound with highest selectivity to release DA/5HT versus NE (PAL-542) were tested in an assay of cocaine versus food choice in rhesus monkeys, and PAL-542 failed to reduce cocaine choice. These results suggest that potency to release NE has minimal influence on abuse liability of dual DA/5HT releasers, and reducing relative potency to release NE versus DA/5HT does not improve anticocaine efficacy.

**CB1 Antagonism: Interference With Affective Properties Of Acute Naloxone-Precipitated Morphine Withdrawal In Rats** Wills KL, Vemuri K, Kalmar A, Lee A, Limebeer CL, Makriyannis A, Parker LA. *Psychopharmacology (Berl)*. 2014 Apr; [Epub ahead of print].

Modulation of the endocannabinoid system has been found to interfere with opiate withdrawal. The potential of activation and blockade of the endocannabinoid system to prevent the aversive-affective state of naloxone-precipitated morphine withdrawal (MWD) was investigated in a one-trial conditioned place aversion (CPA) paradigm. CPA provides a sensitive measure of the motivational effects of acute MWD. The potential of the fatty acid amide hydrolase (FAAH) inhibitors, URB597 and PF-3845, the CB1 antagonist/inverse agonist, AM251, and the neutral CB1 antagonists, AM4113 and AM6527 (oral), to interfere with establishment of a MWD-induced CPA was investigated. As well, the potential of AM251 and AM4113 to interfere with reinstatement of a

previously established MWD-induced CPA was investigated. Using a one-trial place conditioning paradigm, rats were administered naloxone (1 mg/kg, subcutaneous (sc)) 24 h after receiving a high dose of morphine (20 mg/kg, sc) and were placed on the conditioning floor. To determine the effect of each pretreatment drug on the establishment of the MWD-induced CPA, URB597 (0.3 mg/kg, intraperitoneally (ip)), PF-3845 (10 mg/kg, ip), AM251 (1 or 2.5 mg/kg, ip), AM4113 (1 or 2.5 mg/kg, ip), and AM6527 (5 mg/kg, oral) were administered prior to conditioning. AM251 (2.5, but not 1 mg/kg), AM4113, and AM6527, but not URB597 or PF-3845, interfered with the establishment of the MWD-induced CPA. AM251 and AM4113 did not prevent reinstatement of the CPA. Neutral antagonism of the CB1 receptor reduces the aversive affective properties of morphine withdrawal.

**Hypocretin (Orexin) Facilitates Reward By Attenuating the Antireward Effects Of Its Cotransmitter Dynorphin In Ventral Tegmental Area**

Muschamp JW, Hollander JA, Thompson JL, Voren G, Hassinger LC, Onvani S, Kamenecka TM, Borgland SL, Kenny PJ, Carlezon WA. Proc Natl Acad Sci U S A. 2014 Apr; 111(16): E1648-55.

Hypocretin (orexin) and dynorphin are neuropeptides with opposing actions on motivated behavior. Orexin is implicated in states of arousal and reward, whereas dynorphin is implicated in depressive-like states. The authors show that, despite their opposing actions, these peptides are packaged in the same synaptic vesicles within the hypothalamus. Disruption of orexin function blunts the rewarding effects of lateral hypothalamic (LH) stimulation, eliminates cocaine-induced impulsivity, and reduces cocaine self-administration. Concomitant disruption of dynorphin function reverses these behavioral changes. The authors also show that orexin and dynorphin have opposing actions on excitability of ventral tegmental area (VTA) dopamine neurons, a prominent target of orexin-containing neurons, and that intra-VTA orexin antagonism causes decreases in cocaine self-administration and LH self-stimulation that are reversed by dynorphin antagonism. These findings identify a unique cellular process by which orexin can occlude the reward threshold-elevating effects of coreleased dynorphin and thereby act in a permissive fashion to facilitate reward.

**The Novel Dopamine D3 Receptor Antagonist, SR 21502, Reduces Cocaine Conditioned Place Preference In Rats**

Hachimine P, Seepersad N, Ananthan S, Ranaldi R. Neurosci Lett. 2014 May; 569[Epub ahead of print] 137-41.

Research has shown that dopamine (DA) D3 receptors play a crucial role in cocaine addiction. Recently, there has been a strong focus on the development of DA D3 receptor antagonists as potential pharmacological treatments for cocaine addiction. The authors investigated the ability of a novel selective D3 receptor antagonist SR 21502 to block the expression of cocaine-induced conditioned place preference (CPP) in rats. CPP was determined using a two-chamber apparatus. All of the animals had free access to both chambers on day 1, followed by 4 alternating conditioning days of cocaine injection (paired chamber) and 4 alternating non-conditioning days with saline (non-paired chamber). On the test day, animals were systemically treated with 0, 3, 7.5, or 15 mg/kg of SR 21502, 10 min prior to being placed in the CPP apparatus, and the time spent in each chamber was recorded for 15 min. The amount of time spent in the cocaine-paired chamber on the test and pre-exposure days was analyzed. Vehicle-treated animals spent significantly more time in the cocaine-paired side during the test than during the pre-exposure session, indicating a cocaine CPP. SR 21502 produced a dose-related significant reduction in the time spent in the cocaine-paired side compared to vehicle. The DA D3 receptor antagonist SR 21502 blocks the rat's preference for the cocaine-paired chamber, thereby attenuating the rewarding effect of the cocaine cues. This suggests that this compound may be an effective pharmacological

treatment against cocaine addiction.

**Applying A Multitarget Rational Drug Design Strategy: The First Set Of Modulators With Potent and Balanced Activity Toward Dopamine D3 Receptor and Fatty Acid Amide**

**Hydrolase** De Simone A, Ruda GF, Albani C, Tarozzo G, Bandiera T, Piomelli D, Cavalli A, Bottegoni G. Chem Commun (Camb). 2014 May; 50(38): 4904-7.

Combining computer-assisted drug design and synthetic efforts, the authors generated compounds with potent and balanced activities toward both D3 dopamine receptor and fatty acid amide hydrolase (FAAH) enzyme. By concurrently modulating these targets, our compounds hold great potential toward exerting a disease-modifying effect on nicotine addiction and other forms of compulsive behavior.

**Binding Free Energies For Nicotine Analogs Inhibiting Cytochrome P450 2A6 By A**

**Combined Use Of Molecular Dynamics Simulations and QM/MM-PBSA Calculations** Lu H, Huang X, AbdulHameed MD, Zhan CG. Bioorg Med Chem. 2014 Apr; 22(7): 2149-56.

Molecular dynamics (MD) simulations and hybrid quantum mechanical/molecular mechanical (QM/MM) calculations have been performed to explore the dynamic behaviors of cytochrome P450 2A6 (CYP2A6) binding with nicotine analogs (that are typical inhibitors) and to calculate their binding free energies in combination with Poisson-Boltzmann surface area (PBSA) calculations. The combined MD simulations and QM/MM-PBSA calculations reveal that the most important structural parameters affecting the CYP2A6-inhibitor binding affinity are two crucial internuclear distances, that is, the distance between the heme iron atom of CYP2A6 and the coordinating atom of the inhibitor, and the hydrogen-bonding distance between the N297 side chain of CYP2A6 and the pyridine nitrogen of the inhibitor. The combined MD simulations and QM/MM-PBSA calculations have led to dynamic CYP2A6-inhibitor binding structures that are consistent with the observed dynamic behaviors and structural features of CYP2A6-inhibitor binding, and led to the binding free energies that are in good agreement with the experimentally-derived binding free energies. The agreement between the calculated binding free energies and the experimentally-derived binding free energies suggests that the combined MD and QM/MM-PBSA approach may be used as a valuable tool to accurately predict the CYP2A6-inhibitor binding affinities in future computational design of new, potent and selective CYP2A6 inhibitors.

**Reaction Pathways and Free Energy Profiles For Cholinesterase-Catalyzed Hydrolysis Of 6-Monoacetylmorphine**

Qiao Y, Han K, Zhan CG. Org Biomol Chem. 2014 Apr; 12(14): 2214-27. As the most active metabolite of heroin, 6-monoacetylmorphine (6-MAM) can penetrate into the brain for the rapid onset of heroin effects. The primary enzymes responsible for the metabolism of 6-MAM to the less potent morphine in humans are acetylcholinesterase (AChE) and butyrylcholinesterase (BChE). The detailed reaction pathways for AChE- and BChE-catalyzed hydrolysis of 6-MAM to morphine have been explored, for the first time, in the present study by performing first-principles quantum mechanical/molecular mechanical free energy calculations. It has been demonstrated that the two enzymatic reaction processes follow similar catalytic reaction mechanisms, and the whole catalytic reaction pathway for each enzyme consists of four reaction steps. According to the calculated results, the second reaction step associated with the transition state TS2(a)/TS2(b) should be rate-determining for the AChE/BChE-catalyzed hydrolysis, and the free energy barrier calculated for the AChE-catalyzed hydrolysis (18.3 kcal mol<sup>-1</sup>) is 2.5 kcal mol<sup>-1</sup> lower than that for the BChE-catalyzed hydrolysis (20.8 kcal mol<sup>-1</sup>). The free energy barriers calculated for the AChE- and BChE-catalyzed reactions are in good agreement with the experimentally derived activation free energies (17.5 and 20.7 kcal mol<sup>-1</sup>) for the AChE- and

BChE-catalyzed reactions, respectively). Further structural analysis reveals that the aromatic residues Phe295 and Phe297 in the acyl pocket of AChE (corresponding to Leu286 and Val288 in BChE) contribute to the lower energy of TS2(a) relative to TS2(b). The obtained structural and mechanistic insights could be valuable for use in future rational design of a novel therapeutic treatment of heroin abuse.

**Amino-Acid Mutations To Extend the Biological Half-Life Of A Therapeutically Valuable Mutant Of Human Butyrylcholinesterase**

Fang L, Hou S, Xue L, Zheng F, Zhan CG. *Chem Biol Interact.* 2014 May; 214[Epub ahead of print] 18-25.

Cocaine is a widely abused and addictive drug without an FDA-approved medication. The authors' recently designed and discovered cocaine hydrolase, particularly E12-7 engineered from human butyrylcholinesterase (BChE), has the promise of becoming a valuable cocaine abuse treatment. An ideal anti-cocaine therapeutic enzyme should have not only a high catalytic efficiency against cocaine, but also a sufficiently long biological half-life. However, recombinant human BChE and the known BChE mutants have a much shorter biological half-life compared to the native human BChE. The present study aimed to extend the biological half-life of the cocaine hydrolase without changing its high catalytic activity against cocaine. The authors' strategy was to design possible amino-acid mutations that can introduce cross-subunit disulfide bond(s) and, thus, change the distribution of the oligomeric forms and extend the biological half-life. Three new BChE mutants (E364-532, E377-516, and E535) were predicted to have a more stable dimer structure with the desirable cross-subunit disulfide bond(s) and, therefore, a different distribution of the oligomeric forms and a prolonged biological half-life. The rational design was followed by experimental tests in vitro and in vivo, confirming that the rationally designed new BChE mutants, i.e., E364-532, E377-516, and E535, indeed had a remarkably different distribution of the oligomeric forms and prolonged biological half-life in rats from ~7 to ~13h without significantly changing the catalytic activity against (-)-cocaine. This is the first demonstration that rationally designed amino-acid mutations can significantly prolong the biological half-life of a high-activity enzyme without significantly changing the catalytic activity.

**A Novel Aminotetralin-Type Serotonin (5-HT) 2C Receptor-Specific Agonist and 5-HT2A Competitive Antagonist/5-HT2B Inverse Agonist With Preclinical Efficacy For Psychoses**

Canal CE, Morgan D, Felsing D, Kondabolu K, Rowland NE, Robertson KL, Sakhuja R, Booth RG. *J Pharmacol Exp Ther.* 2014 May; 349(2): 310-8.

Development of 5-HT<sub>2C</sub> agonists for treatment of neuropsychiatric disorders, including psychoses, substance abuse, and obesity, has been fraught with difficulties, because the vast majority of reported 5-HT<sub>2C</sub> selective agonists also activate 5-HT<sub>2A</sub> and/or 5-HT<sub>2B</sub> receptors, potentially causing hallucinations and/or cardiac valvulopathy. Herein is described a novel, potent, and efficacious human 5-HT<sub>2C</sub> receptor agonist, (-)-trans-(2S,4R)-4-(3'[meta]-bromophenyl)-N,N-dimethyl-1,2,3,4-tetrahydronaphthalen-2-amine (-)-MBP, that is a competitive antagonist and inverse agonist at human 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> receptors, respectively. (-)-MBP has efficacy comparable to the prototypical second-generation antipsychotic drug clozapine in three C57Bl/6 mouse models of drug-induced psychoses: the head-twitch response elicited by [2,5]-dimethoxy-4-iodoamphetamine; hyperlocomotion induced by MK-801 [(5R,10S)-(+)-5-methyl-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5,10-imine hydrogen maleate (dizocilpine maleate)]; and hyperlocomotion induced by amphetamine. (-)-MBP, however, does not alter locomotion when administered alone, distinguishing it from clozapine, which suppresses locomotion. Finally, consumption of highly palatable food by mice was not increased by (-)-MBP at a dose that produced at least 50% maximal efficacy in the psychoses models. Compared with (-)-MBP, the

enantiomer (+)-MBP was much less active across in vitro affinity and functional assays using mouse and human receptors and also translated in vivo with comparably lower potency and efficacy. Results indicate a 5-HT<sub>2C</sub> receptor-specific agonist, such as (-)-MBP, may be pharmacotherapeutic for psychoses, without liability for obesity, hallucinations, heart disease, sedation, or motoric disorders.

**Identification Of Specific Ligand-Receptor Interactions That Govern Binding and Cooperativity Of Diverse Modulators To A Common Metabotropic Glutamate Receptor 5 Allosteric Site**

Gregory KJ, Nguyen ED, Malosh C, Mendenhall JL, Zic JZ, Bates BS, Noetzel MJ, Squire EF, Turner EM, Rook JM, Emmitte KA, Stauffer SR, Lindsley CW, Meiler J, Conn PJ. ACS Chem Neurosci. 2014 Apr; 5(4): 282-95.

A common metabotropic glutamate receptor 5 (mGlu5) allosteric site is known to accommodate diverse chemotypes. However, the structural relationship between compounds from different scaffolds and mGlu5 is not well understood. In an effort to better understand the molecular determinants that govern allosteric modulator interactions with mGlu5, the authors employed a combination of site-directed mutagenesis and computational modeling. With few exceptions, six residues (P654, Y658, T780, W784, S808, and A809) were identified as key affinity determinants across all seven allosteric modulator scaffolds. To improve our interpretation of how diverse allosteric modulators occupy the common allosteric site, the authors sampled the wealth of mGlu5 structure-activity relationship (SAR) data available by docking 60 ligands (actives and inactives) representing seven chemical scaffolds into our mGlu5 comparative model. To spatially and chemically compare binding modes of ligands from diverse scaffolds, the ChargeRMSD measure was developed. The authors found a common binding mode for the modulators that placed the long axes of the ligands parallel to the transmembrane helices 3 and 7. W784 in TM6 not only was identified as a key NAM cooperativity determinant across multiple scaffolds, but also caused a NAM to PAM switch for two different scaffolds. Moreover, a single point mutation in TM5, G747V, altered the architecture of the common allosteric site such that 4-nitro-N-(1,3-diphenyl-1H-pyrazol-5-yl)benzamide (VU29) was noncompetitive with the common allosteric site. These findings highlight the subtleties of allosteric modulator binding to mGlu5 and demonstrate the utility in incorporating SAR information to strengthen the interpretation and analyses of docking and mutational data.

**Investigating Hapten Clustering As A Strategy To Enhance Vaccines Against Drugs Of Abuse**

Collins KC, Janda KD. Bioconjug Chem. 2014 Mar; 25(3): 593-600.

Vaccines for drugs of abuse have yet to achieve full clinical relevance, largely due to poor/inconsistent immune responses in patients. The use of multivalent scaffolding as a means to tailor drug-hapten density and clustering was examined in the context of drug-immune response modulation. A modular trivalent hapten containing a diglycine spacer, triAM1(Gly)<sub>2</sub>, was synthesized and shown to elicit anti-nicotine antibodies at equivalent affinity and concentration to the monovalent AM1 analog, despite in this instance having a lower effective hapten density. Augmenting this data, the corresponding monovalent hapten AM1(Gly)<sub>2</sub> resulted in enhanced antibody affinity and concentration. Drug-hapten clustering represents a new vaccine paradigm, and, while examined only in the context of nicotine, it should be readily translatable to other drugs of abuse.

**SN79, A Sigma Receptor Antagonist, Attenuates Methamphetamine-Induced Astrogliosis Through A Blockade Of OSMR/Gp130 Signaling and STAT3 Phosphorylation**

Robson MJ, Turner RC, Naser ZJ, McCurdy CR, O'Callaghan JP, Huber JD, Matsumoto RR. *Exp Neurol*. 2014 Apr; 254[Epub ahead of print] 180-9.

Methamphetamine (METH) exposure results in dopaminergic neurotoxicity in striatal regions of the brain, an effect that has been linked to an increased risk of Parkinson's disease. Various aspects of neuroinflammation, including astrogliosis, are believed to be contributory factors in METH neurotoxicity. METH interacts with sigma receptors at physiologically relevant concentrations and treatment with sigma receptor antagonists has been shown to mitigate METH-induced neurotoxicity in rodent models. Whether these compounds alter the responses of glial cells within the central nervous system *in vivo* to METH however has yet to be determined. Therefore, the purpose of the current study was to determine whether the sigma receptor antagonist, SN79, mitigates METH-induced striatal reactive astrogliosis. Male, Swiss Webster mice treated with a neurotoxic regimen of METH exhibited time-dependent increases in striatal gfap mRNA and concomitant increases in GFAP protein, indicative of astrogliosis. This is the first report that similar to other neurotoxicants that induce astrogliosis through the activation of JAK2/STAT3 signaling by stimulating gp-130-linked cytokine signaling resulting from neuroinflammation, METH treatment also increases astrocytic oncostatin m receptor (OSMR) expression and the phosphorylation of STAT3 (Tyr-705) *in vivo*. Pretreatment with SN79 blocked METH-induced increases in OSMR, STAT3 phosphorylation and astrocyte activation within the striatum. Additionally, METH treatment resulted in striatal cellular degeneration as measured by Fluoro-Jade B, an effect that was mitigated by SN79. The current study provides evidence that sigma receptor antagonists attenuate METH-induced astrocyte activation through a pathway believed to be shared by various neurotoxicants.

**Long-Term Reduction Of Cocaine Self-Administration In Rats Treated With Adenoviral Vector-Delivered Cocaine Hydrolase: Evidence For Enzymatic Activity**

Zlebnik NE, Brimijoin S, Gao Y, Saykao AT, Parks RJ, Carroll ME. *Neuropsychopharmacology*. 2014 May; 39(6): 1538-46.

A new pharmacokinetic approach treating cocaine addiction involves rapidly metabolizing cocaine before it reaches brain reward centers using mutated human butyrylcholinesterase (BChE) or cocaine hydrolase (CocH). Recent work has shown that helper-dependent adenoviral (hdAD) vector-mediated plasma CocH reduced the locomotor-activating effects of cocaine and prevented reinstatement of cocaine-seeking behavior up to 6 months in rats. The present study investigated whether hdAD-CocH could decrease ongoing intravenous cocaine (0.4 mg/kg) self-administration. The hdAD-CocH vector was injected into self-administering rats, and after accumulation of plasma CocH, there was a dramatic reduction in cocaine infusions earned under a fixed ratio 1 schedule of reinforcement that lasted for the length of the study (>2 months). Pretreatment with the selective BChE and CocH inhibitor iso-OMPA (1.5 mg/kg) restored cocaine intake; therefore, the decline in self-administration was likely due to rapid CocH-mediated cocaine metabolism. Direct measurements of cocaine levels in plasma and brain samples taken after the conclusion of behavioral studies provided strong support for this conclusion. Further, rats injected with hdAD-CocH did not experience a deficit in operant responding for drug reinforcement and self-administered methamphetamine (0.05 mg/kg) at control levels. Overall, these outcomes suggest that viral gene transfer can yield plasma CocH levels that effectively diminish long-term cocaine intake and may have potential treatment implications for cocaine-dependent individuals seeking to become and remain abstinent.

**Expression Of Human Butyrylcholinesterase With An Engineered Glycosylation Profile Resembling The Plasma-Derived Orthologue**

Schneider JD, Castilho A, Neumann L, Altmann F, Loos A, Kannan L, Mor TS, Steinkellner H. *Biotechnol J*. 2014 Apr; 9(4): 501-10.

Human butyrylcholinesterase (BChE) is considered a candidate bioscavenger of nerve agents for use in pre- and post-exposure treatment. However, the presence and functional necessity of complex N-glycans (i. e. sialylated structures) is a challenging issue in respect to its recombinant expression. Here we transiently co-expressed BChE cDNA in the model plant *Nicotiana benthamiana* with vectors carrying the genes necessary for in planta protein sialylation. Site-specific sugar profiling of secreted recombinant BChE (rBChE) collected from the intercellular fluid revealed the presence of mono- and di-sialylated N-glycans, which largely resembles to the plasma-derived orthologue. Attempts to increase that sialylation content of rBChE by the over-expression of an additional glycosylation enzyme that generates branched N-glycans (i. e.  $\beta$ 1,4-N-acetylglucosaminyl-transferase IV), allowed the production of rBChE decorated with tri-sialylated structures (up to 70%). Sialylated and non-sialylated plant-derived rBChE exhibited functional in vitro activity comparable to that of its commercially available equine-derived counterpart. These results demonstrate the ability of plants to generate valuable proteins with designed sialylated glycosylation profiles optimized for therapeutic efficacy. Moreover, the efficient synthesis of carbohydrates present only in minute amounts on the native protein (tri-sialylated N-glycans) facilitates the generation of a product with superior efficacies and/or new therapeutic functions.

**Effects Of An Oxycodone Conjugate Vaccine On Oxycodone Self-Administration And Oxycodone-Induced Brain Gene Expression In Rats**

Pravetoni M, Pentel PR, Potter DN, Chartoff EH, Tally L, LeSage MG. *PLoS One*. 2014 ; 9(7): e101807.

Prescription opioid abuse is an increasing public health concern in the USA. A vaccine comprising a hapten (OXY) conjugated to the carrier protein keyhole limpet hemocyanin (OXY-KLH) has been shown to attenuate the antinociceptive effects of oxycodone. Here, the vaccine's ability to prevent acquisition of intravenous (i.v) oxycodone self-administration was studied in rats. Effects of vaccination on oxycodone-induced changes in the expression of several genes within the mesolimbic system, which are regulated by chronic opiate use, were also examined. Vaccination with OXY-KLH reduced the proportion of rats acquiring i. v. self-administration of oxycodone under a fixed ratio (FR) 3 schedule of reinforcement compared to control rats immunized with the unconjugated KLH carrier protein. Vaccination significantly reduced the mean number of infusions at FR3, total number of infusions, and total oxycodone intake during the entire protocol. Compared to oxycodone self-administering control rats immunized with the carrier alone, rats vaccinated with the OXY-KLH immunogen showed increased levels of adenylate cyclase 5 (*Adcy5*) and decreased levels of early growth response protein 2 (*Egr2*) and the early immediate gene *c-Fos* in the striatum. These data suggest that vaccination with OXY-KLH can attenuate the reinforcing effects of oxycodone at a clinically-relevant exposure level. Analysis of mRNA expression identified some addiction-relevant markers that may be of interest in understanding oxycodone effects or the protection provided by vaccination.

**Synthesis and Immunological Effects Of Heroin Vaccines**

Li F, Cheng K, Antoline JF, Iyer MR, Matyas GR, Torres OB, Jalah R, Beck Z, Alving CR, Parrish DA, Deschamps JR, Jacobson AE, Rice KC. *Org Biomol Chem*. 2014 Jul; [Epub ahead of print].

Three haptens have been synthesized with linkers for attachment to carrier macromolecules at either the piperidino-nitrogen or via an introduced 3-amino group. Two of the haptens, with a 2-oxopropyl functionality at either C6, or at both the C3 and C6 positions on the 4,5-epoxymorphinan framework, as well as the third hapten (DiAmHap) with diamido moieties at both the C3 and C6

positions, should be much more stable in solution, or in vivo in a vaccine, than a hapten with an ester in one of those positions, as found in many heroin-based haptens. A "classical" opioid synthetic scheme enabled the formation of a 3-amino-4,5-epoxymorphinan which could not be obtained using palladium chemistry. The authors' vaccines are aimed at the reduction of the abuse of heroin and, as well, at the reduction of the effects of its predominant metabolites, 6-acetylmorphine and morphine. One of the haptens, DiAmHap, has given interesting results in a heroin vaccine and is clearly more suited for the purpose than the other two haptens.

### **Treatment With A Monoclonal Antibody Against Methamphetamine and Amphetamine Reduces Maternal And Fetal Rat Brain Concentrations In Late Pregnancy**

White SJ, Hendrickson HP, Atchley WT, Laurenzana EM, Gentry WB, Williams DK, Owens SM. Drug Metab Dispos. 2014 Aug; 42(8): 1285-91.

The authors hypothesized that treatment of pregnant rat dams with a dual reactive monoclonal antibody (mAb4G9) against (+)-methamphetamine [METH; equilibrium dissociation rate constant (KD) = 16 nM] and (+)-amphetamine (AMP; KD = 102 nM) could confer maternal and fetal protection from brain accumulation of both drugs of abuse. To test this hypothesis, pregnant Sprague-Dawley rats (on gestational day 21) received a 1 mg/kg i. v. METH dose, followed 30 minutes later by vehicle or mAb4G9 treatment. The mAb4G9 dose was 0.56 mole-equivalent in binding sites to the METH body burden. Pharmacokinetic analysis showed baseline METH and AMP elimination half-lives were congruent in dams and fetuses, but the METH volume of distribution in dams was nearly double the fetal values. The METH and AMP area under the serum concentration-versus-time curves from 40 minutes to 5 hours after mAb4G9 treatment increased >7000% and 2000%, respectively, in dams. Fetal METH serum did not change, but AMP decreased 23%. The increased METH and AMP concentrations in maternal serum resulted from significant increases in mAb4G9 binding. Protein binding changed from ~15% to > 90% for METH and AMP. Fetal serum protein binding appeared to gradually increase, but the absolute fraction bound was trivial compared with the dams. mAb4G9 treatment significantly reduced METH and AMP brain values by 66% and 45% in dams and 44% and 46% in fetuses (P < 0.05), respectively. These results show anti-METH/AMP mAb4G9 therapy in dams can offer maternal and fetal brain protection from the potentially harmful effects of METH and AMP.

### **Hapten Optimization For Cocaine Vaccine With Improved Cocaine Recognition**

Ramakrishnan M, Kinsey BM, Singh RA, Kosten TR, Orson FM. Chem Biol Drug Des. 2014 May; [Epub ahead of print].  
In the absence of any effective pharmacotherapy for cocaine addiction, immunotherapy is being actively pursued as a therapeutic intervention. While several different cocaine haptens have been explored to develop anti-cocaine antibodies, none of the haptens was successfully designed which had a protonated tropane nitrogen as is found in native cocaine under physiological conditions, including the succinyl norcocaine (SNC) hapten that has been tested in phase II clinical trials. Herein, the authors discuss three different cocaine haptens: hexyl-norcocaine (HNC), bromoacetamido butyl-norcocaine (BNC), and succinyl-butyl-norcocaine (SBNC), each with a tertiary nitrogen structure mimicking that of native cocaine which could optimize the specificity of anti-cocaine antibodies for better cocaine recognition. Mice immunized with these haptens conjugated to immunogenic proteins produced high titer anti-cocaine antibodies. However, during chemical conjugation of HNC and BNC haptens to carrier proteins, the 2 $\beta$  methyl ester group is hydrolyzed and immunizing mice with these conjugate vaccines in mice produced antibodies that bound both cocaine and the inactive benzoylecgonine metabolite. While in the case of the SBNC conjugate vaccine hydrolysis of the methyl ester did not appear to occur, leading to antibodies with

high specificity to cocaine over BE. Though we observed similar specificity with a SNC hapten, the striking difference is that SBNC carries a positive charge on the tropane nitrogen atom, and therefore it is expected to have better binding of cocaine. The 50% cocaine inhibitory concentration (IC<sub>50</sub>) value for SBNC antibodies (2.8  $\mu$ M) was significantly better than the SNC antibodies (9.4  $\mu$ M) when respective hapten-BSA was used as a substrate. In addition, antibodies from both sera had no inhibitory effect from BE. In contrast to BNC and HNC, the SBNC conjugate was also found to be highly stable without any noticeable hydrolysis for several months at 4°C and 2-3 days in pH 10 buffer at 37°C.

**A Recombinant Humanized Anti-Cocaine Monoclonal Antibody Inhibits the Distribution Of Cocaine To the Brain In Rats** Norman AB, Gooden FC, Tabet MR, Ball WJ. Drug Metab Dispos. 2014 Jul; 42(7): 1125-31.

The monoclonal antibody (mAb), h2E2, is a humanized version of the chimeric human/murine anti-cocaine mAb 2E2. The recombinant h2E2 protein was produced in vitro from a transfected mammalian cell line and retained high affinity (4 nM K<sub>d</sub>) and specificity for cocaine over its inactive metabolites benzoylecgonine (BE) and ecgonine methyl ester. In rats, pharmacokinetic studies of h2E2 (120 mg/kg i. v.) showed a long terminal elimination half-life of 9.0 days and a low volume of distribution at steady state (V<sub>dss</sub>) of 0.3 l/kg. Pretreatment with h2E2 produced a dramatic 8.8-fold increase in the area under the plasma cocaine concentration-time curve (AUC) and in brain a concomitant decrease of 68% of cocaine's AUC following an i.v. injection of an equimolar cocaine dose. Sequestration of cocaine in plasma by h2E2, shown via reduction of cocaine's V<sub>dss</sub>, indicates potential clinical efficacy. Although the binding of cocaine to h2E2 in plasma should inhibit distribution and metabolism, the elimination of cocaine remained multicompartmental and was still rapidly eliminated from plasma despite the presence of h2E2. BE was the major cocaine metabolite, and brain BE concentrations were sixfold higher than in plasma, indicating that cocaine is normally metabolized in the brain. In the presence of h2E2, brain BE concentrations were decreased and plasma BE was increased, consistent with the observed h2E2-induced changes in cocaine disposition. The inhibition of cocaine distribution to the brain confirms the humanized mAb, h2E2, as a lead candidate for development as an immunotherapy for cocaine abuse.

## **RESEARCH ON THE MEDICAL CONSEQUENCES OF DRUG ABUSE AND CO-OCCURRING INFECTIONS**

### **HIV and Drug Abuse**

**Changes in HIV Incidence among People Who Inject Drugs in Taiwan following Introduction of a Harm Reduction Program: A Study of Two Cohorts** Huang YF, Yang J-Y, Nelson KE, Kuo H-S, Lew-Ting C-Y, Yang C-H, Chen C-H, Chang F-Y, Liu H-R. PLoS Med 11(4): e1001625. doi:10.1371/journal.pmed.1001625.

Harm reduction strategies for combating HIV epidemics among people who inject drugs (PWID) have been implemented in several countries. However, large-scale studies using sensitive measurements of HIV incidence and intervention exposures in defined cohorts are rare. The aim of this study was to determine the association between harm reduction programs and HIV incidence among PWID. The study included two populations. For 3,851 PWID who entered prison between 2004 and 2010 and tested HIV positive upon incarceration, the authors tested their sera using a BED HIV-1 capture enzyme immunoassay to estimate HIV incidence. Also, they enrolled in a prospective study a cohort of 4,357 individuals who were released from prison via an amnesty on July 16, 2007. The authors followed them with interviews at intervals of 6–12 months and by linking several databases. A total of 2,473 participants who were HIV negative in January 2006 had interviews between then and 2010 to evaluate the association between use of harm reduction programs and HIV incidence. The authors used survival methods with attendance at methadone clinics as a time-varying covariate to measure the association with HIV incidence. They used a Poisson regression model and calculated the HIV incidence rate to evaluate the association between needle/syringe program use and HIV incidence. Among the population of PWID who were imprisoned, the implementation of comprehensive harm reduction programs and a lower mean community HIV viral load were associated with a reduced HIV incidence among PWID. The HIV incidence in this population of PWID decreased from 18.2% in 2005 to 0.3% in 2010. In an individual-level analysis of the amnesty cohort, attendance at methadone clinics was associated with a significantly lower HIV incidence (adjusted hazard ratio: 0.20, 95% CI: 0.06–0.67), and frequent users of needle/syringe program services had lower HIV incidence (0% in high NSP users, 0.5% in non NSP users). In addition, no HIV seroconversions were detected among prison inmates. Although these data are affected by participation bias, they strongly suggest that comprehensive harm reduction services and free treatment were associated with reversal of a rapidly emerging epidemic of HIV among PWID.

### **Expansion of HAART Coverage Is Associated with Sustained Decreases in HIV/AIDS Morbidity, Mortality and HIV Transmission: The “HIV Treatment as Prevention”**

**Experience in a Canadian Setting** Montaner JSG, Lima VD, Harrigan PR, Lourenço L, Yip B, Nosyk B, Wood E, Kerr T, Shannon K, Moore D, Hogg RS, Barrios R, Gilbert M, Krajden M, Gustafson R, Daly P, Kendall P. PLoS ONE 9(2): e87872. doi:10.1371/journal.pone.0087872 PLoS ONE 9(2): e87872. doi:10.1371/journal.pone.0087872.

There has been renewed call for the global expansion of highly active antiretroviral therapy (HAART) under the framework of HIV treatment as prevention (TasP). However, population-level sustainability of this strategy has not been characterized. The authors used population-level longitudinal data from province-wide registries including plasma viral load, CD4 count, drug resistance, HAART use, HIV diagnoses, AIDS incidence, and HIV-related mortality. They fitted two Poisson regression models over the study period, to relate estimated HIV incidence and the number of individuals on HAART and the percentage of virologically suppressed individuals.

HAART coverage, median pre-HAART CD4 count, and HAART adherence increased over time and were associated with increasing virological suppression and decreasing drug resistance. AIDS incidence decreased from 6.9 to 1.4 per 100,000 population (80% decrease,  $p = 0.0330$ ) and HIV-related mortality decreased from 6.5 to 1.3 per 100,000 population (80% decrease,  $p = 0.0115$ ). New HIV diagnoses declined from 702 to 238 cases (66% decrease;  $p = 0.0004$ ) with a consequent estimated decline in HIV incident cases from 632 to 368 cases per year (42% decrease;  $p = 0.0003$ ). Finally, the authors' models suggested that for each increase of 100 individuals on HAART, the estimated HIV incidence decreased 1.2% and for every 1% increase in the number of individuals suppressed on HAART, the estimated HIV incidence also decreased by 1%. These results show that HAART expansion between 1996 and 2012 in BC was associated with a sustained and profound population-level decrease in morbidity, mortality and HIV transmission. These findings support the long-term effectiveness and sustainability of HIV treatment as prevention within an adequately resourced environment with no financial barriers to diagnosis, medical care or antiretroviral drugs. The 2013 Consolidated World Health Organization Antiretroviral Therapy Guidelines offer a unique opportunity to further evaluate TasP in other settings, particularly within generalized epidemics, and resource-limited setting, as advocated by UNAIDS.

### **Effects Of Early Versus Delayed Initiation Of Antiretroviral Treatment On Clinical Outcomes Of HIV-1 Infection: Results From the Phase 3 HPTN 052 Randomised Controlled**

**Trial** Grinsztejn B, Hosseinipour MC, Ribaudo HJ, Swindells S, et al. the HPTN 052-ACTG Study Team; *The Lancet Infectious Diseases* - 1 April 2014; 14(4): 281-290. DOI: 10.1016/S1473-3099(13)70692-3.

Use of antiretroviral treatment for HIV-1 infection has decreased AIDS-related morbidity and mortality and prevents sexual transmission of HIV-1. However, the best time to initiate antiretroviral treatment to reduce progression of HIV-1 infection or non-AIDS clinical events is unknown. The authors reported previously that early antiretroviral treatment reduced HIV-1 transmission by 96%. They aimed to compare the effects of early and delayed initiation of antiretroviral treatment on clinical outcomes. The HPTN 052 trial is a randomised controlled trial done at 13 sites in nine countries. They enrolled HIV-1-serodiscordant couples to the study and randomly allocated them to either early or delayed antiretroviral treatment by use of permuted block randomisation, stratified by site. Random assignment was unblinded. The HIV-1-infected member of every couple initiated antiretroviral treatment either on entry into the study (early treatment group) or after a decline in CD4 count or with onset of an AIDS-related illness (delayed treatment group). Primary events were AIDS clinical events (WHO stage 4 HIV-1 disease, tuberculosis, and severe bacterial infections) and the following serious medical conditions unrelated to AIDS: serious cardiovascular or vascular disease, serious liver disease, end-stage renal disease, new-onset diabetes mellitus, and non-AIDS malignant disease. Analysis was by intention-to-treat. This trial is registered with [ClinicalTrials.gov](http://ClinicalTrials.gov), number [NCT00074581](https://clinicaltrials.gov/ct2/show/study/NCT00074581). 1763 people with HIV-1 infection and a serodiscordant partner were enrolled in the study; 886 were assigned early antiretroviral treatment and 877 to the delayed treatment group (two individuals were excluded from this group after randomisation). Median CD4 counts at randomisation were 442 (IQR 373—522) cells per  $\mu\text{L}$  in patients assigned to the early treatment group and 428 (357—522) cells per  $\mu\text{L}$  in those allocated delayed antiretroviral treatment. In the delayed group, antiretroviral treatment was initiated at a median CD4 count of 230 (IQR 197—249) cells per  $\mu\text{L}$ . Primary clinical events were reported in 57 individuals assigned to early treatment initiation versus 77 people allocated to delayed antiretroviral treatment (hazard ratio 0.73, 95% CI 0.52—1.03;  $p=0.074$ ). New-onset AIDS events were recorded in 40 participants assigned to early antiretroviral treatment versus 61 allocated delayed initiation (0.64, 0.43—0.96;  $p=0.031$ ), tuberculosis developed in 17 versus 34 patients, respectively (0.49,

0.28—0.89,  $p=0.018$ ), and primary non-AIDS events were rare (12 in the early group vs nine with delayed treatment). In total, 498 primary and secondary outcomes occurred in the early treatment group (incidence 24. per 100 person-years, 95% CI 22.5—27.5) versus 585 in the delayed treatment group (29.2 per 100 person-years, 26.5—32.1;  $p=0.025$ ). 26 people died, 11 who were allocated to early antiretroviral treatment and 15 who were assigned to the delayed treatment group. Early initiation of antiretroviral treatment delayed the time to AIDS events and decreased the incidence of primary and secondary outcomes. The clinical benefits recorded, combined with the striking reduction in HIV-1 transmission risk previously reported, provides strong support for earlier initiation of antiretroviral treatment. Funding US National Institute of Allergy and Infectious Diseases.

### **Do Metropolitan HIV Epidemic Histories and Programs For People Who Inject Drugs and Men Who Have Sex With Men Predict AIDS Incidence and Mortality Among Heterosexuals?**

Friedman SR, West BS, Tempalski B, Morton CM, Cleland CM, Des Jarlais DC, Hall HI, Cooper HLF. *Annals of Epidemiology* April 2014; 24(4): 304–311.

The authors focus on a little-researched issue—how human immunodeficiency virus (HIV) epidemics and programs in key populations in metropolitan areas affect epidemics in other key populations. They consider (1) How are earlier epidemics among people who inject drugs (PWID) and men who have sex with men (MSM) related to later AIDS incidence and mortality among heterosexuals?; (2) Were prevention programs targeting PWID or MSM associated with lower AIDS incidence and mortality among heterosexuals?; and (3) Was the size of the potential bridge population of noninjecting drug users (NIDUs) in a metropolitan area associated with later AIDS incidence and mortality among heterosexuals? Using data for 96 large U.S. metropolitan areas, Poisson regression assessed associations of population prevalences of HIV-infected PWID and MSM (1992); NIDU population prevalence (1992–1994); drug use treatment coverage for PWID (1993); HIV counseling and testing coverage for MSM and for PWID (1992); and syringe exchange presence (2000) with CDC data on AIDS incidence and mortality among heterosexuals in 2006–2008, with appropriate socioeconomic controls. Population density of HIV+PWID and of NIDUs were positively related, and prevention programs for PWID negatively related to later AIDS incidence among heterosexuals and later mortality among heterosexuals living with AIDS. HIV+MSM population density and prevention programs for MSM were not associated with these outcomes. Efforts to reduce HIV transmission among PWID and NIDUs may reduce AIDS and AIDS-related mortality among heterosexuals. More research is needed at metropolitan area, network, and individual levels into HIV bridging across key populations and how interventions in one key population affect HIV epidemics in other key populations.

### **Prevention and Treatment Produced Large Decreases In HIV Incidence In A Model Of People Who Inject Drugs**

Marshall BD, Friedman SR, Monteiro JF, Paczkowski M, Tempalski B, Pouget ER, Lurie MN, Galea S. 2014 Mar; 33(3): 401-9. doi: 10.1377/hlthaff.2013.0824.

In the United States, people who inject drugs continue to be at greatly increased risk of HIV infection. To estimate the effectiveness of various prevention scenarios, the authors modeled HIV transmission in a dynamic network of drug users and people who did not use drugs that was based on the New York Metropolitan Statistical Area population. They compared the projected HIV incidence in 2020 and 2040 if current approaches continue to be used to the incidence if one or more of the following hypothetical interventions were applied: increased HIV testing, improved access to substance abuse treatment, increased use of needle and syringe programs, scaled-up treatment as prevention, and a "high impact" combination scenario, consisting of all of the strategies listed above. No strategy completely eliminated HIV transmission. The high-impact combination

strategy produced the largest decrease in HIV incidence—a 62 percent reduction compared to the status quo. These results suggest that increased resources for and investments in multiple HIV prevention approaches will be required to eliminate HIV transmission among people who inject drugs. Health Aff (Millwood).

**Associations Of Cocaine Use and HIV Infection With the Intestinal Microbiota, Microbial Translocation, and Inflammation** Volpe GE, Ward H, Mwamburi M, Dinh D, Bhalchandra S, Wanke C, Kane AV. J Stud Alcohol Drugs. 2014 Mar; 75(2): 347-57.

HIV and illicit drug use have been associated with altered nutrition, immune function, and metabolism. The authors hypothesized that altered composition and decreased diversity of the intestinal microbiota, along with microbial translocation, contribute to nutritional compromise in HIV-infected drug users. They enrolled 26 men and 6 women, 15 HIV infected and 17 HIV uninfected, in this exploratory, cross-sectional study; 7 HIV-infected and 7 HIV-uninfected participants had used cocaine within the previous month. They examined the independent effects of cocaine use and HIV infection on the composition and diversity of the intestinal microbiota, determined by 16S rRNA gene pyrosequencing. Using dietary records, anthropometrics, and dual x-ray absorptiometry, the authors examined the additional effects of nutritional indices on the intestinal microbiota. They compared markers of inflammation and microbial translocation between groups. Cocaine users had a higher relative abundance of Bacteroidetes ( $M \pm SD = 57.0\% \pm 21$  vs.  $37.1\% \pm 23$ ,  $p = .02$ ) than nonusers. HIV-infected individuals had a higher relative abundance of Proteobacteria (Mdn [interquartile range] =  $1.56\%$  [0.5, 2.2] vs.  $0.36\%$  [0.2, 0.7],  $p = .03$ ), higher levels of soluble CD14 and tumor necrosis factor- $\alpha$ , and lower levels of anti-endotoxin core antibodies than uninfected subjects. HIV-infected cocaine users had higher interferon- $\gamma$  levels than all other groups. Food insecurity was higher in HIV-infected cocaine users. The authors identified differences in the relative abundance of major phyla of the intestinal microbiota, as well as markers of inflammation and microbial translocation, based on cocaine use and HIV infection. Nutritional factors, including alcohol use and lean body mass, may contribute to these differences.

**Risk Factors For Vitamin D Deficiency Among HIV-Infected and Uninfected Injection Drug Users** Lambert AA, Drummond MB, Mehta SH, Brown TT, Lucas GM, Kirk GD, Estrella MM. PLoS One. 2014 ; 9(4): e95802.

Vitamin D deficiency is highly prevalent and is associated with bone disease, cardiovascular disease, metabolic syndrome and malignancy. Injection drug users (IDUs), with or without HIV infection, are at risk for these conditions; however, limited data on vitamin D deficiency exist in this population. The authors determined the prevalence and correlates of vitamin D deficiency among urban IDUs in the AIDS Linked to the IntraVenous Experience (ALIVE) Study cohort. For this cross-sectional sub-study, vitamin D deficiency was defined as a serum 25(OH)-vitamin D level  $<20$  ng/mL. Multivariable logistic regression was used to identify factors independently associated with vitamin D deficiency. Of 950 individuals analyzed, 29% were HIV-infected. The median age was 49 years; 65% were male, and 91% were black. The median vitamin D level was 13.5 ng/mL (IQR, 9.0-20.3); 74% were deficient (68% in HIV-infected vs. 76% in HIV-uninfected,  $p=0.01$ ). Non-black race, fall/winter season, multivitamin intake, higher serum albumin, HCV seropositivity and HIV-infection were associated with significantly lower odds of vitamin D deficiency. Vitamin D deficiency is prevalent among IDUs. Notably, HIV-infected IDUs were less likely to be vitamin D deficient. Higher vitamin D levels were associated with multivitamin intake and with higher albumin levels, suggesting that nutritional status contributes substantially to deficiency. The association between HCV serostatus and vitamin D level remains unclear. Further investigation is needed to define the clinical implications of the heavy burden of vitamin D deficiency in this high-

risk, aging population with significant co-morbidities.

**A Cross Sectional Analysis Of the Role Of the Antimicrobial Peptide Cathelicidin In Lung Function Impairment Within the Alive Cohort** Lambert AA, Kirk GD, Astemborski J, Neptune ER, Mehta SH, Wise RA, Drummond MB. PLoS One. 2014 ; 9(4): e95099.

Vitamin D deficiency is associated with reduced lung function. Cathelicidin, an antimicrobial peptide regulated by vitamin D, plays a role within the innate immune system. The association of cathelicidin with lung function decrement and respiratory infection is undefined. The authors determined the independent relationship of cathelicidin with lung function. In a cross-sectional analysis of 650 participants in an urban observational cohort with high smoking prevalence, plasma 25(OH)-vitamin D and cathelicidin levels were measured from stored samples obtained within 6 months of spirometry study visits. Multivariable linear regression was used to determine the independent association between low cathelicidin (defined as the lowest quartile of the cohort) and absolute forced expiratory volume in 1 second (FEV1). The mean age of the cohort was 49 years; 91% were black, 35% female and 41% HIV-infected. Participants with low cathelicidin had a 183 mL lower FEV1 compared to higher cathelicidin ( $p=0.009$ ); this relationship was maintained (115 mL lower;  $p=0.035$ ) after adjusting for demographics, BMI, and smoking. Neither HIV serostatus, heavy smoking history, nor 25(OH)-vitamin D levels were associated with cathelicidin levels. Participants with low cathelicidin had a greater prevalence of prior bacterial pneumonia (21% versus 14%;  $p=0.047$ ). Inclusion of pneumonia in adjusted models did not substantially reduce the FEV1 decrement observed with low cathelicidin (104 mL lower FEV1;  $p=0.05$ ). Lung function decrements associated with low cathelicidin were greatest among individuals with lower 25(OH)-vitamin D levels. In a cohort at risk for airflow obstruction, low cathelicidin was independently associated with lower FEV1. These clinical data support a mechanistic link between 25(OH)-vitamin D deficiency and lung function impairment, independent of pneumonia risk.

### **HCV, HIV/HCV, Drug Abuse Medical Consequences**

**Comparison Of Hepatitis C Virus RNA and Antibody Detection In Dried Blood Spots and Plasma Specimens** Dokubo EK, Evans J, Winkelman V, Cyrus S, Tobler LH, Asher A, Briceno A, Page K. J Clin Virol. 2014 Apr; 59(4): 223-7.

Current diagnostic tests for Hepatitis C Virus (HCV) involve phlebotomy and serologic testing for HCV antibodies (anti-HCV) and RNA, which are not always feasible. Dried blood spots (DBS) present a minimally invasive sampling method and are suitable for sample collection, storage and testing. To assess the utility of DBS in HCV detection, the authors evaluated the sensitivity and specificity of DBS for anti-HCV and HCV RNA detection compared to plasma specimens. This cross-sectional validation study was conducted in the context of an existing prospective study of HCV in young injection drug users. Blood samples were collected by venipuncture into serum separator tubes (SST) and via finger stick onto Whatman 903(®) protein-saver cards. Plasma samples and eluates from the DBS were tested for anti-HCV using either a third generation enzyme-linked or chemiluminescent immunoassay (IA), and HCV RNA using discriminatory HCV transcription-mediated amplification assay (dHCV TMA). DBS results were compared to their corresponding plasma sample results. 148 participants were tested for anti-HCV and 132 participants were tested for HCV RNA. For anti-HCV, the sensitivity of DBS was 70%, specificity was 100%, positive predictive value (PPV) was 100%, negative predictive value (NPV) was 76% and Kappa was 0.69. For HCV RNA, the sensitivity of DBS was 90%, specificity was 100%, PPV was 100%, NPV was 94% and Kappa was 0.92. DBS are sensitive and very specific in detecting

anti-HCV and HCV RNA, demonstrate good correlation with plasma results, and have potential to facilitate diagnosis of HCV infection.

**Kinetic Differences In the Induction Of Interferon Stimulated Genes By Interferon-A and Interleukin 28B Are Altered By Infection With Hepatitis C Virus** Jilg N, Lin W, Hong J,

Schaefer EA, Wolski D, Meixong J, Goto K, Brisac C, Chusri P, Fusco DN, Chevaliez S, Luther J, Kumthip K, Urban TJ, Peng LF, Lauer GM, Chung RT. *Hepatology*. 2014 Apr; 59(4): 1250-61. Several genome-wide association studies (GWAS) have identified a genetic polymorphism associated with the gene locus for interleukin 28B (IL28B), a type III interferon (IFN), as a major predictor of clinical outcome in hepatitis C. Antiviral effects of the type III IFN family have previously been shown against several viruses, including hepatitis C virus (HCV), and resemble the function of type I IFN including utilization of the intracellular Janus kinase signal transducer and activator of transcription (JAK-STAT) pathway. Effects unique to IL28B that would distinguish it from IFN- $\alpha$  are not well defined. By analyzing the transcriptomes of primary human hepatocytes (PHH) treated with IFN- $\alpha$  or IL28B, the authors sought to identify functional differences between IFN- $\alpha$  and IL28B to better understand the roles of these cytokines in the innate immune response. Although the authors' data did not reveal distinct gene signatures, they detected striking kinetic differences between IFN- $\alpha$  and IL28B stimulation for interferon stimulated genes (ISGs). While gene induction was rapid and peaked at 8 hours of stimulation with IFN- $\alpha$  in PHH, IL28B produced a slower, but more sustained increase in gene expression. The authors confirmed these findings in the human hepatoma cell line Huh7. 5. 1. Interestingly, in HCV-infected cells the rapid response after stimulation with IFN- $\alpha$  was blunted, and the induction pattern resembled that caused by IL28B. The kinetics of gene induction is fundamentally different for stimulations with either IFN- $\alpha$  or IL28B in hepatocytes, suggesting distinct roles of these cytokines within the immune response. Furthermore, the observed differences are substantially altered by infection with HCV.

**Direct-Acting Antiviral Agents and the Path To Interferon Independence** Schmidt WN, Nelson DR, Pawlotsky JM, Sherman KE, Thomas DL, Chung RT. *Clin Gastroenterol Hepatol*. 2014 May; 12(5): c728-37.

Chronic infection with hepatitis C virus (HCV) is a major global health problem; there are approximately 120 to 130 million chronic infections worldwide. Since the discovery of HCV 24 years ago, there has been a relentless effort to develop successful antiviral therapies. Studies of interferon- $\alpha$ -based therapies have helped define treatment parameters, and these treatment strategies have cured a substantial percentage of patients. However, interferon- $\alpha$  must be injected; there are problems with tolerability, adherence, and incomplete response in a large percentage of patients. New drug candidates designed to target the virus or the host have recently been introduced at an unprecedented pace. In phase I-III studies, these agents have exceeded expectations and achieved rates of response previously not thought possible. We are, therefore, entering a new era of therapy for HCV infection and interferon independence.

**All-Oral Combination Of Ledipasvir, Vedroprevir, Tegobuvir, and Ribavirin In Treatment-Naïve Patients With Genotype 1 HCV Infection** Wyles DL, Rodriguez-Torres M, Lawitz E,

Shiffman ML, Pol S, Herring RW, Massetto B, Kanwar B, Trenkle JD, Pang PS, Zhu Y, Mo H, Brainard DM, Subramanian GM, McHutchison JG, Habersetzer F, Sulkowski MS. *Hepatology*. 2014 Jul; 60(1): 56-64.

This phase II trial assessed the efficacy and safety of a combination regimen of the nonstructural protein (NS)5A inhibitor ledipasvir (LDV), NS3 protease inhibitor vedroprevir (VDV), non-nucleoside NS5B inhibitor tegobuvir (TGV), and ribavirin (RBV) in treatment-naïve patients with

chronic hepatitis C virus (HCV) genotype 1 without cirrhosis. Patients were randomized 1:2 to LDV 30 mg once daily (QD; Arm 1; n=46) or LDV 90 mg QD (Arm 2; n=94); patients in both arms also received VDV 200 mg QD, TGV 30 mg twice-daily, and RBV 1,000-1,200 mg/day. Patients in Arm 2 with vRVR, defined as HCV RNA below the lower limit of quantification (LLOQ) from treatment weeks 2 to 10, were randomized 1:1 to stop treatment at 12 weeks or continue for 24 weeks. Sustained virologic response 12 weeks after treatment (SVR12) was higher in patients receiving 90 mg of LDV for 24 weeks (63%), compared with LDV 90 mg for 12 weeks (54%) and LDV 30 mg for 24 weeks (48%). In patients with very rapid virologic response (vRVR) in Arm 2, SVR12 was achieved by 68% and 81% of patients treated for 12 and 24 weeks, respectively. Virologic breakthrough was more common in patients with HCV genotype 1a and was associated with resistance-associated variants for all three direct-acting antiviral agents (DAAs); however, in all but 1 patient who relapsed, resistance-associated variants directed against only one or two of the DAAs were detected. The most common adverse events were fatigue, headache, nausea, rash, and diarrhea. In patients with HCV genotype 1, an interferon-free regimen containing LDV/VDV/TGV/RBV was well tolerated and led to SVR12 in up to 63% of patients. LDV 90 mg is currently being investigated in combination with the nucleotide polymerase inhibitor, sofosbuvir.

### **Overall Safety Profile Of Boceprevir Plus Peginterferon Alfa-2B and Ribavirin In Patients With Chronic Hepatitis C Genotype 1: A Combined Analysis Of 3 Phase 2/3 Clinical Trials**

Manns MP, McCone J, Davis MN, Rossaro L, Schiff E, Shiffman ML, Bacon B, Bourliere M, Sulkowski MS, Bruno S, Balart L, Bronowicki JP, Kwo P, Poordad F, Felizarta F, Reddy KR, Helmond FA, Sings HL, Pedicone LD, Burroughs M, Brass CA, Albrecht JK, Vierling JM. *Liver Int.* 2014 May; 34(5): 707-19.

Triple therapy with peginterferon/ribavirin (PR) plus an NS3 protease inhibitor has emerged as the standard-of-care for patients with chronic hepatitis C genotype-1. The authors provide a detailed safety analysis comparing PR to boceprevir plus PR (BOC/PR) across three phase 2/3 studies. SPRINT-1 was an open-label phase 2 study in 595 treatment-naïve patients. In the two phase 3 studies, 1500 patients (1097 treatment-naïve, SPRINT-2; 403 treatment-failure, RESPOND-2) were randomized to receive PR alone, or one of two regimens where BOC was added to PR after a 4-wk PR lead-in. In this analysis, the respective BOC/PR and PR arms were combined for all three trials. The benefit of shortened duration of treatment using response-guided therapy (RGT) was also explored in the SPRINT-2 trial. Only two adverse events, anaemia and dysgeusia, occurred 20% more often with the BOC-containing regimens compared with PR. Nausea, diarrhoea and neutropenia were the only other common events with an incidence of at least 5% greater when BOC was added to the PR backbone. The proportions of patients reporting serious adverse events (AE), life-threatening AEs, and study drug discontinuation because of an AE were similar in the PR and BOC/PR arms. In treatment-naïve patients, RGT generally did not result in a lower frequency of common AEs; however, RGT led to decreased exposure to all 3 study drugs and to a decrease in the mean duration of several clinically relevant AEs such as anaemia, neutropenia, fatigue and depression, as well as earlier normalization of haemoglobin and neutrophil counts. The safety profile of BOC combination therapy largely reflects the known profile of peginterferon and ribavirin, with incremental haematological effects and dysgeusia. Shorter treatment duration with RGT significantly reduced the duration of AEs.

**Safety and Antiviral Activity Of the HCV Entry Inhibitor Itx5061 In Treatment-Naive HCV-Infected Adults: A Randomized, Double-Blind, Phase 1B Study**

Sulkowski MS, Kang M, Matining R, Wyles D, Johnson VA, Morse GD, Amorosa V, Bhattacharya D, Coughlin K, Wong-Staal F, Glesby MJ, . J Infect Dis. 2014 Mar; 209(5): 658-67.

Hepatitis C virus (HCV) entry involves scavenger receptor B1 (SRB1). In vitro, SRB1 inhibition by ITX5061 impedes HCV replication. This was a multicenter study to assess safety/activity of ITX5061 in previously untreated, noncirrhotic, HCV genotype 1 infected adults. The study design included sequential cohorts of 10 subjects with ITX5061 (n = 8) or placebo (n = 2) to escalate duration (3 to 14 to 28 days) or deescalate dose (150 to 75 to 25 mg) based on predefined criteria for safety and activity ( $\geq 4$  of 8 subjects with HCV RNA decline  $\geq 1 \log_{10}$  IU/mL). Thirty subjects enrolled in 3 cohorts: ITX5061 150 mg/day by mouth for 3 (A150), 14 (B150), and 28 (C150) days. Six subjects had grade  $\geq 3$  adverse events (one in placebo); none were treatment related. One of the 7 C150 subjects (14.3%, 95% confidence interval [CI], .7%-55. 4%) had  $\geq 1 \log_{10}$  IU/mL decline in HCV RNA (1.49  $\log_{10}$  IU/mL), whereas none of the 6 placebo, 8 A150 or 8 B150 subjects showed such decline. Oral ITX5061 150 mg/day for up to 28 days was safe and well tolerated. In the 28-day cohort, 1 of 7 subjects showed antiviral activity; however, predefined criteria for antiviral activity were not met at the doses and durations studied.

**HIV and HCV Activate the Inflammasome In Monocytes and Macrophages Via Endosomal Toll-Like Receptors Without Induction Of Type 1 Interferon**

Chattergoon MA, Latanich R, Quinn J, Winter ME, Buckheit RW, Blankson JN, Pardoll D, Cox AL. PLoS Pathog. 2014 May; 10(5): e1004082.

Innate immune sensing of viral infection results in type I interferon (IFN) production and inflammasome activation. Type I IFNs, primarily IFN- $\alpha$  and IFN- $\beta$ , are produced by all cell types upon virus infection and promote an antiviral state in surrounding cells by inducing the expression of IFN-stimulated genes. Type I IFN production is mediated by Toll-like receptor (TLR) 3 in HCV infected hepatocytes. Type I IFNs are also produced by plasmacytoid dendritic cells (pDC) after sensing of HIV and HCV through TLR7 in the absence of productive pDC infection.

Inflammasomes are multi-protein cytosolic complexes that integrate several pathogen-triggered signaling cascades ultimately leading to caspase-1 activation and generation pro-inflammatory cytokines including interleukin (IL)-18 and IL-1 $\beta$ . Here, the authors demonstrate that HIV and HCV activate the inflammasome, but not Type I IFN production, in monocytes and macrophages in an infection-independent process that requires clathrin-mediated endocytosis and recognition of the virus by distinct endosomal TLRs. Knockdown of each endosomal TLR in primary monocytes by RNA interference reveals that inflammasome activation in these cells results from HIV sensing by TLR8 and HCV recognition by TLR7. Despite its critical role in type I IFN production by pDCs stimulated with HIV, TLR7 is not required for inflammasome activation by HIV. Similarly, HCV activation of the inflammasome in monocytes does not require TLR3 or its downstream signaling adaptor TICAM-1, while this pathway leads to type I IFN in infected hepatocytes. Monocytes and macrophages do not produce type I IFN upon TLR8 or TLR7 sensing of HIV or HCV, respectively. These findings reveal a novel infection-independent mechanism for chronic viral induction of key anti-viral programs and demonstrate distinct TLR utilization by different cell types for activation of the type I IFN vs. inflammasome pathways of inflammation.

**Clearance Of Hepatitis C Infection Is Associated With the Early Appearance Of Broad Neutralizing Antibody Responses** Osburn WO, Snider AE, Wells BL, Latanich R, Bailey JR, Thomas DL, Cox AL, Ray SC. *Hepatology*. 2014 Jun; 59(6): 2140-51.

The contribution of humoral immune responses to spontaneous control of hepatitis C virus (HCV) infection remains unclear. The authors assessed neutralizing antibody (nAb) responses during acute HCV infection to determine whether infection outcome is associated with the nAb response, specifically, its timing or breadth (neutralization of multiple genotype-matched variants). A representative genotype 1 HCV pseudoparticle (HCVpp) library, consisting of 19 genetically distinct genotype 1 HCVpp that comprise the natural variability of genotype 1 E1E2 sequences, was used to assess anti-genotype 1 nAb responses during acute infection in at-risk persons followed prospectively. Neutralization of individual library HCVpp by the last viremic plasma sample obtained before clearance was compared to either 1-year post-initial viremia or clearance time-matched specimens obtained from subjects developing persistent infection. In persistently infected persons nAb responses were delayed then progressively broadened, whereas in persons who controlled viremia broader responses were detected early and contracted after clearance of viremia. Surprisingly, the breadth of anti-genotype 1 nAb responses was not dependent on subjects' infection genotype. Also, individual library HCVpp neutralization sensitivity was not associated with any known E2 sequence determinants. Interestingly, two single nucleotide polymorphisms in the HLA-DQ locus were associated with nAb breadth. Control of HCV infection is associated with more rapid development of a broad nAb response, independent of the infection viral genotype, providing further evidence for the role of nAb in controlling HCV infection and the potential benefit of generating broad anti-HCV nAb responses by vaccination.

### **Non-HIV/AIDS Drug Abuse Medical Consequences**

**Craving Predicts Opioid Use In Opioid-Dependent Patients Initiating Buprenorphine Treatment: A Longitudinal Study** Tsui JI, Anderson BJ, Strong DR, Stein MD. *Am J Drug Alcohol Abuse*. 2014 Mar; 40(2): 163-9.

Few studies have assessed associations between craving and subsequent opioid use. The authors prospectively evaluated the relative utility of two craving questionnaires to predict opioid use among opioid-dependent patients in outpatient treatment. Opioid-dependent patients (n=147) initiating buprenorphine treatment were assessed every two weeks for 3 months. Craving was measured using the: (1) Desires for Drug Questionnaire (DDQ) and (2) Penn Alcohol-Craving Scale adapted for opioid craving (PCS). Multi-level logistic regression models estimated the effects of craving on the likelihood of opioid use. Craving assessed at time t was entered as a time-varying predictor of opioid use at time t+1. Craving scores plateaued at approximately 2 weeks after initiation of buprenorphine. In adjusted regression models, a 1-point increase in PCS scores (on a 7-point scale) was associated with a significant increase in the odds of opioid use at the subsequent assessment (OR=1.27, 95% CI 1.08; 1.49, p<0.01). The odds of opioid use at the subsequent follow-up assessment increased significantly as DDQ desire and intention scores increased (OR=1.25, 95% CI 1.03; 1.51, p<0.05), but was not significantly associated with DDQ negative reinforcement (OR=1.01, 95% CI 0.88; 1.17, p>0.05) or DDQ control (OR=0.97, 95% CI 0.85; 1.11, p>0.05) scores. Self-reported craving for opioids was modestly associated with subsequent relapse to opioid use among a cohort of patients treated with buprenorphine. Assessment of craving may provide clinical utility in predicting relapse among treated opioid-dependent patients.

**The Lifetime Prevalence Of Anabolic-Androgenic Steroid Use and Dependence In Americans: Current Best Estimates** Pope HG, Kanayama G, Athey A, Ryan E, Hudson JI, Baggish A. *Am J Addict.* 2014 Jul; 23(4): 371-7.

Although various surveys have tracked the prevalence of anabolic-androgenic steroid (AAS) use in American teenagers and young adults, no recent surveys have assessed the lifetime prevalence of AAS use in Americans overall. The authors therefore analyzed serial youth-survey data to derive estimates of the lifetime prevalence of AAS use in the current American general population. They first determined the distribution of age of onset of AAS use, based on pooled data from nine studies. Using this distribution, they then developed equations to project the eventual lifetime prevalence of AAS use among young survey respondents, once they aged and completed the period of risk for initiating AAS. The authors similarly calculated the denominator of lifetimes of risk for AAS use in the total American population. They next applied these equations to four independent national youth datasets to derive current American general-population estimates for lifetime AAS use. Finally, using data from 10 pooled studies, the authors estimated the lifetime prevalence of AAS dependence among AAS users. Age-of-onset studies consistently showed that AAS use begins later than most drugs, with only 22% of users (95% confidence interval: 19-25%) starting before age 20. Applying the age-of-onset findings to national youth datasets, we estimated that among Americans currently age 13-50 years, 2.9-4.0 million have used AAS. Within this group, roughly 1 million may have experienced AAS dependence. Although subject to various limitations, our estimation techniques suggest a surprisingly high prevalence of AAS use and dependence among Americans.

**Comparison Of Tobacco-Containing and Tobacco-Free Waterpipe Products: Effects On Human Alveolar Cells** Shihadeh A, Eissenberg T, Rammah M, Salman R, Jaroudi E, El-Sabban M. *Nicotine Tob Res.* 2014 Apr; 16(4): 496-9.

In recent years, a class of products marketed as "tobacco-free" alternatives for the "health conscious user" has become widely available for waterpipe (hookah, narghile, or shisha) smoking. Their adoption may be in part driven by regulations banning tobacco smoking in public places and by an increasing awareness of the hazards of waterpipe tobacco smoking. Although these products are presented in advertising as a "healthier" choice, very little is known about their health effects. In this study, the authors compared the effects of smoke generated with tobacco-free and conventional tobacco-derived products on human alveolar cells. Smoke was generated with a smoking machine that precisely mimicked the puffing behavior of 15 experienced waterpipe smokers when they used conventional waterpipe tobacco products of their choice and flavor-matched tobacco-free products. Human alveolar epithelial cells (A549) were treated with particulate matter sampled from the smoke, and the effects on cell cycle, proliferation, and doubling time were measured during the subsequent 72 hr. The authors found that smoke from both types of waterpipe products markedly reduced cell proliferation, caused cell cycle arrest at G0/G1, and increased cell doubling time. There were no significant differences across product in any measure. Tobacco-free and tobacco-based waterpipe products exert substantial and similar deleterious effects on human lung cells. This study adds to the nascent evidence base indicating that except for exposure to nicotine and its derivatives, use of tobacco-free waterpipe products does not present a reduced health risk relative to the use of conventional tobacco-based products.

**Drug Interactions And Antiretroviral Drug Monitoring** Foy M, Sperati CJ, Lucas GM, Estrella MM. *Curr HIV/AIDS Rep.* 2014 Jun; [Epub ahead of print].

Owing to the improved longevity afforded by combination antiretroviral therapy (cART), HIV-infected individuals are developing several non-AIDS-related comorbid conditions. Consequently, medical management of the HIV-infected population is increasingly complex, with a growing list of

potential drug-drug interactions (DDIs). This article reviews some of the most relevant and emerging potential interactions between antiretroviral medications and other agents. The most common DDIs are those involving protease inhibitors or non-nucleoside reverse transcriptase inhibitors, which alter the cytochrome P450 enzyme system and/or drug transporters such as p-glycoprotein. Of note are the new agents for the treatment of chronic hepatitis C virus infection. These new classes of drugs and others drugs that are increasingly used in this patient population represent a significant challenge with regard to achieving the goals of effective HIV suppression and minimization of drug-related toxicities. Awareness of DDIs and a multidisciplinary approach are imperative in reaching these goals.

**Electrochemical Sensing Of Cortisol: A Recent Update** Singh A, Kaushik A, Kumar R, Nair M, Bhansali S. Appl Biochem Biotechnol. 2014 Apr; [Epub ahead of print].

Psychological stress caused by everyday lifestyle contributes to health disparities experienced by individuals. It affects many biomarkers, but cortisol - "a steroid hormone" - is known as a potential biomarker for psychological stress detection. Abnormal levels of cortisol are indicative of conditions such as Cushing's syndrome, Addison's disease, adrenal insufficiencies, and more recently, post-traumatic stress disorder (PTSD). Chromatographic techniques, which are traditionally used to detect cortisol, are a complex system requiring multistep extraction/purification. This limits its application for point-of-care (POC) detection of cortisol. However, electrochemical immunosensing of cortisol is a recent advancement towards POC application. This review highlights simple, low-cost, and label-free electrochemical immunosensing platforms which have been developed recently for sensitive and selective detection of cortisol in bio-fluids. Electrochemical detection is utilized for the detection of cortisol using Anti-Cortisol antibodies (Anti-Cab) covalently immobilized on nanostructures, such as self-assembled monolayer (SAM) and polymer composite, for POC integration of sensors. The observed information can be used as a prototype to understand behavioral changes in humans such as farmers and firefighters. Keeping the future directions and challenges in mind, the focus of the BioMEMS and Microsystems Research Group at Florida International University is on development of POC devices for immunosensing, integration of these devices with microfluidics, cross validation with existing technologies, and analysis of real sample.

## **SERVICES RESEARCH**

**The Ability of Single Screening Questions for Unhealthy Alcohol and Other Drug Use to Identify Substance Dependence in Primary Care** Saitz R, Cheng DM, Allensworth-Davies D, Winter MR, Smith PC. *J Stud Alcohol Drugs*. 2014; 75 (1): 153-7.

The ability of single screening questions for unhealthy alcohol and other drug use to identify substance dependence in primary care. Single screening questions (SSQs) are recommended for the evaluation of unhealthy alcohol use and other drug use (risky use through dependence). In addition, SSQs could provide information on severity that is necessary for brief intervention, information thought to be available only from longer questionnaires. The authors assessed SSQ accuracy for identifying dependence. In a cross-sectional study, 286 primary care patients were administered SSQs for alcohol and for other drugs (each asks how many times they were used in the past year), the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C), the Drug Abuse Screening Test (DAST), and a diagnostic interview reference standard for dependence. For each test, the authors calculated area under the receiver operating characteristic (ROC) curve and the ability to discriminate dependence at an optimal cutoff. The prevalence of alcohol and other drug dependence was 9% and 12%, respectively. Optimal cut points were eight or more times for the alcohol SSQ, a score of three or more for AUDIT-C, three or more times for the other drug SSQ, and a score of four or more for the DAST. The areas under the ROC curve ranged from 0.87 to 0.96. Sensitivity, specificity, and positive and negative likelihood ratios at optimal cut points for the alcohol SSQ were 88%, 84%, 5.6, and 0.1, respectively; for the other drug SSQ were 97%, 79%, 4.6, 0.04, respectively; for the AUDIT-C were 92%, 71%, 3.2, 0.1, respectively; and for the DAST were 100%, 84%, 6.3, 0, respectively. Alcohol SSQ and AUDIT-C positive likelihood ratio 95% confidence intervals did not overlap. SSQs can identify substance dependence as well as and sometimes better than longer screening tools. SSQs may be useful for both screening and preliminary assessment, thus overcoming a barrier (seen with lengthy questionnaires) to dissemination of screening and brief intervention in primary care settings.

**Prevalence of Tuberculosis Symptoms and Latent Tuberculosis Infection among Prisoners in Northeastern Malaysia** Margolis B, Al-Darraj HA, Wickersham JA, Kamarulzaman A, Altice FL. *Int J Tuberc Lung Dis*. 2013; 17 (12): 1538-44.

There are currently no routine screening procedures for active tuberculosis (TB) or latent tuberculosis infection (LTBI) in Malaysian prisons. The objective of this study was to determine the prevalence and correlates of LTBI and active TB symptoms among Malaysian prisoners with and without human immunodeficiency virus (HIV) infection using the tuberculin skin test (TST) and the World Health Organization TB symptom-based screening instrument. A cross-sectional survey of 266 prisoners was performed in Kelantan, Malaysia. Consenting participants underwent two-step TST and were screened for active TB symptoms. Standardized cut-offs of respectively 5 and 10 mm was used to define reactive TST among prisoners with and without HIV. Clinical and behavioral data were assessed and HIV-infected prisoners were stratified by CD4 status. Overall LTBI prevalence was 87.6%, with significantly lower TST reactivity among HIV-infected than non-HIV-infected prisoners (83.6% vs. 91.5%,  $P < 0.05$ ); however, TB symptoms were similar (16.9% vs. 10.1%,  $P = 0.105$ ). On multivariate analysis, previous incarceration (aOR 4.61, 95%CI 1.76-12.1) was the only significant correlate of LTBI. Increasing age (aOR 1.07, 95%CI 1.01-1.13), lower body mass index (aOR 0.82, 95%CI 0.70-0.96) and TST-reactive status (aOR 3.46, 95%CI 1.20-9.97) were correlated with TB symptoms. The authors conclude that LTBI is highly prevalent, associated with previous incarceration, and suggests the need for routine TB screening on entry to Malaysian prisons.

**DSM-IV Antisocial Personality Disorder and Conduct Disorder: Evidence for Taxonic Structures Among Individuals With and Without Substance Use Disorders in the General Population** Kerridge BT, Saha TD, Hasin DS. *DSM-IV J Stud Alcohol Drugs*. 2014; 75 (3): 496-509.

The categorical-dimensional status of DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) conduct disorder (CD) and antisocial personality disorder (ASPD) is a source of controversy. This study examined whether the underlying structure of DSM-IV CD and ASPD was dimensional or categorical (taxonic) among individuals with and without substance use disorders. Using a national large representative survey of U.S. adults (n = 43,093), taxometric analyses of DSM-IV CD and ASPD diagnostic criteria were conducted on the total sample and among those with and without substance use disorders. Results of three taxometric procedures were consistent in showing that the structures underlying DSM-IV CD and ASPD were clearly taxonic in the total sample and among individuals with and without substance use disorders. Comparison curve fit indices exceeded 0.57 for each model. Taxonic findings of the present study were in contrast to the dimensional results of prior taxometric research among incarcerated samples with substantial comorbidity of antisocial syndromes and substance use disorders. Results supported the categorical representation and diagnostic thresholds of ASPD and CD as defined in DSM-IV and DSM-5. That the structure of ASPD and CD may be taxonic suggests that further research on these disorders use group comparative designs in which samples with and without these disorders are compared in terms of socio-demographic and clinical correlates, comorbidity, and treatment utilization. The taxonic structure of ASPD and CD may contribute to future research on causal processes through which these antisocial syndromes develop.

**No Detectable Association between Frequency of Marijuana Use and Health Or Healthcare Utilization among Primary Care Patients Who Screen Positive For Drug Use** Fuster D, Cheng DM, Allensworth-Davies D, Palfai TP, Samet JH, Saitz R. *J Gen Intern Med*. 2014; 29 (1): 133-9. Marijuana is the most commonly used illicit drug, yet its impact on health and healthcare utilization has not been studied extensively. To assess the cross-sectional association between frequency of marijuana use and healthcare utilization (emergency department and hospitalization) and health (comorbidity, health status), the authors studied patients in an urban primary care clinic who reported any recent (past 3-month) drug use (marijuana, opioids, cocaine, others) on screening. Frequency of marijuana use in the past 3 months was the main independent variable [daily/ almost daily, less than daily and no use (reference group)]. Outcomes assessed were past 3-month emergency department or hospital utilization, the presence of medical comorbidity (Charlson index  $\geq 1$ ), and health status with the EuroQol. The authors used separate multivariable regression models adjusting for age, sex, tobacco and other substance use. All 589 participants reported recent drug use: marijuana 84 % (29 % daily, 55 % less than daily), cocaine 25 %, opioid 23 %, and other drugs 8 %; 58 % reported exclusive marijuana use. Frequency of marijuana use was not significantly associated with emergency department use {adjusted odds ratio [AOR] 0.67, [95 % confidence interval (CI) 0.36, 1.24] for daily; AOR 0.69 [95 % CI 0.40, 1.18] for less than daily versus no use}, hospitalization [AOR 0.79 (95 % CI 0.35, 1.81) for daily; AOR 1.23 (95 % CI 0.63, 2.40) for less than daily versus no use], any comorbidity [AOR 0.62, (95 % CI 0.33, 1.18) for daily; AOR 0.67 (95 % CI 0.38, 1.17) for less than daily versus no use] or health status (adjusted mean EuroQol 69.1, 67.8 and 68.0 for daily, less than daily and none, respectively, global  $p=0.78$ ). Among adults in primary care who screen positive for any recent illicit or non-medical prescription drug use, we were unable to detect an association between frequency of marijuana use and health, emergency department use, or hospital utilization.

**Optimization of Human Immunodeficiency Virus Treatment During Incarceration: Viral Suppression at The Prison Gate**

Meyer JP, Cepeda J, Wu J, Trestman RL, Altice FL, Springer S.

JAMA Intern Med. 2014; 174 (5): 721-9.

Human immunodeficiency virus (HIV) management in correctional settings is logistically feasible, but HIV-related outcomes before release have not been recently systematically examined. The objective of this study was to evaluate HIV treatment outcomes throughout incarceration, including jail and prison. This was a retrospective cohort study of longitudinally linked demographic, pharmacy, and laboratory data on 882 prisoners within the Connecticut Department of Correction (2005-2012) with confirmed HIV infection, who were continually incarcerated 90 days or more, had at least 2 HIV-1 RNA and CD4 lymphocyte measurements, and were prescribed antiretroviral therapy. Three electronic databases (correctional, laboratory, and pharmacy) were integrated to assess HIV viral suppression (HIV-1 RNA levels, 400 copies/mL) on intake and release. Secondary outcomes were mean change in log-transformed HIV-1 RNA levels and mean change in CD4 lymphocyte count during incarceration. Demographic characteristics, prescribed pharmacotherapies, receipt of directly observed therapy, and duration of incarceration were analyzed as possible explanatory variables for HIV viral suppression in logistic regression models. Among 882 HIV-infected prisoners with 1185 incarceration periods, mean HIV-1 RNA level decreased by 1.1 log10 and CD4 lymphocyte count increased by 98 cells/L over time, with a higher proportion achieving viral suppression by release compared with entry (70.0% vs 29.8%; P=.001); 36.9% of antiretroviral therapy (ART) regimens were changed during incarceration. After adjusting for baseline HIV-1 RNA level, prerelease viral suppression correlated with female sex (adjusted odds ratio, 1.81; 95% CI, 1.26-2.59) and psychiatric disorder severity below the sample median (adjusted odds ratio, 1.50; 95% CI, 1.12-1.99), but not race/ethnicity, incarceration duration, ART regimen or dosing strategy, or directly observed therapy. Though just one-third of HIV-infected prisoners receiving ART entered correctional facilities with viral suppression, HIV treatment was optimized during incarceration, resulting in the majority achieving viral suppression by release. Treatment for HIV within prison is facilitated by a highly structured environment and, when combined with simple well-tolerated ART regimens, can result in viral suppression during incarceration. In the absence of important and effective community-based resources, incarceration can be an opportunity of last resort to initiate continuous ART for individual health and, following the "treatment as prevention" paradigm, potentially reduce the likelihood of HIV transmission to others after release if continuity of HIV care is sustained.

**Cannabis Use Disorders Are Comparatively Prevalent among Nonwhite Racial/Ethnic Groups and Adolescents: A National Study**

Wu L-T, Brady KT, Mannelli P, Killeen TK, NIDA

Workgroup. J Psychiatr Res. 2014; 50: 26-35.

The racial/ethnic composition of the US population is shifting, with the nonwhite population growing faster than whites. The authors examined cannabis use disorder (CUD) prevalence's and correlate in seven racial/ethnic groups. They included cannabis use (CU) prevalence as a comparison. Data were from the 2005-2011 National Surveys on Drug Use and Health (N=394,400). Substance use among respondents aged 12 years and older was assessed by computer-assisted, self-interviewing methods. The following were included as control variables: age, sex, family income, government assistance, county type, residential stability, major depressive episode history, arrest history, nicotine dependence, alcohol disorder, and survey year. Past-year CU prevalence increased significantly from 10.45% in 2005 to 11.41-11.54% during 2009-2011. Compared with whites, mixed-race individuals had higher odds of CU; Asian Americans and Hispanics had lower odds of CU. There were no significant yearly changes in CUD prevalence in the sample during 2005-2011 (1.58-1.73%). Compared with whites, individuals who were mixed-

race, black, and Native American had higher odds of CUD; Asian Americans had lower odds. In aggregate, 15.35% of past-year cannabis users met criteria for a CUD in the 12-month period. Past-year cannabis users who were black, Native American, Hispanic, or Asian American had higher odds of CUD than white users. In each racial/ethnic group, adolescent cannabis users generally showed greater odds of CUD than adult users. Behavioral health indicators (major depressive episode, arrest history, nicotine dependence, and alcohol disorder) were associated with CU and CUD. In conclusion, CUD disproportionately affects nonwhite groups and youth.

**Extended Release Naltrexone Injection is Performed in the Majority Of Opioid Dependent Patients Receiving Outpatient Induction: A Very Low Dose Naltrexone and Buprenorphine Open Label Trial** Mannelli P, Wu L-T, Peindl KS, Swartz MS, Woody GE. Drug Alcohol Depend. 2014; 138: 83-8.

Extended release naltrexone injection is performed in the majority of opioid dependent patients receiving outpatient induction: a very low dose naltrexone and buprenorphine open label trial. The approval of extended release injectable naltrexone (XR-NTX; Vivitrol®) has introduced a new option for treating opioid addiction, but studies are needed to identify its place within the spectrum of available therapies. The absence of physiological opioid dependence is a necessary and challenging first step for starting XR-NTX. Outpatient detoxification gives poor results and inpatient detoxification is either unavailable or too brief for the physiological effects of opioids to resolve. Here the authors present findings from an open label study that tested whether the transition from opioid addiction to XR-NTX can be safely and effectively performed in an outpatient setting using very low dose naltrexone and buprenorphine. Twenty treatment seeking opioid addicted individuals were given increasing doses of naltrexone starting at 0.25mg with decreasing doses of buprenorphine starting at 4 mg during a 7-day outpatient XR-NTX induction procedure. Withdrawal discomfort, craving, drug use, and adverse events were assessed daily until the XR-NTX injection, then weekly over the next month. Fourteen of the 20 participants received XR-NTX and 13 completed weekly assessments. Withdrawal, craving, and opioid or other drug use were significantly lower during induction and after XR-NTX administration compared with baseline, and no serious adverse events were recorded. Outpatient transition to XR-NTX combining upward titration of very low dose naltrexone with downward titration of low dose buprenorphine was safe, well tolerated, and completed by most participants. Further studies with larger numbers of subjects are needed to see if this approach is useful for naltrexone induction.

**E-Cigarette Prevalence and Correlates of Use among Adolescents versus Adults: A Review and Comparison** Carroll Chapman SL, Wu L-T. J Psychiatr Res. 2014; 54C: 43-54.

Perceived safer than tobacco cigarettes, prevalence of electronic cigarette (e-cigarette) use is increasing. Analyses of cartridges suggest that e-cigarettes may pose health risks. In light of increased use and the potential for consequences, the authors searched Google Scholar and Pubmed in July of 2013 using keywords, such as e-cigarette and vaping, to compare differences and similarities in prevalence and correlates of e-cigarette use among adolescents (grades 6-12) versus adults (aged greater than or equal to 18 years). Twenty-one studies focused on e-cigarette use. Ever-use increased among various age groups. In 2011, ever-use was highest among young adults (college students and those aged 20-28; 4.9%-7.0%), followed by adults (aged 18 and older; 0.6%-6.2%), and adolescents (grades 6-12 and aged 11-19; <1%-3.3%). However, in 2012 adolescent ever-use increased to 6.8% and, among high school students, went as high as 10.0%. While the identified common correlate of e-cigarette use was a history of cigarette smoking, a notable proportion of adolescents and young adults who never smoked cigarettes had ever-used e-cigarettes. E-cigarette use was not consistently associated with attempting to quit tobacco among young adults.

Adults most often reported e-cigarettes as a substitute for tobacco, although not always to quit. Reviewed studies showed a somewhat different pattern of e-cigarette use among young people (new e-cigarette users who had never used tobacco) versus adults (former or current tobacco users). Research is needed to better characterize prevalence's, use correlates, and motives of use in different population groups, including how adolescent and young adult experimentation with e-cigarettes relates to other types of substance use behaviors.

### **Organizational Capacity for Service Integration in Community-Based Addiction Health**

**Services** Guerrero EG, Aarons GA, Palinkas LA. Am J Public Health. 2014; 104 (4): e40-7.

The authors examined factors associated with readiness to coordinate mental health, public health, and HIV testing among community-based addiction health services programs. They analyzed client and program data collected in 2011 from publicly funded addiction health services treatment programs in Los Angeles County, California. They analyzed a sample of 14,379 clients nested in 104 programs by using logistic regressions examining odds of service coordination with mental health and public health providers. They conducted a separate analysis to examine the percentage of clients receiving HIV testing in each program. Motivational readiness and organizational climate for change were associated with higher odds of coordination with mental health and public health services. Programs with professional accreditation had higher odds of coordinating with mental health services, whereas programs receiving public funding and methadone and residential programs (compared with outpatient) had a higher percentage of clients receiving coordinated HIV testing. These findings provide an evidentiary base for the role of motivational readiness, organizational climate, and external regulation and funding in improving the capacity of addiction health services programs to develop integrated care.

### **Association between Cannabis Use, Psychosis, and Schizotypal Personality Disorder: Findings from the National Epidemiologic Survey on Alcohol and Related Conditions**

Davis GP, Compton MT, Wang S, Levin FR, Blanco C. Schizophr Res. 2013; 151 (1-3): 197-202.

Studies to date showing an association between cannabis use and schizophrenia-spectrum disorders are of relatively small sample sizes with limitations in generalizability. The present study addresses this gap by examining the relationship between cannabis use and psychotic-like symptoms in a large representative community sample. Data were derived from the 2004-2005 National Epidemiologic Survey on Alcohol and Related Conditions (NESARC, Wave 2), a large, nationally representative sample of 34,653 adults from the United States population. The authors evaluated the association between lifetime cannabis use, psychosis, and schizotypal personality features. The prevalence of psychosis and schizotypal personality disorder increased significantly with greater cannabis use in a dose-dependent manner. The associations between cannabis use and psychosis were 1.27 (95% CI 1.03-1.57) for lifetime cannabis use, 1.79 (95% CI 1.35-2.38) for lifetime cannabis abuse, and 3.69 (95% CI 2.49-5.47) for lifetime cannabis dependence. There was a similar dose-response relationship between the extent of cannabis use and schizotypal personality disorder (OR=2.02 for lifetime cannabis use, 95% CI 1.69-2.42; OR=2.83 for lifetime cannabis abuse, 95% CI 2.33-2.43; OR=7.32 for lifetime cannabis dependence, 95% CI 5.51-9.72). Likelihood of individual schizotypal features increased significantly with increased extent of cannabis use in a dose-dependent manner. This is the first population-based study to examine the association between lifetime cannabis use, psychosis, and schizotypal personality traits. These results add to evidence that cannabis use may be a risk factor for psychosis liability.

**Two Cases of Intranasal Naloxone Self-Administration in Opioid Overdose** Green TC, Ray M, Bowman SE, McKenzie M, Rich JD, Subst Abus. 2014; 35(2): 129-32.

Overdose is a leading cause of death for former prisoners, exacting its greatest toll during the first 2 weeks post release. Protective effects have been observed with training individuals at high risk of overdose and prescribing them naloxone, an opioid antagonist that reverses the effects of the opioid-induced respiratory depression that causes death. Cases: The authors report 2 people with opiate use histories who self-administered intranasal naloxone to treat their own heroin overdoses following release from prison. Patient A is a 34-year-old male, who reported having experienced an overdose on heroin the day after he was released from incarceration. Patient B is a 29-year-old female, who reported an overdose on her first injection of heroin, 17 days post release from incarceration. Both patients self-administered the medication but were assisted at some point during the injury by a witness whom they had personally instructed in how to prepare and administer the medication. Neither patient experienced withdrawal symptoms following exposure to naloxone. Self-administration of naloxone should not be a goal of overdose death prevention training. A safer, more reliable approach is to prescribe naloxone to at-risk patients and train and also equip members of their household and social or drug-using networks in overdose prevention and response.

**MAPIT: Development of a Web-Based Intervention Targeting Substance Abuse Treatment in the Criminal Justice System** Walters ST, Ondersma SJ, Ingersoll KS, Rodriguez M, Lerch J, Rossheim ME, Taxman FS. J Subst Abuse Treat. 2014; 46 (1): 60-5.

Although drug and alcohol treatment are common requirements in the U.S. criminal justice system, only a minority of clients actually initiate treatment. This paper describes a two-session, web-based intervention to increase motivation for substance abuse treatment among clients using illicit substances. MAPIT (Motivational Assessment Program to Initiate Treatment) integrates the extended parallel process model, motivational interviewing, and social cognitive theory. The first session (completed near the start of probation) targets motivation to complete probation, to make changes in substance use (including treatment initiation), and to obtain HIV testing and care. The second session (completed approximately 30 days after session 1) focuses on goal setting, coping strategies, and social support. Both sessions can generate emails or mobile texts to remind clients of their goals. MAPIT uses theory-based algorithms and a text-to-speech engine to deliver custom feedback and suggestions. In an initial test, participants indicated that the program was respectful, easy to use, and would be helpful in making changes in substance use. MAPIT is being tested in a randomized trial in two large U.S. probation agencies. MAPIT addresses the difficulties of many probation agencies to maximize client involvement in treatment, in a way that is cost effective and compatible with the existing service delivery system.

**Substance Use Disorders and Psychiatric Comorbidity in Mid and Later Life: A Review** Wu L-T, Blazer DG. Int J Epidemiol. 2014; 43 (2): 304-17.

Globally, adults aged 65 years or older will increase from 516 million in 2009 to an estimated 1.53 billion in 2050. Due to substance use at earlier ages that may continue into later life, and aging-related changes in medical conditions, older substance users are at risk for substance-related consequences. MEDLINE and Psych Info databases were searched using keywords: alcohol use disorder, drug use disorder, drug misuse, substance use disorder, prescription drug abuse, and substance abuse. Using the related-articles link, additional articles were screened for inclusion. This review focused on original studies published between 2005 and 2013 to reflect recent trends in substance use disorders. Studies on psychiatric comorbidity were also reviewed to inform treatment needs for older adults with a substance use disorder. Among community non-institutionalized adults aged 50+ years, about 60% used alcohol, 3% used illicit drugs and 1-2% used nonmedical

prescription drugs in the past year. Among adults aged 50+, about 5% of men and 1.4% of women had a past-year alcohol use disorder. Among alcohol users, about one in 14 users aged 50-64 had a past-year alcohol use disorder vs one in 30 elder users aged 65+. Among drug users aged 50+, approximately 10-12% had a drug use disorder. Similar to depressive and anxiety disorders, substance use disorders were among the common psychiatric disorders among older adults. Older drug users in methadone maintenance treatment exhibited multiple psychiatric or medical conditions. There have been increases in treatment admissions for illicit and prescription drug problems in the United States. Substance use in late life requires surveillance and research, including tracking substance use in the racial/ethnic populations and developing effective care models to address comorbid medical and mental health problems.

**Suicide and Substance Use among Female Veterans: A Need for Research** Chapman SLC, Wu L-T *Drug Alcohol Depend.* 2014; 136: 1-10.

The number of female veterans is increasing. Veterans Administration (VA) enrollment increased over 40% from past eras. However, little research has focused on their mental health. The authors reviewed literature to examine associations of substance use with suicide in female veterans, identify research gaps, and inform future studies. Google Scholar, Pub Med, and Psych INFO were searched using: substance use, female veteran, and suicide. Exclusion criteria (e.g., not discussing U.S. veterans) left 17 articles. Nine studies examined completed suicide among veterans. In most recent years, rates of deaths were greater for veterans than nonveterans, including females. Completed suicide was associated with past trauma, young age, and a mental disorder. Studies have often not addressed substance use. Three studies examined completed suicide among VA treated veterans without examining substance use as an associated factor. Rates of completed suicides were also higher among veterans than nonveterans, including females. A large proportion of females also had a mental diagnosis. Five studies examined substance use and attempted or completed suicide among VA treated veterans. Veterans in poor mental health had increased odds of suicide mortality; women with a substance use disorder (SUD) had a higher hazard ratio for completed suicide than men with a SUD. Engagement in substance abuse treatment decreased odds of suicide attempt among veterans. Available data suggest that suicide rates are higher among female veterans than women in the general population. Substance use may increase the likelihood of suicidal behaviors among female veterans, particularly those with a mental diagnosis.

**Method of Administration Of PROMIS Scales Did Not Significantly Impact Score Level, Reliability, or Validity** Bjorner JB, Rose M, Gandek B, Stone AA, Junghaenel DU, Ware Jr JE. *J Clin Epidemiol.* 2014; 67 (1): 108-13.

The objective of this study was to test the impact of the method of administration (MOA) on score level, reliability, and validity of scales developed in the Patient Reported Outcomes Measurement Information System (PROMIS). Two non-overlapping parallel forms each containing eight items from each of three PROMIS item banks (Physical Function, Fatigue, and Depression) were completed by 923 adults with chronic obstructive pulmonary disease, depression, or rheumatoid arthritis. In a randomized crossover design, subjects answered one form by interactive voice response (IVR) technology, paper questionnaire (PQ), personal digital assistant (PDA), or personal computer (PC) and a second form by PC, in the same administration. Method equivalence was evaluated through analyses of difference scores, intraclass correlations (ICCs), and convergent/discriminant validity. In difference score analyses, no significant mode differences were found and all confidence intervals were within the pre-specified minimal important difference of 0.2 standard deviation. Parallel-forms reliabilities were very high (ICC = 0.85-0.93). Only one across-mode ICC was significantly lower than the same-mode ICC. Tests of validity showed no differential effect by

MOA. Participants preferred screen interface over PQ and IVR. The authors found no statistically or clinically significant differences in score levels or psychometric properties of IVR, PQ, or PDA administration compared with PC.

### **New English and Spanish Social Health Measures Will Facilitate Evaluating Health**

**Determinants** Hahn EA, DeWalt DA, Bode RK, Garcia SF, DeVellis RF; Correia H, Cella D, PROMIS Cooperative Group. *Health Psychol.* 2014; 33 (5): 490-9.

The objective of this study was to develop psychometrically sound, culturally relevant, and linguistically equivalent English and Spanish self-report measures of social health guided by a comprehensive conceptual model and applicable across chronic illnesses. The Patient-Reported Outcomes Measurement Information System (PROMIS) Social Health Workgroup implemented a mixed methods approach to evaluate earlier results (v1.0); expand and refine domain definitions and items; translate items into Spanish; and obtain qualitative feedback. Computer-based and paper/pencil questionnaire administration was conducted with a variety of U.S. respondent samples during 2009-2012. Analyses included exploratory factor analysis (EFA), confirmatory factor analysis (CFA), two-parameter logistic item response theory (IRT) modeling, evaluation of differential item functioning (DIF), and evaluation of criterion and construct validity. Qualitative feedback supported the conceptualization of the Social Health domain framework (Social Function and Social Relationships subcomponents). Validation testing participants (n = 2,208 English; n = 644 Spanish) were diverse in terms of gender, age, education, and ethnicity/race. EFA, CFA, and IRT identified 7 unidimensional factors with good model fit. There was no DIF by language, and good evidence of criterion and construct validity. PROMIS English and Spanish language instruments (v2.0), including computer-adaptive tests and fixed-length short forms, are publicly available for assessment of Social Function (Ability to Participate in Social Roles and Activities, and Satisfaction with Social Roles and Activities) and Social Relationships (Companionship; Emotional, Informational and Instrumental Support; and Social Isolation). Measures of social health will play a key role in applications that use ecologic (or determinants of health) models that emphasize how patients' social environments influence their health.

### **Tuberculosis Screening in a Novel Substance Abuse Treatment Center in Malaysia:**

**Implications for a Comprehensive Approach for Integrated Care** Al-Darraji HAA, Wong KC, Yeow DGE, Fu JJ, Loeliger K, Paiji C, Kamarulzaman A, Altice FL. *J Subst Abuse Treat.* 2014; 46 (2): 144-9.

People who use drugs (PWUD) represent a key high risk group for tuberculosis (TB). The prevalence of both latent TB infection (LTBI) and active disease in drug treatment centers in Malaysia is unknown. A cross-sectional convenience survey was conducted to assess the prevalence and correlates of LTBI among attendees at a recently created voluntary drug treatment center using a standardized questionnaire and tuberculin skin testing (TST). Participants (N=196) were mostly men (95%), under 40 (median age=36 years) and reported heroin use immediately before treatment entry (75%). Positive TST prevalence was 86.7%. Nine (4.6%) participants were HIV-infected. Previous arrest/incarcerations (AOR=1.1 for every entry, p<0.05) and not being HIV-infected (AOR=6.04, p=0.03) were significantly associated with TST positivity. There is an urgent need to establish TB screening and treatment programs in substance abuse treatment centers and to tailor service delivery to the complex treatment needs of patients with multiple medical and psychiatric co-morbidities.

### **Efficacy of Dual Focus Mutual Aid for Persons with Mental Illness and Substance Misuse**

Rosenblum A, Matusow H, Fong C, Vogel H, Uttaro T, Moore TL, Magura S. *Drug Alcohol Depend.* 2014; 135: 78-87.

Previous studies have indicated that persons with co-occurring mental health and substance use problems can benefit by attending dual-focus mutual aid groups. However, to date, a trial to test the efficacy of these groups has not been published. This study randomly assigned 203 substance misusing clients attending a mental health or dual-diagnosis facility to either a dual-focus 12-step group (Double Trouble in Recovery; DTR) or a waiting list control group. Participants were followed for 3-6 months. The primary outcome was substance use (days used in the past 30 with saliva testing to detect under-reporting); secondary outcomes included psychiatric medication adherence, attendance at traditional (single-focus) 12-step meetings (e.g., AA/NA); and improvement in mental health and substance use problems (quality of life). Multilevel model (MLM) regression was used to analyze the nested effect of participants within 8 facilities (7 in New York City and 1 in Michigan). Regression imputation was used to adjust for drug use under-reporting. At follow-up 79% of the subjects were interviewed. In intent to treat analysis, DTR subjects compared with control subjects used alcohol ( $p=.03$ ) and any substances ( $p=.02$ ) on fewer days. DTR compared with control subjects were also more likely to rate themselves as experiencing better mental health and fewer substance use problems ( $p=.001$ ). There were no effects for DTR on drug use only, medication adherence or NA/AA attendance. Findings reported in previous studies on the association between exposure to DTR and reductions in substance use were partially supported in this efficacy trial.

### **Interest in Couples-based Voluntary HIV Counseling and Testing in A National U.S. Sample of Gay and Bisexual Men: The Role of Demographic and HIV Risk Factors**

Rendina HJ, Breslow AS, Grov C, Ventuneac A, Starks TJ, Parsons JT. *Arch Sex Behav.* 2014; 43(1): 149-59.

Main partnerships represent one context in which HIV transmission may occur that has been insufficiently addressed to date for gay and bisexual men, but few studies have focused on the acceptability of couples-based voluntary HIV counseling and testing (CVCT) for male couples in the U.S. The authors' aim in this study was to explore the acceptability of CVCT among a national U.S. sample of 1,532 gay and bisexual men surveyed online using a sexual networking site. The authors examined the role of demographic (i.e., geographic region, age, relationship status, sexual orientation, race/ethnicity) and HIV risk (i.e., substance use, number of sexual partners, unprotected anal intercourse, sexual role identity, and sexual compulsivity) factors that may be associated with CVCT among the full sample and among partnered men separately. They found that single men expressed higher interest in CVCT than partnered men and that greater age was more strongly associated with lower interest in CVCT for partnered men than for single men. The intersection of sexual orientation and race/ethnicity was also significantly associated with CVCT interest, with a higher proportion of Black bisexual men being interested than White bisexual men. These findings suggest that the uptake of CVCT may be less impacted by HIV risk factors than by demographic factors and that young gay and bisexual men of color-for whom rates of HIV continue to rise-may be the group with the highest levels of interest in CVCT.

### **Patient Navigation Facilitates Medical and Social Services Engagement among HIV-Infected Individuals Leaving Jail and Returning to the Community**

Koester KA, Morewitz M, Pearson C, Weeks J, Packard R, Estes M, Tulskey J, Kang-Dufour MS, Myers J. *J AIDS Patient Care STDS.* 2014; 28 (2): 82-90.

HIV-infected individuals leaving jails, facilities typically used to confine accused persons awaiting trial or to incarcerate persons for minor offenses, often face barriers to engagement with medical

and social-support services. Patient navigation is a model that may ease these barriers by supporting individuals in negotiating fragmented and highly bureaucratic systems for services and care. While there is evidence linking navigation to a reduction in health disparities, little is known about the mechanisms by which the model works. The authors present findings of an ethnographic study of interactions between navigators and their clients: HIV-infected men and women recently released from jails in San Francisco, California. They conducted 29 field observations of navigators as they accompanied their clients to appointments, and 40 in-depth interviews with clients and navigators. Navigators worked on strengthening clients' abilities to engage with social-services and care systems. Building this strength required navigators to gain clients' trust by leveraging their own similar life experiences or expressing social concordance. After establishing meaningful connections, navigators spent time with clients in their day-to-day environments serving as mentors while escorting clients to and through their appointments. Intensive time spent together, in combination with a shared background of incarceration, HIV, and drug use, was a critical mechanism of this model. This study illustrates that socially concordant navigators are well positioned to facilitate successful transition to care and social-services engagement among a vulnerable population.

**Perceived Neighborhood Safety, Recovery Capital, and Successful Outcomes among Mothers 10 years After Substance Abuse Treatment** Evans E, Li L, Buoncristiani S, Hser Y-I. *Subst Use Misuse*. 2014.

This study examines perceived neighborhood characteristics associated with successful outcome among mothers 10 years after being treated for substance use disorders. Data were obtained from 713 mothers first studied at admission to drug treatment in California in 2000-2002 and followed up in 2009-2011. At follow-up, 53.6% of mothers had a successful outcome (i.e., no use of illicit drugs and not involved with the criminal justice system). Perceived neighborhood safety almost doubled the odds of success. Perceived neighborhood safety interacted with social involvement, decreasing the odds of success among mothers who reported more versus less neighborhood social involvement. Perceived neighborhood climate is associated with long-term outcomes among mothers with substance use disorders independent of individual-level characteristics, underscoring the need for further efforts to understand its interaction with recovery capital in ways that promote and impede health.

**Prospective Risk Factors for Traumatic Event Re-exposure in Community Syringe Exchange Participants** Peirce JM, Schacht RL, Brooner RK, King VL, Kidorf MS. *Drug Alcohol Depend*. 2014; 138: 98-102.

Traumatic event re-exposure in injecting drug users is associated with increased drug use and potential for psychiatric symptoms. This is the first study to examine fixed and time-varying factors that are prospectively associated with new traumatic event re-exposure in injecting drug users. Injecting drug users registered in a syringe exchange program were enrolled in a 16-month parent study comparing strategies to increase drug abuse treatment enrollment. Participants (N=162) completed baseline measures of demographics, psychiatric treatment history, and lifetime traumatic event exposure. Monthly follow-ups assessed past-month traumatic event exposure, days of heroin and cocaine use, criminal activity, and drug abuse treatment participation. Generalized estimating equations models tested the influence of fixed baseline and time-varying factors on traumatic event re-exposure in the same month, the following month, and two months later. Significant fixed risk factors for traumatic event re-exposure include female gender and past psychiatric treatment. In addition, each past traumatic event exposure was associated with an increased likelihood of re-exposure. After accounting for all other factors, each day of cocaine use was associated with a small

but persistent increased risk of traumatic event re-exposure. Re-exposure to a traumatic event in the prior month more than doubled the risk of subsequent re-exposure. Injecting drug users experience a pattern in which drug use is associated with increased risk of subsequent traumatic event re-exposure, and traumatic event re-exposure is associated with further drug use and continued re-exposure. Implications for addressing these concerns in injecting drug users are presented.

**Self-Management of Buprenorphine/Naloxone among Online Discussion Board Users** Brown S-E, Altice FL. *Subst Use Misuse*. 2014; 49(8): 1017-24.

Buprenorphine/naloxone is an effective medication used to treat opioid dependence. Patients in treatment and those using it illegally without prescriptions have discussed using buprenorphine/naloxone anonymously on Internet discussion boards. Their beliefs about self-treatment and efforts to self-treat are not well known. The objective of this study was to identify facilitators of self-treatment by online buprenorphine/naloxone users. This was a qualitative, retrospective study of discussion board postings from September 2010 to November 2012 which analyzed 121 threads from 13 discussion boards using grounded theory. Facilitators of self-management themes that emerged included: (1) a ready supply of buprenorphine/naloxone from a variety of sources; (2) distrust of buprenorphine prescribers and pharmaceutical companies; (3) the declaration that buprenorphine/naloxone is a "bad-tasting" medicine; (4) the desire to adopt a different delivery method other than sublingually; and (5) a desire to become completely "substance-free." The sublingual film formulation appears to be an important facilitator in self-treatment because it can more easily be apportioned to extend the medication because of limited supply, cost, or to taper. The findings indicate a range of self-management activities ranging from altering the amount taken to modifying the physical medication composition or changing the administration route; some of these behaviors constitute problematic extra-medical use. Contributors to discussion boards seem to trust each other more than they trust pharmacists and prescribing physicians. The shared knowledge and behaviors of this understudied online community are important to healthcare providers because of the previously unknown precautions and risks taken to self-treat.

**Substance Use Trends among Younger vs. Older Homeless Parolees** Nyamathi A, Salem B, Marshall L, Idemundia F, Mata R, Khalilifard F, Farabee D, Leake B. *J Addict Dis*. 2014.

This was a cross-sectional study of 540 homeless ex-offenders exiting prisons and jails which assessed socio-demographic, childhood and drug-related differences. Older ex-offenders from prison were more likely to have been married, come from a two-parent family and used crack while younger ex-offenders were more likely to have used methamphetamine. Older ex-offenders from jail were more likely to be African-American, have children, and report a history of crack and injection drug use, while those younger were more likely to have engaged in binge drinking and be in a gang. These findings showcase the need to understand unique correlates of younger and older incarcerated populations.

**The Feasibility of Implementing the HIV Seek, Test, and Treat Strategy in Jails** Beckwith C, Bazerman L, Gillani F, Tran L, Larson B, Rivard S, Flanigan T, Rich J. *AIDS Patient Care STDS*. 2014; 28(4): 183-7.

To successfully implement the Seek, Test, and Treat (STT) strategy to curb the HIV epidemic, the criminal justice system must be a key partner. Increasing HIV testing and treatment among incarcerated persons has the potential to decrease HIV transmission in the broader community, but whether it is feasible to consider the implementation of the STT within jail facilities is not known. The authors conducted a retrospective review of Rhode Island Department of Corrections (RIDOC) medical records to assess whether persons newly diagnosed in the jail were able to start ART and be

linked to community HIV care after release. From 2001 to 2007, 64 RIDOC detainees were newly diagnosed with HIV. During their index incarcerations, 64% were informed of positive confirmatory HIV test results, 50% completed baseline evaluations, and 9% began ART. Linkage to community care was confirmed for 58% of subjects. Subjects incarcerated for >14 days were significantly more likely to receive HIV test results and complete baseline evaluation ( $p<0.001$ ). A similar association was not observed for ART initiation until incarceration length reached 60 days ( $p<0.001$ ). There was no association between incarceration length and linkage to care. This comprehensive analysis demonstrates that length of incarceration impacts HIV test result delivery, baseline evaluation, and ART initiation in the RIDOC. Jails are an important venue to "Seek" and "Test"; however, completing the "Treat" part of the STT strategy is hindered by the transient nature of this criminal justice population and may require new strategies to improve linkage to care.

**Time to Relapse Following Treatment for Methamphetamine Use: A Long-Term Perspective on Patterns and Predictors** Brecht M-L, Herbeck D. *Drug Alcohol Depend.* 2014; 139: 18-25.

This paper describes methamphetamine (MA) use patterns, specifically the duration of continuing abstinence ("time to relapse") for periods averaging 5 years post-discharge from treatment for MA use, and the relationship with selected user and treatment characteristics. A sample of 350 treatment admissions from a large county substance use disorder (SUD) treatment system was randomly selected (within gender, race/ethnicity, and treatment modality strata). Retrospective self-report data are from natural history interviews (NHI) conducted approximately 3 years after treatment and a follow-up of 2-3 years later. Relapse is defined as any use of MA with time as the number of months of continuous MA abstinence after treatment discharge until relapse. This outcome was constructed from a monthly MA use timeline using NHI data. A Cox model was used to examine time to relapse and predictors. Sixty-one percent of the sample relapsed to MA use within 1 year after treatment discharge and 14% during years 2-5. Significant protective factors predicting longer time to relapse included having experienced serious MA-related psychiatric/behavioral problems (hazard ratio [HR]=0.75,  $p=0.027$ ), longer duration of the index treatment episode (HR=0.93,  $p=0.001$ ), and participating in self-help or other treatment during the post-treatment abstinence period (HR=0.29,  $p<0.001$ ); risk factors for shorter time to relapse included having a parent with alcohol and/or drug use problems (HR=1.35,  $p=0.020$ ) and involvement in MA sales (HR=1.48,  $p=0.002$ ). Results contribute a long-term perspective on patterns of MA use following treatment and support a need for early post-treatment and long-term continuing care and relapse-prevention services.

**A Psychometric Assessment of the GAIN Individual Severity Scale (GAIN-GISS) and Short Screeners (GAIN-SS) among Adolescents in Outpatient Treatment Programs** Stucky BD, Edelen MO, Ramchand R. *J Subst Abuse Treat.* 2014; 46(2): 165-73.

The global appraisal of individual needs (GAIN)-general individual severity scale (GAIN-GISS), and GAIN-short screener (GAIN-SS) are widely used diagnostic measures of internalizing disorders, externalizing disorders, substance abuse, and criminal and violent behavior. Although prevalent in clinical and research settings, there is only limited psychometric evidence of the dimensional structure of these scales. This investigation used intake data from 6,909 adolescents presenting to outpatient substance abuse treatment facilities in the United States. The authors' analytic approach used exploratory and item factor analyses to evaluate the underlying factor structure. Multi- and unidimensional item response theory models were employed to evaluate the utility of the scales at providing precise score estimates at various locations of severity. Most scales were confirmed as unidimensional; scales with evidence of multidimensionality, identified as

having a weak general dimension and strong specific dimensions using a bi-factor IRT model, include the Crime and Violence Scale and the GAIN-SS.

**A Qualitative Study of the Adoption of Buprenorphine for Opioid Addiction Treatment** Green CA, Mccarty D, Mertens J, Lynch FL, Hilde A, Firemark A, Weisner CM, Pating D, Anderson BM. J Subst Abuse Treat. 2014; 46(3): 390-401.

Qualified physicians may prescribe buprenorphine to treat opioid dependence, but medication use remains controversial. The authors examined adoption of buprenorphine in two not-for-profit integrated health plans, over time, completing 101 semi-structured interviews with clinicians and clinician-administrators from primary and specialty care. Transcripts were reviewed, coded, and analyzed. A strong leader championing the new treatment was critical for adoption in both health plans. Once clinicians began using buprenorphine, patients' and other clinicians' experiences affected decisions more than did the champion. With experience, protocols developed to manage unsuccessful patients and changed to support maintenance rather than detoxification. Diffusion outside addiction and mental health settings was nonexistent; primary care clinicians cited scope-of-practice issues and referred patients to specialty care. With greater diffusion came questions about long-term use and safety. Recognizing how implementation processes develop may suggest where, when, and how to best expend resources to increase adoption of such treatments.

**A Systematic Review of Strategies for Implementing Empirically Supported Mental Health Interventions** Powell BJ, Proctor EK, Glass JE. Res Soc Work Pract. 2014; 24(2): 192-212.

This systematic review examines experimental studies that test the effectiveness of strategies intended to integrate empirically supported mental health interventions into routine care settings. The authors' goal was to characterize the state of the literature and to provide direction for future implementation studies. A literature search was conducted using electronic databases and a manual search. Eleven studies were identified that tested implementation strategies with a randomized (n = 10) or controlled clinical trial design (n = 1). The wide range of clinical interventions, implementation strategies, and outcomes evaluated precluded meta-analysis. However, the majority of studies (n = 7; 64%) found a statistically significant effect in the hypothesized direction for at least one implementation or clinical outcome. There is a clear need for more rigorous research on the effectiveness of implementation strategies, and we provide several suggestions that could improve this research area.

**Assessing the Generalizability of the CSAT-Sponsored GAIN Dataset: Are the CSAT Sites Representative of Adolescent Treatment Programs in the U.S.?** Hunter SB, Griffin BA, Booth MS, Ramchand R, McCaffrey DF. J Subst Abuse Treat. 2014; 46(2): 238-43.

The CSAT-sponsored GAIN dataset represents one of the largest longitudinal datasets of adolescent substance use treatment currently available. Understanding the characteristics of the included treatment programs is needed to help inform whether the data are generalizable to adolescent treatment more broadly. Data from a national sample of adolescent treatment programs were compared to the CSAT-funded programs to assess generalizability and understand trends over time in quality service provision. The results indicated that CSAT-funded programs had higher rates of comprehensive mental health assessments, discharge planning, HIV, STD and TB testing, and HIV/AIDS education and support. Conversely, CSAT and non-CSAT-funded programs had similar rates of comprehensive substance use screening and assessment, family and aftercare counseling, drug and alcohol urine screening, case management support, and licensing. The results also showed that service provision has not changed much over the past decade and is in critical need of improvement to reflect expert-informed quality standards.

**Barriers to Drug Use Behavior Change among Primary Care Patients in Urban United States Community Health Centers** Padwa H, Ni Y-M, Barth-Rogers Y, Arangua L, Andersen R, Gelberg L. *Subst Use Misuse*. 2014; 49(6): 743-51.

In 2011 and 2012, 147 patients in urban United States Community Health Centers who misused drugs, but did not meet criteria for drug dependence, received a brief intervention as part of a National Institute on Drug Abuse-funded clinical trial of a screening and brief intervention protocol. Potential study participants were identified using the World Health Organization (WHO) Alcohol, Smoking, and Substance Involvement Screening Test. Data gathered during brief interventions were analyzed using grounded theory strategies to identify barriers patients believed inhibited drug use behavior change. Numerous perceived barriers to drug use behavior change were identified. Study implications and limitations are discussed.

**Characterizing Longitudinal Health State Transitions among Heroin, Cocaine, and Methamphetamine Users** Nosyk B, Li L, Evans E, Huang D, Min J, Kerr T, Brecht ML, Hser Y- I. *Drug Alcohol Depend*. 2014.

The purpose of this study was to characterize longitudinal patterns of drug use careers and identify determinants of drug use frequency across cohorts of primary heroin, methamphetamine (MA) and cocaine users. This was a pooled analysis of prospective cohort studies. Illicit drug users recruited from community, criminal justice and drug treatment settings in California, USA. The authors used longitudinal data on from five observational cohort studies featuring primary users of heroin (N=629), cocaine (N=694) and methamphetamine (N=474). The mean duration of follow-up was 20.9 years. Monthly longitudinal data was arranged according to five health states (incarceration, drug treatment, abstinence, non-daily and daily use). The authors fitted proportional hazards (PH) frailty models to determine independent differences in successive episode durations. They then executed multi-state Markov (MSM) models to estimate probabilities of transitioning between health states, and the determinants of these transitions. Across primary drug use types, PH frailty models demonstrated durations of daily use diminished in successive episodes over time. MSM models revealed primary stimulant users had more erratic longitudinal patterns of drug use, transitioning more rapidly between periods of treatment, abstinence, non-daily and daily use. MA users exhibited relatively longer durations of high-frequency use. Criminal engagement had a destabilizing effect on health state durations across drug types. Longer incarceration histories were associated with delayed transitions toward cessation. PH frailty and MSM modeling techniques provided complementary information on longitudinal patterns of drug abuse. This information can inform clinical practice and policy, and otherwise be used in health economic simulation models, designed to inform resource allocation decisions.

**Development of the Clinician Assessment of Financial Incapability (CAFI)** Black AC, McMahon TJ, Rosenheck RA, Ball SA, Ries RK, Ames D, Rosen MI. *Psychiatry Res*. 2014; 215(3): 784-9.

The Social Security Administration (SSA) provides financial support to adults disabled by psychiatric conditions to provide for their basic needs. For beneficiaries identified as incapable of managing their funds, representative payee assignment is mandated. However, studies indicate that the current SSA method of determining capability leads to idiosyncratic payee assignment, with a tendency to under-identify beneficiaries needing payees. Over two phases with data from 78 mental health clinicians treating 134 patient-beneficiaries, The authors describe the development of a new assessment, the Clinician Assessment of Financial Incapability (CAFI). Item generation, subscale construction, and preliminary assessments of validity are described. They also describe the simultaneous development of a criterion measure of capability, a comprehensive review of all data.

Experts identified four subscales mapping to four criteria of incapability; factor analysis provided support for this item structure. Close to one-half of patients were determined to be incapable by review of all data. CAFI and SSA methods correctly classified 73% of cases, but errors with CAFI were more evenly distributed between false negatives and false positives. The implications of classification error are considered, and advantages of CAFI over the SSA method are enumerated. Plans for future instrument revision are briefly described.

**Effectiveness of a Theoretically-Based Judgment and Decision Making Intervention for Adolescents** Knight DK, Dansereau DF, Becan JE, Rowan GA, Flynn PM. *J Youth Adolesc.* 2014.

Although adolescents demonstrate capacity for rational decision making, their tendency to be impulsive, place emphasis on peers, and ignore potential consequences of their actions often translates into higher risk-taking including drug use, illegal activity, and physical harm. Problems with judgment and decision making contribute to risky behavior and are core issues for youth in treatment. Based on theoretical and empirical advances in cognitive science, the Treatment Readiness and Induction Program (TRIP) represent a curriculum-based decision making intervention that can be easily inserted into a variety of content-oriented modalities as well as administered as a separate therapeutic course. The current study examined the effectiveness of TRIP for promoting better judgment among 519 adolescents (37% female; primarily Hispanic and Caucasian) in residential substance abuse treatment. Change over time in decision making and premeditation (i.e., thinking before acting) was compared among youth receiving standard operating practice (n=281) versus those receiving standard practice plus TRIP (n=238). Change in TRIP-specific content knowledge was examined among clients receiving TRIP. Premeditation improved among youth in both groups; TRIP clients showed greater improvement in decision making. TRIP clients also reported significant increases over time in self-awareness, positive-focused thinking (e.g., positive self-talk, goal setting), and recognition of the negative effects of drug use. While both genders showed significant improvement, males showed greater gains in metacognitive strategies (i.e., awareness of one's own cognitive process) and recognition of the negative effects of drug use. These results suggest that efforts to teach core thinking strategies and apply/practice them through independent intervention modules may benefit adolescents when used in conjunction with content-based programs designed to change problematic behaviors.

**Financial versus Health Motivation to Quit Smoking: A Randomized Field Study** Sindelar JL, O'Malley SS. *Prev Med.* 2014; 59: 1-4.

Smoking is the most preventable cause of death, thus justifying efforts to effectively motivate quitting. The authors compared the effectiveness of financial versus health messages to motivate smoking cessation. Low-income individuals disproportionately smoke and, given their greater income constraints, the authors hypothesized that making financial costs of smoking more salient would encourage more smokers to try quitting. Further, they predicted that financial messages would be stronger in financial settings where pecuniary constraints are most salient. The authors conducted a field study in low-income areas of New Haven, Connecticut using brochures with separate health vs. financial messages to motivate smoking cessation. Displays were rotated among community settings-check-cashing, health clinics, and grocery stores. They randomized brochure displays with gain-framed cessation messages across locations. The authors' predictions were confirmed. Financial messages attracted significantly more attention than health messages, especially in financial settings. These findings suggest that greater emphasis on the financial gains to quitting and use of financial settings to provide cessation messages may be more effective in motivating quitting. Importantly, use of financial settings could open new, non-medical venues for

encouraging cessation. Encouraging quitting could improve health, enhance spending power of low-income smokers, and reduce health disparities in both health and purchasing power.

### **Laboratory-Induced Cue Reactivity among Individuals with Prescription Opioid Dependence**

Back SE, Gros DF, McCauley JL, Flanagan JC, Cox E, Barth KS, Brady KT. *Addict Behav.* 2014; 39(8): 1217-1223.

Prescription opioid (PO) dependence is a critical health problem. Although examination of drug cue reactivity paradigms has advanced the understanding of risk factors for relapse for a variety of substances (e.g., cocaine, alcohol, nicotine), no PO specific drug cue paradigm has been developed. The current study addressed this gap in the literature and evaluated the ability of a newly developed PO drug cue paradigm to elicit subjective, physiological, and neuroendocrine changes among PO-dependent participants (n=20) as compared to controls (n=17). The drug cue paradigm included an induction script, viewing and handling paraphernalia (e.g., bottle of OxyContin pills, pill crusher) and watching a video depicting people using POs as well as places related to POs (e.g., pharmacies). Consistent with hypotheses, the PO group demonstrated significant pre- to post-cue increases on subjective ratings of craving, difficulty resisting POs, stress, and anger. The control group did not demonstrate significant changes on any of the subjective measures. Both the PO group and the control group evidenced significant pre- to post-cue increases in physiological responses (e.g., blood pressure, skin conductance), as expected given the arousing nature of the drug cue stimuli. The PO group, but not the control group, evidenced a significant pre- to post-cue increase in heart rate and salivary cortisol levels. The development and validation of a drug cue paradigm for POs may help inform future research and treatment development efforts for patients with PO dependence.

### **Looking for the Uninsured in Massachusetts? Check Opioid Dependent Persons Seeking**

**Detoxification** Stein MD, Bailey GL, Thurmond P, Paull N. *Drug Alc Depend.* 2014; 136: 166-9.

The authors examined the rate of un-insurance among persons seeking detoxification at a large drug treatment program in Massachusetts in 2013, five years after insurance mandates. They interviewed three hundred and forty opioid dependent persons admitted for inpatient detoxification in Fall River, Massachusetts. Potential predictors of self-reported insurance status included age, gender, ethnicity, employment, homelessness, years of education, current legal status, and self-perceived health status. Participants mean age was 32 years, 71% were male, and 87% were non-Hispanic Caucasian. Twenty-three percent were uninsured. In the multivariate model, the odds of being uninsured was positively associated with years of education (OR=1.22, 95% CI=1.03; 1.46, p<.05), higher among males than females (OR=2.63, 95% CI=1.33; 5.20, p<.01), and inversely associated with age (OR=0.94, 95% CI=0.90; 0.98, p<.01). Opioid dependent persons recruited from a detoxification program in Massachusetts are uninsured at rates far above the state average. With the arrival of the Affordable Care Act, drug treatment programs in Massachusetts and nationally will be important sites to target to expand health coverage.

### **Opportunity Costs and Financial Incentives for Hispanic Youth Participating in a Family-Based HIV and Substance Use Preventive Intervention**

McCollister KE, Freitas DM, Prado G, Pantin H. *J Prim Prev.* 2014; 35(1): 13-20.

This paper presents results from a pilot study of the synergies between the opportunity costs incurred by research participants, participant compensation, and program attendance in a family-based substance use and HIV preventive intervention for Hispanic adolescents in Miami-Dade County, Florida. To estimate parent/caretaker cost per session and cost for the duration of the intervention, the authors administered the Caretaker Drug Abuse Treatment Cost Analysis Program

to a random sample of 34 families who participated in a recent clinical trial of Familias Unidas. The total opportunity cost per parent/caretaker was under \$40 per group session, under \$30 per family session, and just over \$570 for the duration of the intervention. Participants were compensated between \$40 and \$50 per session and attended more than 79% of family and group sessions. Parents and caretakers incurred a cost of approximately \$30-40 per intervention session for which they were adequately compensated. Attendance was very good overall for this group (>79%) and significantly higher than attendance in a comparable uncompensated study group from another recent Familias Unidas trial that targeted similar youth. Findings suggest that incentives should be considered important for future implementations of Familias Unidas and similar family-based interventions that target minority and low-SES populations.

**Participant and Staff Experiences in A Peer-Delivered HIV Intervention with Injection Drug Users** Kostick KM, Weeks M, Mosher H. J Empir Res Hum Res Ethics. 2014; 9(1): 6-18.

The authors explore ethical issues faced by investigators as they conduct research as part of a peer-delivered HIV/AIDS risk reduction program for injection drug users (IDUs). Staff and participant experiences in peer-delivered interventions among IDUs have come under scrutiny by ethics researchers because of their potential to inadvertently and negatively impact participant rehabilitation due to continued engagement with drug-using networks during the course of outreach. This study explores whether enhanced communication of participant concerns and experiences with clinic and research staff helps to reduce inadvertent malfeasance in peer-delivered drug treatment interventions. Results contribute to the development of patient support infrastructure in peer-delivered risk reduction programs involving IDUs.

**Pathologizing Poverty: New Forms of Diagnosis, Disability, and Structural Stigma under Welfare Reform** Hansen H, Bourgois P, Drucker E. Soc Sci Med. 2014; 103: 76-83.

In 1996 the U.S. severely restricted public support for low income people, ending "welfare as we know it." This led to dramatic increases in medicalized forms of support for indigent people, who increasingly rely on disability benefits justified by psychiatric diagnoses of chronic mental illness. The authors present case studies drawn from ethnographic data involving daily participant-observation between 2005 and 2012 in public clinics and impoverished neighborhoods in New York City, to describe the subjective experience of structural stigma imposed by the increasing medicalization of public support for the poor through a diagnosis of permanent mental disability. In some cases, disability benefits enable recipients to fulfill important social roles (sustaining a vulnerable household and promoting stable parenting). The status of family members who receive a monthly disability check improves within their kin and neighborhood-based networks, counterbalancing the felt stigma of being identified by doctors as "crazy". When a diagnosis of mental pathology becomes a valuable survival strategy constituting the basis for fulfillment of household responsibilities, stigmatizing processes are structurally altered. Through the decades, the stigmatized labels applied to the poor have shifted: from being a symptom of racial weakness, to the culture of poverty, and now to permanent medical pathology. The neoliberal bureaucratic requirement that the poor must repeatedly prove their "disabled" status through therapy and psychotropic medication appears to be generating a national and policy-maker discourse condemning SSI malingerers, resurrecting the 16th century specter of the "unworthy poor".

**Screening and Assessment Tools for Measuring Adolescent Client Needs and Functioning in Substance Abuse Treatment** Knight DK, Becan JE, Landrum B, Joe GW, Flynn PM. *Subst Use Misuse*. 2014; 49(7): 902-18.

The purpose of this study is to establish the psychometric properties of a noncommercial, publicly available, modular screening and assessment system for adolescents in substance abuse treatment. Data were collected in 2011-2012 from 1,189 adolescents admitted to eight residential treatment programs in urban and rural locations in the United States. Results from three sets of analyses documented the instruments to be reliable. Females reported more problems than males, and younger adolescents reported more problems than older youth. Implications and limitations are discussed, and suggestions for future research are provided.

**Terrorism, Civil War and Related Violence and Substance Use Disorder Morbidity and Mortality: A Global Analysis** Kerridge BT, Khan MR, Rehm J, Sapkota A. *J Epidemiol Glob Health*. 2014; 4(1): 61-72.

The purpose of this study is to examine associations between deaths owing to terrorism, civil war, and one-sided violence from 1994-2000 and substance use disorder disability-adjusted life years (DALYs). The relationship between terrorism, and related violence and substance use disorder morbidity and mortality among World Health Organization Member States in 2002, controlling for adult per capita alcohol consumption, illicit drug use, and economic variables at baseline in 1994. Deaths as a result of terrorism and related violence were related to substance use disorder DALYs: a 1.0% increase in deaths as a result of terrorism, war and one-sided violence was associated with an increase of between 0.10% and 0.12% in alcohol and drug use disorder DALYs. Associations were greater among males and 15-44 year-old. Terrorism, war and one-sided violence may influence morbidity and mortality attributable to substance use disorders in the longer-term suggests that more attention to be given to rapid assessment and treatment of substance use disorders in conflict-affected populations with due consideration of gender and age differences that may impact treatment outcomes in these settings. Priorities should be established to rebuild substance abuse treatment infrastructures and treat the many physical and mental comorbid disorders.

**Testing the Effects of Peer Socialization versus Selection on Alcohol and Marijuana Use among Treated Adolescents** Becker SJ, Curry JF. *Subst Use Misuse*. 2014; 49(3): 234-42.

This study examined the relative influence of peer socialization and selection on alcohol and marijuana use among 106 adolescents who received a brief intervention. Adolescents were recruited between 2003 and 2007 and followed for 12 months as part of a SAMHSA-funded study. Cross-lagged panel models using four assessment points examined the longitudinal relationship between adolescent substance use and peer substance involvement separately for alcohol and marijuana. Consistent with community studies, there was evidence of both peer socialization and peer selection for alcohol use, and only evidence of peer selection for marijuana use. Implications for research and intervention are discussed.

**Reducing Risky Relationships: A Multisite Randomized Trial of a Prison-Based Intervention for Reducing HIV Sexual Risk Behaviors among Women with A History of Drug Use**

Knudsen HK, Staton-Tindall M, Oser CB, Havens JR, Leukefeld CG. *AIDS Care*. 2014.

Women involved in the criminal justice system, particularly those with a history of drug use, are at elevated risk of HIV infection, yet few HIV prevention interventions have been tailored for delivery to incarcerated women. Drawing on the Relational Model, the Reducing Risky Relationships for HIV (RRR-HIV) intervention was developed and evaluated in a multisite randomized clinical trial. Women with weekly drug use prior to incarceration (n = 444) who were incarcerated within

correctional institutions in four states were randomized to (1) the RRR-HIV intervention consisting of an HIV educational video, five group sessions, and one post-release booster session or (2) a control condition consisting of the HIV educational video. The RRR-HIV intervention combined didactic and interactive content regarding seven "thinking myths" about intimate relationships that may result in decisions to engage in risky sexual behaviors. Data were collected while women were still incarcerated and approximately 90 days following release from prison by trained interviewers. A negative binomial regression (NBR) model of unprotected sexual behaviors at the 90-day follow-up indicated that RRR-HIV participants reported fewer unprotected sexual behaviors than women in the control condition once the analysis was adjusted for study site. Future studies should examine the sustainability of the RRR-HIV intervention's effect on risk reduction. Implementation research is needed to determine whether delivery of this intervention by correctional staff or peers, rather than research staff, yields similar reductions in unprotected sexual behaviors.

### **The Association between Changes in Alternative Reinforcers and Short-Term Smoking Cessation**

Goelz PM, Audrain-McGovern JE, Hitsman B, Leone FT, Veluz-Wilkins A, Jepson C, Wileyto EP, D'Avanzo PA, Rivera JG, Schnoll RA. *Drug Alcohol Depend.* 2014; 138: 67-74.

While more than 50% of smokers make a serious quit attempt each year, less than 10% quit permanently. Evidence from studies of adolescent smoking and other substances of abuse suggest that alternative reinforcers, a construct of Behavioral Economic Theory, may contribute to the likelihood of smoking cessation in adults. This study examined the behavioral economics of smoking cessation within a smoking cessation clinical trial and evaluated how depressive symptoms and behavioral economic variables are associated with smoking cessation. A sample of 469 smokers, enrolled in an effectiveness trial that provided counseling and 8 weeks of 21 mg nicotine patches, was analyzed. Alternative reinforcers (substitute and complementary reinforcers) and depressive symptoms were examined in relation to 7-day point prevalence abstinence, verified with breath carbon monoxide, 8 weeks after the quit date. Controlling for covariates associated with cessation (nicotine dependence, age of smoking initiation, patch adherence), participants who were abstinent at week 8 showed significantly higher substitute reinforcers at all time-points, compared to those who were smoking ( $p < .05$ ). Participants who were abstinent at week 8 showed lower complementary reinforcers and depressive symptoms at all time-points, compared to those who were smoking, but significant differences were confined to week 8 ( $p < .01$ ). There was no significant interaction between alternative reinforcers and depressive symptoms across the 8 weeks on week 8 abstinence. These results support continued examination of Behavioral Economic Theory in understanding adult smoking cessation in order to inform future treatments and guidelines.

### **Use of Hospital-Based Services among Young Adults With Behavioral Health Diagnoses Before and After Health Insurance Expansions**

Meara E, Golberstein E, Zaha R, Greenfield SF, Beardslee WR, Busch SH. *JAMA Psychiatry.* 2014; 71(4): 404-11.

Young adults have high levels of behavioral health needs but often lack health insurance. Recent health reforms have increased coverage, but it is unclear how use of hospital-based care changed after expanding insurance. The objective of this study was to evaluate the association between health insurance coverage expansions and use of hospital-based care among young adults with behavioral health diagnoses. This was a quasi-experimental analyses of community hospital inpatient and emergency department use from 2003-2009 based on hospital discharge data, comparing differential changes in service use among young adults with behavioral health diagnoses in Massachusetts vs other states before and after Massachusetts' 2006 health reform. This population-based sample included inpatient admissions ( $n = 2,533,307$ , representing 12,821,746 weighted admissions across 7 years) nationwide and emergency department visits

(n = 6,817,855 across 7 years) from Maryland and Massachusetts for 12- to 25-year-old patients. Inpatient admission rates per 1000 population for primary diagnosis of any behavioral health disorder by diagnosis; emergency department visit rates per 1000 population by behavioral health diagnosis; and insurance coverage for hospital discharges. After 2006, un-insurance among 19- to 25-year-old individuals in Massachusetts decreased from 26% to 10% (16 percentage points; 95% CI, 13-20). Young adults experienced relative declines in inpatient admission rates of 2.0 per 1000 for primary diagnoses of any behavioral health disorder (95% CI, 0.95-3.2), 0.38 for depression (95% CI, 0.18-0.58), and 1.3 for substance use disorder (95% CI, 0.68-1.8). The increase in emergency department visits with any behavioral health diagnosis after 2006 was lower among young adults in Massachusetts compared with Maryland (16.5 per 1000; 95% CI, 11.4-21.6). Among young adults in Massachusetts, the percentage of behavioral health discharges that were uninsured decreased by 5.0 (95% CI, 3.0-7.2) percentage points in inpatient settings and 5.0 (95% CI, 1.7-7.8) percentage points in emergency departments relative to other states. Expanded health insurance coverage for young adults was not associated with large increases in hospital-based care for behavioral health, but it increased financial protection for young adults with behavioral health diagnoses and for the hospitals that care for them.

**Willingness to Use HIV Pre-Exposure Prophylaxis among Opiate Users** Stein M, Thurmond P, Bailey G. AIDS Behav. 2014.

Few studies of pre-exposure prophylaxis (PrEP) to prevent HIV infection have focused on drug users. Between February to September 2013, the authors asked 351 opiate injectors entering detoxification treatment about HIV risk, knowledge about PrEP, and willingness to use a once daily PrEP pill under one of two randomly assigned effectiveness scenarios-40% (low) or 90% (high) effective in reducing HIV risk. Participants were 70% male and 87% non-Hispanic White. Only 7% had heard of a drug to reduce HIV risk, yet once informed, 47% would be willing to take such a pill [35% of those in the low effectiveness scenario and 58% in the high group (p<0.001)]. Higher perceived HIV risk was associated with greater willingness to take medication. Increasing knowledge of PrEP and the rate of HIV reduction-effectiveness promised will influence its use among targeted high-risk drug users.

**Design and Methods of a Double Blind Randomized Placebo-controlled Trial of Extended-release Naltrexone for Alcohol Dependent and Hazardous Drinking Prisoners with HIV Who Are Transitioning to the Community** Springer SA, Altice FL, Herme M, Di Paola A. Contemp Clin Trials. 2014; 37(2): 209-18.

HIV-infected prisoners have a high prevalence of alcohol use disorders and commonly relapse to alcohol soon after release to the community which is linked to high morbidity, poor antiretroviral therapy (ART) adherence and increased sexual risk-taking behaviors. Extended-release naltrexone (XR-NTX) effectively reduces relapse to alcohol in alcohol dependent persons, yet it remains unexamined among criminal justice system (CJS) populations transitioning to the community. This was a randomized double-blind, placebo-controlled trial of XR-NTX to improve HIV treatment outcomes via reducing relapse to alcohol use after prison release for HIV-infected hazardous drinking and alcohol dependent prisoners is discussed. Acceptability of study participation is high with 86% of those referred who met eligibility criteria and 85% of those who were able to receive injections prior to release accepted injections, yet important implementation issues are identified and addressed during the study and are discussed in this paper. Medication-assisted therapies for prevention of relapse to alcohol use for CJS populations transitioning to the community, especially for HIV-infected patients, are urgently needed in order to reduce alcohol relapse after release and improve HIV treatment outcomes and contribute to improved individual and public health.

**Addiction Treatment Centers' Progress in Preparing for Health Care Reform** Molfenter TD. J Subst Abuse Treat. 2014; 46(2): 158-64.

The Patient Protection and Affordable Care Act (PPACA) is expected to significantly alter addiction treatment service delivery. Researchers designed the Health Reform Readiness Index (HRRI) for addiction treatment organizations to assess their readiness for the PPACA. Four-hundred twenty-seven organizations completed the HRRI throughout a 3-year period, using a four-point scale to rank their readiness on 13 conditions. HRRI results completed during two different time periods (between 10/1/2010-6/30/2011 and 9/1/2011-9/30/2012) were analyzed and compared. Most respondents self-assessed as being in the early stages of preparation for 9 of the 13 conditions. Survey results showed that organizations with annual budgets < \$5 million (n=295) were less likely to be prepared for the PPACA than organizations with annual budgets > \$5 million (n=132). The HRRI results suggest that the addiction field, and in particular smaller organizations, is not preparing adequately for health care reform; organizations that are making preparations are making only modest gains.

**Alcohol and Drug Treatment Involvement, 12-Step Attendance and Abstinence: 9-Year Cross-Lagged Analysis of Adults in an Integrated Health Plan** Witbrodt J, Ye Y, Bond J, Chi F, Weisner C, Mertens J. J Subst Abuse Treat. 2014; 46(4): 412-9.

This study explored causal relationships between post-treatment 12-step attendance and abstinence at multiple data waves and examined indirect paths leading from treatment initiation to abstinence 9-years later. Adults (N = 1945) seeking help for alcohol or drug use disorders from integrated healthcare organization outpatient treatment programs were followed at 1-, 5-, 7- and 9-years. Path modeling with cross-lagged partial regression coefficients was used to test causal relationships. Cross-lagged paths indicated greater 12-step attendance during years 1 and 5 and were casually related to past-30-day abstinence at years 5 and 7 respectively, suggesting 12-step attendance leads to abstinence (but not vice versa) well into the post-treatment period. Some gender differences were found in these relationships. Three significant time-lagged, indirect paths emerged linking treatment duration to year-9 abstinence. Conclusions are discussed in the context of other studies using longitudinal designs. For outpatient clients, results reinforce the value of lengthier treatment duration and 12-step attendance in year 1.

**Climate for Innovation, 12-Step Orientation, and Tobacco Cessation Treatment** Muilenburg JL, Laschober TC, Eby LT. J Subst Abuse Treat. 2014; 46(4): 447-55.

This study examined the relationship between (1) three indicators of climate for innovation (clinician skills, absence of program obstacles, policy-related incentives) and adoption extensiveness of both behavioral treatments for tobacco cessation (TC) and system-level support for TC in substance use disorder treatment programs, (2) a program's 12-step treatment orientation and adoption extensiveness, and (3) whether 12-step treatment orientation moderates the relationship between climate for innovation and adoption extensiveness. Data were obtained from a random sample of 1006 program administrators. Hierarchical regression results showed that both absence of program obstacles and policy-related incentives are positively related to adoption extensiveness. Twelve-step treatment orientation is neither related to adoption extensiveness nor a moderator of the relationship between climate for innovation and adoption extensiveness. Although the adoption of both behavioral treatments for TC and system-level support for TC is not extensive, the authors conclude that a 12-step treatment orientation neither hampers nor promotes adoption extensiveness.

**Comparing Barriers to Mental Health Treatment and Substance Use Disorder Treatment among Individuals with Comorbid Major Depression and Substance Use Disorders** Mojtabai

R, Chen L-Y, Kaufmann CN, Crum RM. *J Subst Abuse Treat.* 2014; 46(2): 268-73.

Barriers to both mental health and substance use disorder treatments have rarely been examined among individuals with comorbid mental health and substance use disorders. In a sample of 393 adults with 12-month major depressive episodes and substance use disorders, the authors compared perceived barriers to these two types of treatments. Data were drawn from the 2005-2011 U.S. National Surveys on Drug Use and Health. Overall, the same individuals experienced different barriers to mental health treatment versus substance use disorder treatment. Concerns about negative views of the community, effects on job, and inconvenience of services were more commonly reported as reasons for not receiving substance use disorder treatment. Not affording the cost of care was the most common barrier to both types of treatments, but more commonly reported as a barrier to mental health treatment. Improved financial access through the Affordable Care Act and parity legislation and integration of mental health and substance use disorder services may help to reduce treatment barriers among individuals with comorbid mental health and substance disorders.

**Does Age at First Treatment Episode Make a Difference in Outcomes Over 11 Years?** Chi FW,

Weisner C, Grella CE, Hser Y-I, Moore C, Mertens J. *J Subst Abuse Treat.* 2014; 46(4): 482-90.

This study examines the associations between age at first substance use treatment entry and trajectory of outcomes over 11 years. The authors found significant differences in individual and treatment characteristics between adult intakes first treated during young adulthood (25 years or younger) and those first treated at an older age. Compared to their first treated older age counterparts matched on demographics and dependence type, those who entered first treatment during young adulthood had on average an earlier onset for substance use but a shorter duration between first substance use and first treatment entry; they also had worse alcohol and other drug outcomes 11 years post treatment entry. While subsequent substance use treatment and 12-step meeting attendance are important for both age groups in maintaining positive outcomes, relationships varied by age group. Findings underline the importance of different continuing care management strategies for those entering first treatment at different developmental stages.

**It Made My Life a Little Easier: Primary Care Providers' Beliefs and Attitudes About Using Opioid Treatment Agreements** Starrels JL, Wu B, Peyser D, Fox AD, Batchelder A, Barg FK,

Arnsten JH, Cunningham CO. *J Opioid Manag.* 2014; 10(2): 95-102.

The objective of this study was to understand primary care provider's (PCPs); experiences, beliefs, and attitudes about using opioid treatment agreements (OTAs) for patients with chronic pain. Qualitative research study. Twenty-eight internists and family medicine physicians at two health centers. Semi structured telephone interviews, informed by the Integrative Model of Behavioral Prediction. Themes were analyzed using a Grounded Theory approach, and similarities and differences in themes were examined among OTA adopters, non-adopters, and selective adopters. Participants were 64 percent female and 68 percent white, and practiced for a mean of 9.5 years. Adoption of OTAs varied: seven were adopters, five were non-adopters, and 16 were selective adopters. OTA adoption reflected PCPs' beliefs and attitudes in the following three thematic categories: 1) perceived effect of OTA use on the therapeutic alliance, 2) beliefs about the utility of OTAs for patients or providers, and 3) perception of patients' risk for opioid misuse. PCPs commonly believed that OTAs were useful for physician self-protection, but few believed that they prevent opioid misuse. Selective adopters expressed ambivalent beliefs and made decisions about OTA use for individual patients based on both observed data and a subjective sense of each

patient's risk for misuse. Substantial variability in PCP use of OTAs reflects differences in PCP beliefs and attitudes. Research to understand the impact of OTA use on providers, patients, and the therapeutic alliance is urgently needed to guide best practices.

**Physical Abuse is Associated with HIV-Related Drug Risk** Reddy MK, Anderson BJ, Liebschutz J, Stein MD. *Addict Behav.* 2014; 39(5): 965-8.

Those who have experienced abuse may be prone to engaging in risky sexual behavior and risky drug use. The relationship between sexual abuse and risky behavior has been well established in the literature, but the association between physical abuse and risky drug use has been equivocal. The authors hypothesize that the experience of PTSD symptoms following physical abuse leads to risky drug use. Therefore, they examined the associations among physical abuse history, PTSD symptoms, and HIV-related drug risk in a sample of 121 opioid-dependent persons to determine whether PTSD symptoms mediated the relationship between physical abuse history and drug risk. Participants were recruited during an acute care hospital inpatient stay. Physical abuse history was associated with increased drug risk, and PTSD symptoms were associated with increased drug risk. However, PTSD symptoms were not found to be a mediator of the association between physical abuse history and HIV-related drug risk. These findings highlight the importance of assessing abuse history in high-risk samples of opioid users.

**Recovery among Adolescents: Models for Post-Treatment Gains In Drug Abuse Treatments**

Joe GW, Kalling Knight D, Becan JE, Flynn PM. *J Subst Abuse Treat.* 2014; 46(3): 362-73.

Recovery among adolescents undergoing substance abuse treatment was modeled in terms of pre-treatment motivation, therapeutic relationships, psychological functioning, treatment retention, legal pressures, DSM diagnoses, and client demographics. To address between program differences, a within-covariance matrix, based on 547 youth, was used. Applicability of the results across treatment modalities was also examined. The data were from the NIDA-sponsored DATOS Adolescent study. Results from structural equation models (estimated using Mplus) indicated that higher pre-treatment motivation predicted stronger counselor and in-treatment peer relationships, better counselor relationships and retention predicted less illegal drug use at follow-up, and DSM diagnosis was important in the treatment process. Overall, illegal drug use at follow-up was associated with post-treatment alcohol consumption, cigarette use, condom nonuse, psychological distress, criminality, and school non-attendance. The results document the importance of motivation and therapeutic relationships on recovery, even when taking into account the relative effects of legal pressures, DSM diagnoses, and demographics.

**Treating Pain in Addicted Patients: Recommendations from an Expert Panel** Cheattle M, Comer D, Wunsch M, Skoufalos A, Reddy Y. *Popul Health Manag.* 2014; 17(2): 79-89.

Clinicians may face pragmatic, ethical, and legal issues when treating addicted patients. Equal pressures exist for clinicians to always address the health care needs of these patients in addition to their addiction. Although controversial, mainly because of the lack of evidence regarding their long-term efficacy, the use of opioids for the treatment of chronic pain management is widespread. Their use for pain management in the addicted population can present even more challenges, especially when evaluating the likelihood of drug-seeking behavior. As the misuse and abuse of opioids continues to burgeon, clinicians must be particularly vigilant when prescribing chronic opioid therapy. The purpose of this article is to summarize recommendations from a recent meeting of experts convened to recommend how primary care physicians should approach treatment of chronic pain for addicted patients when an addiction specialist is not available for a referral. As there is a significant gap in guidelines and recommendations in this specific area of care, this article serves to

create a foundation for expanding chronic pain guidelines in the area of treating the addicted population. This summary is designed to be a practical how-to guide for primary care physicians, discussing risk assessment, patient stratification, and recommended therapeutic approaches.

**Test-Retest Reliability of a Self-Administered Alcohol, Smoking and Substance Involvement Screening Test (Assist) in Primary Care Patients** McNeely J, Strauss SM, Wright S, Rotrosen J, Khan R, Lee JD, Gourevitch MN. J Subst Abuse Treat. 2014; 47(1): 93-101.

The time required to conduct drug and alcohol screening has been a major barrier to its implementation in mainstream healthcare settings. Because patient self-administered tools are potentially more efficient, the authors translated the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) into an audio guided computer assisted self-interview (ACASI) format. This study reports on the test-retest reliability of the ACASI ASSIST in an adult primary care population. Adult primary care patients completed the ACASI ASSIST, in English or Spanish, twice within a 1-4 week period. Among the 101 participants, there were no significant differences between test administrations in detecting moderate to high risk use for tobacco, alcohol, or any other drug class. Substance risk scores from the two administrations had excellent concordance (90-98%) and high correlation (ICC 0.90-0.97) for tobacco, alcohol, and drugs. The ACASI ASSIST has good test-retest reliability, and warrants additional study to evaluate its validity for detecting unhealthy substance use.

## **CLINICAL TRIALS NETWORK-RELATED RESEARCH**

**Identifying Patients With Problematic Drug Use In The Emergency Department: Results Of A Multisite Study** Macias Konstantopoulos WL, Dreifuss JA, McDermott KA, Parry BA, Howell ML, Mandler RN, Fitzmaurice GM, Bogenschutz MP, Weiss RD. Ann Emerg Med. 2014 Jul 3. [Epub ahead of print].

Drug-related emergency department (ED) visits have steadily increased, with substance users relying heavily on the ED for medical care. The present study aims to identify clinical correlates of problematic drug use that would facilitate identification of ED patients in need of substance use treatment. Using previously validated tests, 15,224 adult ED patients across 6 academic institutions were prescreened for drug use as part of a large randomized prospective trial. Data for 3,240 participants who reported drug use in the past 30 days were included. Self-reported variables related to demographics, substance use, and ED visit were examined to determine their correlative value for problematic drug use. Of the 3,240 patients, 2,084 (64.3%) met criteria for problematic drug use (Drug Abuse Screening Test score  $\geq 3$ ). Age greater than or equal to 30 years, tobacco smoking, daily or binge alcohol drinking, daily drug use, primary noncannabis drug use, resource-intense ED triage level, and perceived drug-relatedness of ED visit were highly correlated with problematic drug use. Among primary cannabis users, correlates of problematic drug use were age younger than 30 years, tobacco smoking, binge drinking, daily drug use, and perceived relatedness of the ED visit to drug use. Clinical correlates of drug use problems may assist the identification of ED patients who would benefit from comprehensive screening, intervention, and referral to treatment. A clinical decision rule is proposed. The correlation between problematic drug use and resource-intense ED triage levels suggests that ED-based efforts to reduce the unmet need for substance use treatment may help decrease overall health care costs.

**Reasons For Opioid Use Among Patients With Dependence On Prescription Opioids: The Role Of Chronic Pain** Weiss RD, Potter JS, Griffin ML, McHugh RK, Haller D, Jacobs P, Gardin J 2nd, Fischer D, Rosen KD. J Subst Abuse Treat. 2014 Aug;47(2): 140-5. Epub 2014 Apr 4.

The number of individuals seeking treatment for prescription opioid dependence has increased dramatically, fostering a need for research on this population. The aim of this study was to examine reasons for prescription opioid use among 653 participants with and without chronic pain, enrolled in the Prescription Opioid Addiction Treatment Study, a randomized controlled trial of treatment for prescription opioid dependence. Participants identified initial and current reasons for opioid use. Participants with chronic pain were more likely to report pain as their primary initial reason for use; avoiding withdrawal was rated as the most important reason for current use in both groups. Participants with chronic pain rated using opioids to cope with physical pain as more important, and using opioids in response to social interactions and craving as less important, than those without chronic pain. Results highlight the importance of physical pain as a reason for opioid use among patients with chronic pain.

**Multisite, Randomized, Double-Blind, Placebo-Controlled Pilot Clinical Trial To Evaluate the Efficacy Of Buspirone As A Relapse-Prevention Treatment For Cocaine Dependence**

Winhusen TM, Kropp F, Lindblad R, Douaihy A, Haynes L, Hodgkins C, Chartier K, Kampman KM, Sharma G, Lewis DF, VanVeldhuisen P, Theobald J, May J, Brigham GS. J Clin Psychiatry. 2014 May 27. [Epub ahead of print].

The objective of this study was to evaluate the potential efficacy of buspirone as a relapse-prevention treatment for cocaine dependence. A randomized, double-blind, placebo-controlled, 16-week pilot trial was conducted at 6 clinical sites between August 2012 and June 2013. Adult crack

cocaine users meeting DSM-IV-TR criteria for current cocaine dependence who were scheduled to be in inpatient/residential substance use disorder (SUD) treatment for 12-19 days when randomized and planning to enroll in local outpatient treatment through the end of the active treatment phase were randomized to bupirone titrated to 60 mg/d (n=35) or placebo (n=27). All participants received psychosocial treatment as usually provided by the SUD treatment programs in which they were enrolled. Outcome measures included maximum days of continuous cocaine abstinence (primary), proportion of cocaine use days, and days to first cocaine use during the outpatient treatment phase (study weeks 4-15) as assessed by self-report and urine drug screens. There were no significant treatment effects on maximum continuous days of cocaine abstinence or days to first cocaine use. In the female participants (n=23), there was a significant treatment-by-time interaction effect ( $\chi^2_1=15.26$ ,  $P<.0001$ ), reflecting an increase in cocaine use by those receiving bupirone, relative to placebo, early in the outpatient treatment phase. A similar effect was not detected in the male participants (n=39;  $\chi^2_1=0.14$ ,  $P=.70$ ). The results suggest that bupirone is unlikely to have a beneficial effect on preventing relapse to cocaine use and that bupirone for cocaine-dependent women may worsen their cocaine use outcomes. TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT01641159.

**HIV Risk Reduction With Buprenorphine-Naloxone Or Methadone: Findings From A Randomized Trial** Woody G, Bruce D, Korhuis PT, Chhatre S, Hillhouse M, Jacobs P, Sorensen J, Saxon AJ, Metzger D, Ling W. J Acquir Immune Defic Syndr. 2014 Apr 18. [Epub ahead of print].

The objective of this study was to compare HIV injecting and sex risk in patients being treated with methadone (MET) or buprenorphine-naloxone (BUP). This was a secondary analysis from a study of liver enzyme changes in patients randomized to MET or BUP who completed 24-weeks of treatment and had 4 or more blood draws. The initial 1:1 randomization was changed to 2:1 (BUP: MET) after 18 months due to higher dropout in BUP. The Risk Behavior Survey (RBS) measured past 30-day HIV risk at baseline and weeks 12 and 24. Among 529 patients randomized to MET, 391 (74%) were completers; among 740 randomized to BUP, 340 (46%) were completers; 700 completed the RBS. There were significant reductions in injecting risk ( $p<0.0008$ ) with no differences between groups in mean number of times reported injecting heroin, speedball, other opiates, and number of injections; or percent who shared needles, did not clean shared needles with bleach, shared cookers, or engaged in front/back loading of syringes. The percent having multiple sex partners decreased equally in both groups ( $p<0.03$ ). For males on BUP the sex risk composite increased; for males on MET, the sex risk decreased resulting in significant group differences over time ( $p<0.03$ ). For females, there was a significant reduction in sex risk ( $p<0.02$ ) with no group differences. Among MET and BUP patients that remained in treatment, HIV injecting risk was equally and markedly reduced, however MET retained more patients. Sex risk was equally and significantly reduced among females in both treatment conditions, but increased for males on BUP, and decreased for males on MET.

**Validity of Brief Screening Instrument For Adolescent Tobacco, Alcohol, and Drug Use** Kelly SM, Gryczynski J, Mitchell SG, Kirk A, O'Grady KE, Schwartz RP. Pediatrics. 2014 Apr 21. [Epub ahead of print].

The National Institute on Alcohol Abuse and Alcoholism developed an alcohol screening instrument for youth based on epidemiologic data. This study examines the concurrent validity of this instrument, expanded to include tobacco and drugs, among pediatric patients, as well as the acceptability of its self-administration on an iPad. Five hundred and twenty-five patients (54.5% female; 92.8% African American) aged 12 to 17 completed the Brief Screener for Tobacco,

Alcohol, and other Drugs (BSTAD) via interviewer-administration or self-administration using an iPad. Diagnostic and Statistical Manual, Fifth Edition substance use disorders (SUDs) were identified using a modified Composite International Diagnostic Interview-2 Substance Abuse Module. Receiver operating characteristic curves, sensitivities, and specificities were obtained to determine optimal cut points on the BSTAD in relation to SUDs. One hundred fifty-nine (30.3%) adolescents reported past-year use of  $\geq 1$  substances on the BSTAD: 113 (21.5%) used alcohol, 84 (16.0%) used marijuana, and 50 (9.5%) used tobacco. Optimal cut points for past-year frequency of use items on the BSTAD to identify SUDs were  $\geq 6$  days of tobacco use (sensitivity=0.95; specificity=0.97);  $\geq 2$  days of alcohol use (sensitivity=0.96; specificity=0.85); and  $\geq 2$  days of marijuana use (sensitivity=0.80; specificity=0.93). iPad self-administration was preferred over interviewer administration ( $z=5.8$ ;  $P<.001$ ). The BSTAD is a promising screening tool for identifying problematic tobacco, alcohol, and marijuana use in pediatric settings. Even low frequency of substance use among adolescents may indicate need for intervention.

### **Acceptability Of A Web-Based Community Reinforcement Approach For Substance Use Disorders With Treatment-Seeking American Indians/Alaska Natives**

Campbell AN, Turrigiano E, Moore M, Miele GM, Rieckmann T, Hu MC, Kropp F, Ringor-Carty R, Nunes EV. Community Ment Health J. 2014 Jul 15. [Epub ahead of print].

Longstanding disparities in substance use disorders and treatment access exist among American Indians/Alaska Natives (AI/AN). Computerized, web-delivered interventions have potential to increase access to quality treatment and improve patient outcomes. Prior research supports the efficacy of a web-based version [therapeutic education system (TES)] of the community reinforcement approach to improve outcomes among outpatients in substance abuse treatment; however, TES has not been tested among AI/AN. The results from this mixed method acceptability study among a diverse sample of urban AI/AN ( $N = 40$ ) show that TES was acceptable across seven indices (range 7.8-9.4 on 0-10 scales with 10 indicating highest acceptability). Qualitative interviews suggest adaptation specific to AI/AN culture could improve adoption. Additional efforts to adapt TES and conduct a larger effectiveness study are warranted.

### **Who Benefits From Additional Drug Counseling Among Prescription Opioid-Dependent Patients Receiving Buprenorphine-Naloxone and Standard Medical Management?**

Weiss RD, Griffin ML, Potter JS, Dodd DR, Dreifuss JA, Connery HS, Carroll KM. Drug Alcohol Depend. 2014 Jul 1; 140: 118-22. Epub 2014 Apr 24.

In the multi-site Prescription Opioid Addiction Treatment Study (POATS), conducted within the National Drug Abuse Clinical Trials Network, participants randomly assigned to receive individual drug counseling in addition to buprenorphine-naloxone and medical management did not have superior opioid use outcomes. However, research with other substance-dependent populations shows that subgroups of participants may benefit from a treatment although the entire population does not. The authors conducted a secondary analysis of POATS data to determine whether a subgroup of participants benefited from drug counseling in addition to buprenorphine-naloxone and medical management, either due to greater problem severity or more exposure to counseling as a result of greater treatment adherence. Problem severity was measured by a history of heroin use, higher Addiction Severity Index drug composite score, and chronic pain. Adequate treatment adherence was defined a priori as attending at least 60% of all offered sessions. Patients who had ever used heroin and received drug counseling were more likely to be successful (i.e., abstinent or nearly abstinent from opioids) than heroin users who received medical management alone, but only if they were adherent to treatment and thus received adequate exposure to counseling (OR=3.7, 95% CI=1.1-11.8,  $p=0.03$ ). The association between severity and outcome did not vary by treatment

condition for chronic pain or ASI drug severity score. These findings emphasize the importance of treatment adherence, and suggest that patients with prescription opioid dependence are a heterogeneous group, with different optimal treatment strategies for different subgroups.

**Preliminary Findings On the Association Between Clients' Perceived Helpfulness Of Substance Abuse Treatment and Outcomes: Does Race Matter?**

Montgomery L, Sanning B, Litvak N, Peters EN. *Drug Alcohol Depend.* 2014 Jun 1; 139: 152-8. Epub 2014 Apr 5.

Few studies examine the helpfulness and effectiveness of substance abuse treatment from the clients' perspective. The current secondary analysis examined the perceived helpfulness of substance abuse treatment components and its relationship to treatment outcomes among 387 Black and White adults participating in a multisite randomized clinical trial (RCT) of Motivational Enhancement Therapy. Throughout the 16-week RCT, participants self-reported substance use. Upon completion of treatment, participants completed a self-report measure assessing the perceived helpfulness of treatment components. Black participants rated 9 out of 12 treatment components (e.g., "learning skills that will help me cope with my problems") as being more helpful than their White counterparts, even after controlling for age, gender, employment status, primary drug type, and treatment assignment. However, perceived helpfulness ratings were not associated with substance use outcomes among Black or White participants. Clients' perceived helpfulness of treatment components is an important factor to consider in improving the delivery of substance abuse treatment, especially for Black adults.

**Is Level Of Exposure To A 12-Step Facilitation Therapy Associated With Treatment Outcome?**

Wells EA, Donovan DM, Daley DC, Doyle SR, Brigham G, Garrett SB, Ingalsbe MH, Hatch-Maillette MA, Perl HI, Walker R. *J Subst Abuse Treat.* 2014 Jun 14 [Epub ahead of print].

This study examined whether level of exposure to Stimulant Abuser Groups to Engage in 12-Step (STAGE-12), a 12-Step facilitative therapy, is related to treatment outcome. Data were from a large National Drug Abuse Treatment Clinical Trials Network (CTN) study comparing STAGE-12 combined with treatment-as-usual (TAU) to TAU alone. These analyses include only those randomized to STAGE-12 ( $n=234$ ). Assessments occurred at baseline and 30, 60, 90, and 180 days following randomization. High-exposure patients ( $n=158$ ; attended at least 2 of 3 individual, and 3 of 5 group, sessions), compared to those with less exposure ( $n=76$ ), demonstrated: (1) higher odds of self-reported abstinence from, and lower rates of, stimulant and non-stimulant drug use; (2) lower probabilities of stimulant-positive urines; (3) more days of attending and lower odds of not attending 12-Step meetings; (4) greater likelihood of reporting no drug problems; (5) more days of duties at meetings; and (6) more types of 12-Step activities. Many of these differences declined over time, but several were still significant by the last follow-up. Treatment and research implications are discussed.

**Treatment Adherence and Competency Ratings Among Therapists, Supervisors, Study-Related Raters and External Raters In A Clinical Trial Of A 12-Step Facilitation For Stimulant Users**

Peavy KM, Guydish J, Manuel JK, Campbell BK, Lisha N, Le T, Delucchi K, Garrett S. *J Subst Abuse Treat.* 2014 Jun 10. [Epub ahead of print].

This study investigated the correspondence among four groups of raters on adherence to STAGE-12, a manualized 12-step facilitation (TSF) group and individual treatment targeting stimulant abuse. The four rater groups included the study therapists, supervisors, study-related ("TSF expert") raters, and non-project related ("external") raters. Results indicated that external raters rated most critically mean adherence - the mean of all the adherence items - and global performance. External raters also demonstrated the highest degree of reliability with the designated expert. Therapists rated

their own adherence lower, on average, than did supervisors and TSF expert raters, but therapist ratings also had the poorest reliability. Findings highlight the challenges in developing practical, but effective methods of fidelity monitoring for evidence based practice in clinical settings. Recommendations based on study findings are provided.

**Improving Treatment For Opioid Dependence: A Perspective From The Ohio Valley Node Of the NIDA Clinical Trials Network** Winstanley EL, Brigham GS, Babcock D, Winhusen T. Prog Community Health Partnersh. 2014 Spring; 8(1): 99-107.

Rates of adoption of evidenced-based practices, including the use of medications, to treat opioid dependence are low and severely limit secondary prevention efforts to curtail the prescription drug epidemic. The goal of this article was to describe how involvement in a research clinical trials network (CTN) facilitated the adoption of medications to treat opioid dependence at two community-based treatment programs (CTPs) affiliated with the Ohio Valley Node (OVN) of the National Institute on Drug Abuse's (NIDA) CTN. Participation in a CTN may facilitate adoption by providing the infrastructure for trialability and observability, but the most critical function may be the knowledge translation that occurs through the individual-level professional relationships that develop. Community-based treatment providers' involvement in research networks may increase the rate of evidence-based practice (EBP) adoption and improve outcomes for patients with opioid dependence.

**Racial/Ethnic Match and Treatment Outcomes For Women With PTSD and Substance Use Disorders Receiving Community-Based Treatment** Ruglass LM, Hien DA, Hu MC, Campbell AN, Caldeira NA, Miele GM, Chang DF. Community Ment Health J. 2014 May 10. [Epub ahead of print].

This study examined the relationship between racial/ethnic match and treatment outcomes for 224 women who participated in a clinical trial of group treatments for posttraumatic stress disorder (PTSD) and substance use disorders. Generalized estimating equations were used to examine the effect of client-therapist racial/ethnic match on outcomes. Results revealed racial/ethnic match was not significantly associated with session attendance. There was a significant three-way interaction between client race/ethnicity, baseline level of PTSD symptoms, and racial/ethnic match on PTSD outcomes. White clients, with severe PTSD symptoms at baseline, who attended treatment groups where they were matched with their therapist, had greater reductions in PTSD symptoms at follow-up than their counterparts who were racially/ethnically mismatched with their group therapist. Racial/ethnic match did not confer additional benefits for Black clients in terms of PTSD outcomes. Racial/ethnic match interacted with baseline substance use to differentially influence substance use outcomes at follow-up for all women. Clinical implications are discussed.

**Clinically Relevant Characteristics Associated With Early Treatment Drug Use Versus Abstinence** Cochran G, Stitzer M, Nunes EV, Hu MC, Campbell A. Addict Sci Clin Pract. 2014 Apr 4; 9:6.

This study describes early treatment drug use status and associated clinical characteristics in a diverse sample of patients entering outpatient substance abuse psychosocial counseling treatment. The goal is to more fully characterize those entering treatment with and without active use of their primary drug in order to better understand associated treatment needs and resilience factors. The authors examined baseline data from a NIDA Clinical Trials Network (CTN) study (Web-delivery of Treatment for Substance Use) with an all-comers sample of patients (N=494) entering 10 outpatient treatment centers. Patients were categorized according to self-identified primary drug of abuse (alcohol, cocaine/stimulants, opioids, marijuana) and by baseline drug use status

(positive/negative) based on urine testing or self-reports of recent use (alcohol). Characteristics were examined by primary drug and early use status. Classified as drug-negative were 84%, 76%, 62%, and 33% of primary opioid, stimulant, alcohol, and marijuana users respectively. Drug-positive versus -negative patients did not differ on demographics or rates of substance abuse/dependence diagnoses. However, those negative for active use had better physical and mental health profiles, were less likely to be using a secondary drug, and were more likely to be attending 12-step self-help meetings. Early treatment drug abstinence is common among substance users entering outpatient psychosocial counseling programs, regardless of primary abused drug. Abstinence (by negative UA) is associated with better health and mental health profiles, less secondary drug use, and more days of 12-step attendance. These data highlight differential treatment needs and resiliencies associated with early treatment drug use status. TRIAL REGISTRATION: NCT01104805.

**Expanding the National Drug Abuse Treatment Clinical Trials Network To Address the Management Of Substance Use Disorders In General Medical Settings** Tai, B, Sparenborg S,

Ghitza UE, Liu D. *Subst Abuse Rehabil* 2014; 5: 75-80.

The Patient Protection and Affordable Care Act (2010) and the Mental Health Parity and Addiction Equity Act (2008) expand substance use disorder (SUD) care services in the USA into general medical settings. Care offered in these settings will engage substance-using patients in an integrated and patient-centered environment that addresses physical and mental health comorbidities and follows a chronic care model. This expansion of SUD services presents a great need for evidence-based practices useful in general medical settings, and reveals several research gaps to be addressed. The National Drug Abuse Treatment Clinical Trials Network of the National Institute on Drug Abuse can serve an important role in this endeavor. High-priority research gaps are highlighted in this commentary. A discussion follows on how the National Drug Abuse Treatment Clinical Trials Network can transform to address changing patterns in SUD care to efficiently generate evidence to guide SUD treatment practice within the context of recent US health care legislation.

**Patient Registries For Substance Use Disorder** Tai B, Hu L, Ghitza UE, Sparenborg S,

VanVeldhusien P, Lindblad R. *Subst Abuse Rehabil* 2014, 5: 81-86.

This commentary discusses the need for developing patient registries of substance use disorders (SUD) in general medical settings. A patient registry is a tool that documents the natural history of target diseases. Clinicians and researchers use registries to monitor patient comorbidities, care procedures and processes, and treatment effectiveness for the purpose of improving care quality. Enactments of the Affordable Care Act 2010 and the Mental Health Parity and Addiction Equity Act 2008 open opportunities for many substance users to receive treatment services in general medical settings. An increased number of patients with a wide spectrum of SUD will initially receive services with a chronic disease management approach in primary care. The establishment of computer-based SUD patient registries can be assisted by wide adoption of electronic health record systems. The linkage of SUD patient registries with electronic health record systems can facilitate the advancement of SUD treatment research efforts and improve patient care.

## **WOMEN & SEX/GENDER DIFFERENCES RELATED RESEARCH**

### **Cerebral Gray Matter Volumes and Low-Frequency Fluctuation of BOLD Signals in Cocaine**

**Dependence: Duration of Use and Gender Difference** Ide JS, Zhang S, Hu S, Sinha R, Mazure CM, Li CS. *Drug Alcohol Depend.* 2014 Jan 1; 134: 51-62.

Magnetic resonance imaging has provided a wealth of information on altered brain activations and structures in individuals addicted to cocaine. However, few studies have considered the influence of age and alcohol use on these changes. The authors examined gray matter volume with voxel based morphometry (VBM) and low frequency fluctuation (LFF) of BOLD signals as a measure of cerebral activity of 84 cocaine dependent (CD) and 86 healthy control (HC) subjects. They performed a covariance analysis to account for the effects of age and years of alcohol use. Compared to HC, CD individuals showed decreased gray matter (GM) volumes in frontal and temporal cortices, middle/posterior cingulate cortex, and the cerebellum, at  $p < 0.05$ , corrected for multiple comparisons. The GM volume of the bilateral superior frontal gyri (SFG) and cingulate cortices were negatively correlated with years of cocaine use, with women showing a steeper loss in the right SFG in association with duration of use. In contrast, the right ventral putamen showed increased GM volume in CD as compared to HC individuals. Compared to HC, CD individuals showed increased fractional amplitude of LFF (fALFF) in the thalamus, with no significant overlap with regions showing GM volume loss. These results suggested that chronic cocaine use is associated with distinct changes in cerebral structure and activity that can be captured by GM volume and fALFF of BOLD signals.

**Clinical Correlates of Prescription Opioid Analgesic Use in Pregnancy** Smith MV, Costello D, Gotman N, Yonkers KA. *Maternal and Child Health Journal.* 2014 June. [Epub ahead of print].

A 2012 committee opinion from the American College of Obstetricians and Gynecologists highlights the considerable increase in opioid addiction in recent years, yet little is known about clinical correlates of prescribed opioids among pregnant women. This study examines clinical and demographic factors associated with the use of opioid analgesics in pregnancy. Data were derived from a prospective cohort study of pregnant women. Participants were administered the Composite International Diagnostic Interview to identify depressive and anxiety disorders and data on medication use were gathered at three assessment points and classified according to the Anatomical Therapeutic Chemical Code (ATC) classification system ATC group N02A. Participants included 2,748 English or Spanish speaking pregnant women. Six percent ( $n = 165$ ) of women used opioid analgesics at any point in pregnancy. More pregnant women using opioids met diagnostic criteria for major depressive disorder (16 vs. 8% for non users), generalized anxiety disorder (18 vs. 9% for non users), post-traumatic stress disorder (11 vs. 4% for non users) and panic disorder (6 vs. 4% for non users). Women who reported opioid use were also significantly more likely than non users to report using illicit drugs and almost three times as likely to report smoking cigarettes in the second or third trimester of pregnancy (4 and 23%, respectively) as compared to non-opioid users (0.5 and 8%). The use of opioids in pregnancy was associated with higher levels of psychiatric comorbidity and use of other substances as compared to non-opioid users.

### **Sex Differences in Guanfacine Effects on Drug Craving and Stress Arousal in Cocaine-**

**Dependent Individuals** Fox HC, Morgan PT, Sinha R. *Neuropsychopharmacology.* 2014 May; 39(6): 1527-1537.

Currently, no FDA-approved medication exists for the treatment of cocaine use disorder. Furthermore, as women become increasingly more at risk for the consequences of cocaine addiction, the need to establish better-tailored treatment medications is paramount. The authors

examine the effects of the alpha2 adrenergic agonist, guanfacine HCl, on responses to stress and drug cue in a group of cocaine-dependent men and women who also abuse alcohol and nicotine. Forty early abstinent treatment-seeking cocaine-dependent males and females were randomly assigned to receive either daily placebo (12 M/7 F) or guanfacine (2 or 3 mg) (15 M/6 F) for 3 weeks. In week 4, they participated in a laboratory experiment and were exposed to three 10-min guided imagery conditions (stress/stress, cue/cue, and stress/cue), one per day, consecutively in a random, counterbalanced order. Craving, negative emotion, anxiety, and cardiovascular function were assessed at baseline, immediately following imagery exposure, and at various recovery time points. Guanfacine significantly attenuated cocaine craving, alcohol craving, anxiety, and negative emotion following exposure to all three imagery conditions in females, but not males. Guanfacine did, however, reduce sympathetic tone as well as stress and cue-induced nicotine craving and systolic blood pressure (SBP) in both males and females. These findings highlight sex-specific effects of guanfacine on drug craving, anxiety, and negative mood with significant effects in women and not men. The findings suggest further evaluation of guanfacine in the treatment of cocaine use disorder with a specific focus on sex differences in treatment response.

**Yohimbine Administration and Cue-Reactivity in Cocaine-Dependent Individuals.** Moran-Santa Maria MM, McRae-Clark A, Baker NL, Ramakrishnan V, Brady KT. *Psychopharmacology (Berl)*. 2014 Apr 8. [Epub ahead of print].

Preclinical studies suggest that stress potentiates cue-induced cocaine seeking and that this effect is more pronounced in females. These findings have not been characterized in clinical populations. The objectives of this study were to examine the impact a pharmacological stressor, alpha-2 adrenergic receptor antagonist yohimbine, on the subjective, endocrine, and physiologic responses to drug-paired cues cocaine-dependent men and women. In a double-blind placebo-controlled cross-over study, cocaine-dependent men (n=32), cocaine-dependent women (n=30), control men (n=32), and control women (n=25) received either yohimbine or placebo prior to two cocaine cue exposure sessions. Yohimbine increased ratings of anxiety both before (p<0.001) and after (p=0.035) cues, and the post-cue increase in anxiety was more pronounced in women (p=0.001). Yohimbine also significantly increased craving, compared with placebo (p<0.05), following the cue presentation, and this effect was greater in women than men (gender by treatment interaction; p=0.006). Yohimbine also increased salivary cortisol (p<0.001) and dehydroepiandrosterone (p=0.003) levels, regardless of diagnostic group. Women had a significantly greater heart rate response following yohimbine as compared with men (p<0.001). Stress may increase the salience of cocaine cues for cocaine-dependent women as compared with men. This suggests gender differences in vulnerability to craving and relapse under stressful conditions.

**Smoking Initiation after Marriage and Parenting among Black and White Women** Thompson AB. *American Journal of Health Behavior*. 2014 July; 38(4): 577-585. [Epub ahead of print].

The objective of this study was to examine the hypothesis that Black-White differences in smoking initiation after transitions into marriage and/or parenting is associated with racial disparities in quitting. Cox models were used on data from the National Longitudinal Survey of Young Women, a cohort of women surveyed from 1968-2003. Black women (58%) were more likely than white women (40%) to initiate after marriage and/or parenting. Adjustment for these differences did not reduce disparities in quitting (HR 0.53, CI 0.30-0.95). Only after adjustment for sociodemographics were disparities reduced (HR 0.67, HR 0.36-1.22). Other factors associated with smoking initiation among young adult black women (i.e., limited economic opportunities, racial discrimination) should be examined for their influence on quitting.

### **Prenatal Cocaine Exposure and Adolescent Neural Responses to Appetitive and Stressful Stimuli**

Yip SW, Potenza EB, Balodis IM, Lacadie CM, Sinha R, Mayes LC, Potenza MN.

Neuropsychopharmacology. 2014 June 6 [Epub ahead of print].

Preclinical research has demonstrated the effects of prenatal cocaine exposure (PCE) on brain regions involved in emotional regulation, motivational control, and addiction vulnerability-e.g., the ventral striatum (VS), anterior cingulate (ACC), and prefrontal cortex (PFC). However, little is known about the function of these regions in human adolescents with PCE. Twenty-two adolescents with PCE and 22 age-, gender-, and IQ-matched non-cocaine exposed (NCE) adolescents underwent functional magnetic resonance imaging (fMRI) during exposure to individually personalized neutral/relaxing, stressful, and favorite-food cues. fMRI data were compared using group-level two-tailed t-tests in the BioImage Suite. In comparison with NCE adolescents, PCE adolescents had reduced activity within cortical and subcortical brain regions, including the VS, ACC, and medial and dorsolateral PFC during exposure to favorite-food cues but did not differ in neural responses to stress cues. Subjective food craving was inversely related to dorsolateral PFC activation among PCE adolescents. Among PCE adolescents, subjective anxiety ratings correlated inversely with activations in the orbitofrontal cortex and brainstem during the stress condition and with ACC, dorsolateral PFC, and hippocampus activity during the neutral-relaxing condition. Thus adolescents with PCE display hypoactivation of brain regions involved in appetitive processing, with subjective intensities of craving and anxiety correlating inversely with extent of activation. These findings suggest possible mechanisms by which PCE might predispose to the development of addictions and related disorders, e.g., substance-use disorders and binge-eating.

### **Sex Differences in Resting State Neural Networks of Nicotine-dependent Cigarette Smokers**

Wetherill RR, Jagannathan K, Shin J, Franklin TR. Addict Behav. 2014 Apr; 39: 789-792.

Although several sex differences in nicotine dependence have been identified, the neural mechanisms underlying these sex differences are not clear. The present study examines sex differences in resting-state brain activity using an arterial spin labeling (ASL) perfusion imaging technique. Fifty-one (31 males) sated nicotine-dependent cigarette smokers underwent perfusion functional magnetic resonance imaging during the resting state. Using functionally defined hippocampus/amygdala (HIP/AMY) seed regions, the authors observed sex differences in correlation strength between the HIP/AMY and the bilateral anterior insula, rostral anterior cingulate cortex, and inferior parietal lobule with females showing stronger functional coupling than males. This pattern of synchronous variations in dynamic cerebral blood flow is consistent with recent models of nicotine dependence, and as such, these findings provide a novel perspective on the neural mechanisms that may contribute to sex differences in nicotine dependence.

### **Sex Differences In Response To Reduced Nicotine Content Cigarettes**

Vogel RI, Hertsgaard LA, Dermody SS, Luo X, Moua L, Allen S, al'Absi M, Hatsukami DK. Addict Behav. 2014; 39(7): 1197-204.

When switching from usual brand cigarettes, very low nicotine content (VLNC) cigarettes lead to a reduction in the number of cigarettes smoked, toxicant exposure, withdrawal symptoms and dependence. One area that has been relatively unexplored is what factors might moderate the effects of VLNC cigarettes. This exploratory analysis focuses on sex differences in responses to VLNC cigarettes and nicotine replacement therapy. An exploratory secondary analysis of a randomized trial of 235 participants (58% female, mean age 47 years) comparing a) 0.05-0.09 mg nicotine yield cigarettes; b) 21 mg nicotine patch and 3) 0.05-0.09 nicotine yield cigarettes with 21 mg nicotine patch was conducted. The authors focused on sex differences in product use, and impact of products on withdrawal response from usual brand cigarettes and abstinence by randomized group. The

combination of VLNC cigarettes and nicotine patch was more effective in reducing use of VLNC cigarettes and withdrawal symptoms among males than females, whereas females were equally responsive to VLNC cigarettes with and without the nicotine patch. Females were more likely to quit smoking than males when assigned to either of the conditions that incorporated the VLNC cigarettes; however, males were more likely to quit smoking in the nicotine patch alone condition than females. Sex of the smoker may be an important determinant for effects of VLNC cigarettes and nicotine patch. Future large randomized trials to confirm these results are needed.

**Sex Differences In Nicotine Self-Administration In Rats During Progressive Unit Dose Reduction: Implications For Nicotine Regulation Policy** Grebenstein P, Burroughs D, Zhang Y, LeSage MG. *Pharmacol Biochem Behav.* 2013 Dec; 114-115: 70-81.

Reducing the nicotine content in tobacco products is being considered by the FDA as a policy to reduce the addictiveness of tobacco products. Understanding individual differences in response to nicotine reduction will be critical to developing safe and effective policy. Animal and human research demonstrating sex differences in the reinforcing effects of nicotine suggests that males and females may respond differently to nicotine-reduction policies. However, no studies have directly examined sex differences in the effects of nicotine unit-dose reduction on nicotine self-administration (NSA) in animals. The purpose of the present study was to examine this issue in a rodent self-administration model. Male and female rats were trained to self-administer nicotine (0.06mg/kg) under an FR 3 schedule during daily 23h sessions. Rats were then exposed to saline extinction and reacquisition of NSA, followed by weekly reductions in the unit dose (0.03 to 0.00025mg/kg) until extinction levels of responding were achieved. Males and females were compared with respect to baseline levels of intake, resistance to extinction, degree of compensatory increases in responding during dose reduction, and the threshold reinforcing unit dose of nicotine. Exponential demand-curve analysis was also conducted to compare the sensitivity of males and females to increases in the unit price (FR/unit dose) of nicotine (i.e., elasticity of demand or reinforcing efficacy). Females exhibited significantly higher baseline intake and less compensation than males. However, there were no sex differences in the reinforcement threshold or elasticity of demand. Dose-response relationships were very well described by the exponential demand function ( $r^2$  values > 0.96 for individual subjects). These findings suggest that females may exhibit less compensatory smoking in response to nicotine reduction policies, even though their nicotine reinforcement threshold and elasticity of demand may not differ from males.

**Subjective, Physiological, and Cognitive Responses To Intravenous Nicotine: Effects Of Sex and Menstrual Cycle Phase** DeVito EE, Herman AI, Waters AJ, Valentine GW, Sofuoglu M. *Neuropsychopharmacology.* 2014 May; 39(6): 1431-40. doi: 10.1038/npp.2013.339. Epub 2013 Dec 18.

Nicotine dependence is a serious public health concern. Optimal treatment of nicotine dependence will require greater understanding of the mechanisms that contribute to the maintenance of smoking behaviors. A growing literature indicates sex and menstrual phase differences in responses to nicotine. The aim of this study was to assess sex and menstrual phase influences on a broad range of measures of nicotine response including subjective drug effects, cognition, physiological responses, and symptoms of withdrawal, craving, and affect. Using a well-established intravenous nicotine paradigm and biochemical confirmation of overnight abstinence and menstrual cycle phase, analyses were performed to compare sex (age 18-50 years; 115 male and 45 female) and menstrual cycle phase (29 follicular and 16 luteal) effects. Females had diminished subjective drug effects of, but greater physiological responses to, nicotine administration. Luteal-phase females showed diminished subjective drug effects and better cognition relative to follicular-phase women. These

findings offer candidate mechanisms through which the luteal phase, wherein progesterone is dominant relative to estradiol, may be protective against vulnerability to smoking.

**Gender Differences In Stressful Life Events, Social Support, Perceived Stress, and Alcohol Use Among Older Adults: Results From A National Survey** Sacco P, Bucholz KK, Harrington D. *Subst Use Misuse*. 2014; 49(4): 456-65.

Stressful life events, perceived stress, and social support relationships with consumption, at-risk drinking, and alcohol use disorder (AUD) were studied in a population-based sample of current drinkers age 60+ in the National Epidemiologic Survey of Alcohol and Related Conditions (Wave 2; 2004-2005; n = 4,360). Stressful life events were associated with AUD among men and women, and crime victimization among men only. However, greater perceived stress was associated with lower consumption among women and greater odds of AUD in men, highlighting differences in the relationship between stress and alcohol use by gender that may be the result of the stress alcohol link.

## **INTRAMURAL RESEARCH**

### **Molecular Targets and Medications Discovery Research Branch**

#### **Medicinal Chemistry Section**

**Chiral Resolution and Serendipitous Fluorination Reaction For the Selective Dopamine D3 Receptor Antagonist BAK2-66** Kumar V, Banala AK, Garcia EG, Cao J, Keck TM, Bonifazi A, Deschamps JR, Newman AH. ACS Med Chem Lett 2014, 5(6) 647–51.

The improved chiral synthesis of the selective dopamine D3 receptor (D3R) antagonist (R)-N-(4-(4-(2,3-dichlorophenyl)piperazin-1-yl)-3-hydroxybutyl)1H-indole-2-carboxamide ((R)-PG648) is described. The same chiral secondary alcohol intermediate was used to prepare the enantiomers of a 3-F-benzofuranyl analogue, BAK 2-66. The absolute configurations of the 3-F enantiomers were assigned from their X-ray crystal structures that confirmed retention of configuration during fluorination with N,N-diethylaminosulfur trifluoride (DAST). (R)-BAK2-66 showed higher D3R affinity and selectivity than its (S)-enantiomer, however it had lower D3R affinity and enantioselectivity than (R)-PG648. Further, importance of the 4-atom linker length between the aryl amide and 4-phenylpiperazine was demonstrated with the 4-fluorobutyl-product (8).

**Novel and High Affinity Fluorescent Ligands For the Serotonin Transporter Based On (S)-Citalopram** Kumar V, Rahbek-Clemmensen T, Billesbolle CB, Jorgensen TN, Gether U, Newman AH. ACS Med Chem Lett 2014, 5(6), 696–9.

Novel rhodamine-labeled ligands, based on (S)-citalopram, were synthesized and evaluated for uptake inhibition at the human serotonin, dopamine and norepinephrine transporters (hSERT, hDAT and hNET respectively) and for binding at SERT, in transiently transfected COS7 cells. Compound 14 demonstrated high affinity binding and selectivity for SERT (K<sub>i</sub>=3 nM). Visualization of SERT, using confocal laser scanning microscopy, validated compound 14 as a novel tool for studying SERT expression and distribution in living cells.

**Dopamine D3 Receptors Contribute To Methamphetamine-Induced Alterations In Dopaminergic Neuronal Function: Role Of Hyperthermia** Baladi MG, Newman AH, Nielsen SM, Hanson GR, Fleckenstein AE. Eur J Pharmacol. 2014, 732, 105-11.

Methamphetamine administration causes long-term deficits to dopaminergic systems that, in humans, are thought to be associated with motor slowing and memory impairment. Methamphetamine interacts with the dopamine transporter (DAT) and increases extracellular concentrations of dopamine that, in turn, binds to a number of dopamine receptor subtypes. Although the relative contribution of each receptor subtype to the effects of methamphetamine is not fully known, non-selective dopamine D2/ D3 receptor antagonists can attenuate methamphetamine-induced changes to dopamine systems. The present study extended these findings by testing the role of the dopamine D3 receptor subtype in mediating the long-term dopaminergic, and for comparison serotonergic, deficits caused by methamphetamine. Results indicate that the dopamine D3 receptor selective antagonist, PG01037, attenuated methamphetamine-induced decreases in striatal DAT, but not hippocampal serotonin (5HT) transporter (SERT), function, as assessed 7 days after treatment. However, PG01037 also attenuated methamphetamine-induced hyperthermia. When methamphetamine-induced hyperthermia was maintained by treating rats in a warm ambient environment, PG01037 failed to attenuate the effects of methamphetamine on DAT uptake. Furthermore, PG01037 did not attenuate methamphetamine-induced decreases in dopamine and 5HT content. Taken together, these data demonstrate that the

degree of METH-induced hyperthermia might contribute to the role of dopamine D3 receptors in methamphetamine-induced dopaminergic deficits. The present study demonstrates that dopamine D3 receptors mediate, in part, the long-term deficits in DAT function caused by methamphetamine, and that this effect likely involves an attenuation of methamphetamine-induced hyperthermia.

**Enantiomers Of Tranlycypromine Substituted Cis-Hydroxycyclobutyl-naphthamides As Potent and Selective Dopamine D3 Receptor Antagonists** Chen J, Jiang C, Levant B, Keck TM, Newman AH, Wang S. J Med Chem 2014, 57(11), 4962-8.

The authors report herein a class of potent and selective dopamine D3 receptor antagonists based upon tranlycypromine. Although tranlycypromine binds to the rat D3 receptor with low affinity ( $K_i=12.8 \mu\text{M}$ ), our efforts have yielded (1R,2S)-11 (CJ-1882), which has  $K_i$  values of 2.7 nM and 2.8 nM at the rat and human dopamine D3 receptors, respectively, and displays good selectivity over both the rat and human D2 receptors. Evaluation in a  $\beta$ -arrestin functional assay showed that (1R,2S)-11 is a potent and competitive antagonist at the human D3 receptor.

**Quinpirole-Elicited Yawning In Monkeys: Relationship With D3 Receptor Availability, Sex Differences and Effects On Chronic Drug Exposure** Martelle, SE, Nader SH, Czoty PW, John WS, Duke AN, Garg PK, Garg S, Newman AH, Nader MA. J Pharmacol Exp Ther 2014, 350, 205-11.

The dopamine (DA) D3 receptor (DRD3) has been associated with impulsivity, pathological gambling and drug addiction making it a potential target for pharmacotherapy development. Positron emission tomography (PET) studies using the DRD3-preferring radioligand [11C]-(+)-propyl-hexahydro-naphtho-oxazin ([11C]PHNO) have shown higher binding potentials in drug abusers compared to control subjects. Preclinical studies have examined DRD3 receptor activation using the DA agonist quinpirole and the unconditioned behavior of yawning. However, the relationship between quinpirole-elicited yawning and DRD3 receptor availability has not been determined. In Experiment 1, 10 drug-naïve male rhesus monkeys were scanned with [11C]PHNO and the ability of quinpirole (0.01-0.3 mg/kg, i.m.) to elicit yawning was examined. Significant relationships between DRD3 receptor availability and quinpirole-induced yawns were noted in several brain regions. Experiment 2 replicated earlier findings that a history of cocaine self-administration did not affect quinpirole-induced yawning and extended this to examine monkeys with a history of methamphetamine (MA) self-administration and found that monkeys with experience self-administering MA showed greater potency and significantly higher quinpirole-elicited yawning compared to controls. Finally, quinpirole-elicited yawning was studied in drug-naïve female monkeys and compared to drug-naïve male. Sex differences were noted, with quinpirole being more potent and significantly eliciting more yawns in males compared to females. Taken together these findings support the use of quinpirole-elicited yawning as a behavioral tool for examining DRD3 activation in monkeys and that both drug history and sex may influence individual sensitivity to the behavioral effects of DRD3 compounds.

**Functional Dopamine Transporter Deficiency Associated With Adult Parkinsonism and ADHD** Hansen FH, Skorringer T, Yasmeen S, Arends NV, Sahai M, Erreger K, Andreassen TF, Neergheen V, Karlsborg M Newman AH., Pope S, Heales S, Friberg L, Pinborg LH, Loland CJ, Shi L, Weinstein H, Galli A, Hjermind LE, Moller LB, Gether U. J Clin Invest 2014, 124(7) 3107-20. The sodium-coupled dopamine transporter (DAT) controls dopamine homeostasis and is encoded by SLC6A3. Loss-of-function mutations in SLC6A3 were recently described as a cause of infantile parkinsonism-dystonia. To further assess DAT's contribution to movement disorders, the authors searched for DAT variants in patients with early-onset parkinsonism and related atypical movement

disorders. SLC6A3 exons were sequenced in 91 patients. DAT mutants were characterized in heterologous cells by uptake and binding experiments, surface biotinylation, confocal microscopy, amperometry and by modelling. Neuropathological features were assessed through single photon emission computed tomography (SPECT) scans, and CSF metabolite analysis. The authors present an adult male, diagnosed with parkinsonism and ADHD, who is compound heterozygous for DAT-I312F and the presumed de novo mutant, DAT-D421N. Both mutants exhibit reduced dopamine uptake in cells (~56% and ~10% of WT for DAT-I312F and DAT-D421N respectively), consistent with strong bilateral reduction of [<sup>123</sup>I]-FP-CIT binding in DAT-SPECT scans. The reduced uptake by DAT-D421N was not caused by impaired membrane targeting, but rather by disrupted sodium binding to the second sodium site in DAT, as supported by computational simulations and uptake experiments. DAT-D421N was moreover characterized by constitutive, anomalous dopamine efflux. The data link, to the authors' knowledge, for the first time DAT coding variants, including a de novo mutation, to parkinsonism in an adult. Furthermore, it is the first patient with ADHD, who is compound heterozygous for SLC6A3 mutations. The findings support a key role of altered DAT function in human disease and provide an important framework for improved understanding of dopaminergic pathologies.

## Designer Drug Research Unit

**Abuse-Related Effects Of Dual Dopamine/Serotonin Releasers With Varying Potency To Release Norepinephrine In Male Rats and Rhesus Monkeys** Banks ML, Bauer CT, Blough BE, Rothman RB, Partilla JS, Baumann MH, Negus SS. *Exp Clin Psychopharmacol.* 2014 Jun; 22(3): 274-84.

d-Amphetamine selectively promotes release of both dopamine (DA) and norepinephrine (NE) versus serotonin (5HT), and chronic d-amphetamine treatment decreases cocaine-taking behavior in rats, nonhuman primates, and humans. However, abuse liability limits the clinical utility of amphetamine maintenance for treating cocaine abuse. One strategy to improve safety and efficacy of monoamine releasers as candidate anticocaine medications has been to develop dual DA/5HT releasers like 1-naphthyl-2-aminopropane (PAL-287), but the pharmacology of this class of compounds has not been extensively examined. In particular, PAL-287 has similar potencies to release DA, 5HT, and NE, and the role of manipulating NE release potency on abuse-related or anticocaine effects of dual DA/5HT releasers is not known. To address this issue, the present study compared effects of four novel DA/5HT releasers that varied >800-fold in their selectivities to release DA/5HT versus NE: [1-(5-chloro-1H-indol-3-yl)propan-2-amine (PAL-542), 1-(5-fluoro-1H-indol-3-yl)propan-2-amine (PAL-544), 1-(1H-indol-5-yl)propan-2-amine (PAL-571), and (R)-1-(1H-indol-1-yl)propain-2-amine (PAL-569). Abuse-related effects of all four compounds were evaluated in assays of intracranial self-stimulation (ICSS) in rats and cocaine discrimination in rats and monkeys, and none of the compounds reliably facilitated ICSS or substituted for cocaine. Anticocaine effects of the compound with highest selectivity to release DA/5HT versus NE (PAL-542) were tested in an assay of cocaine versus food choice in rhesus monkeys, and PAL-542 failed to reduce cocaine choice. These results suggests that potency to release NE has minimal influence on abuse liability of dual DA/5HT releasers, and reducing relative potency to release NE versus DA/5HT does not improve anticocaine efficacy.

**Evidence For A Role Of Transporter-Mediated Currents In the Depletion Of Brain Serotonin Induced By Serotonin Transporter Substrates**

Baumann MH, Bulling S, Benaderet TS, Saha K, Ayestas MA, Partilla JS, Ali SF, Stockner T, Rothman RB, Sandtner W, Sitte HH. *Neuropsychopharmacology*. 2014 May; 39(6): 1355-65.

Serotonin (5-HT) transporter (SERT) substrates like fenfluramine and 3,4-methylenedioxy-methamphetamine cause long-term depletion of brain 5-HT, while certain other substrates do not. The 5-HT deficits produced by SERT substrates are dependent upon transporter proteins, but the exact mechanisms responsible are unclear. Here, the authors compared the pharmacology of several SERT substrates: fenfluramine, d-fenfluramine, 1-(m-chlorophenyl)piperazine (mCPP) and 1-(m-trifluoromethylphenyl)piperazine (TFMPP), to establish relationships between acute drug mechanisms and the propensity for long-term 5-HT depletions. In vivo microdialysis was carried out in rat nucleus accumbens to examine acute 5-HT release and long-term depletion in the same subjects. In vitro assays were performed to measure efflux of [(3)H]5-HT in rat brain synaptosomes and transporter-mediated ionic currents in SERT-expressing *Xenopus* oocytes. When administered repeatedly to rats (6 mg/kg, i.p., four doses), all drugs produce large sustained elevations in extracellular 5-HT (>5-fold) with minimal effects on dopamine. Importantly, 2 weeks after dosing, only rats exposed to fenfluramine and d-fenfluramine display depletion of brain 5-HT. All test drugs evoke fluoxetine-sensitive efflux of [(3)H]5-HT from synaptosomes, but d-fenfluramine and its bioactive metabolite d-norfenfluramine induce significantly greater SERT-mediated currents than phenylpiperazines. These data confirm that drug-induced 5-HT release probably does not mediate 5-HT depletion. However, the magnitude of transporter-mediated inward current may be a critical factor in the cascade of events leading to 5-HT deficits. This hypothesis warrants further study, especially given the growing popularity of designer drugs that target SERT.

**Hybrid Dopamine Uptake Blocker-Serotonin Releaser Ligands: A New Twist On Transporter-Focused Therapeutics**

Blough BE, Landavazo A, Partilla JS, Baumann MH, Decker AM, Page KM, Rothman RB. *ACS Med Chem Lett*. 2014 Apr 15; 5(6): 623-7.

As part of their program to study neurotransmitter releasers, the authors report herein a class of hybrid dopamine reuptake inhibitors that display serotonin releasing activity. Hybrid compounds are interesting since they increase the design potential of transporter related compounds and represent a novel and unexplored strategy for therapeutic drug discovery. A series of N-alkylpropiofenones was synthesized and assessed for uptake inhibition and release activity using rat brain synaptosomes. Substitution on the aromatic ring yielded compounds that maintained hybrid activity, with the two disubstituted analogues (PAL-787 and PAL-820) having the most potent hybrid activity.

**Age Differences In (±) 3,4-Methylenedioxymethamphetamine (MDMA)-Induced Conditioned Taste Aversions and Monoaminergic Levels**

Cobuzzi JL, Siletti KA, Hurwitz ZE, Wetzell B, Baumann MH, Riley AL. *Dev Psychobiol*. 2014 May; 56(4): 635-46.

Preclinical work indicates that adolescent rats appear more sensitive to the rewarding effects and less sensitive to the aversive effects of abused drugs. The present investigation utilized the conditioned taste aversion (CTA) design to measure the relative aversive effects of (±)3,4-methylenedioxymethamphetamine (MDMA; 0, 1.0, 1.8, or 3.2mg/kg) in adolescent and adult Sprague-Dawley rats. After behavioral testing was complete, monoamine and associated metabolite levels in discrete brain regions were quantified using high-performance liquid chromatography coupled to electrochemical detection (HPLC-ECD) to determine if adolescent animals displayed a different neurochemical profile than did adult animals after being exposed to subcutaneous low doses of MDMA. Adolescent rats displayed less robust MDMA-induced taste aversions than adults

during acquisition and on a final two-bottle aversion test. MDMA at these doses had no consistent effect on monoamine levels in either age group, although levels did vary with age. The relative insensitivity of adolescents to MDMA's aversive effects may engender an increased vulnerability to MDMA abuse in this specific population.

## **Psychobiology Section**

**2-isoxazol-3-phenyltropane Derivatives of Cocaine: Molecular and Atypical System Effects at the Dopamine Transporter** Hiranita T, Wilkinson DS, Hong WC, Zou M-F, Kopajtic TA, Soto PL, Lupica CR, Newman AH, Katz JL. *Journal of Pharmacology and Experimental Therapeutics*, 2014; 349: 297-309.

The present study examined RTI-371 (3 $\beta$ -(4-methylphenyl)-2 $\beta$ -[3-(4-chlorophenyl)-isoxazol-5-yl]tropane), a phenyltropane cocaine analog with effects distinct from cocaine, and assessed potential mechanisms for those effects by comparison with its constitutional isomer, RTI-336 (3 $\beta$ -(4-chlorophenyl)-2 $\beta$ -[3-(4-methylphenyl)-isoxazol-5-yl]tropane). In mice RTI-371 was less effective than cocaine and RTI-336 in stimulating locomotion, and incompletely substituted (~60% maximum at 5-min or 1-hr post-injection) in a cocaine (10 mg/kg, i.p.)/saline discrimination procedure; RTI-336 completely substituted. In contrast to RTI-336, RTI-371 was not self-administered, and its pretreatment (1.0-10 mg/kg, i.p.) dose-dependently decreased maximal cocaine self-administration more potently than food-maintained responding. RTI-336 pretreatment dose-dependently left-shifted the cocaine self-administration dose-effect curve. Both RTI-336 and RTI-371 displaced [3H]WIN35,428 binding to striatal dopamine transporters (DATs) with  $K_i$  values of 10.8 and 7.81 nM, respectively, and had lower affinities at serotonin or norepinephrine transporters, or muscarinic and sigma receptors. The relative low affinity at these sites suggests the DAT as the primary target of RTI-371 with minimal contributions from these other targets. In biochemical assays probing the outward-facing DAT conformation, both RTI-371 and RTI-336 had effects similar to cocaine, suggesting little contribution of DAT conformation to the unique pharmacology of RTI-371. The locomotor-stimulant effects of RTI-371 (3.0-30 mg/kg, i.p.) were comparable in CB1R WT and KO mice, indicating that previously reported CB1 allosteric effects do not decrease cocaine-like effects of RTI-371. DAT occupancy *in vivo* was most rapid with cocaine and least with RTI-371. The slow apparent association rate may allow compensatory actions that in turn dampen cocaine-like stimulation, and give RTI-371 its unique pharmacological profile.

## **Clinical Pharmacology and Therapeutics Branch**

### **Chemistry and Drug Metabolism Section**

**Morphine and Codeine Concentrations In Human Urine Following Controlled Poppy Seeds Administration Of Known Opiate Content** Smith ML, Nichols DC, Underwood P, Fuller Z, Moser MA, LoDico C, Gorelick DA, Newmeyer MN, Concheiro M, Huestis MA. *Forensic Science International* 2014, e-pub May 14, 2014.

Opiates are an important component for drug testing due to their high abuse potential. Proper urine opiate interpretation includes ruling out poppy seed ingestion; however, detailed elimination studies after controlled poppy seed administration with known morphine and codeine doses are not available. Therefore, the authors investigated urine opiate pharmacokinetics after controlled oral

administration of uncooked poppy seeds with known morphine and codeine content. Participants were administered two 45 g oral poppy seed doses 8 h apart, each containing 15.7 mg morphine and 3 mg codeine. Urine was collected ad libitum up to 32 h after the first dose. Specimens were analyzed with the Roche Opiates II immunoassay at 2000 and 300 mg/L cutoffs, and the ThermoFisher CEDIA1 heroin metabolite (6-acetylmorphine, 6-AM) and Lin-Zhi 6-AM immunoassays with 10 mg/L cutoffs to determine if poppy seed ingestion could produce positive results in these heroin marker assays. In addition, all specimens were quantified for morphine and codeine by GC/MS. Participants (N = 22) provided 391 urine specimens over 32 h following dosing; 26.6% and 83.4% were positive for morphine at 2000 and 300 mg/L GC/MS cutoffs, respectively. For the 19 subjects who completed the study, morphine concentrations ranged from <300 to 7522 mg/L with a median peak concentration of 5239 mg/L. The median first morphine-positive urine sample at 2000 mg/L cutoff concentration occurred at 6.6 h (1.2–12.1), with the last positive from 2.6 to 18 h after the second dose. No specimens were positive for codeine at a cutoff concentration of 2000 mg/L, but 20.2% exceeded 300 mg/L, with peak concentrations of 658 mg/L (284–1540). The Roche Opiates II immunoassay had efficiencies greater than 96% for the 2000 and 300 mg/L cutoffs. The CEDIA 6-AM immunoassay had a specificity of 91%, while the Lin-Zhi assay had no false positive results. These data provide valuable information for interpreting urine opiate results.

#### **Cannabinoids In Oral Fluid By On-Site Immunoassay And By GC-MS Using Two Different Oral Fluid Collection Devices**

Desrosiers NA, Milman G, Mendu DR, Lee D, Barnes AJ, Gorelick DA, and Huestis MA. Anal Bioanal Chem. 2014, Jul; 406(17): 4117-28.

Oral fluid (OF) enables non-invasive sample collection for on-site drug testing, but performance of on-site tests with occasional and frequent smokers' OF to identify cannabinoid intake requires further evaluation. Furthermore, as far as the authors are aware, no studies have evaluated differences between cannabinoid disposition among OF collection devices with authentic OF samples after controlled cannabis administration. Fourteen frequent ( $\geq 4$  times per week) and 10 occasional (less than twice a week) adult cannabis smokers smoked one 6.8 %  $\Delta 9$ -tetrahydrocannabinol (THC) cigarette ad libitum over 10 min. OF was collected with the StatSure Saliva Sampler, Oral-Eze, and Draeger DrugTest 5000 test cassette before and up to 30 h after cannabis smoking. Test cassettes were analyzed within 15 min and gas chromatography–mass spectrometry cannabinoid results were obtained within 24 h. Cannabinoid concentrations with the StatSure and Oral-Eze devices were compared and times of last cannabinoid detection (tlast) and DrugTest 5000 test performance were assessed for different cannabinoid cutoffs. 11-nor-9-Carboxy-THC (THCCOOH) and cannabinol concentrations were significantly higher in Oral-Eze samples than in Stat-Sure samples. DrugTest 5000 tlast for a positive cannabinoid test were median (range) 12 h (4–24 h) and 21 h (1– $\geq 30$  h) for occasional and frequent smokers, respectively. Detection windows in screening and confirmatory tests were usually shorter for occasional than for frequent smokers, especially when including THCCOOH  $\geq 20$  ng L<sup>-1</sup> in confirmation criteria. No differences in tlast were observed between collection devices, except for THC  $\geq 2$   $\mu$ g L<sup>-1</sup>. The authors thus report significantly different THCCOOH and cannabinol, but not THC, concentrations between OF collection devices, which may affect OF data interpretation. The DrugTest 5000 on-site device had high diagnostic sensitivity, specificity and efficiency for cannabinoids

#### **Cannabis Withdrawal In Chronic, Frequent Cannabis Smokers During Sustained Abstinence Within A Closed Residential Environment**

Lee D, Schroeder JR, Karschner EL, Goodwin RS, Hirvonen J, Gorelick DA, Huestis MA. Am J Addict. 2014, May-Jun; 23(3): 234-42.

Chronic, frequent cannabis smokers may experience residual and offset effects, withdrawal, and

craving when abstaining from the drug. The authors characterized the prevalence, duration, and intensity of these effects in chronic frequent cannabis smokers during abstinence on a closed research unit. Non-treatment-seeking participants (N=29 on admission, 66% and 34% remaining after 2 and 4 weeks) provided subjective effects data. A battery of five instruments was computer-administered daily to measure psychological, sensory, and physical symptoms associated with cannabinoid intoxication and withdrawal. Plasma and oral fluid specimens were concurrently collected and analyzed for cannabinoids. Outcome variables were evaluated as change from admission (Day 0) with regression models. Most abstinence effects, including irritability and anxiety were greatest on Days 0-3 and decreased thereafter. Cannabis craving significantly decreased over time, whereas decreased appetite began to normalize on Day 4. Strange dreams and difficulty getting to sleep increased over time, suggesting intrinsic sleep problems in chronic cannabis smokers. Symptoms likely induced by residual drug effects were at maximum intensity on admission and positively correlated with plasma and oral fluid cannabinoid concentrations on admission but not afterward; these symptoms showed overall prevalence higher than cannabis withdrawal symptoms. The combined influence of residual/offset drug effects, withdrawal, and craving was observed in chronic cannabis smokers during monitored abstinence. Abstinence symptoms were generally more intense in the initial phase, implying importance of early intervention in cannabis quit attempts. Sleep disturbance persisting for an extended period suggests that hypnotic medications could be beneficial in treating cannabis dependence.

**Metabolism Of RCS-8, A Synthetic Cannabinoid With Cyclohexyl Structure, In Human Hepatocytes By High-Resolution MS** Wohlfarth A, Pang S, Zhu M, Gandhi AS, Scheidweiler KB, Huestis MA. *Bioanalysis*. 2014, May; 6(9): 1187-200.

Since 2008, synthetic cannabinoids are major new designer drugs of abuse. They are extensively metabolized and excreted in urine, but limited human metabolism data are available. As there are no reports on the metabolism of RCS-8, a scheduled phenylacetylindole synthetic cannabinoid with an N-cyclohexylethyl moiety, the authors investigated metabolism of this new designer drug by human hepatocytes and high resolution MS. After human hepatocyte incubation with RCS-8, samples were analyzed on a TripleTOF 5600+ mass spectrometer with time-of-flight survey scan and information-dependent acquisition triggered product ion scans. Data mining of the accurate mass full scan and product ion spectra employed different data processing algorithms. More than 20 RCS-8 metabolites were identified, products of oxidation, demethylation, and glucuronidation. Major metabolites and targets for analytical methods were hydroxyphenyl RCS-8 glucuronide, a variety of hydroxycyclohexyl-hydroxyphenyl RCS-8 glucuronides, hydroxyphenyl RCS-8, as well as the demethyl-hydroxycyclohexyl RCS-8 glucuronide.

**3,4-Methylenedioxypyrovalerone (MDPV) and Metabolites Quantification In Human and Rat Plasma By Liquid Chromatography-High Resolution Mass Spectrometry** Anizan S, Ellefsen K, Concheiro M, Suzuki M, Rice KC, Baumann MH, Huestis MA. *Anal Chim Acta*. 2014, May 27; 827: 54-63.

Synthetic cathinones are recreational drugs that mimic the effects of illicit stimulants like cocaine, amphetamine or Ecstasy. Among the available synthetic cathinones in the United States, 3,4-methylenedioxypyrovalerone (MDPV) is commonly abused and associated with dangerous side effects. MDPV is a dopamine transporter blocker 10-fold more potent than cocaine as a locomotor stimulant in rats. Previous in vitro and in vivo studies examining MDPV metabolism reported 3,4-dihydroxypyrovalerone (3,4-catechol-PV) and 4-hydroxy-3-methoxypyrovalerone (4-OH-3-MeO-PV) as the two primary metabolites. The authors developed and validated a liquid chromatography-high resolution mass spectrometry method to quantify MDPV and its primary metabolites in 100 µL

human and rat plasma. Plasma hydrolysis was followed by protein precipitation before analysis. Limits of detection were 0.1  $\mu\text{g L}^{-1}$ , with linear ranges from 0.25 to 1000  $\mu\text{g L}^{-1}$ . Process efficiency, matrix effect, total imprecision (%CV) and accuracy (%target) were 36-93%, from -8 to 12%, 2.1 to 7.3% and 86 to 109%, respectively. MDPV and metabolites were stable at room temperature for 24 h, 4 °C for 72 h and after 3 freeze-thaw cycles with less than 10% variability. Human-rat plasma cross validation demonstrated that rat plasma could be accurately quantified against a human plasma calibration curve. As proof of this method, rat plasma specimens were analyzed after intraperitoneal and subcutaneous dosing with MDPV (0.5 mg kg<sup>-1</sup>). MDPV, 3,4-catechol-PV and 4-OH-3-MeO-PV concentrations ranged from not detected to 107.5  $\mu\text{g L}^{-1}$  prior to and up to 8h after dosing. This method provides a simultaneous quantification of MDPV and two metabolites in plasma with good selectivity and sensitivity.

**High-Resolution Mass Spectrometric Metabolite Profiling Of A Novel Synthetic Designer Drug, N-(Adamantan-1-Yl)-1-(5-Fluoropentyl)-1H-Indole-3-Carboxamide (STS-135), Using Cryopreserved Human Hepatocytes and Assessment Of Metabolic Stability With Human Liver Microsomes** Gandhi AS, Wohlfarth A, Zhu M, Pang S, Scheidweiler KB, Huestis MA. Drug Testing and Analysis 2014, May 14.

N-(Adamantan-1-yl)-1-(5-fluoropentyl)-1H-indole-3-carboxamide (STS-135) is a new synthetic cannabinoid in herbal incense products discussed on Internet drug user forums and identified in police seizures. To date, there are no STS-135 clinical or in vitro studies identifying STS-135 metabolites. However, characterizing STS-135 metabolism is critical because synthetic cannabinoid metabolites can possess pharmacological activity and parent compounds are rarely detectable in urine. To characterize the metabolite profile, human hepatocytes were incubated with 10  $\mu\text{mol/L}$  STS-135 for up to 3 h. High-resolution mass spectrometry with software-assisted data mining identified 29 STS-135 metabolites. Less than 25% of STS-135 parent compound remained after 3 h incubation. Primary metabolites were generated by mono-, di- or trihydroxylation with and without ketone formation, dealkylation, and oxidative defluorination of N-fluoropentyl side chain or possible oxidation to carboxylic acid, some of them further glucuronidated. Hydroxylations occurred mainly on the aliphatic adamantane ring and less commonly on the N-pentyl side chain. At 1 h, phase I metabolites predominated, while at 3 h, phase II metabolites were present in higher amounts. The major metabolites were monohydroxy STS-135 (M25) and dihydroxy STS-135 (M21), both hydroxylated on the adamantane system. Moreover, metabolic stability of STS-135 (1  $\mu\text{mol/L}$ ) was assessed in human liver microsomes experiments. The in vitro half-life of STS-135 was 3.1 $\pm$ 0.2 min and intrinsic clearance ( $CL_{int}$ ) was 208.8 mL $\cdot$ min<sup>-1</sup> kg<sup>-1</sup>. This is the first report characterizing STS-135 hepatic metabolic pathways. These data provide potential urinary targets to document STS-135 intake in clinical and forensic settings and potential candidates for pharmacological testing.

**Evaluation Of A Homogenous Enzyme Immunoassay For The Detection Of Synthetic Cannabinoids In Urine** Barnes AJ, Young S, Spinelli E, Martin TM, Klette KL, Huestis MA. Forensic Sci Int. 2014, Apr 24; 241C: 27-34.

The recent emergence and widespread availability of many new synthetic cannabinoids support the need for an accurate and high-throughput urine screen for these new designer drugs. The authors evaluated performance of the immunalysis homogeneous enzyme immunoassay (HEIA) to sensitively, selectively, and rapidly identify urinary synthetic cannabinoids. 2443 authentic urine samples were analyzed with the HEIA that targets JWH-018 N-pentanoic acid, and a validated LC-MS/MS method for 29 synthetic cannabinoids and metabolites. Semi-quantitative HEIA results were obtained, permitting performance evaluation at and around three cutoffs (5, 10 and 20 $\mu\text{g/L}$ ),

and diagnostic sensitivity, specificity and efficiency determination. Performance challenges at  $\pm 25$  and  $\pm 50\%$  of each cutoff level, cross-reactivity and interferences also were evaluated. Sensitivity, specificity, and efficiency of the immunoassay HEIA K2 Spice kit with the manufacturer's recommended  $10\mu\text{g/L}$  cutoff were 75.6%, 99.6% and 96.8%, respectively, as compared to the reference LC-MS/MS method with limits of detection of 0.1- $10\mu\text{g/L}$ . Performance at  $5\mu\text{g/L}$  was 92.2%, 98.1% and 97.4%, and for the  $20\mu\text{g/L}$  cutoff were 62.9%, 99.7% and 95.4%. Semi-quantitative results for in-house prepared standards were obtained from 2.5- $30\mu\text{g/L}$ , and documented acceptable linearity from 5- $25\mu\text{g/L}$ , with inter-day imprecision  $<30\%$  ( $n=17$ ). Thirteen of 74 synthetic cannabinoids evaluated were classified as highly cross-reactive ( $\geq 50\%$  at  $10\mu\text{g/L}$ ); 4 showed moderate cross-reactivity (10-50% at  $10\mu\text{g/L}$ ), 30 low cross-reactivity ( $<10\%$  at  $500\mu\text{g/L}$ ), and 27  $<1\%$  cross-reactivity at  $500\mu\text{g/L}$ . There was no interference from 102 investigated compounds. Only a mixture containing  $1000\mu\text{g/L}$  each of buprenorphine/norbuprenorphine produced a positive result above our proposed cutoff ( $5\mu\text{g/L}$ ) but below the manufacturer's recommended cutoff concentration ( $10\mu\text{g/L}$ ). The Immunoassay HEIA K2 Spice kit required no sample preparation, had a high-throughput, and acceptable sensitivity, specificity and efficiency, offering a viable method for screening synthetic cannabinoids in urine that cross-react with JWH-018 N-pentanoic acid antibodies.

**Plasma Cannabinoid Concentrations During Dronabinol Pharmacotherapy For Cannabis Dependence** Milman G, Bergamaschi MM, Lee D, Mendu DR, Barnes AJ, Vandrey R, Huestis MA. *Ther Drug Monit.* 2014, Apr; 36(2): 218-24.

Recently, high-dose oral synthetic delta-9-tetrahydrocannabinol (THC) was shown to alleviate cannabis withdrawal symptoms. The present data describe cannabinoid pharmacokinetics in chronic, daily cannabis smokers who received high-dose oral THC pharmacotherapy and later a smoked cannabis challenge. Eleven daily cannabis smokers received 0, 30, 60, or 120 mg/d THC for four 5-day medication sessions, each separated by 9 days of ad libitum cannabis smoking. On the fifth day, participants were challenged with smoking one 5.9% THC cigarette. Plasma collected on the first and fifth days was quantified by two-dimensional gas chromatography mass spectrometer for THC, 11-hydroxy-THC (11-OH-THC), and 11-nor-9-carboxy-THC (THCCOOH). Linear ranges (ng/mL) were 0.5-100 for THC, 1-50 for 11-OH-THC, and 0.5-200 for THCCOOH. During placebo dosing, THC, 11-OH-THC, and THCCOOH concentrations consistently decreased, whereas all cannabinoids increased dose dependently during active dronabinol administration. THC increase over time was not significant after any dose, 11-OH-THC increased significantly during the 60- and 120-mg/d doses, and THCCOOH increased significantly only during the 120-mg/d dose. THC, 11-OH-THC, and THCCOOH concentrations peaked within 0.25 hours after cannabis smoking, except after 120 mg/d THC when THCCOOH peaked 0.5 hours before smoking. The significant withdrawal effects noted during placebo dronabinol administration were supported by significant plasma THC and 11-OH-THC concentration decreases. During active dronabinol dosing, significant dose-dependent increases in THC and 11-OH-THC concentrations support withdrawal symptom suppression. THC concentrations after cannabis smoking were only distinguishable from oral THC doses for 1 hour, too short a period to feasibly identify cannabis relapse. THCCOOH/THC ratios were higher 14 hours after overnight oral dronabinol abstinence but cannot distinguish oral THC dosing from the smoked cannabis intake.

## Molecular Neuropsychiatry Research Branch

**Stress, Sex, and Addiction: Potential Roles Of Corticotropin-Releasing Factor, Oxytocin, and Arginine-Vasopressin** Bisagno V1, Cadet JL. Behav Pharmacol. 2014 Jun 19. [Epub ahead of print].

Stress sensitivity and sex are predictive factors for the development of neuropsychiatric disorders. Life stresses are not only risk factors for the development of addiction but also are triggers for relapse to drug use. Therefore, it is imperative to elucidate the molecular mechanisms underlying the interactions between stress and drug abuse, as an understanding of this may help in the development of novel and more effective therapeutic approaches to block the clinical manifestations of drug addiction. The development and clinical course of addiction-related disorders do appear to involve neuroadaptations within neurocircuitries that modulate stress responses and are influenced by several neuropeptides. These include corticotropin-releasing factor, the prototypic member of this class, as well as oxytocin and arginine-vasopressin that play important roles in affiliative behaviors. Interestingly, these peptides function to balance emotional behavior, with sexual dimorphism in the oxytocin/arginine-vasopressin systems, a fact that might play an important role in the differential responses of women and men to stressful stimuli and the specific sex-based prevalence of certain addictive disorders. Thus, this review aims to summarize (i) the contribution of sex differences to the function of dopamine systems, and (ii) the behavioral, neurochemical, and anatomical changes in brain stress systems.

**Transcriptional and Epigenetic Substrates Of Methamphetamine Addiction and Withdrawal: Evidence From A Long-Access Self-Administration Model In the Rat** Cadet JL, Brannock C, Jayanthi S, Krasnova IN. Mol Neurobiol. 2014 Jun 18. [Epub ahead of print].

Methamphetamine use disorder is a chronic neuropsychiatric disorder characterized by recurrent binge episodes, intervals of abstinence, and relapses to drug use. Humans addicted to methamphetamine experience various degrees of cognitive deficits and other neurological abnormalities that complicate their activities of daily living and their participation in treatment programs. Importantly, models of methamphetamine addiction in rodents have shown that animals will readily learn to give themselves methamphetamine. Rats also accelerate their intake over time. Microarray studies have also shown that methamphetamine taking is associated with major transcriptional changes in the striatum measured within a short or longer time after cessation of drug taking. After a 2-h withdrawal time, there was increased expression of genes that participate in transcription regulation. These included cyclic AMP response element binding (CREB), ETS domain-containing protein (ELK1), and members of the FOS family of transcription factors. Other genes of interest include brain-derived neurotrophic factor (BDNF), tyrosine kinase receptor, type 2 (TrkB), and synaptophysin. Methamphetamine-induced transcription was found to be regulated via phosphorylated CREB-dependent events. After a 30-day withdrawal from methamphetamine self-administration, however, there was mostly decreased expression of transcription factors including junD. There was also downregulation of genes whose protein products are constituents of chromatin-remodeling complexes. Altogether, these genome-wide results show that methamphetamine abuse might be associated with altered regulation of a diversity of gene networks that impact cellular and synaptic functions. These transcriptional changes might serve as triggers for the neuropsychiatric presentations of humans who abuse this drug. Better understanding of the way that gene products interact to cause methamphetamine addiction will help to develop better pharmacological treatment of methamphetamine addicts.

## Chemical Biology Research Branch

### Drug Design and Synthesis Section

#### **The Role Of 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub> and mGlu<sub>2</sub> Receptors In the Behavioral Effects Of Tryptamine Hallucinogens N,N-Dimethyltryptamine and N,N-Diisopropyltryptamine In Rats and Mice** Carbonaro TM, Eshleman AJ, Forster MJ, Cheng K, Rice KC, Gatch MB.

Psychopharmacology, 2014, e-pub Jul 3, 2014.

Serotonin 5-HT<sub>2A</sub> and 5-HT<sub>2C</sub> receptors are thought to be the primary pharmacological mechanisms for serotonin-mediated hallucinogenic drugs, but recently there has been interest in metabotropic glutamate (mGluR<sub>2</sub>) receptors as contributors to the mechanism of hallucinogens. The present study assesses the role of these 5-HT and glutamate receptors as molecular targets for two tryptamine hallucinogens, N,N-dimethyltryptamine (DMT) and N,N-diisopropyltryptamine (DiPT). Drug discrimination, head twitch, and radioligand binding assays were used. A 5-HT<sub>2AR</sub> inverse agonist (MDL100907), 5-HT<sub>2CR</sub> antagonist (SB242084), and mGluR<sub>2/3</sub> agonist (LY379268) were tested for their ability to attenuate the discriminative stimulus effects of DMT and DiPT; an mGluR<sub>2/3</sub> antagonist (LY341495) was tested for potentiation. MDL100907 was used to attenuate head twitches induced by DMT and DiPT. Radioligand binding studies and inositol-1-phosphate (IP-1) accumulation were performed at the 5-HT<sub>2CR</sub> for DiPT. MDL100907 fully blocked the discriminative stimulus effects of DMT, but only partially blocked DiPT. SB242084 partially attenuated the discriminative stimulus effects of DiPT, but produced minimal attenuation of DMT's effects. LY379268 produced potent, but only partial blockade of the discriminative stimulus effects of DMT. LY341495 facilitated DMT- and DiPT-like effects. Both compounds elicited head twitches (DiPT > DMT) which were blocked by MDL1000907. DiPT was a low-potency full agonist at 5-HT<sub>2CR</sub> in vitro. The 5-HT<sub>2AR</sub> likely plays a major role in mediating the effects of both compounds. 5-HT<sub>2C</sub> and mGluR<sub>2</sub> receptors likely modulate the discriminative stimulus effects of both compounds to some degree.

#### **Synthesis and Immunological Effects Of Heroin Vaccines** Li F, Cheng K, Antoline JF, Iyer MR, Matyas GR, Torres OB, Jalah R, Beck Z, Alving CR, Parrish DA, Deschamps JR, Jacobson AE, Rice KC. Org Biomol Chem. 2014, e-pub Jul 4, 2014.

Three haptens have been synthesized with linkers for attachment to carrier macromolecules at either the piperidino-nitrogen or via an introduced 3-amino group. Two of the haptens, with a 2-oxopropyl functionality at either C<sub>6</sub>, or at both the C<sub>3</sub> and C<sub>6</sub> positions on the 4,5-epoxymorphinan framework, as well as the third hapten (DiAmHap) with diamido moieties at both the C<sub>3</sub> and C<sub>6</sub> positions, should be much more stable in solution, or in vivo in a vaccine, than a hapten with an ester in one of those positions, as found in many heroin-based haptens. A "classical" opioid synthetic scheme enabled the formation of a 3-amino-4,5-epoxymorphinan which could not be obtained using palladium chemistry. The authors' vaccines are aimed at the reduction of the abuse of heroin and, as well, at the reduction of the effects of its predominant metabolites, 6-acetylmorphine and morphine. One of the haptens, DiAmHap, has given interesting results in a heroin vaccine and is clearly more suited for the purpose than the other two haptens.

**Automated Touch Screen Device For Recording Complex Rodent Behaviors** Mabrouk OS, Dripps IJ, Ramani S, Chang C, Han JL, Rice KC, Jutkiewicz EM. *J Neurosci Methods*, 2014, 233C, 129-36.

Monitoring mouse behavior is a critical step in the development of modern pharmacotherapies. Here the authors describe the application of a novel method that utilizes a touch display computer (tablet) and software to detect, record, and report fine motor behaviors. A consumer-grade tablet device is placed in the bottom of a specially made acrylic cage allowing the animal to walk on the device (MouseTrapp). The authors describe its application in open field (for general locomotor studies) which measures step lengths and velocity. The device can perform light-dark (anxiety) tests by illuminating half of the screen and keeping the other half darkened. A divider is built into the lid of the device allowing the animal free access to either side. Treating mice with amphetamine and the delta opioid peptide receptor agonist SNC80 stimulated locomotor activity on the device. Amphetamine increased step velocity but not step length during its peak effect (40-70min after treatment), thus indicating detection of subtle amphetamine-induced effects. Animals showed a preference (74% of time spent) for the darkened half compared to the illuminated side. Animals were videotaped within the chamber to compare quadrant crosses to detect motion on the device. The slope, duration and magnitude of quadrant crosses tightly correlated with overall locomotor activity as detected by MouseTrapp. The authors suggest that modern touch display devices such as MouseTrapp will be an important step toward automation of behavioral analyses for characterizing phenotypes and drug effects.

**3,4-Methylenedioxypyrovalerone (MDPV) and Metabolites Quantification In Human and Rat Plasma By Liquid Chromatography-High Resolution Mass Spectrometry** Anizan S, Ellefsen K, Concheiro M, Suzuki M, Rice KC, Baumann MH, Huestis MA. *Anal Chim Acta*, 2014, 827, 54-63.

Synthetic cathinones are recreational drugs that mimic the effects of illicit stimulants like cocaine, amphetamine or Ecstasy. Among the available synthetic cathinones in the United States, 3,4-methylenedioxypyrovalerone (MDPV) is commonly abused and associated with dangerous side effects. MDPV is a dopamine transporter blocker 10-fold more potent than cocaine as a locomotor stimulant in rats. Previous in vitro and in vivo studies examining MDPV metabolism reported 3,4-dihydroxyprovalerone (3,4-catechol-PV) and 4-hydroxy-3-methoxyprovalerone (4-OH-3-MeO-PV) as the two primary metabolites. The authors developed and validated a liquid chromatography-high resolution mass spectrometry method to quantify MDPV and its primary metabolites in 100  $\mu$ L human and rat plasma. Plasma hydrolysis was followed by protein precipitation before analysis. Limits of detection were 0.1  $\mu$ g L<sup>(-1)</sup>, with linear ranges from 0.25 to 1000  $\mu$ g L<sup>(-1)</sup>. Process efficiency, matrix effect, total imprecision (%CV) and accuracy (%target) were 36-93%, from -8 to 12%, 2.1 to 7.3% and 86 to 109%, respectively. MDPV and metabolites were stable at room temperature for 24 h, 4 °C for 72 h and after 3 freeze-thaw cycles with less than 10% variability. Human-rat plasma cross validation demonstrated that rat plasma could be accurately quantified against a human plasma calibration curve. As proof of this method, rat plasma specimens were analyzed after intraperitoneal and subcutaneous dosing with MDPV (0.5 mg kg<sup>(-1)</sup>). MDPV, 3,4-catechol-PV and 4-OH-3-MeO-PV concentrations ranged from not detected to 107.5  $\mu$ g L<sup>(-1)</sup> prior to and up to 8h after dosing. This method provides a simultaneous quantification of MDPV and two metabolites in plasma with good selectivity and sensitivity.

### **Synthesis Of Enantiopure 10-Nornaltrexones In The Search For Toll-Like Receptor 4**

**Antagonists and Opioid Ligands** Selfridge BR, Deschamps JR, Jacobson, AE Rice KC. J Org Chem, 2014, 79(11), 5007-18.

10-Nornaltrexones (3-(cyclopropylmethyl)-4a,9-dihydroxy-2,3,4,4a,5,6-hexahydro-1H-benzofuro[3,2-e]isoquinolin-7(7aH)-one, 1) have been underexploited in the search for better opioid ligands, and their enantiomers have been unexplored. The synthesis of trans-isoquinolinone 2 (4-aH, 9-O-trans-9-methoxy-3-methyl-2,3,4,4a,5,6-hexahydro-1H-benzofuro[3,2-e]isoquinolin-7(7aH)-one) was achieved through a nonchromatographic optimized synthesis of the intermediate pyridinyl compound 12. Optical resolution was carried out on 2, and each of the enantiomers were used in efficient syntheses of the "unnatural" 4aR,7aS,12bR-(+)-1) and its "natural" enantiomer (-)-1. Addition of a 14-hydroxy (the 4a-hydroxy) group in the enantiomeric isoquinolinones, (+)- and (-)-2), gave (+)- and (-)-10-nornaltrexones. A structurally unique tetracyclic enamine, (12bR)-7,9-dimethoxy-3-methyl-1,2,3,7-tetrahydro-7,12b-methanobenzo[2,3]oxocino[5,4-c]pyridine, was found as a byproduct in the syntheses and offers a different opioid-like skeleton for future study.

### **Wistar Rats Acquire and Maintain Self-Administration Of 20 % Ethanol Without Water Deprivation, Saccharin/Sucrose Fading, Or Extended Access Training**

Augier E, Flanigan M, Dulman RS, Pincus A, Schank JR, Rice KC, Kejun C, Heilig M, Tapocik JD. Psychopharmacology, 2014, e-pub May 25, 2014.

Operant self-administration (SA) is an important model of motivation to consume ethanol (EtOH), but low rates of voluntary consumption in rats are thought to necessitate water deprivation and saccharin/sucrose fading for acquisition of responding. Here, the authors sought to devise an effective model of SA that does not use water deprivation or saccharin/sucrose fading. First, they tested if Wistar rats would acquire and maintain SA behavior of 20 % EtOH under two conditions, water deprivation (WD) and non-water deprivation (NWD). Second, they tested the efficacy of our SA procedure by confirming a prior study which found that the NK1 antagonist L822429 specifically blocked stress-induced reinstatement of EtOH seeking but not SA. Finally, they assessed the effect of naltrexone, an FDA-approved medication for alcohol dependence that has been shown to suppress EtOH SA in rodents. Lever presses (LPs) and rewards were consistent with previous reports that utilized WD and saccharin/sucrose fading. Similar to previous findings, the authors found that L822429 blocked stress-induced reinstatement but not baseline SA of 20 % EtOH. Moreover, naltrexone dose-dependently decreased alcohol intake and motivation to consume alcohol for rats that are self-administering 20 % EtOH. These findings provide a method for voluntary oral EtOH SA in rats that is convenient for experimenters and eliminates the potential confound of sweeteners in EtOH-operant SA studies. Unlike models that use intermittent access to 20 % EtOH, this method does not induce escalation, and based on pharmacological experiments, it appears to be driven by the positive reinforcing effects of EtOH.

### **Effects Of Corticotrophin-Releasing Factor Receptor 1 Antagonists On Amyloid-B and Behavior In Tg2576 Mice**

Dong, H, Wang S, Zeng Z, Li F, Montalvo-Ortiz J, Tucker C, Akhtar S, Shi J, Meltzer HY, Rice KC, Csernansky JG. Psychopharmacology, 2014, e-pub May 27, 2014.

Previous studies indicate that psychosocial stressors could accelerate amyloid- $\beta$  ( $A\beta$ ) levels and accelerate plaque deposition in mouse models of Alzheimer disease (AD). Stressors enhanced the release of corticotrophin-releasing factor (CRF), and exogenous CRF administration mimicked the effects of stress on  $A\beta$  levels in mouse models of AD. However, whether CRF receptor 1 (CRF1) antagonists could influence the stress-induced acceleration of an AD-like process in mouse models has not been well studied. The authors sought to examine whether CRF1 antagonists inhibit the effects of isolation stress on tissue  $A\beta$  levels,  $A\beta$  plaque deposition, and behaviors related to anxiety

and memory in Tg2576 mice, and to investigate the molecular mechanism underlying such effects. Cohorts of Tg2576 mouse pups were isolated or group-housed at 21 days of age, and then the subgroups of these cohorts received daily intraperitoneal injections of the CRF1 antagonists, antalarmin or R121919 (5, 10, and 20 mg/kg), or vehicle for 1 week. Other cohorts of Tg2576 mouse pups were isolated or group-housed at 21 days of age, and then at 4 months of age, subgroups of these mice were administered antalarmin (20 mg/kg) or vehicle in their drinking water for 6 months. Finally, cultured primary hippocampal neurons from regular Tg2576 pups (P0) were incubated with CRF (0.1, 1, and 10 nM), antalarmin (100 nM) or H-89 (1  $\mu$ M) for 48 h. Brain tissues or cultured neurons were collected for histological and biochemical analyses, and behavioral measures were collected in the cohorts of mice that were chronically stressed. Administration of antalarmin at 20 mg/kg dose for 1 week significantly reduced A $\beta$ 1-42 levels in isolation stressed mice. Administration of antalarmin for 6 months significantly decreased plasma corticosterone levels, tissue A $\beta$ 1-42 levels, and A $\beta$  plaque deposition in the brain and blocked the effects of isolation stress on behaviors related to anxiety and memory. Finally, incubation of neurons with 100 nM antalarmin inhibited the ability of 10 nM CRF to increase A $\beta$ 1-42 levels and protein kinase A II $\beta$  expression. The effect of CRF1 on A $\beta$ 1-42 levels was also diminished by treatment with H-89, a c-AMP/PKA inhibitor. These results suggest that CRF1 antagonists can slow an AD-like process in Tg2576 mice and that the c-AMP/PKA signaling pathway may be involved in this effect.

### **Patent Applications Filed**

Kunos G, Iyer MR, Resa C, and Rice KC: Cannabinoid Receptor Mediating Compounds. U.S. Provisional Patent Appl. 61/991,333 was filed May 9, 2014.

### **Molecular Neurobiology Branch**

#### **Cell Adhesion Molecules: Druggable Targets For Modulating The Connectome and Brain Disorders?** Uhl GR, Drgonova J. *Neuropsychopharmacology*. 2014 Jan;39(1):235. doi:

10.1038/npp.2013.240. PMID: 24317312.

Since the brain develops and modulates more than a trillion connections in ways that depend fundamentally on ligand recognition mediated by cell adhesion molecules (CAMs), understanding the CAM language for establishing and shaping brain connections is key to understanding the connectome. Variants in CAM genes have been associated with addiction and other interesting brain phenotypes; tests of a growing number of mouse models of altered CAM expression support many of their associations with addiction human disorders and phenotypes. We should thus think about CDH13, PTPRD, and other CAMs as potentially druggable targets for modulating brain phenotypes, establish robust screening assays, test libraries of small-molecule ligands for in vitro effects, and test for in vivo effects of lead and more optimized structures. Small molecules that recognize members of several of these CAM subfamilies can provide valuable starting points. Disease association and mouse model data can provide targets and estimates of potential toxicities. Data for the detailed pattern of CAM expression in brain, and in other organs, can also help us to estimate the specificity of possible CAM ligands. Studies in conditional knockout mice will help to define the contributions of developmental vs adult CAM expression to disease phenotypes. CAMs may be among the most promising and understudied druggable targets for modulating the connectome and influencing brain disorders.

**Specific Regions Display Altered Gray Matter Volume In M-Opioid Receptor Knockout (MOP-KO) Mice: MRI Voxel - Based Morphometry**

Sasaki K, Sumiyoshi A, Nonaka H, Kasahara Y, Ikeda K, Hall FS, Uhl GR, Watanabe M, Kawashima R, Sora I. *Br J Pharmacol*. 2014 Jun 10. doi: 10.1111/bph.12807. [Epub ahead of print] PMID: 24913308.

$\mu$ -opiate receptor knockout mice display several behavioral differences from wild-type (WT) littermates including differential responses to nociceptive stimuli. Brain structural changes have been tied to behavioral alternations noted in transgenic mice with targeting of different genes. The authors thus assessed the brain structure of MOP-KO mice using MRI-voxel based morphometry (VBM) and histological methods. The knockout mice display robust increases in regional gray matter volume in olfactory bulb, several hypothalamic nuclei, periaqueductal gray (PAG), and several cerebellar areas; most confirmed by VBM analysis. The largest increases in gray matter volume were detected in the glomerular layer of the olfactory bulb, arcuate nucleus of hypothalamus, ventrolateral PAG (VLPAG) and cerebellar regions that include paramedian and cerebellar lobules. Histological analyses confirmed several of these results, with increased VLPAG cell numbers and increased thickness of the olfactory bulb granule cell layer and cerebellar molecular and granular cell layers. Deleting expression of the mu receptor gene thus causes previously undescribed structural changes in specific brain regions, but not in all regions with high receptor densities (e.g. thalamus, nucleus accumbens) or that exhibit adult neurogenesis (e.g. hippocampus). Volume differences in hypothalamus and PAG may relate to behavioral alternations that include the hyperalgesia. Although the precise relationship between volume change and receptor deletion could not be determined based on this study alone, these findings suggest that levels of mu receptor expression may influence a broader range of neural structure and function in humans than previously suspected.

**Developmental Alterations In Anxiety and Cognitive Behavior In Serotonin Transporter**

**Mutant Mice** Sakakibara Y, Kasahara Y, Hall FS, Lesch KP, Murphy DL, Uhl GR, Sora I. *Psychopharmacology (Berl)*. 2014 Apr 13. [Epub ahead of print] PMID: 24728652.

Heterozygous (SERT+/-) and homozygous (SERT-/-) SERT mutant mice are valuable tools for understanding the mechanisms of altered SERT levels. Although these genetic effects are well investigated in adulthood, the developmental trajectory of altered SERT levels for behavior has not been investigated. The authors assessed anxiety-like and cognitive behaviors in SERT mutant mice in early adolescence and adulthood to examine the developmental consequences of reduced SERT levels. Spine density of pyramidal neurons was also measured in corticolimbic brain regions. Adult SERT-/- mice exhibited increased anxiety-like behavior, but these differences were not observed in early adolescent SERT-/- mice. Conversely, SERT+/- and SERT-/- mice did display higher spontaneous alternation during early adolescence and adulthood. SERT+/- and SERT-/- also exhibited greater neuronal spine densities in the orbitofrontal but not the medial prefrontal cortices. Adult SERT-/- mice also showed an increased spine density in the basolateral amygdala. Developmental alterations of the serotonergic system caused by genetic inactivation of SERT can have different influences on anxiety-like and cognitive behaviors through early adolescence into adulthood, which may be associated with changes of spine density in the prefrontal cortex and amygdala. The altered maturation of serotonergic systems may lead to specific age-related vulnerabilities to psychopathologies that develop during adolescence.

**Agmatine (Decarboxylated L-Arginine), A Putative Neuromodulator, Affected Selected Aspects Agmatine Attenuates Methamphetamine-Induced Hyperlocomotion and Stereotyped Behavior In Mice**

Kitanaka N, Kitanaka J, Hall FS, Uhl GR, Watabe K, Kubo H, Takahashi H, Tanaka K, Nishiyama N, Takemura M. Behav Pharmacol. 2014 Apr;25(2):158-65. doi: 10.1097/FBP.0000000000000030. PMID: 24557322.

Agmatine pretreatment produced a dose-dependent attenuation of locomotion and the total incidence of stereotyped behavior induced by a low dose of METH (5 mg/kg). The stereotypy induced by this dose was predominantly characterized by stereotyped sniffing. Agmatine did not affect the total incidence of stereotypy induced by a higher dose of METH (10 mg/kg) but it significantly reduced stereotyped biting while increasing stereotyped sniffing and persistent locomotion. Pretreatment with the putative agmatinase inhibitor piperazine-1-carboxamide had no effect on locomotion or stereotypy induced by METH, suggesting that endogenous agmatine may not regulate the METH action.

**Smoking Quit Success Genotype Score Predicts Quit Success and Distinct Patterns Of Developmental Involvement With Common Addictive Substances**

Uhl GR, Walther D, Musci R, Fisher C, Anthony JC, Storr CL, Behm FM, Eaton WW, Ialongo N, Rose JE. Mol Psychiatry. 2014 Jan;19(1):50-4. doi:10.1038/mp.2012.155. PMID: 23128154.

Genotype scores that predict relevant clinical outcomes may detect other disease features and help direct prevention efforts. The authors validate a previously established v1.0 smoking cessation quit success genotype score and describe striking differences in the score in individuals who display differing developmental trajectories of use of common addictive substances. In a cessation study, v1.0 genotype scores predicted ability to quit with good p values and area under receiver-operating characteristic curve. About 43% vs 13% quit in the upper vs lower genotype score terciles. Latent class growth analyses of a developmentally assessed sample identified three latent classes based on substance use. Higher v1.0 scores were associated with (a) higher probabilities of participant membership in a latent class that displayed low use of common addictive substances during adolescence and (b) lower probabilities of membership in a class that reported escalating use. These results indicate that: (a) we have identified genetic predictors of smoking cessation success, (b) genetic influences on quit success overlap with those that influence the rate at which addictive substance use is taken up during adolescence and (c) individuals at genetic risk for both escalating use of addictive substances and poor abilities to quit may provide especially urgent focus for prevention efforts.

**A Novel Synthesis: Influences Of Addiction Vulnerability Gene Variants On Dose-Response Relationships For Addictive Substances**

Uhl GR, Drgonova J, Hall FS. Pharmacol Ther. 2014 Mar; 141(3): 335-46. doi: 10.1016/j.pharmthera.2013.10.013.PMID: 24189489.

Dose-response relationships for most addictive substances are "inverted U"-shaped. Addictive substances produce both positive features that include reward, euphoria, anxiolysis, withdrawal-relief, and negative features that include aversion, dysphoria, anxiety and withdrawal symptoms. A simple model differentially associates ascending and descending limbs of dose-response curves with rewarding and aversive influences, respectively. However, Diagnostic and Statistical Manual (DSM) diagnoses of substance dependence fail to incorporate dose-response criteria and don't directly consider balances between euphoric and dysphoric drug effects. Classical genetic studies document substantial heritable influences on DSM substance dependence. Linkage and genome-wide association studies identify modest-sized effects at any locus. Nevertheless, clusters of SNPs within selected genes display  $10^{-2} > p > 10^{-8}$  associations with dependence in many independent samples. For several of these genes, evidence for cis-regulatory, level-of-expression differences

supports the validity of mouse models in which levels of expression are also altered. This review documents surprising, recently defined cases in which convergent evidence from humans and mouse models supports central influences of altered dose-response relationships in mediating the impact of relevant genomic variation on addiction phenotypes. For variation at loci for the  $\alpha 5$  nicotinic acetylcholine receptor, cadherin 13, receptor type protein tyrosine phosphatase  $\Delta$  and neuronal cell adhesion molecule genes, changed dose-response relationships conferred by gene knockouts in mice are accompanied by supporting human data. These observations emphasize desirability of carefully elucidating dose-response relationships for both rewarding and aversive features of abused substances wherever possible. They motivate consideration of individual differences in dose-response relationships in addiction nosology and therapeutics.

**Reducing Aggression and Impulsivity Through School-Based Prevention Programs: A Gene By Intervention Interaction** Musci RJ, Bradshaw CP, Maher B, Uhl GR, Kellam SG, Ialongo NS. *Prev Sci.* 2013 Nov 1. [Epub ahead of print]PMID:24178584.

A variety of school-based, universal preventive interventions have been developed to address behavioral and mental health problems. Unfortunately, few have been evaluated within the context of randomized controlled trials with long-term follow-up. Even fewer still have examined the potential genetic factors that may drive differential impact of the intervention. In the present analysis, the authors examine the extent to which the longitudinal effects of two elementary school-based interventions were moderated by the brain-derived neurotrophic factor (BDNF) gene, which has been linked with aggression and impulsive behaviors. The sample included 678 urban, primarily African American children who were randomly assigned along with their teachers to one of three first grade classroom conditions: classroom-centered (CC) intervention, Family School Partnership (FSP), or a control condition. The teacher ratings of the youth's aggressive and impulsive behavior were obtained at baseline and in grades 6-12. Single-nucleotide polymorphisms (SNPs) from the BDNF gene were extracted from the genome-wide data. Longitudinal latent trait-state-error models indicated a significant interaction between a particular profile of the BDNF SNP cluster (46 % of sample) and CC intervention on impulsivity ( $\beta = -.27, p < .05$ ). A similar interaction was observed for the BDNF SNP cluster and the CC intervention on aggression ( $\beta = -.14, p < .05$ ). The results suggest that the impacts of preventive interventions in early elementary school on late adolescent outcomes of impulsivity and aggression can be potentially modified by genetic factors, such as BDNF.

**Decreased Vesicular Monoamine Transporter 2 (VMAT2) and Dopamine Transporter (DAT) Function In Knockout Mice Affects Aging Of Dopaminergic Systems** Hall FS, Itokawa K, Schmitt A, Moessner R, Sora I, Lesch KP, Uhl GR. *Neuropharmacology.* 2014 Jan; 76 Pt A: 146-55. doi: 10.1016/j.neuropharm.2013.07.031. Epub 2013 Aug 24. PMID: 23978383.

Dopamine (DA) is accumulated and compartmentalized by the dopamine transporter (DAT; SLC3A6) and the vesicular monoamine transporter 2 (VMAT2; SLC18A2). These transporters work at the plasma and vesicular membranes of dopaminergic neurons, respectively, and thus regulate levels of DA in neuronal compartments that include the extravesicular cytoplasmic compartment. DA in this compartment has been hypothesized to contribute to oxidative damage that can reduce the function of dopaminergic neurons in aging brains and may contribute to reductions in dopaminergic neurochemical markers, locomotor behavior and responses to dopaminergic drugs that are found in aged animals. The studies reported here examined aged mice with heterozygous deletions of VMAT2 or of DAT, which each reduce transporter expression to about 50% of levels found in wild-type (WT) mice. Aged mice displayed reduced locomotor responses under a variety of circumstances, including in response to locomotor stimulants, as well as changes in monoamine levels and metabolites in a regionally dependent manner. Several effects of aging were more

pronounced in heterozygous VMAT2 knockout (KO) mice, including aging induced reductions in locomotion and reduced locomotor responses to cocaine. By contrast, some effects of aging were reduced or not observed in heterozygous DAT KO mice. These findings support the idea that altered DAT and VMAT2 expression affect age-related changes in dopaminergic function. These effects are most likely mediated by alterations in DA compartmentalization, and might be hypothesized to be exacerbated by other factors that affect the metabolism of cytosolic DA.

## **Behavioral Neuroscience Branch**

### **Neurobiology of Relapse Section**

#### **Critical Role Of Peripheral Vasoconstriction In Fatal Brain Hyperthermia Induced By MDMA (Ecstasy) Under Conditions That Mimic Human Drug Use** Kiyatkin EA, Kim A, Wakabayashi KT, Baumann MH, Shaham Y *The Journal of Neuroscience* 2014; 34:7754 –7762.

MDMA (Ecstasy) is an illicit drug used by young adults at hot, crowded “rave” parties, yet the data on potential health hazards of its abuse remain controversial. Here, the authors examined the effect of MDMA on temperature homeostasis in male rats under standard laboratory conditions and under conditions that simulate drug use in humans. They chronically implanted thermocouple microsensors in the nucleus accumbens (a brain reward area), temporal muscle, and facial skin to measure temperature continuously from freely moving rats. While focusing on brain hyperthermia, temperature monitoring from the two peripheral locations allowed the authors to evaluate the physiological mechanisms (i.e., intra-cerebral heat production and heat loss via skin surfaces) that underlie MDMA-induced brain temperature responses. Their data confirm previous reports on high individual variability and relatively weak brain hyperthermic effects of MDMA under standard control conditions (quiet rest, 22-23°C), but demonstrate dramatic enhancements of drug-induced brain hyperthermia during social interaction (exposure to male conspecific) and in warm environments (29°C). Importantly, the authors identified peripheral vasoconstriction as a critical mechanism underlying the activity- and state-dependent potentiation of MDMA-induced brain hyperthermia. Through this mechanism, which prevents proper heat dissipation to the external environment, MDMA at a moderate non-toxic dose (9 mg/kg or ~1/5 of LD50 in rats) can cause fatal hyperthermia under environmental conditions commonly encountered by humans. These results demonstrate that doses of MDMA that are non-toxic under cool, quiet conditions can become highly dangerous under conditions that mimic recreational use of MDMA at rave parties or other hot, crowded venues.

### **Neurocircuitry of Motivation Section**

#### **Phasic Excitation Of Ventral Tegmental Dopamine Neurons Potentiates the Initiation Of Conditioned Approach Behavior: Parametric and Reinforcement-Schedule Analyses** Ilango A, Kesner AJ, Broker CJ, Wang DV, Ikemoto S. *Front Behav Neurosci.* 2014 May 6; 8: 155. doi: 10.3389/fnbeh.2014.00155.

Midbrain dopamine neurons are implicated in motivation and learning. However, it is unclear how phasic excitation of dopamine neurons, which is implicated in learning, is involved in motivation. Here the authors used a self-stimulation procedure to examine how mice seek for optogenetically-induced phasic excitation of dopamine neurons, with an emphasis on the temporal dimension. TH-Cre transgenic mice received adeno-associated viral vectors encoding channelrhodopsin-2 into the

ventral tegmental area, resulting in selective expression of the opsin in dopamine neurons. These mice were trained to press on a lever for photo-pulse trains that phasically excited dopamine neurons. They learned to self-stimulate in a fast, constant manner, and rapidly reduced pressing during extinction. The authors first determined effective parameters of photo-pulse trains in self-stimulation. Lever-press rates changed as a function of the manipulation of pulse number, duration, intensity, and frequency. They then examined effects of interval and ratio schedules of reinforcement on photo-pulse train reinforcement, which was contrasted with food reinforcement. Reinforcement with food inhibited lever pressing for a few seconds, after which pressing was robustly regulated in a goal-directed manner. In contrast, phasic excitation of dopamine neurons robustly potentiated the initiation of lever pressing; however, this effect did not last more than 1 s and quickly diminished. Indeed, response rates markedly decreased when lever pressing was reinforced with inter-reinforcement interval schedules of 3 or 10 s or ratio schedules requiring multiple responses per reinforcement. Thus, phasic excitation of dopamine neurons briefly potentiates the initiation of approach behavior with apparent lack of long-term motivational regulation.

## **Molecular Mechanisms of Behavior Unit**

**Role Of Nucleus Accumbens Shell Neuronal Ensembles In Context-Induced Reinstatement Of Cocaine Seeking** Cruz FC, Babin KR, Leao RM, Goldart EM, Bossert JM, Shaham Y, Hope BT. *Journal of Neuroscience* 2014, 34: 7437-7446.

Environmental contexts previously associated with drug use provoke relapse to drug use in humans and reinstatement of drug-seeking in animal models of drug relapse. The authors examined whether context-induced reinstatement of cocaine-seeking is mediated by activation of context-selected nucleus accumbens neurons. They trained rats to self-administer cocaine in context A and extinguished their lever-pressing in a distinct context B. On test day, re-exposure to the cocaine-associated context A reinstated cocaine-seeking and increased expression of the neural activity marker Fos in 3.3% of accumbens shell and 1.6% of accumbens core neurons. To assess a causal role for these activated neurons, the authors used the Daun02 inactivation procedure to selectively inactivate these neurons. They trained c-fos-lacZ transgenic rats to self-administer cocaine in context A and extinguished their lever-pressing in context B. On induction day, the authors exposed rats to either context A or a novel context C for 30 min and injected Daun02 or vehicle into accumbens shell or core 60 min later. On test day, three days after induction day, the ability of context A to reinstate cocaine-seeking and increase neuronal activity in accumbens shell was attenuated when Daun02 was previously injected following exposure to context A. Daun02 injections following exposure to the novel context C had no effect on context-induced reinstatement of cocaine-seeking despite much greater numbers of Fos-expressing neurons induced by context C. Daun02 injections in accumbens core had no effect. These data suggest that context-induced reinstatement of cocaine-seeking is mediated by activation of context-selected accumbens shell but not core neuronal ensembles.

## Preclinical Pharmacology Section

### **Effects Of 3,4-Methylenedioxymethamphetamine (MDMA) and Its Main Metabolites On Cardiovascular Function In Conscious Rats**

Schindler CW, Thorndike EB, Blough BE, Tella SR, Goldberg SR, Baumann MH. *British Journal of Pharmacology* 2014; 171(1): 83-91.

The cardiovascular effects produced by 3,4-methylenedioxymethamphetamine (MDMA; 'Ecstasy') contribute to its acute toxicity, but the potential role of its metabolites in these cardiovascular effects is not known. Here the authors examined the effects of MDMA metabolites on cardiovascular function in rats. Radiotelemetry was employed to evaluate the effects of s.c. administration of racemic MDMA and its phase I metabolites on BP, heart rate (HR) and locomotor activity in conscious male rats. MDMA (1-20 mg•kg<sup>-1</sup>) produced dose-related increases in BP, HR and activity. The peak effects on HR occurred at a lower dose than peak effects on BP or activity. The N-demethylated metabolite, 3,4-methylenedioxyamphetamine (MDA), produced effects that mimicked those of MDMA. The metabolite 3,4-dihydroxymethamphetamine (HHMA; 1-10 mg•kg<sup>-1</sup>) increased HR more potently and to a greater extent than MDMA, whereas 3,4-dihydroxyamphetamine (HHA) increased HR, but to a lesser extent than HHMA. Neither dihydroxy metabolite altered motor activity. The metabolites 4-hydroxy-3-methoxymethamphetamine (HMMA) and 4-hydroxy-3-methoxyamphetamine (HMA) did not affect any of the parameters measured. The tachycardia produced by MDMA and HHMA was blocked by the β-adrenoceptor antagonist propranolol. These results demonstrate that HHMA may contribute significantly to the cardiovascular effects of MDMA in vivo. As such, determining the molecular mechanism of action of HHMA and the other hydroxyl metabolites of MDMA warrants further study.

### **Differential Effects Of Presynaptic Versus Postsynaptic Adenosine A2A Receptor Blockade On Δ9-Tetrahydrocannabinol (THC) Self-Administration In Squirrel Monkeys**

Justinová Z, Redhi GH, Goldberg SR, Ferré S. *Journal of Neuroscience*, 2014, 34(19): 6480-4.

Different doses of an adenosine A2A receptor antagonist MSX-3 [3,7-dihydro-8-[(1E)-2-(3-ethoxyphenyl)ethenyl]-7-methyl-3-[3-(phosphoxy)propyl-1-(2-propynyl)-1H-purine-2,6-dione] were found previously to either decrease or increase self-administration of cannabinoids delta-9-tetrahydrocannabinol (THC) or anandamide in squirrel monkeys. It was hypothesized that the decrease observed with a relatively low dose of MSX-3 was related to blockade of striatal presynaptic A2A receptors that modulate glutamatergic neurotransmission, whereas the increase observed with a higher dose was related to blockade of postsynaptic A2A receptors localized in striatopallidal neurons. This hypothesis was confirmed in the present study by testing the effects of the preferential presynaptic and postsynaptic A2A receptor antagonists SCH-442416 [2-(2-furanyl)-7-[3-(4-methoxyphenyl)propyl]-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-5-amine] and KW-6002 [(E)-1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methyl-3,7-dihydro-1H-purine-2,6-dione], respectively, in squirrel monkeys trained to intravenously self-administer THC. SCH-442416 produced a significant shift to the right of the THC self-administration dose-response curves, consistent with antagonism of the reinforcing effects of THC. Conversely, KW-6002 produced a significant shift to the left, consistent with potentiation of the reinforcing effects of THC. These results show that selectively blocking presynaptic A2A receptors could provide a new pharmacological approach to the treatment of marijuana dependence and underscore corticostriatal glutamatergic neurotransmission as a possible main mechanism involved in the rewarding effects of THC.

## **Integrative Neurobiology Section**

### **Differential Effects Of Presynaptic Versus Postsynaptic Adenosine A2A Receptor Blockade On Δ9-Tetrahydrocannabinol (THC) Self-Administration In Squirrel Monkeys**

Justinová Z, Redhi GH, Goldberg SR, Ferré S. *Journal of Neuroscience*, 2014, 34, 6480-6484.

Different doses of an adenosine A2A receptor antagonist MSX-3 [3,7-dihydro-8-[(1E)-2-(3-ethoxyphenyl)ethenyl]-7-methyl-3-[3-(phosphoxy)propyl-1-(2-propynyl)-1H-purine-2,6-dione] were found previously to either decrease or increase self-administration of cannabinoids delta-9-tetrahydrocannabinol (THC) or anandamide in squirrel monkeys. It was hypothesized that the decrease observed with a relatively low dose of MSX-3 was related to blockade of striatal presynaptic A2A receptors that modulate glutamatergic neurotransmission, whereas the increase observed with a higher dose was related to blockade of postsynaptic A2A receptors localized in striatopallidal neurons. This hypothesis was confirmed in the present study by testing the effects of the preferential presynaptic and postsynaptic A2A receptor antagonists SCH-442416 [2-(2-furanyl)-7-[3-(4-methoxyphenyl)propyl]-7H-pyrazolo[4,3-e][1,2,4]triazolo[1,5-c]pyrimidin-5-amine] and KW-6002 [(E)-1,3-diethyl-8-(3,4-dimethoxystyryl)-7-methyl-3,7-dihydro-1H-purine-2,6-dione], respectively, in squirrel monkeys trained to intravenously self-administer THC. SCH-442416 produced a significant shift to the right of the THC self-administration dose-response curves, consistent with antagonism of the reinforcing effects of THC. Conversely, KW-6002 produced a significant shift to the left, consistent with potentiation of the reinforcing effects of THC. These results show that selectively blocking presynaptic A2A receptors could provide a new pharmacological approach to the treatment of marijuana dependence and underscore corticostriatal glutamatergic neurotransmission as a possible main mechanism involved in the rewarding effects of THC.

### **Cocaine Disrupts Histamine H3 Receptor Modulation Of Dopamine D1 Receptor Signaling: σ1-D1-H3 Receptor Complexes As Key Targets For Reducing Cocaine's Effects**

Moreno E, Moreno-Delgado D, Navarro G, Hoffmann HM, Fuentes S, Rosell-Vilar S, Gasperini P, Rodríguez-Ruiz M, Medrano M, Mallol J, Cortés A, Casadó V, Lluís C, Ferré S, Ortiz J, Canela E, McCormick PJ. *Journal of Neuroscience*, 2014, 34, 3545-3558.

The general effects of cocaine are not well understood at the molecular level. What is known is that the dopamine D1 receptor plays an important role. Here the authors show that a key mechanism may be cocaine's blockade of the histamine H3 receptor-mediated inhibition of D1 receptor function. This blockade requires the  $\sigma_1$  receptor and occurs upon cocaine binding to  $\sigma_1$ -D1-H3 receptor complexes. The cocaine-mediated disruption leaves an uninhibited D1 receptor that activates Gs, freely recruits  $\beta$ -arrestin, increases p-ERK 1/2 levels, and induces cell death when over activated. Using in vitro assays with transfected cells and in ex vivo experiments using both rats acutely treated or self-administered with cocaine along with mice depleted of  $\sigma_1$  receptor, the authors show that blockade of  $\sigma_1$  receptor by an antagonist restores the protective H3 receptor-mediated brake on D1 receptor signaling and prevents the cell death from elevated D1 receptor signaling. These findings suggest that a combination therapy of  $\sigma_1$ R antagonists with H3 receptor agonists could serve to reduce some effects of cocaine.

### **G Protein-Coupled Receptor Oligomerization Revisited: Functional and Pharmacological Perspectives**

Ferré S, Casadó V, Devi LA, Filizola M, Jockers R, Lohse MJ, Milligan G, Pin JP, Guitart X. *Pharmacological Reviews*, 2014 66, 413-434.

Most evidence indicates that, as for family C G protein-coupled receptors (GPCRs), family A GPCRs form homo- and heteromers. Homodimers seem to be a predominant species, with potential dynamic formation of higher-order oligomers, particularly tetramers. Although monomeric GPCRs

can activate G proteins, the pentameric structure constituted by one GPCR homodimer and one heterotrimeric G protein may provide a main functional unit, and oligomeric entities can be viewed as multiples of dimers. It still needs to be resolved if GPCR heteromers are preferentially heterodimers or if they are mostly constituted by heteromers of homodimers. Allosteric mechanisms determine a multiplicity of possible unique pharmacological properties of GPCR homomers and heteromers. Some general mechanisms seem to apply, particularly at the level of ligand-binding properties. In the frame of the dimer-cooperativity model, the two-state dimer model provides the most practical method to analyze ligand-GPCR interactions when considering receptor homomers. In addition to ligand-binding properties, unique properties for each GPCR oligomer emerge in relation to different intrinsic efficacy of ligands for different signaling pathways (functional selectivity). This gives a rationale for the use of GPCR oligomers, and particularly heteromers, as novel targets for drug development. Herein, the authors review the functional and pharmacological properties of GPCR oligomers and provide some guidelines for the application of discrete direct screening and high-throughput screening approaches to the discovery of receptor-heteromer selective compounds.

**Personality Traits and Vulnerability Or Resilience To Substance Use Disorders** Belcher AM, Volkow ND, Moeller FG, Ferré S. Trends in Cognitive Sciences, 2014, 18, 211-217.

Clear evidence supports a genetic basis for substance use disorders (SUD). Yet, the search to identify individual gene contributions to SUD has been unsuccessful. Here, the authors argue for the study of endophenotypes within the frame of individual differences, and identify three high-order personality traits that are tied to specific brain systems and genes, and that offer a tractable approach to studying SUD. These personality traits, and the genes that moderate them, interact dynamically with the environment and with the drugs themselves to determine ultimately an individual's vulnerability or resilience to developing SUD.

## **Neuroimaging Research Branch**

**Machine Learning Classification Of Resting State Functional Connectivity Predicts Smoking Status** Pariyadath, V, Ross, TJ, Stein, EA. Frontiers in Human Neuroscience 6 June 2014 | doi: 10.3389/fnhum.2014.00425.

Machine learning-based approaches are now able to examine functional magnetic resonance imaging data in a multivariate manner and extract features predictive of group membership. The authors applied support vector machine-based classification to resting state functional connectivity data from nicotine-dependent smokers and healthy controls to identify brain-based features predictive of nicotine dependence. By employing a network-centered approach, the authors observed that within network functional connectivity measures offered maximal information for predicting smoking status, as opposed to between-network connectivity, or the representativeness of each individual node with respect to its parent network. Further, their analysis suggests that connectivity measures within higher-order resting state networks, including the executive control and frontoparietal networks, are particularly informative in predicting smoking status. These findings suggest that machine learning-based approaches to classifying resting state functional connectivity data offer a valuable alternative technique to understanding large-scale differences in addiction-related neurobiology.

## Cellular Neurobiology Research

### Behavioral Neurophysiology Research Section

**Orbitofrontal Neurons Infer the Value and Identity Of Predicted Outcomes** Stalnaker, TA, Cooch, NK, McDannald, MA, Liu, TL, Wied, H, and Schoenbaum, G. Nature Communications. 2014, 5: 3926. doi: 10.1038/ncomms4926.

The best way to respond flexibly to changes in the environment is to anticipate them. Such anticipation often benefits us if we can infer that a change has occurred, before we have actually experienced the effects of that change. Here the authors test for neural correlates of this process by recording single-unit activity in the orbitofrontal cortex in rats performing a choice task in which the available rewards changed across blocks of trials. Consistent with the proposal that orbitofrontal cortex signals inferred information, firing changes at the start of each new block as if predicting the not-yet-experienced reward. This change occurs whether the new reward is different in number of drops, requiring signalling of a new value, or in flavour, requiring signalling of a new sensory feature. These results show that orbitofrontal neurons provide a behaviourally relevant signal that reflects inferences about both value-relevant and value-neutral information about impending outcomes.

### Clinical Psychoneuroendocrinology and Neuropsychopharmacology Section

**Intravenous Ghrelin Administration Increases Alcohol Craving In Alcohol-Dependent Heavy Drinkers: A Preliminary Investigation** Leggio L, Zywiak WH, Fricchione SR, Edwards SM, de la Monte SM, Swift RM, Kenna GA. Biological Psychiatry 2014. Available Online March 25, 2014. In this proof-of-concept human laboratory study, it was shown that intravenous (IV) administration of exogenous ghrelin increased alcohol craving in alcohol-dependent heavy-drinking individuals. This represents the first study testing the effects of IV ghrelin administration to an addictive population. These findings are consistent with previous preclinical work and provide preliminary human evidence that ghrelin may play a role in the neurobiology of alcohol craving, thus demonstrating a novel pharmacologic target for treatment.

**A Preliminary Double-Blind, Placebo-Controlled Randomized Study Of Baclofen Effects In Alcoholic Smokers** Leggio L, Zywiak WH, Edwards SM, Tidey JW, Swift RM, Kenna GA. Psychopharmacology (Berl). 2014 Jun 29. [Epub ahead of print] PubMed PMID: 24973894. This was a pilot randomized clinical trial testing the effects of the GABA-B receptor agonist baclofen in the treatment of alcoholism and smoking comorbidity. This study provides preliminary evidence suggesting a possible role of baclofen in the treatment of alcoholic smokers, but larger studies are needed to replicate these preliminary findings.

**Ondansetron Reduces Naturalistic Drinking In Nontreatment-Seeking Alcohol-Dependent Individuals With the LL 5'-HTTLPR Genotype: A Laboratory Study** Kenna GA, Zywiak WH, Swift RM, McGeary JE, Clifford JS, Shoaff JR, Vuittonet C, Fricchione S, Brickley M, Beaucage K, Haass-Koffler CL, Leggio L. Alcohol Clin Exp Res. 2014; 38: 1567-74. This was a within-subject human laboratory study testing the effects of ondansetron and sertraline in reducing alcohol use. The results of this study support the hypothesis that ondansetron may reduce alcohol use in alcohol-dependent individuals with the LL genotype as measured naturalistically.

## **EXTRAMURAL POLICY AND REVIEW ACTIVITIES**

### **Receipt, Referral, and Review**

- Total # of grant applications: 1795
- DA primary: 938
- Institute-based reviews: 19 Grant SEPS (106 applications) and 10 Contract SEPS (145 proposals)

### **Grant Reviews**

- RFA-MH-14-214 (R01); EUREKA Review: Exceptional Unconventional Research Enabling Knowledge Acceleration (EUREKA) for Neuroscience and Disorders of the Nervous System (R01)
- PAR-14-010 (UH2/UH3); Identification of Gene Variants for Addiction Related Traits by Next-Gen Sequencing in Model Organisms Selectively Bred for Addiction Traits ( UH2/UH3)
- Random FOA; Multi-site clinical trials SEP
- PA-14-042 (Parent K99/R00); NIH Pathway to Independence Award (K99)
- PAR-12-066 (R03); NIDA I/START Small Grant Review
- PAR-13-270 (U01); GOMED U01: Grand Opportunity in Medications Development for Substance-Related Disorders (U01)
- PAR12-279 (R34); "Pilot Intervention and Services Research Grants (R34)
- PAR-13-334 (R01); Strategic Alliances for Medications Development to Treat Substance Use Disorders (R01) (PAR-13-334)
- PAR-12-222 (U01); Cohort Studies of HIV/AIDS and Substance Use (U01)
- PAR-13-104 (R25); NIH Summer Research Experience Programs (R25)
- Random FOA; Multi-site clinical trials SEP II
- PA12-212 (R13); R13 Conference Grant Review (PA12-212)
- PAR-12-222 (U01); Conflicts SEP: Cohort Studies of HIV/AIDS and Substance Use (U01)
- Random FOA; Multi-site clinical trials SEP III
- RFA-DA-15-001 (R43/R44); Tools for Monitoring and Manipulating Modified RNAs in the Nervous System (R43/R44)
- RFA-DA-15-002 (R41/R42); Tools for Monitoring and Manipulating Modified RNAs in the Nervous System (R41/R42)
- RFA-DA-15-003 (U54); Medications Development Centers of Excellence Cooperative Program (U54)
- PAR-12-297 (R21); Mechanism for Time-Sensitive Drug Abuse Research (R21)
- PAR-13-270 (U01); SEP for GOMED

### **Contract Reviews**

- OD13-081 (L30); OD13-083 (L40); NOT-OD-13-082, NOT-OD-13-083, NOT-OD-13-084, NOT-OD-13-085 Loan Repayment 2014
- N01DA-14-8918; Analytical Chemistry & Stability Testing of Treatment Drugs (8918)
- N44DA-14-4417; SBIR Phase II For Life: An Online Relapse Prevention Tool (4417)
- N44DA-14-4419; SBIR Phase II Video Game Targeting Relapse Prevention in (4419)
- N01DA-14-1153; Communication Support (8a) (1153)

- N01DA-15-4422; NIH Pain Consortium Centers of Excellence in Pain Education (4422)
- N01DA-14-2241 Clinical Trials Research Coordination Center (2241)
- N01DA-15-7792 Preparation & Distribution of Research Drug Products (7792)
- N01DA-14-8915 (on hold); GMP Synthesis of Bulk Drug Substances (8915)
- N01DA-15-8919 In Vitro Metabolism and Metabolite Quantification (8919)

### **Certificates of Confidentiality**

Between March 5, 2014 and August 5, 2014 NIDA OEA processed 119 Certificate of Confidentiality applications. These numbers are frequency counts and do not provide insight into the complexity of the applications.

### **Staff Training and Development**

The OEA Symposium Series, a forum for staff training and sharing of ideas and information, continued to provide open forums for discussions and presentations.

### **Other Review Activities**

The CTN Data and Safety Monitoring Board met July 2, 2014, to discuss progress of protocol CTN 0056-Ot, Testing and Linkage to HIV Care in China.

**CONGRESSIONAL AFFAIRS SECTION**  
**(Prepared August 11, 2014)**

**CONGRESSIONAL HEARINGS/MEETINGS**

**May 9, 2014:** At the request of the Congressional Hepatitis Caucus, NIDA Deputy Director Dr. Wilson Compton participated in a briefing entitled Hepatitis on the Hill. The Assistant Secretary for Health and HRSA also participated. The briefing was organized by the Harm Reduction Coalition and the National Association of State and Territorial AIDS Directors.

**May 14, 2014:** The Senate Caucus on International Narcotics control held a hearing on the Causal Role Prescription Drug Abuse has had on the Increased Use of Heroin in the United States. Dr. Nora Volkow, Director, NIDA, testified, along with Michael Botticelli, Acting Director, Office of National Drug Control Policy; Dr. H. Westley Clark, Director, Substance Abuse and Mental Health Services Administration; and Dr. Andrew Kolodny, Chief Medical Officer, Phoenix House.

**May 28, 2014:** NIDA Associate Director for Scientific Affairs Dr. Susan Weiss briefed Senator Elizabeth Warren's (D-MA) staff on marijuana research at NIDA.

**June 3, 2014:** NIDA Deputy Director Dr. Wilson Compton briefed Senator Jack Reed's (D-RI) staff on opiate abuse and addiction research at NIDA.

**June 10, 2014:** NIDA Director Dr. Nora Volkow met with and briefed Senator Lisa Murkowski (R-AK) on marijuana health and research issues.

**June 18, 2014:** NIDA Director Dr. Nora Volkow participated in a Senate Forum focused on buprenorphine use in the treatment of opiate addiction. The Forum was sponsored by Senator Carl Levin (D-MI) and Senator Orrin Hatch (R-UT).

**June 19, 2014: Friends of NIDA Capitol Hill Briefing** – NIDA Deputy Director Wilson Compton participated in a briefing titled “**Marijuana: Health Effects, Changing Patterns of Use and Societal Impact.**” This was a heavily attended congressional event which also featured Dr. Robert Booth and former Congressman Patrick Kennedy. Please see <http://www.apa.org/science/about/psa/2014/07/marijuana-impacts.aspx> for a full description from our colleagues at the American Psychological Association.

**June 20, 2014:** NIDA Director Dr. Nora Volkow briefed U.S. Representative John Fleming (R-LA) on the health effects of and NIDA research into marijuana abuse and addiction.

**June 20, 2014:** The House Oversight and Government Reform Subcommittee on Government Operations [Chairman, John Mica, (R-FL)] held a hearing on marijuana. Dr. Nora Volkow, Director, NIDA, testified. This was the third in a series of hearings held by this Subcommittee on this topic. Also testifying at this hearing were Dr. Douglas Throckmorton of FDA, and Dr. Carl Hart of Columbia University.

**June 27, 2014:** NIDA Director Dr. Nora Volkow briefed the Clerks of the Senate Appropriations Subcommittee on Labor, Health and Human Services, and Pensions on NIDA research priorities and challenges.

**July 9, 2014:** NIDA Deputy Director Dr. Wilson Compton briefed Senator Mitch McConnell's (R-TN) staff for McConnell staff on opiate abuse and addiction research at NIDA.

**July 15, 2014:** NIDA Director Dr. Nora Volkow participated in a Capitol Hill briefing focused on Womens Health. The briefing was sponsored by the Womens Health Caucus, and organized by Womens Policy, Inc., with support from the Robert Wood Johnson Foundation.

**July 22, 2014:** NIDA Division of Epidemiology, Services and Prevention Acting Director Dr. Redonna Chandler chaired a panel at the second Senate Addiction Forum. The Forum focused on women and drug abuse/addiction issues, and also featured some NIDA grantees.

**August 6, 2014:** NIDA Director Dr. Nora Volkow participated in a community forum in Boston, MA. The event, organized and sponsored by U.S. Senator Edward Markey (D-MA), focused on opiate addiction and overdose issues. Other federal agencies participating were ONDCP, SAMHSA, and DEA.

**August 13-14, 2014:** NIDA Director Dr. Nora Volkow participated in a community forum and "coalfields tour" in southeastern West Virginia. The events, organized and sponsored by U.S. Representative Nick Rahall (D-WV), focused on opiate addiction and overdose issues. Other federal agencies participating were ONDCP, SAMHSA, CDC, DOJ/BJA.

## **SOME BILLS OF INTEREST**

**HR 486** – On February 4, 2013, Representative William Keating (D-MA) introduced the Stop Tampering of Prescription Pills act of 2013, to amend the Food, Drug and Cosmetic Act to incentivize the development of abuse-deterrent drugs. The bill was referred to the Committee on Energy and Commerce.

**HR 498** – On February 5, 2013, Representative Lucille Roybal-Allard (D-CA) introduced a bill to reauthorize the Sober Truth on Preventing Underage Drinking (STOP) Act. The bill was referred to the House Committee on Energy and Commerce.

**HR 499** – On February 5, 2013, Representative Jared Polis (D-CO) introduced the Ending Federal Marijuana Prohibition Act of 2013, to generally decriminalize and change the way the Controlled Substances Act is applied to marijuana. The bill was referred to the Committee on the Judiciary, the Committee on Ways and Means, the Committee on Energy and Commerce, the Committee on Natural Resources, and the Committee on Agriculture.

**HR 672** – On February 13, 2013, Representative Nick Rahall (D-WV) introduced the Prescription Drug Abuse Prevention and Treatment Act of 2013, to provide for increased federal oversight of prescription opioid treatment and assistance to states in reducing opioid abuse, diversion, and deaths. The bill was referred to the Committee on Energy and Commerce and the Committee on the Judiciary. See also S 348.

**HR 1263** – On March 19, 2013, Representative Doris Matsui (D-CA) introduced the Excellence in Mental Health Act, to increase access to community behavioral health services for all Americans and to improve Medicaid reimbursement for community behavioral health services. The bill was referred to the Committee on Energy and Commerce. See also S 264, S 265.

**HR 1285** – On March 20, 2013, Representative Vern Buchanan (R-FL) introduced Safe Prescribing Act of 2013, to amend the Controlled Substances Act to make any substance containing hydrocodone a schedule II drug. The bill was referred to the Committee on the Judiciary, and Judiciary. See also S 621. [NOTE: The FDA has recommended to HHS the reclassification of hydrocodone combination products as Schedule II controlled substances.]

**HR 1366** – On March 21, 2013, Representative Stephen Lynch (D-MA) introduced the Stop Oxycontin Abuse Act of 2013, to direct the Commissioner of Food and Drugs to modify the approval of any drug containing controlled-release oxycodone hydrochloride to limit such approval to use for the relief of severe-only instead of moderate-to-severe pain, and for other purposes. The bill was referred to the Committee on Energy and Commerce.

**HR 1523** – On April 12, 2013, Representative Dana Rohrbacher (R-CA) introduced the Respect State Marijuana Laws Act of 2013, to amend the Controlled Substances Act to provide for a new rule regarding the application of the Act to marijuana, and for other purposes. The bill was referred to the Committee on the Judiciary and the Committee on Energy and Commerce.

**HR 3717** – On December 12, 2013, Representative Tim Murphy (R-PA) introduced the Helping Families in Mental Health Crisis Act of 2013, to make available needed psychiatric, psychological, and supportive services for individuals diagnosed with mental illness and families in mental health crisis, and for other purposes. The bill was referred to the House Committees on: Energy and Commerce; Judiciary; Energy and the Workforce; Ways and Means; and Science, Space and Technology.

**HR 4046** – On February 11, 2014, Representative Steve Cohen (D-TN) introduced the Unmuzzle the Drug Czar Act of 2014, to strike provisions that prohibit the Director of the ONDCP from studying the legalization of marijuana, that require the Director to oppose any attempt to legalize marijuana, and for other purposes. The bill was referred to the Committees on Oversight and Government Reform and Energy and Commerce.

**HR 4169** – On March 6, 2014, Representative Donna Edwards (D-MD) introduced the Stop Overdose Stat Act, to prevent deaths occurring from drug overdoses. The bill was referred to the Committee on Energy and Commerce. See S 2755.

**HR 4241** – On March 13, 2014, Representative Stephen Lynch (D-MA) introduced the Act to Ban Zohydro, to withdraw approval for the drug Zohydro ER and prohibit the FDA from approving such drug unless it is reformulated to prevent abuse. The bill was referred to the Committee on Energy and Commerce. See S. 2134

**HR 5226** – On July 28, 2014, Representative Scott Perry (R-PA) introduced the Charlotte's Web Medical Hemp Act of 2014, to amend the Controlled Substances Act to exclude therapeutic hemp and cannabidiol from the definition of marijuana, and for other purposes. The bill was referred to the Committees on Energy and Commerce, and Judiciary.

**HR 5136** – On July 17, 2014, Representative Marcia Fudge (D-OH) introduced the Breaking Addiction Act of 2014, to direct the Secretary of HHS to establish a demonstration project under the Medicaid program under title XIX of the Social Security Act under which payment may be made to states for expenditures for medical assistance with respect to substance abuse disorder services, and for other purposes. The bill was referred to the Committee on Energy and Commerce.

**HR 5294** – On July 30, 2014, Representative Roybal-Allard (D-CA) along with 65 other Members of Congress introduced the Health Equity and Accountability Act of 2014. The bill contains ten titles, many of which include provisions for NIH. The titles include: Data Collection and Reporting; Culturally and Linguistically Appropriate Health Care; Health Workforce Diversity; Improvement of Health Care Services; Improving Health Outcomes for Women, Children, and Families; Mental Health; Addressing High Impact Minority Diseases (including cancer, viral hepatitis and liver cancer control and prevention, acquired bone marrow failure disease, cardiovascular disease, and chronic disease, HIV/AIDS, diabetes, lung disease, osteoarthritis and musculoskeletal diseases, and sleep and circadian rhythm disorders); Health Information Technology; Accountability and Evaluation; and Addressing Social Determinants and Improving Environmental Justice. The bill was referred to the Committee on Energy and Commerce, and in addition to the Committees on Ways and Means, Agriculture, Education and Workforce, the Budget, Veteran’s Affairs, Armed Services, the Judiciary, and Natural Resources.

**HR 5339** – On July 31, 2014, Representative Bill Foster (D-IL) introduced the Expanding Opportunities for Recovery Act of 2014, to authorize the Administrator of SAMHSA, acting through the director of CSAT, to award grants to states to expand access to clinically appropriate services for opioid abuse, dependence, or addiction. The bill was referred to the Committee on Energy and Commerce.

**S 237** – On February 7, 2013, Senator Lisa Murkowski (R-AK) introduced the Advancing FASD Research, Prevention and Services Act, to amend the Public Health Service Act to reauthorize and extend the FAS prevention and services program, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions.

**S 264** – On February 7, 2013, Senator Debbie Stabenow (D-MI) introduced the Excellence in Mental Health Act, to expand access to community mental health centers and improve the quality of mental health care for all Americans. The bill was referred to the Committee on Health, Education, Labor, and Pensions. See also S 265, HR 1263

**S 265** – On February 7, 2013 Senator Jack Reed (D-RI) introduced Community-Based Mental Health Infrastructure Improvements Act, to amend the Public Health Service Act to provide grants for community-based mental health infrastructure improvement. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also S 264, HR 1263

**S 348** – On February 14, 2013, Senator John Rockefeller (D-WV) introduced the Prescription Drug Abuse Prevention and Treatment Act of 2013, to provide for increased federal oversight of prescription opioid treatment and assistance to states in reducing opioid abuse, diversion, and deaths. The bill was referred to the Committee on Health, Education, Labor and Pensions. See also HR 672.

**S 621** – On March 20, 2013, Senator Joe Manchin (D-WV) introduced the Safe Prescribing Act of 2013, to amend the Controlled Substances Act to make any substance containing hydrocodone a schedule II drug. The bill was referred to the Committee on the Judiciary. See also HR 1285. [NOTE: The FDA has recommended to HHS the reclassification of hydrocodone combination products as Schedule II controlled substances.]

**S 644** – On March 21, 2013, Senator Robert Casey (D-PA) introduced the Preventing Abuse of Cough Treatments Act of 2013, to amend the Food, Drug, and Cosmetic Act to prevent the abuse of dextromethorphan, and for other purposes. The bill was referred to the Committee on Health, Education, Labor, and Pensions.

**S 1277** – On July 10, 2013, Senator Barbara Boxer (D-CA) introduced the Combating Prescription Drug Abuse Act, to establish a commission for the purpose of coordinating efforts to reduce prescription drug abuse, and for other purposes. The bill was referred to the Committee on Health, Education, Labor and Pensions.

**S 2134** – On March 13, 2014, Senator Joe Manchin ((D-WV) introduced the Act to Ban Zohydro, to withdraw approval for the drug Zohydro ER and prohibit the FDA from approving such drug unless it is reformulated to prevent abuse. See H.R. 4241

**S 2755** – On July 31, 2014, Senator Jack Reed (D-RI) introduced the Overdose Prevention Act, to support community-based efforts to prevent fatal drug overdoses from opioid pain medications, heroin, and other drugs. The bill was referred to the Committee on Health, Education, Labor and Pensions. See H.R. 4169.

## **INTERNATIONAL ACTIVITIES**

### **NIDA Meetings**

#### ***NIDA International Forum Focuses on Marijuana, New Psychoactive Substances, and the 25th Anniversary of the NIDA Hubert H. Humphrey Fellowships***

More than 265 participants from 65 countries explored the adverse health effects of marijuana and related policy issues during the opening plenary session of the 19th Annual NIDA International Forum. The meeting, which was held June 13-16, 2014, in San Juan, Puerto Rico, also focused on new psychoactive substances and the 25th anniversary of NIDA's participation in the Hubert H. Humphrey Drug Abuse Research Fellowships. NIDA IP Director Steven W. Gust, Ph.D., chaired the meeting, which was cosponsored by the Canadian Institutes of Health Research (CIHR). A joint College on Problems of Drug Dependence (CPDD)/NIDA International Forum poster session featured presentations on international research by 130 scientists from the United States and 40 other countries.

NIDA Director Nora D. Volkow, M.D., opened the plenary session by exploring gaps in the scientific evidence on adverse health effects of marijuana. Susan Weiss, Ph.D., OD, chaired a panel discussion on marijuana policy, research, and knowledge gaps that provided global perspectives from Asia and Oceania, Europe, and Latin America, and the United States. Paul Griffiths, M.Sc., scientific director of the European Monitoring Centre for Drugs and Drug Addiction, chaired a plenary session panel discussion on new psychoactive substances (NPS) and discussed recent European findings on the synthetic drugs. Other speakers addressed the Italian National Action Plan to prevent NPS use, a joint United Nations Office on Drugs and Crime/ Inter-American Drug Abuse Control Commission project to monitor, analyze, and report on regional NPS trends, and NIDA grantee Jane Maxwell, Ph.D., University of Texas at Austin, who reported on the U.S. situation.

NIDA staff chaired several breakout sessions. IP Associate Director Dale S. Weiss co-chaired the NIDA International Networking Forum with J. Randy Koch, Ph.D., Virginia Commonwealth University. Speakers reviewed the positive role the NIDA Humphrey fellowships have played both for individual fellows and for international drug abuse research infrastructures and cooperation. During the networking session, Susan Weiss, Ph.D., OD, discussed NIDA's National Drug Facts Week, and Joni Rutter, Ph.D., DBNBR, reviewed opportunities for collaborative research through NIH programs. Ivan D. Montoya, M.D., M.P.H, DPMCDA, participated in a panel discussion of former Humphrey fellows and chaired another breakout session on treatment advances for marijuana dependence. Jacques Normand, Ph.D., ARP, and Yu "Woody" Lin, Ph.D., DCNBR, co-chaired a session on vaccination for addiction and AIDS. Betty Tai, Ph.D., and Carmen Rosa, M.S., both of CCTN, co-chaired a session on secondary analyses using the CTN datashare. Speakers representing CIHR, the meeting cosponsor, reported on recent advances and new initiatives to address dual diagnoses, cultural interventions, and capacity building in addiction research.

#### ***IP Presents Awards of Excellence to Four Individuals***

NIDA International Awards of Excellence, which recognize individuals for outstanding contributions to international cooperation in drug abuse research and training, were presented during the NIDA International Forum for:

- Excellence in mentoring, to Dennis McCarty, Ph.D., Oregon Health & Science University,

for his work with the United Nations Office on Drug Control TreatNet program, the Peruvian National Institutes of Health, colleagues in Vietnam, and as scientific director of the Dutch Summer Institute on Alcohol, Drugs, and Addiction.

- Excellence in international leadership, to Charles O’Keeffe, M.B.A., Virginia Commonwealth University (VCU), for his work on U.S. and international drug policy, securing approval for buprenorphine, and creating the International Programme in Addiction Studies, an online master’s degree program.
- Excellence in collaborative research, to Marek C. Chawarski, Ph.D., Yale University, and Vicknasingam B Kasinather, Ph.D., Universiti Sains Malaysia, Malaysia, for their work developing culturally appropriate prevention and treatment interventions for co-occurring opioid and amphetamine dependence and drug-related HIV in Malaysia.
- Special Recognition to William L. Dewey, Ph.D., VCU, for his significant scientific accomplishments and his devoted service to the addiction research community.

### ***NIDA and French Research Agency Host Satellite at AIDS 2014, Announce New Fellows in HIV and Drug Use***

U.S. and French scientists presented a satellite session Monday, July 21, 2014, at the International AIDS meeting in Melbourne, Australia. ARP Director Jacques Normand, Ph.D., and Jean-François Delfraissy, M.D., Ph.D., director of Agence Nationale de Recherche sur le Sida et les hépatitis virales (ANRS), co-chaired the meeting, which focused on drug use, HIV, and hepatitis C (HCV). NIDA grantee Don C. Des Jarlais, Ph.D., Mount Sinai Beth Israel, presented a global overview on the general context of research on HIV/HCV infection and drug use. Another NIDA grantee, Shruti H. Mehta, Ph.D., Johns Hopkins, reported on HCV among people who inject drugs in India. Other speakers addressed treatment and access to treatment in low- and middle-income countries, global health policy and the position of international organizations and the United Nations, the role of harm reduction in HCV prevention in France, injecting drug use and HIV - HCV infections in Dakar, Senegal, and a partnership studying people who inject drugs in Vietnam.

Françoise Barré-Sinoussi, Ph.D., president of the International AIDS Society (IAS), joined Drs. Normand and Delfraissy to award NIDA-IAS-ANRS Postdoctoral Research Fellowships in HIV and Drug Use to five researchers. The Fellowship provides 18 months of postdoctoral training with a mentor who is an expert in the fields of HIV and drug abuse research. The new fellows are:

- Mojtaba Habibi Asgharabad, Ph.D., Iran, who will examine the role of global neurocognitive function by comparing risky decision-making learning among individuals who abuse methamphetamine and have either acute and early or chronic HIV infection. His mentor is David Moore, Ph.D., University of California San Diego.
- Ernest Tafara Chivero, Ph.D., Zimbabwe, who will investigate the roles of the HIV Tat gene and cocaine-mediated modulation of cyclic adenosine monophosphate in neuroAIDS. His mentor is Shilpa Buch, Ph.D., University of Nebraska Medical Center.
- Trupti Ishwar, Gilada, M.D., India, who will study the effect of alcohol and substance abuse disorders on viral and host events during early HIV infection, including genital viral load decay, transmitted drug resistance, and host inflammatory markers. Her mentor is Ann C. Duerr, M.D., Fred Hutchinson Cancer Research Center.
- Andrew Guise, Ph.D., United Kingdom, who will conduct a qualitative study of implementing methadone for HIV prevention and treatment in Kenya. His mentor is Steffanie Strathdee, Ph.D., University of California San Diego.
- Nicholas Peter Fraser Thomson, Ph.D., Australia, who will identify and evaluate the impact

of partnerships between law enforcement and HIV programs on HIV and HCV incidence and risk behaviors among people who use drugs in selected high-priority countries across South, Southeast, and Central Asia. His mentor is Chris Beyrer, M.D., Johns Hopkins University.

### ***SPR Poster Session Features NIDA International Research***

NIDA IP and DESPR cosponsored a poster session for international research at the Society for Prevention Research (SPR). The poster session opened the SPR Annual Meeting, which was held May 27–30, 2014, in Washington, D.C. SPR President Felipe Gonzalez Castro, Ph.D., University of Texas at El Paso; DESPR Prevention Research Deputy Branch Chief Jacqueline Lloyd, Ph.D., M.S.W.; and IP Associate Director Dale S. Weiss welcomed attendees to the poster session. NIDA supported the participation of five international researchers: Joachim Jacobs, South Africa; Antonio Cesar Pazinato, Brazil; Gergely Radacsi, Hungary; Shreeletha Solomon, India; and Angela Trujillo, Colombia. Ms. Weiss also participated in the preconference meeting of the SPR International Networking Forum, which discussed plans to develop a guide for sustaining successful international collaborations. The guide will review developing research questions, the impact of cultural influences on working relationships, and collaborative strategies for analyses, writing, and dissemination.

### **NIDA Participates in the French-American Networking Event in Science and Technology (NEST), Inserm’s 50<sup>th</sup> Anniversary Workshop**

On July 1, 2014 several NIDA staff attended the NEST event at the Embassy of France in Washington, DC. As noted in the agenda for the workshop, “Through the annual NEST event, the Office for Science and Technology of the Embassy of France in Washington, DC seeks to bring together and honor these scientific alumni who are familiar with research in both France and the United States. The members of this community serve as true scientific ambassadors”. Featured speakers at the workshop were NIDA Director Nora Volkow, M.D., and NIAAA Director George Koob, Ph.D.

### **Research Results**

#### ***Former INVEST Fellow Edits Journal Supplement on Inhalant Abuse***

A special issue of the *Journal of Drug and Alcohol Research* (Volume 3, 2014) features papers based on inhalant abuse research originally presented at a symposium during the 4th Meeting of the International Drug Abuse Research Society (IDARS) held in Mexico City April 15–19, 2013. The symposium, “Research on Inhalant Misuse: From Epidemiology to Epigenetics,” was sponsored by the NIDA IP and organized and chaired by former NIDA INVEST fellow Silvia L. Cruz, Ph.D., Cinvestav, Mexico, and NIDA grantee John J. Woodward, Ph.D., Medical University of South Carolina. Drs. Cruz and Woodward also edited the special issue, which is available online at <http://www.ashdin.com/journals/JDAR/special.issues/ANBA/>. The papers focus on recent research advances and unanswered questions in five areas:

- The challenges new substances and patterns of inhalant abuse pose to neuroscience and public policy.
- Long-term behavioral consequences of prenatal binge toluene exposure in animal models.
- The molecular and behavioral actions of toluene, the most widely abused inhalant.
- Behavioral pharmacological data that allow comparisons of the abuse liability of different inhalants.
- The neural effects of toluene on the mesolimbic dopaminergic system.

## **Fellowships**

### ***NIDA Selects Australian and Chinese Researchers as INVEST/CTN Fellows***

Two researchers have been awarded INVEST/CTN fellowships, which provide 12 months of postdoctoral research training in the United States with a scientist affiliated with 1 of the 13 CTN Regional Research and Training Centers. The new fellows are:

- Chandra K. Jha, Ph.D., Australia. Dr. Jha will investigate factors related to relapse among former and relapsed Nepali drug users, and how public health strategies can minimize relapse risks. His mentor is Dennis M. Donovan, Ph.D., University of Washington. The fellowship evolved from previous collaboration between the two researchers, who co-authored a paper together in 2013 (Jha, C. & Donovan, D. [2013]. Prison – A Missing Target to Address Issues Related to Drug Detoxification and Rehabilitation: Nepalese Experiences. *International Journal of Prisoners Health*, 9(4): 208-219).
- Jinsong Tang, M.D., China. Dr. Tang will conduct a secondary analysis based on NIDA funded clinical research investigating the safety and efficacy of extended-release depot naltrexone plus extended-release bupropion to treat methamphetamine dependence. He will then design a study comparing the safety and efficacy of varenicline to a placebo as a treatment for methamphetamine dependence for patients already receiving behavioral therapies such as contingency management or cognitive behavioral therapy. His mentor is Walter Ling, M.D., University of California, Los Angeles.

## **Travel Support**

### ***NIDA Supports Two Participants in Dutch Summer Institute on Alcohol, Drugs, and Addiction***

IP provided full tuition scholarships to researchers from Texas and New Mexico to participate in the 2014 Dutch Summer Institute on Alcohol, Drugs, and Addiction. Oralia Loza, Ph.D., an assistant professor at the University of Texas at El Paso, conducts research documenting substance abuse and risk behaviors for HIV, hepatitis C, and other sexually transmitted infections among high-risk populations in the U.S.-Mexico border region in order to develop or adapt prevention interventions. Mandy Owens, a doctoral student in clinical psychology at the University of New Mexico, investigates interventions for individuals with substance use disorders who are involved in the criminal justice system. The multidisciplinary summer training program in addiction research was held June 29 – July 11, 2014, at the University of Amsterdam. Graduate and postdoctoral students join addiction professionals to learn about the intersection of policy models, prevention, and evidence-based treatment and ways to bridge the gap between research and practice. Dennis McCarty, Ph.D., Oregon Health and Science University, is academic director of the Dutch Summer Institute.

## **CTN INVEST Fellows**

Since 2008, NIDA's International Program and the Clinical Trials Network (CTN) have jointly offered fellowships to non-U.S. scientists. Each INVEST fellow works with a CTN mentor affiliated with one of the 13 CTN Nodes. Fellows may conduct their research in any aspect of the CTN research agenda on drug abuse and addiction, such as intervention research, clinical trials methodology, or drug abuse treatment, as well as HIV/AIDS prevention. Two new fellows from China and Australia were selected in 2014.

## **Other International Activities**

Dr. Ruben Baler, OSPC, delivered several presentations while representing NIDA at the XVI National Conference of the Spanish Society on Dual Pathology in Valencia, Spain on June 8-15, 2014.

Dr. Jonathan Pollock, Chief, Genetics, DBNBR, was an invited speaker for the Barcelona 2014 Summer Course "Cellular Biology of Addiction," for a webinar presentation entitled, Funding Opportunities at NIDA. The audience came from the USA, Canada, Europe, and Asia. Dr. Pollock gave an introduction to NIDA's organization and provided information on the grant funding process. NIDA International Program Associate Director, Ms. Dale Weiss, spoke about international funding and training opportunities. Ms. Beth Babecki, Training Coordinator, DBNBR discussed extramural training, career development and new investigator funding available at NIDA.

Dr. Rao Rapaka, DBNBR, attended The International Narcotics Research Conference 2014, Montréal, Québec, Canada, July 13-18, 2014.

Dr. Jag Khalsa, DPMCDA, chaired a session on Cost Aspects of Directly Acting Antivirals for HCV Treatment, and discuss grant writing/funding opportunities at NIDA/NIH at the 10<sup>th</sup> International Workshop on HIV/HCV Co-infection, Paris, France, June 12-13, 2014.

Dr. Meyer Glantz, DESPR, attended the 2014 World Mental Health Consortium meeting as NIDA's representative and scientific collaborator. The WHO meeting was held in Boston, Massachusetts from July 9 to July 13, 2014. Dr. Glantz collaborates with the Substance Use Disorder, the Psychiatric Comorbidity, and the College Student Online Surveys design and analysis workgroups. The WMH Consortium is a multinational set of coordinated community psychiatric epidemiology surveys. The U.S. implementation was the National Comorbidity Survey Replication Survey. Dr. Glantz proposed projects, all of which were accepted, and collaborated in the design and analyses plans in the workgroups.

On May 27, 2014, Dr. Harold Perl, DESPR, co-organized and led a 2-day workshop on "New Advances in Addiction Prevention Research" in Jazan, Saudi Arabia. The workshop was hosted by the Substance Abuse Research Center at Jazan University, the Saudi National Committee on Narcotics Control, and the Saudi Ministry of Higher Education. Dr. Perl gave three major talks, in which he (1) reviewed the fundamentals of prevention research and presented the current state of evidence-based addiction prevention knowledge; (2) highlighted addiction surveillance systems in the US; and (3) gave a tutorial on designing addiction prevention research. The workshop was very well-received and Saudi officials intend to increase their support of prevention research and plan to hold a large national conference on addiction prevention in 2015.

On April 1-4, 2014, Dr. Richard Jenkins, DESPR, represented NIDA for the Overview of the International Agency Investment and also presented "Harmonization of Protocols, the NIDA Experience" the 2014 Treatment as Prevention Workshop in Vancouver BC.

Dr. Lorenzo Leggio, IRP, was one of three invited guest speakers, together with NIDA-funded extramural investigators Drs. Cunningham and Kalivas, at the Research Day entitled "Developing Medications to Treat Addiction: Challenges for Science and Practice" at the Ross University Medical School in Portsmouth, Commonwealth of Dominica, West Indies.

Dr. Bruce Hope, IRP, gave an invited lecture at the European Winter Conference on Brain Research in Brides-les-Bains, France in March 2014.

Dr. Bruce Hope gave an invited lecture at the 12th annual Endo-Neuro-Psycho (ENP) meeting in Lunteren, Netherlands in May 2014.

Dr. Jonathan Katz, IRP, presented a special lecture invited for presentation at the 41st Annual Meeting of the Japanese Society of Toxicology, Kobe, Japan, July 3, 2014.

Dr. Marilyn A. Huestis, IRP, was an invited keynote speaker for two lectures at the Hjelt Institute, Faculty of Medicine, University of Helsinki. The title of the symposium was Trends in New Drugs and Drug Abuse, and the lectures were entitled " Characterizing Metabolic Profiles of Synthetic Cannabinoids: Human Hepatocyte Incubation and High-Resolution Mass Spectrometry," and "Identifying Recent Cannabis Intake in Chronic and Occasional Cannabis Smokers."

Dr. Marilyn A. Huestis was invited faculty for the first international Robert F. Borckenstein course held in Glasgow, Scotland. She has taught the course on the "Effects of Drugs on Human Performance" in the United States since its inception, and presented extensively on the pharmacodynamics and pharmacokinetics of acute and chronic cannabis use.

Dr. Marilyn A. Huestis was an invited speaker at the International Conference "New Drugs" 2014—Scientific and Technical Update on New Psychoactive Substances on May 13-16, 2014 in Rome, Italy. Her lecture was entitled- "In Vitro Metabolism Studies of Synthetic Cannabinoids."

Dr. Marilyn A. Huestis was an invited keynote speaker at the 9th International Symposium on Advances in Legal Medicine (ISALM) held in Fukuoka, Japan in June 2014. Dr. Huestis presented her group's research on deciphering the metabolism of new synthetic cannabinoids by incubation of the new designer drug with human hepatocytes and harnessing the power of high-resolution mass spectrometry. Dr. Huestis also was invited to present at the National Institute of Health Sciences by Dr Ruri Kikura-Hanajiri in Tokyo on June 16, 2014.

Dr. George Uhl, IRP, recently presented an invited talk at the University of Bergen.

Dr. Michael Baumann, IRP, presented data describing the pharmacology of novel drugs of abuse at a conference entitled, "New Drugs 2014: Scientific and technical update on new psychoactive substances", held in Rome, Italy on May 14, 2014.

Dr. Yavin Shaham, IRP, gave an invited lecture at the University of Puerto Rico.

Dr. Yavin Shaham gave the 2014 Distinguished Lectureship in Behavioral Pharmacology at the University of Toronto.

## **PROGRAM ACTIVITIES/FOAS**

### **New NIDA RFAs**

On July 22, 2014, NIDA issued an RFA entitled **Interventions for Youth who Misuse/Abuse Prescription Stimulant Medications in High School and/or College-Attending Youth (U01) [RFA-DA-15-010](#)**. This RFA solicits U01 applications conducting either hypothesis-driven or hypothesis-generating controlled research to build an evidence base to address the problem of prescription stimulant medication (PSM) misuse in youth. Specifically this RFA solicits research applications that develop and test the efficacy of interventions to either prevent or reduce the misuse and diversion of PSMs among high school students and/or college students. Open date: October 13, 2014. Application due date(s): November 13, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): November 13, 2014, by 5:00 PM local time of applicant organization.

On July 16, 2014, NIDA issued an RFA entitled **Extracellular Vesicles in HIV/AIDS and Substance Abuse (R01) [RFA-DA-15-011](#) (R21) [RFA-DA-15-012](#)**. The purpose of this RFA is to encourage research projects that investigate extracellular vesicles in HIV infection/progression or as potential HIV/AIDS biomarkers or therapeutics. Proposed projects must also explore the potential impact of exposure to substances of abuse. Open date: November 15, 2014. Application due date(s): December 15, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): December 15, 2014, by 5:00 PM local time of applicant organization.

On July 3, 2014, NIDA issued an RFA entitled **The National Drug Abuse Treatment Clinical Trials Network (UG1) [RFA-DA-15-008](#)**. This RFA invites applications from clinical investigators to participate in the National Drug Abuse Treatment Clinical Trials Network (CTN). NIDA intends to expand its research to develop and test interventions for the management of the wide spectrum of substance use disorders (SUD) with input from and collaboration with clinical research investigators, healthcare providers, patients and relevant stakeholders. It is expected that successful applicants will describe working alliances with existing and newly created practice-based primary care or other general medical research networks. Open date: November 3, 2014. Application due date(s): December 3, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): Not Applicable.

### **New NIDA Program Announcements**

On May 19, 2014, NIDA, in conjunction with NIMH, NCI and NIAAA, issued a PAR entitled **Exploratory Studies of Smoking Cessation Interventions for People with Schizophrenia (R21/R33) [PAR-14-230](#), (R33) [PAR-14-231](#)**. The purpose of this PAR is to provide support for grant applications to generate and conduct preliminary tests of targeted smoking cessation treatments for individuals with schizophrenia. Smokers with schizophrenia who have co-occurring alcohol and/or substance abuse disorders are also a population of interest. This PAR encourages Phased Innovation (R21/R33) applications that focus on early-stage, treatment generation and pilot clinical trials that are consistent with an experimental therapeutic approach. This approach requires the identification of a theory-derived target based on putative mechanisms of nicotine addiction in individuals with schizophrenia, and clear hypotheses about how an intervention directed at changing

the target can lead to clinical benefits. Open date: July 15, 2014. Application due date(s): August 15, 2014, December 16, 2014, April 15, 2015, August 17, 2015, December 15, 2015, April 15, 2016, August 16, 2016, December 15, 2016, April 17, 2017, by 5:00 PM local time of applicant organization. AIDS application due date(s): August 15, 2014, December 16, 2014, April 15, 2015, August 17, 2015, December 15, 2015; April 15, 2016, August 16, 2016, December 15, 2016, April 17, 2017, by 5:00 PM local time of applicant organization.

On May 15, 2014, NIDA, in conjunction with NCCAM and NCI, issued a PAR entitled **Clinical Evaluation of Adjuncts to Opioid Therapies for the Treatment of Chronic Pain (R01)** [PAR-14-225](#). This announcement aims to fund applications designed to assess the clinical value of adjuncts prescribed to chronic pain patients together with opioid analgesics. Adjuncts of interest are either approved by the FDA or have previously been studied as an Investigational New Drug. Studies with adjuncts of interest should be focused on enhancing analgesia, rather than on reducing an adverse effect. A secondary purpose is to increase awareness among opioid prescribers of the potential value of adjunctive therapies by focused data dissemination. Open date: September 5, 2014. Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization AIDS application due date(s): [Standard AIDS dates](#) apply, by 5:00 PM local time of applicant organization.

On May 15, 2014, NIDA issued a PA entitled **Long-Term Retention in Care for U.S. Substance Using Populations (R01)** [PA-14-224](#), **(R21)** [PA-14-223](#), **(R34)** [PA-14-222](#). Until there is a cure, people living with HIV (PLWH) will have to be retained in care throughout their lives. Therefore, the purpose of this Funding Opportunity Announcement (FOA) is to encourage research on long-term retention in care leading to sustained viral suppression among substance abusers. Open date(s): August 7, 2014. Application due date(s): [Standard dates](#) apply, by 5:00 PM local time of applicant organization AIDS application due date(s): [Standard AIDS dates](#) apply, by 5:00 PM local time of applicant organization.

On April 23, 2014, NIDA issued a PAR entitled **NIDA Core "Center of Excellence" Grant Program (P30)** [PAR-14-186](#). NIDA Core Center of Excellence Grants (P30) are intended to bring together investigators currently funded by NIH or other Federal or non-Federal sources, to enhance the effectiveness of existing research and also to extend the focus of research to drug abuse and addiction. It is expected that a Center will transform knowledge in the sciences it is studying. Incremental work should not be the focus of Center activities; rather, new and creative directions are encouraged. A P30 should integrate and promote research in existing funded projects, to achieve new and creative directions. It is expected that individual core activities reflect a relationship to the integrating theme of the Center and the Center is expected to support the education, training, and mentoring of new investigators, and share findings, data and their resources. Open date(s): August 25, 2014. Application due date(s): September 25, 2014; September 25, 2015; September 26, 2016, by 5:00 PM local time of applicant organization. AIDS application due date(s): January 7, 2015; January 7, 2016; January 7, 2017, by 5:00 PM local time of applicant organization.

## **New FOAs Issued by the NIH Blueprint for Neuroscience Research**

**Neuroscience Information Framework (U24) [RFA-DA-15-009](#).**

**Blueprint Neurotherapeutics Network (BPN): Small Molecule Drug Discovery and Development for Disorders of the Nervous System (U44) [PAR-14-292](#)**

**Blueprint Neurotherapeutics Network (BPN): Small Molecule Drug Discovery and Development for Disorders of the Nervous System (UH2/UH3) [PAR-14-293](#)**

**Limited Competition for a Connectome Coordination Facility (R24) [RFA-MH-15-750](#)**

## **New FOAs Issued by the NIH Roadmap**

On July 24, 2014, the NIH Common Fund issued a Roadmap RFA entitled **NIH Transformative Research Awards (R01) [RFA-RM-14-003](#)**. The NIH Transformative Research Awards complement NIH's traditional, investigator-initiated grant programs by supporting individual scientists or groups of scientists proposing groundbreaking, exceptionally innovative, original and/or unconventional research with the potential to create new scientific paradigms, establish entirely new and improved clinical approaches, or develop transformative technologies. Little or no preliminary data are expected. Projects must clearly demonstrate the potential to produce a major impact in a broad area of biomedical or behavioral research. Open date: September 10, 2014. Application due date(s): October 10, 2014, by 5:00 PM local time of applicant organization. AIDS application due date(s): October 10, 2014, by 5:00 PM local time of applicant organization.

## **New RFAs Issued by Other NIH/HHS Components in which NIDA is a participant**

**U.S.-China Program for Research Toward a Cure for HIV/AIDS (R01) [RFA-AI-14-057](#)**

**Revisions to Add Biomedical Big Data Training to Active Institutional Training Grants (T32) [RFA-HG-14-005](#)**

**Predoctoral Training in Biomedical Big Data Science (T32) [RFA-HG-14-004](#)**

## **New PAs Issued by Other NIH/HHS Components in which NIDA is a participant**

**Administrative Supplements for Tobacco Regulatory Research on the Role and Impact of Flavors in Cigarettes, Cigars, E-Cigarettes and Smokeless Tobacco (Admin Supp) [PA-14-320](#)**

**Platform Delivery Technologies for Nucleic Acid Therapeutics (R43/R44) [PA-14-307](#)**

**Platform Delivery Technologies for Nucleic Acid Therapeutics (R41/R42) [PA-14-308](#)**

**High Throughput Screening (HTS) to Discover Chemical Probes (R21) [PAR-14-283](#)**

**High Throughput Screening (HTS) to Discover Chemical Probes (R01) [PAR-14-284](#)  
Connectomes Related to Human Disease (U01) [PAR-14-281](#)**

**Discovery of in vivo Chemical Probes (R01) [PAR-14-279](#)  
Ethical, Legal, and Social Implications (ELSI) of Genomic Research Small Research Grant  
Program (R03) [PA-14-277](#)**

**Ethical, Legal, and Social Implications (ELSI) of Genomic Research Regular Research  
Program (R01) [PA-14-276](#)**

**Ethical, Legal, and Social Implications (ELSI) of Genomic Research Exploratory/  
Developmental Research Program (R21) [PA-14-278](#)**

**Interventions for Health Promotion and Disease Prevention in Native American Populations  
(R01) [PAR-14-260](#)**

**Multidisciplinary Studies of HIV and Viral Hepatitis Co-Infection (R01) [PAR-14-255](#)**

**Administrative Supplements for the U.S.-Japan Brain Research Cooperative Program  
(BRCP) - U.S. Entity (Administrative Supplement) [PA-14-249](#)**

**Basic Research on HIV Persistence (R21) [PAR-14-248](#)**

**Basic Research on HIV Persistence (R01) [PAR-14-247](#)**

**National Cooperative Drug Discovery/Development Groups (NCDDG) for the Treatment of  
Mental Disorders, Drug or Alcohol Addiction (U19) [PAR-14-234](#)**

**Limited Competition for NIH-Industry Program: Discovering New Therapeutic Uses for  
Existing Molecules (UH3) [PAR-14-211](#)**

**Limited Competition for NIH-Industry Program: Discovering Pediatric New Therapeutic  
Uses for Existing Molecules (UH2/UH3) [PAR-14-210](#)**

**Limited Competition for NIH-Industry Program: Discovering New Therapeutic Uses for  
Existing Molecules (UH2/UH3) [PAR-14-212](#)**

**National Cooperative Drug Discovery/Development Groups (NCDDG) for the Treatment of  
Mental Disorders, Drug or Alcohol Addiction (U01) [PAR-14-184](#)**

### **Other Program Activities**

The Office of Diversity and Health Disparities (ODHD) led the **18<sup>th</sup> Annual 2014 NIDA Summer Internship Program**. Coordinated by Julie Huffman, Program Analyst, the program provided 55 high school and undergraduate students with eight to ten week summer research experiences in NIDA funded research labs around the country. This year, NIDA received over 300 applications from highly qualified high school and undergraduate students in the area of biomedical, behavioral,

clinical and the social sciences as it relates to substance-abuse research. A total of 77 applicants received offers, and 55 students accepted an internship. Selected interns were from all backgrounds including: African-American, American-Indian/Alaska Native, Asian-American, Hispanic/Latino, Native Hawaiian/Pacific Islander, and White/Caucasian. The NIDA Summer Internship program is designed to build the research pipeline among our budding scientists. Since its inception, over 900 students have been provided with invaluable research opportunities. NIDA funded investigators who volunteered to serve as mentors, as well as NIDA staff who assisted with reviewing applications, were instrumental to the program's success.

During FY 2014, The Office of Diversity and Health Disparities supported the **Diversity Supplements Program**. Coordinated by Pamela Goodlow, Public Health Analyst, the program funded 32 new diversity supplements (from 37 applications received), totaling \$1,918,839. The 32 funded recipients consisted of 1 undergraduate student, 12 pre-doctoral students, 11 postdoctoral fellows, and 8 early investigators; 17 of the recipients were female and 15 male. African American, Hispanic, Native American, Pacific Islander, and Asian American ethnicities were represented in this year's funded recipients.

NIDA's Women & Sex/Gender Differences Research Program awarded 27 **Women & Gender Junior Investigator Travel Awards** for the annual meeting of the College on Problems of Drug Dependence (CPDD), June 14-19, 2014 in San Juan, PR. These \$750 awards provide travel support to first author junior investigators who make presentations on the topic of women or sex/gender differences. These travel awards have been made annually beginning in 1999, and are designed to promote entry of junior investigators into drug abuse research on women and sex/gender differences. To further promote research in this field, NIDA published a mini-program book, Focus on Women & Sex/Gender Differences, for the CPDD meeting. Excerpted from the CPPD program book, it contains only those program listings related to women and sex/gender differences. The mini-program also contains a listing of all awardees since 1999, information about the Women & Gender Junior Investigator Travel Awardees presentations, announcement of the travel award program for CPDD 2015, and information on current NIDA funding opportunity announcements in this area. These efforts were led by Dr. Samia Noursi and were supported by Drs. Cora Lee Wetherington, Lynda Erinoff and Joe Frascella.

On May 14, 2014, the NIDA IRP Office of Education and Career Development hosted the **NIDA Poster Day and Mentoring Awards Ceremony**. IRP postdocs, grad students, and postbacs presented 51 posters. Mentoring Awards were presented to Drs. Nathan Marchant, Michael Baumann, Satoshi Ikemoto, and Irina Krasnova. Additionally, seven Program Officers from NIDA attended the event to view posters and meet with postdocs about grant submissions.

From April to June 2014, the Office of Education and Career Development, together with the NIH Office of Intramural Training and Education, have offered the following workshops or seminars: Advanced PubMed Training; How to Succeed in Medical School; Medical School Applications and Personal Statements; Mentoring a Summer Student; K99 Grant Writing Workshop; Postbac Poster Day (Bethesda); Scientists Teaching Science (9-week course); NIDA Poster Day and Mentoring Awards; NIH Career Symposium; Postbac Graduation Luncheon; Graduate School Planning and Applying; Applying to Medical School and Preparing for the MCAT; and Skill Blitz sessions on Assertiveness and Negotiating a Non-academic Position.

### **CTN Update**

A total of 55 protocols have been initiated since 2001, including multi-site clinical trials (39), multi-site surveys (3), studies in special populations (8), and secondary analyses of data across various trials (5). In addition, 28 ancillary studies have been supported by CTN and non-CTN funds. Nearly 17,000 participants have been enrolled in CTN studies. Information on protocols can be found at: <http://www.drugabuse.gov/about-nida/organization/cctn/ctn/research-studies>

### **NIDA's Blending Initiative**

Accelerating the dissemination of research-based drug abuse treatment into clinical practice is a priority for the National Institute on Drug Abuse (NIDA) and represents the core mission of the **Blending Initiative** (<http://www.drugabuse.gov/blending-initiative>). Through the Blending Initiative, NIDA partners with professional organizations and other institutions dedicated to the training and education of junior fellows/residents to support the development of expertise in substance use disorders (SUDs) within medical and clinical settings. These training awards aim: 1) to promote knowledge of evidence-based SUD treatment within medical specialties, 2) to advance medical care for patients with substance use disorders, and 3) to facilitate the academic growth, advanced education, and development of future researchers and clinicians in SUDs and medicine and thereby invest in the future of the field. Two training award partnerships have been initiated with the Society of Teachers of Family Medicine and the Society for Adolescent Health and Medicine.

### **New Common Data Elements Resource**

NIDA launched its **Common Data Elements (CDE)** website on June 12, 2014 ([cde.drugabuse.gov](http://cde.drugabuse.gov)). This website is available to all investigators and developers, to encourage them to use a core set of CDEs when developing case report forms. Use of this resource will help establish a standardized collection of CDEs compatible with Electronic Health Record Systems (EHRS) data elements and will support the meaningful exchange and integration of data between EHRS and research data systems to answer future research questions on substance use disorder (SUD) treatment. Many of these CDEs originated in the Substance Abuse and Addiction (SAA) project and other components of the Phenotypes and Exposures (PhenX) Toolkit. Different sets of CDEs are available and have been crafted to meet specific data needs such as clinical research and EHRS. EHR vendors are strongly encouraged to select SUD-relevant data elements for their systems from this list, with the goal of developing a core set of common standards nationwide. This current CDE list is expected to grow as new data elements are developed and validated by investigators and as the science evolves; it is thus hoped that the CDEs housed in this website will be universally useful for both EHRS and clinical research.

## COMMUNICATIONS

### PUBLICATIONS/VIDEOS

#### NIDA Publications and Online Resources

##### NIDA Notes (now online only)

A new podcast with Dr. Kevin Gray initiates a project to engage NIDA Notes readers in research in action. In the podcast, Dr. Gray presents a clinical trial (acetylcysteine for marijuana addiction) that is just starting. Coverage of two studies related to marijuana abuse have proven to be big readership draws as some states legalize the drug and others debate doing so. NIDA Notes currently receives around 35,000 article page views per month.

##### **Videos**

- **NIDA NOTES: NIDA @Work Presents, Dr. Elizabeth F. Howell**  
<http://youtu.be/3SOaxPZ-EG0>
- **NIDA TV Spotlight: Tobacco Partnership with FDA**  
<http://youtu.be/h82TqGml-JQ>
- **NIDA NOTES: NIDA @Work Presents, Dr. Joni Rutter**  
[http://youtu.be/W\\_kq2fWrQps](http://youtu.be/W_kq2fWrQps)
- **What's New at NIDA: Office of Science Policy & Communication Director's Notes for April**  
<http://youtu.be/IL62x6HLGiw>
- **NIDA's 2014 Avant-Garde Awards Announced**  
<http://youtu.be/pvV95T67uQQ>
- **NIDA TV Spotlight: Dr. ElSohly and the University of Mississippi Marijuana Farm**  
<http://youtu.be/IEJf2-TdU68>
- **National Institutes of Health-Take Your Child To Work Day @ NSC**  
[http://youtu.be/ayLr0\\_mIYuw](http://youtu.be/ayLr0_mIYuw)
- **What's New at NIDA: Office of Science Policy & Communication Director's Notes for June**  
<http://youtu.be/X7rIhbqXP8A>
- **Investigating Drug Abuse: Brain Neurons**  
<http://youtu.be/NI0nwKcNJ0Y>
- **Investigating Drug Abuse: Brain Imaging**  
<http://youtu.be/DaifOWSKjdA>
- **Investigating Drug Abuse: Building Molecular Tools**  
<http://youtu.be/H4rx7Nkw4Wk>
- **NIDA Notes: Researchers Speak Presents Dr. Antonello Bonci**  
<http://youtu.be/j1yf0eFs3aM>

##### CTN-Related Publications

Five editions of the CTN Bulletin Board were distributed. The Bulletin Board is an electronic report on the progress of the protocols, committees, and Node activity in the CTN. The Bulletin has wide readership within and outside the CTN and NIDA.

Data from 32 CTN studies are now available on the NIDA Data Share website <http://datashare.nida.nih.gov/>. Over 2,700 data sets have been downloaded by researchers from 55 countries. These data sets are in compliance with HIPAA and CDISC (Clinical Data Interchange Standards Consortium) standards in support of the interoperability required by the NIH Roadmap. The NIDA Data Share is also part of the Neuroscience Information Framework (NIF), which is a dynamic inventory of Web-based neuroscience resources: data, materials, and tools accessible via any computer connected to the Internet.

## **OTHER PUBLICATIONS**

Gordon AJ, Galanter M, Khalsa JH. Addressing addiction across borders: An international perspective on policies, scholarship, and collaboration. *Subst Abus.* 2014 Jun 3: [Epub ahead of print].

Macias Konstantopoulos WL, Dreifuss JA, McDermott KA, Parry BA, Howell ML, Mandler RN, Fitzmaurice GM, Bogenschutz MP, Weiss RD. Identifying patients with problematic drug use in the Emergency Department: Results of a multisite study. *Ann Emerg Med.* 2014 Jul 3. [Epub ahead of print].

Reider EE, Robertson EB, Sims BE. Does early intervention prevent health-risking sexual behaviors related to HIV/AIDS? *Prevention Science* 2014; 15 (S1): 1-5. DOI 10.1007/s11121-013-0455-x.

Tai B, Hu L, Ghitza UE, Sparenborg S, VanVeldhusien P, Lindblad R. Patient registries for substance use disorder. *Subst Abuse Rehabil* 2014; 5: 81-86.

Tai, B, Sparenborg S, Ghitza UE, Liu D. Expanding the National Drug Abuse Treatment Clinical Trials Network to address the management of substance use disorders in general medical settings. *Subst Abuse Rehabil* 2014; 5: 75-80.

## **COMMUNITY AND PRESS EVENTS**

### **NIDA's Deputy Director Speaks at US-Mexico Addiction Summit**

On April 28, 2014, NIDA Deputy Director Dr. Wilson Compton presented at the U.S.-Mexico Addiction Summit in Albuquerque, NM about addiction. In anticipation of his participation, he was interviewed by the *Albuquerque Journal* about the effects of marijuana on the body and brain.

### **NIDA Director Presents at APA Conference about Addiction**

On May 3, 2014, NIDA Director Dr. Nora Volkow presented *Frontiers of Science: Advances in Addiction Research* to attendees at the 167th American Psychiatry Association Annual Meeting in New York City, NY. The NIDA press team arranged for an interview with APA TV as well as provided social media outreach.

### **NIDA Director Speaks at World Science Festival**

On May 31, 2014, Dr. Volkow presented on “*The Brain and Addiction*” at the World Science Festival in New York City, NY, where several leading scientists discussed the latest developments

in the fields of addiction neuroscience to over 600 attendees. The NIDA press team provided logistical and social media support for the event.

#### **NIDA Director Receives Nathan B. Eddy Award**

On June 15, 2014, NIDA Director Dr. Nora Volkow received the Nathan B. Eddy Award from the College on Problems of Drug Dependence (CPDD) in San Juan, Puerto Rico. The Nathan B. Eddy Award is named after a pioneer in the field of drug dependence and acknowledges outstanding research efforts that have advanced our knowledge of drug dependence. Dr. Volkow delivered a keynote address on the state of addiction research at the annual meeting of the CPDD, which featured 800 presentations by scientists from the United States and other nations, many of them supported by grants from NIDA. The NIDA press team issued a media advisory and provided social media support for the event.

#### **Dr. Wilson Compton Presents at 2014 ESOF Conference in Copenhagen**

Deputy Director Dr. Wilson Compton presented on three panels about brain addiction, e-cigarettes and global policy on drug abuse at the ESOF 2014 Copenhagen Euroscience Open Forum held in Denmark June 21-26, 2014. The NIDA press team coordinated local press interviews on these topics.

#### **Dr. Nora Volkow Receives Students Against Destructive Decisions (SADD) Award**

On June 24, 2014, Dr. Volkow received the 2014 National Outstanding Contribution Award at the SADD national conference in Washington, D.C. The award is presented to “that individual or group who has made a contribution that stands out in size, creativity, sacrifice or commitment to SADD or to the themes of SADD, including the health and safety of teens.” NIDA promoted the award through social media, including Twitter and Facebook.

#### **Addiction Science Award Winners Present at NIDA**

On June 30, 2014, the 2014 winners of NIDA’s Addiction Science Awards, part of the Intel International Science and Engineering Fair (ISEF) -- the world’s largest science competition for high school students -- presented their projects to NIDA Director Nora Volkow and other NIDA scientists and were given a tour of the NIH campus. The Addiction Science Awards are coordinated by NIDA as well as Friends of NIDA, a private group dedicated to furthering NIDA’s mission. The ISEF awards ceremony occurred on May 15, 2014, at the Los Angeles Convention Center in CA and NIDA Press Officer Dr. Sheri Grabus served as judge for the Addiction Science Awards. The press team sent information about each winner to their hometown newspapers and schools, to internal NIDA and NIH publications, and provided social media outreach.

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### **PRESS RELEASES**

**May 6, 2014 - Dr. Joni Rutter to lead NIDA’s genetics and basic science research division.**  
*Rutter to lead institute’s efforts to explore the relationship between genes, environment, and the neuroscience of addiction*

NIDA is pleased to announce that Joni Rutter, Ph.D., has been named Division Director for the Division of Basic Neuroscience and Behavioral Research (DBNBR). For the past three years, Dr. Rutter has served as acting director of DBNBR, leading her staff to build strategic directions for the science supported by the division.

“We are excited to welcome Dr. Rutter as the new DBNBR Division Director,” said NIDA Director Dr. Nora D. Volkow. “Her extensive experience with how the study of genetics ties into drug abuse strengthens her role as a leader in a division dedicated to fundamentally preventing and stopping drug abuse.”

The division’s primary goal is to support basic biomedical and behavioral research to address the public health problem of drug addiction, including the neurobiological and behavioral mechanisms of drugs of abuse and their consequences. DBNBR’s research portfolio includes research into the role of drug use in accelerating the progression and the transmission of HIV/AIDS and the effects of chronic pain and its treatments on drug use and addiction processes. DBNBR also supports research into sex and gender differences as they relate to drug use and addiction.

Dr. Rutter’s career spans 15 years of excellent basic and clinical research in human genetics and the study of genetic and environmental risk factors in the fields of cancer and addiction. She has earned a national and international reputation for her diverse and unique expertise in more than 50 publications in journals, and she received several scientific achievement awards, including a SmithKline Beecham Student Award in Pharmacology, a Janssen Research Foundation Young Investigator Award, and a Fellowship Achievement Award from the National Cancer Institute. Rutter has also built, supported, and maintained the NIDA Genetics Consortium, a group of more than 20 investigators who study addiction genetics.

“I am delighted to lead this division’s efforts to advance the basic science of drug abuse and addiction,” said Dr. Rutter. “My background as a geneticist fits well with NIDA’s commitment to staying at the forefront of scientific discovery, maximizing available resources to foster innovative ideas and scientific collaborations.”

Prior to joining NIDA in 2003, Dr. Rutter received her Ph.D. from the Department of Pharmacology and Toxicology, Dartmouth Medical School, Hanover, New Hampshire. Upon completing her doctoral degree, she remained at Dartmouth Medical School as a research associate for a short period of time. She then accepted a fellowship at the National Cancer Institute within the Division of Cancer Epidemiology and Genetics to fortify her training in human genetics. Her scientific objective is to integrate genetic principles with the study of how drugs and chemicals act on the brain. <http://www.drugabuse.gov/news-events/news-releases/2014/05/dr-joni-rutter-to-lead-nidas-genetics-basic-science-research-division>

### **May 16, 2014 – Study of third hand nicotine from e-cigarette exposure wins top NIH Addiction Science Award**

*Other honors awarded to project using theoretical model of GABA(A) receptor to screen potential medications; study exploring cognitive control in multitaskers*

An exploration of third hand nicotine exposure from e-cigarettes was given the top Addiction Science Award at the 2014 Intel International Science and Engineering Fair (ISEF)—the world’s largest science competition for high school students. The awards are coordinated by the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health, and Friends of NIDA, a coalition that supports NIDA’s mission. The Intel ISEF Addiction Science Awards were presented at a ceremony Thursday night at the Los Angeles Convention Center.

First place distinction was awarded to Lily Wei Lee, a high school senior at Stuyvesant High School in New York City for her project, Assessment of Third Hand Exposure to Nicotine from Electronic Cigarettes. The 18 year-old wondered whether e-cigarette use could pose a risk of third hand exposure, where nicotine from vapors sticks to surfaces to affect non-users even if they aren't exposed to the e-cigarette use. She took three brands of e-cigarettes and filled them with varying nicotine concentrations. Using a syringe to ensure consistent puffs, e-cigarettes were vaped, after which nicotine concentrations were measured from surrounding surfaces – a glass window, vinyl walls, tiled floor, metal, and wood. Lee found significant increases in the amount of nicotine on all five surfaces; the floor and window had the greatest nicotine levels. The amount of residual nicotine depended on the particular brand used. Lee hopes to next explore whether e-cigarette usage is also related to increased third hand exposure to cancer-causing agents.

“This bright, young scientist showed that non-users can be exposed to nicotine residue from just one e-cigarette, even if the e-cigarette usage occurred some time ago,” said NIDA Director Nora D. Volkow, M.D. “Chronic e-cigarette use would be expected to produce even higher levels of third hand nicotine exposure, and it’s unclear how such exposure could impact the health of close family members, friends, and coworkers who are regularly exposed to these environments.”

The second place distinction went to Aakash Jain, a high school senior at Brophy College Preparatory in Phoenix. His project, Computational Analysis of the GABA(A) Receptor, used computational and statistical techniques to provide insight into the three-dimensional structure of the GABA(A) receptor – which is believed to be involved in various disease conditions such as depression, schizophrenia, Parkinson’s disease, and addiction. After developing his model, Jain then screened approximately 2,500 drugs to determine if their structure would be a tight fit for the GABA(A) receptor. Through this process, Jain was able to identify several compounds that deserved further research into their possible clinical applications.

Winning third place distinction were two high school juniors, Alexandra Ulmer and Sarayu Caulfield from Oregon Episcopal School in Portland. Their project, Capacity Limits of Working Memory: The Impact of Multitasking on Cognitive Control and Emotion Recognition in the Adolescent Mind, explored whether experience with multitasking affected behaviors controlled by the prefrontal cortex, an area involved in self-control that is negatively impacted by drug use. They found that experienced multitaskers were better at multitasking, switching priorities, and filtering out distracting, irrelevant tasks. However, they were less able to focus on a single task, possibly because they are anticipating new information. These results may be especially relevant to today’s young, who are exposed to more streams of electronic information compared to previous generations.

Judges for this year’s Addiction Science Award included NIDA-funded researchers from the University of California, Los Angeles: Keith Heinzerling, M.D., Mitchell Wong, M.D., Ph.D., and Bridget Freisthler, Ph.D.; and NIDA’s Sheri Grabus, Ph.D.

The Friends of NIDA provides funding for the awards as part of its ongoing support of research into the causes, consequences, prevention, and treatment of drug abuse and addiction.

“These incredibly gifted, young students demonstrated innovation well beyond their years,” said William Dewey, Ph.D., president and chair of the Executive Committee, Friends of NIDA, as well as the Louis S. and Ruth S. Harris Professor and chair, Department of Pharmacology and Toxicology, Virginia Commonwealth University, in Richmond. “From looking at the effects of

new technologies on health and cognition to computerized receptor modeling, this year's winners covered a wide range of topics. We hope this award will encourage them to pursue a career in addiction science.”

This year, about 1,700 students from 70 countries, regions and territories participated in the Intel ISEF competition, coordinated by the Society for Science and the Public. The nonprofit organization partners with Intel—along with dozens of other corporate, academic, government and science-focused sponsors—to provide support and awards each year. Addiction Science Winners receive cash awards provided by Friends of NIDA, with a \$2,500 scholarship for the first-place honoree. NIDA has developed a special section on its website, which includes other resources on addiction science, to highlight the winning projects and to help science fair entrants understand the criteria for the awards: The NIDA Science Fair Award for Addiction Science.

<http://www.drugabuse.gov/news-events/news-releases/2014/05/study-third-hand-nicotine-e-cigarette-exposure-wins-top-nih-addiction-science-award>

### **May 19, 2014 - 2014 Avant-Garde Awards focus on strengthening the immune system**

*NIH's HIV/AIDS research awards offer hope in battling HIV infection and improving long-term outcomes in HIV-infected drug users*

With proposals ranging from enhancing the immune system's ability to fight HIV infection to improving long-term immune health in HIV-infected drug users, three scientists have been chosen to receive the 2014 Avant-Garde Award for HIV/AIDS Research from the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health. The three scientists, Drs. Stephen Waggoner, Heinrich Gottlinger, and Melanie Ott, will each receive \$500,000 per year for five years to support their research. NIDA's annual Avant-Garde award competition, now in its seventh year, is intended to stimulate high-impact research that may lead to groundbreaking opportunities for the prevention and treatment of HIV/AIDS in drug users.

**Awardee: Stephen Waggoner, Ph.D.,**  
Cincinnati Children's Hospital Medical Center

#### **Project: A revolutionary vaccine approach to prevent HIV infection in substance abuse**

Dr. Waggoner's group will play an important role in the ongoing science of HIV vaccine development. His project will focus on preventing natural killer cells from destroying activated helper CD4 cells, to strengthen vaccine effectiveness. The CD4 helper cells support the functioning of the immune system against infections, including HIV. A vaccine that enhances the immune system's long-term ability to resist infection could enhance the antibodies against HIV and delay progression to AIDS in vulnerable populations. This will be particularly valuable among drug users who are much less likely to be treated and to have some of the worst outcomes.

“Millions of people, including those with substance use disorders, would benefit from the development of an effective HIV vaccine,” said Waggoner. “This award will permit our group to pursue a revolutionary vaccination approach designed to overcome natural roadblocks imposed by the immune system in order to prevent new HIV infections.”

**Awardee: Heinrich Gottlinger, M.D.,**  
University of Massachusetts Medical School, Worcester

#### **Project: Mechanism of HIV cell-cell transmission of relevance to substance users**

Dr. Gottlinger will explore the roles of two specific proteins involved in HIV's movement from an infected to an uninfected cell. Because this route of infection allows HIV to evade the immune system's antibodies, a clearer understanding of this process can inform new strategies to prevent HIV and slow HIV disease progression. Such strategies could be especially relevant for injection drug users, who may be exposed to HIV through sharing syringes that contain infected cells. "HIV transmission via direct cell-to-cell contact is vastly more efficient than the transmission of cell-free virus, and could contribute substantially to the transmission of HIV by blood contact, as may occur among injection drug users. The Avant-Garde award provides us with a unique opportunity to explore in detail how certain cellular pathways are exploited by HIV to move from one cell to another so efficiently," said Gottlinger. "We hope that the planned research will yield translational insights into how to block this important mode of transmission and thus benefit all patients infected with HIV, especially substance users."

**Awardee: Melanie Ott, M.D., Ph.D.,**

Gladstone Institutes, San Francisco

**Project: A new model of accelerated immune aging in HIV-infected drug users**

Dr. Ott will investigate the role of an enzyme (SIRT-1) in slowing accelerated immune aging resulting from either long-term HIV infection or regular drug use. Because SIRT-1 appears to protect against overworked immune activation that can eventually exhaust immune cell functions, new therapies aimed at this enzyme could delay immune aging and its related health risks in HIV-infected drug users. "The goal of our research is to transform our understanding of how HIV and drug abuse affect the immune system and the aging process," Ott said. "We hope to identify novel links between HIV, abused substances and the biological pathways of aging that lead to potential therapeutic strategies to slow the accelerated immune aging in this patient population."

"These innovative approaches can shed light on mechanisms through which HIV damages or circumvents the immune system, and how these effects interact with those of drugs of abuse" said NIDA Director Nora D. Volkow, M.D. "By learning more about these underlying processes, not only might this research slow the progression and transmission of HIV infection, but it could improve the long-term health of those already infected."

These awardees were among the many applicants whose proposals reflect diverse scientific disciplines and approaches to HIV/AIDS research. The Avant-Garde Awards are modeled after the NIH Pioneer Awards and are granted to scientists of exceptional creativity who propose high-impact research that could open new avenues for prevention and treatment of HIV/AIDS among drug abusers.

For information about NIDA's AIDS Research Program, including the [Avant-Garde Award Program for HIV/AIDS Research](http://www.drugabuse.gov/AIDS), go to [www.drugabuse.gov/AIDS](http://www.drugabuse.gov/AIDS).

Waggoner, Gottlinger, and Ott are funded under grant numbers DA038017, DA038034 and DA038043, respectively. <http://www.drugabuse.gov/news-events/news-releases/2014/05/2014-avant-garde-awards-focus-strengthening-immune-system>

**May 20, 2014 - NIDA offers tools for talking to teens about marijuana**

*Guides target both teens and parents with up-to-date science-based facts on marijuana*

Two updated booklets about marijuana for teens and their parents will help families sort out marijuana myths from science-based facts. The revamped tools come from the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health. These booklets are being released during the Substance Abuse and Mental Health Services Administration's [National Prevention Week 2014](#) on the day dedicated to the Prevention of Prescription Drug Abuse and Marijuana Use.

[Marijuana Facts for Teens](#) discusses the often confusing themes of health consequences of marijuana use in this age group, its effect on the developing brain, its addiction risk, and what we know about its potential as a medicine. [Marijuana: Facts Parents Need to Know](#) has updated tips for parents on how to tell if their child is using marijuana and how to talk about the issue with their teen in a climate of heated public debates over legalization. Both revised publications are now available online. Marijuana Facts for Teens is also available in [print](#), and Marijuana: Facts Parents Need to Know will be available in print soon.

Along with updated data and research-based information, new sections in both guides cover the dangers of K2/Spice (often referred to as synthetic marijuana) and new research that shows smoking marijuana regularly as a teen can lower IQ. Both guides also include new information on the state of the science related to potential therapeutic uses for chemical compounds found in the marijuana plant.

NIDA's 2013 [Monitoring the Future](#) survey results indicate that by the time they graduate high school, 45.5 percent of U.S. teens will have tried marijuana at least once. Also, 36.4 percent of 12<sup>th</sup> graders, 29.8 percent of 10<sup>th</sup> graders, and 12.7 percent of eighth graders say they smoked it during the past year. More than 6 percent of seniors say they smoke it daily, putting them at higher risk for addiction.

“Our goal for teens is to give them the straight, science-based facts so that they can make smart choices and be their best selves—without drugs,” said NIDA director Dr. Nora D. Volkow. “We hope that they will continue the conversation and share this information with their peers, parents, teachers, and others.” For more information for teens about drug abuse, please visit the [NIDA for Teens](#) website. <http://www.drugabuse.gov/news-events/news-releases/2014/05/nida-offers-tools-talking-to-teens-about-marijuana>

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### **May 21, 2014 - NIH Pain Consortium's first pain care curriculum improves clinical skills**

*Interactive module improves medical student care for elderly back pain patient "Edna"*

An online training module designed for the evaluation and care of chronic pain greatly improved medical student clinical skills, according to a report in the Journal of the American Geriatrics Society. The module, built by the University of Pittsburgh and using an elderly woman with chronic lower back pain as a case study, is the first curriculum resource created through the efforts of the National Institutes of Health Pain Consortium's Centers of Excellence in Pain Education program (CoEPEs). The program was developed in response to the Affordable Care Act's mandate to advance the science, research, care and education of pain.

“Management of chronic lower back pain is one of the most common and difficult problems that patients and health care providers face,” said Josephine P. Briggs, M.D., director of the NIH's National Center for Complementary and Alternative Medicine (NCCAM) and member of the NIH

Pain Consortium Executive Committee. “The educational materials that have been developed through this partnership will be a great asset in helping the next generation of physicians build clinical skills to support their chronic pain patients.”

The CoEPEs were selected in 2012 to act as hubs for the development, evaluation, and distribution of pain management curriculum resources for medical, dental, nursing, and pharmacy schools. The NIH Pain Consortium developed the centers to improve how health care professionals are taught about pain and its treatment. The module is the first to be completed and evaluated for effectiveness.

A team of six experts in education, information technology, pain management, and geriatrics at the University of Pittsburgh developed the module, focusing on common errors in clinical exams, expert modeling, interactivity, and feedback. The module presented a standardized case of an elderly back pain patient called Edna, with brief video clips that showed her interacting with her clinician. The module also contains a multiple choice pre-test, interactive questions, and a multiple choice post-test. Twenty-seven medical students were exposed to the module and 28 were not. The students in the group exposed to the module did significantly better on their objective structured clinical examinations, an exam during which medical students rotate through multiple stations, each with an objective examiner, demonstrating clinical skills and knowledge while interviewing real or simulated patients. Ninety-three percent of the students in the exposed group passed the exam, compared to 60 percent of the non-exposed group. To view the paper (published May 15), go to <http://onlinelibrary.wiley.com/doi/10.1111/jgs.12871/abstract>.

“To our knowledge, this is the first study that has demonstrated the potential of an online interactive module to improve medical student clinical skills related to evaluating a patient with chronic pain,” said the study’s lead author Debra K. Weiner, M.D. “While our module focused specifically on an older adult with chronic low back pain, we see this type of educational intervention as a powerful and efficient curriculum tool for a variety of patient scenarios. We look forward to continuing to work with the NIH Pain Consortium in its effort to improve pain care across the country for many different pain conditions that plague patients of all ages.”

The CoEPE program is coordinated by the National Institute on Drug Abuse (NIDA), one of 27 Institutes and Centers at the National Institutes of Health. “We are so pleased that the first successful curriculum product created by the CoEPEs relates to solutions for chronic back pain, one of the most common pain conditions in America,” said NIDA Director Nora D. Volkow, M.D. “While we know opioids can be powerful clinical allies, a balanced approach that includes a range of pain management options is needed to ensure that people suffering from chronic pain can get the relief they need while minimizing the potential for abuse.”

The CoEPEs are creating and testing online, case-based pain education modules for use in their own teaching institutions. Edna and several other modules will be made available to other teaching institutions beginning in the fall of 2014 at <http://painconsortium.nih.gov/CoEPEs.html>. These modules are also accessible by the general public to help them learn how to discuss chronic pain with their doctors. A preview of the module is available at <http://bit.ly/1g3HTo4>. Chronic pain affects approximately 100 million Americans, costing up to \$635 billion in medical treatment and lost productivity and contributing to poor quality of life. Yet, pain treatment is not taught extensively in many health professional schools. The curriculum resources developed by the CoEPEs aim to advance the assessment and safe treatment of multiple pain conditions for diverse

population groups, while minimizing the abuse of opioid pain relievers. The curriculum resources developed by this program will teach about the various types of chronic pain, medications to treat specific pain conditions, and factors that contribute to both under- and over-prescribing of pain medications. The courses will include the latest research in complementary and integrative pain management. The news release announcing the selection of the specific CoEPEs can be found here: <http://painconsortium.nih.gov/CoEPEs.html>.

The sponsors of this Pain Consortium initiative are NIDA: Lead; Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), National Center for Complementary and Alternative Medicine (NCCAM), National Institute of Dental and Craniofacial Research (NIDCR), National Institute of Nursing Research (NINR), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Institute of Neurological Disorders and Stroke (NINDS), National Institute on Aging (NIA), Office of Behavioral and Social Sciences Research (OBSSR), and the Office of Research on Women's Health (ORWH).

NIH supports the full spectrum of pain research from basic understanding of pain mechanisms through translation of discoveries into treatments and prevention strategies. In FY 2013, NIH supported an estimated \$400 million in research focused on chronic pain, not including the related diseases that often cause chronic pain, such as cancer, arthritis, diabetes, and stroke. The details of individual pain-focused grants are publicly available on the NIH RePORTER website. Enhancing education of pain care professionals was highlighted in the June 2011 Institute of Medicine report "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research," a report mandated by the 2010 Patient Protection and Affordable Care Act. <http://www.drugabuse.gov/news-events/news-releases/2014/05/nih-pain-consortiums-first-pain-care-curriculum-improves-clinical-skills>

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### **June 3, 2014 - MDMA can be fatal in warm environments**

*NIH preclinical study suggests higher risk of death is associated with warmer brain temperature* A moderate dose of [MDMA](#), commonly known as Ecstasy or Molly, that is typically nonfatal in cool, quiet environments can be lethal in rats exposed to conditions that mimic the hot, crowded, social settings where the drug is often used by people, a study finds. Scientists have identified the therapeutically-relevant cooling mechanism to enable effective interventions when faced with MDMA-induced hyperthermia. The study, publishing tomorrow in the *Journal of Neuroscience*, was conducted by researchers at the National Institute on Drug Abuse's Intramural Research Program (NIDA IRP). NIDA is a part of the National Institutes of Health.

While MDMA can have a range of adverse health effects, previous studies have shown that high doses of MDMA increase body temperature, while results with moderate doses were inconsistent. This has led some people to assume that the drug is harmless if taken in moderation. However, this study shows that in rats even moderate doses of MDMA in certain environments can be dangerous because it interferes with the body's ability to regulate temperature.

"We know that high doses of MDMA can sharply increase body temperature to potentially lead to organ failure or even death," said NIDA Director Dr. Nora D. Volkow. "However, this current study opens the possibility that even moderate doses could be deadly in certain conditions."

It is impossible to predict who will have an adverse reaction even to a low dose of MDMA.

However, in this study scientists gave the rats low to moderate doses that have been shown in past

studies to not be fatal. They monitored the rats to determine drug-induced changes in brain and body temperature and in the body's ability to cool itself through blood vessel dilation. When rats were alone and in a room-temperature environment, a moderate dose of MDMA modestly increased brain and body temperature and moderately diminished the rats' ability to eliminate excessive heat. However, when researchers injected the same dose in rats that were either in a warmer environment or in the presence of another rat in the cage, brain temperature increased, causing death in some rats. These fatal temperature increases were because the drug interfered with the body's ability to eliminate heat.

“These results demonstrate that the use of MDMA in certain warm, social settings could be more dangerous than commonly believed,” said Dr. Eugene Kiyatkin, first author on the study and NIDA IRP scientist. “Even with moderate doses, we saw drug-induced, fatal brain hyperthermia during conditions of social interaction and in warm environments.”

These findings further suggest that medical interventions aimed at increasing the efficiency of whole-body cooling by targeting blood vessel constriction in the skin could be therapeutically relevant for counteracting the development of MDMA-induced hyperthermia.

For a copy of the study, please visit [www.jneurosci.org/](http://www.jneurosci.org/). For more information on Ecstasy, please visit <http://www.drugabuse.gov/drugs-abuse/mdma-ecstasy> or <http://www.drugabuse.gov/news-events/news-releases/2014/06/mdma-can-be-fatal-in-warm-environments>.

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#### **June 4, 2014 - NIDA review summarizes research on marijuana's negative health effects**

*Comprehensive review published in the New England Journal of Medicine also discusses why risks are greatest for teen users*

The current state of science on the adverse health effects of marijuana use links the drug to several significant adverse effects including addiction, a review reports. The article, published today in the New England Journal of Medicine, is authored by scientists from the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health.

The review describes the science establishing that marijuana can be addictive and that this risk for addiction increases for daily or young users. It also offers insights into research on the gateway theory indicating that marijuana use, similar to nicotine and alcohol use, may be associated with an increased vulnerability to other drugs.

The authors review literature showing that marijuana impairs driving, increasing the risk of being involved in a car accident and that these risks are further enhanced when combining marijuana with alcohol. The authors also discuss the implications of rising marijuana potencies and note that, because older studies are based on the effects of marijuana containing lower THC – the main psychoactive chemical found in marijuana – stronger adverse health effects may occur with today's more potent marijuana.

The reviewers consider areas in which little research has been conducted. This includes possible health consequences of secondhand marijuana smoke; the long-term impact of prenatal marijuana exposure; the therapeutic potential of the individual chemicals found in the marijuana plant; and effects of marijuana legalization policies on public health.

The scientists focus on marijuana's harmful effects on teens, an age group in which the brain rapidly develops, which is one factor that could help explain increased risks from marijuana use in this population. Research suggests that marijuana impairs critical thinking and memory functions during use and that these deficits persist for days after using. In addition, a [long-term study](#) showed that regular marijuana use in the early teen years lowers IQ into adulthood, even if users stopped smoking marijuana as adults.

The NIDA-supported 2013 Monitoring the Future Survey says that 6.5 percent of 12th graders report daily or near-daily marijuana use, with 60 percent not perceiving that regular marijuana use can be harmful. "It is important to alert the public that using marijuana in the teen years brings health, social, and academic risk," said lead author and NIDA Director Dr. Nora D. Volkow. "Physicians in particular can play a role in conveying to families that early marijuana use can interfere with crucial social and developmental milestones and can impair cognitive development."

This review emphasizes that marijuana use is likely to increase as state and local policies move toward legalizing marijuana for medical or recreational purposes. As use increases, so might the number of people likely to suffer negative health consequences, the review says.

For more information on marijuana and its health consequences, go to:

[www.drugabuse.gov/publications/drugfacts/marijuana](http://www.drugabuse.gov/publications/drugfacts/marijuana).

Reference: Adverse Health Effects of Marijuana Use, by Nora D. Volkow, M.D., Ruben D. Baler, Ph.D., Wilson M. Compton, M.D., and Susan R.B. Weiss, Ph.D., published online June 4, 2014 in The New England Journal of Medicine <http://www.drugabuse.gov/news-events/news-releases/2014/06/nida-review-summarizes-research-marijuanas-negative-health-effects>

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### **July 17, 2014 - NIH system to monitor emerging drug trends**

*Data from the National Drug Early Warning System will promote rapid and effective public health responses*

An innovative National Drug Early Warning System (NDEWS) is being developed to monitor emerging trends that will help health experts respond quickly to potential outbreaks of illicit drugs such as heroin and to identify increased use of designer synthetic compounds. The system will scan social media and Web platforms to identify new trends as well as use conventional national- and local-level data resources.

The University of Maryland's Center for Substance Abuse Research (CESAR) will receive five years of funding from the National Institute on Drug Abuse (NIDA), part of the National Institutes of Health, to develop NDEWS.

"NDEWS will generate critically needed information about new drug trends in specific locations around the country so rapid, informed, and effective public health responses can be developed precisely where needed," said NIDA Director Dr. Nora D. Volkow. "By monitoring trends at the local level, we hope to prevent emerging drug problems from escalating or spreading to surrounding regions."

Information about designer synthetic drugs – including different ways to possess and use them – is rapidly spread to millions of people through the Internet and social media. Also, other drug trends may quickly change. An example is the recent [increases in heroin use](#) among many regions across

the country. Conventional methods to monitor drug trends may not ask about emerging drugs, do not always provide information about the types of drugs used at the community level, and may need a year or more to collect and report information.

Currently, NIDA conducts local-level surveillance on drug use through the [Community Epidemiology Work Group \(CEWG\) network](#). For the last 38 years, CEWG has relied on drug addiction experts to analyze data from various other sources and summarize this information in semiannual reports from sentinel sites - major metropolitan areas and some states from around the United States. NDEWS will continue to monitor drug trends in sentinel sites around the country using many of the national and local data sources that have been utilized by CEWG. To expand upon these efforts and produce an enhanced national system to reflect that new drug trends may emerge outside of sentinel sites, NDEWS will establish a virtual community - a network of addiction experts across the country who will regularly communicate with each other to:

- Detect emerging drug trends using national and local data sources (existing surveys, various drug-related listservs and networks, and social media and web scans).
- Dispatch a rapid response team at hot spots - local areas with reported rapid increases in emerging drugs. This team will assess the outbreak and collect anonymous urine samples – provided by criminal justice drug testing programs – for enhanced analysis that includes testing for synthetic drug metabolites.
- Quickly disseminate information to the public using traditional and social media, websites, publications and newsletters.

“NDEWS promises to provide the country with critically needed real-time information about changing drug use patterns in communities across the country,” said lead investigator Dr. Eric Wish of CESAR. “It will utilize social media and other innovative technologies to identify emerging drugs and trends and to quickly disseminate important findings to experts and interested citizens. This opportunity builds on CESAR’s over 20 years of experience monitoring and reporting on emerging drugs.”

The five-year project begins in August 2014. For more information on the current system, CEWG, please go to: [www.drugabuse.gov/about-nida/organization/workgroups-interest-groups-consortia/community-epidemiology-work-group-cewg](http://www.drugabuse.gov/about-nida/organization/workgroups-interest-groups-consortia/community-epidemiology-work-group-cewg).

Development of NDEWS will be funded under DA038360.

<http://www.drugabuse.gov/news-events/news-releases/2014/07/nih-system-to-monitor-emerging-drug-trends>

### **SCIENCE SPOTLIGHTS AND ANNOUNCEMENTS**

**May 9, 2014** - *Early interventions can decrease drug use in young women.* A NIDA-funded study shows that adolescent girls who were involved in the juvenile justice system and participated in Multidimensional Treatment Foster Care (MTFC) showed decreased drug use over a two-year period in young adulthood. MTFC is a family-focused prevention program to encourage healthy behaviors in at-risk teens within the foster care system. <http://www.drugabuse.gov/news-events/news-releases/2014/05/early-interventions-can-decrease-drug-use-in-young-women>

**May 27, 2014** - *More Colorado drivers in fatal car crashes testing positive for marijuana.* A new NIAAA- and NIDA-funded study shows an increased number of marijuana-positive Colorado drivers involved in fatal motor vehicle crashes since Colorado's legalization of medical marijuana in 2009. A similar increase was not seen in the 34 states that did not have medical marijuana laws when this study was conducted. During the same time period, there was no change in the number of alcohol-impaired drivers in fatal motor vehicle crashes in either Colorado or the 34 then non-medical marijuana states. <http://www.drugabuse.gov/news-events/news-releases/2014/05/more-colorado-drivers-in-fatal-car-crashes-testing-positive-marijuana>

**June 10, 2014** - *CPDD conference features NIDA Director Dr. Nora Volkow as well as Media Forum.* Dr. Nora Volkow, Director of NIDA, will deliver a keynote address on the state of addiction research at the annual meeting of the College on Problems of Drug Dependence (CPDD) in San Juan, Puerto Rico on June 15. The conference features 800 presentations by scientists from the United States and other nations, many of them supported by grants from NIDA. Dr. Volkow will also receive CPDD's Nathan B. Eddy Award, named after a pioneer in the field of drug dependence. <http://www.drugabuse.gov/news-events/news-releases/2014/06/cpdd-conference-features-nida-director-dr-nora-volkow-well-media-forum>

**June 16, 2014** - *Study compares effectiveness of oral drug tests for recent marijuana use.* A variety of oral drug testing devices are available to determine recent marijuana use. For the first time, a new NIDA study compares the ability of these devices to accurately detect specific cannabinoids – the chemical compounds found in marijuana. The researchers looked at diagnostic sensitivity, specificity, and efficiency of the tests. In particular, the study identified devices that perform better at determining cannabinoid concentrations within certain time periods of detection in occasional and frequent users. <http://www.drugabuse.gov/news-events/news-releases/2014/06/study-compares-effectiveness-oral-drug-tests-recent-marijuana-use>

**July 1, 2014** - *Social media can influence teens with pro-drug messages.* A NIDA-funded study analyzed the content and demographic reach of a popular pro-marijuana Twitter handle in 2013 and found that only ten percent of the messages mentioned any risky behaviors associated with marijuana use. <http://www.drugabuse.gov/news-events/news-releases/2014/07/social-media-can-influence-teens-pro-drug-messages>

**July 3, 2014** – *New brain imaging dataset now available to enhance reliability and reproducibility.* A new NIDA-supported dataset will now allow researchers to compare their MRI-based scans against more than 10,000 brain images, thereby enhancing reliability and reproducibility. The Consortium for Reproducibility and Reliability (CoRR) dataset is managed by the Child Mind Institute (CMI). CoRR was organized by a team of scientists, engineers, and technicians from CMI, the Nathan Kline Institute, the Institute of Psychology, and the Chinese Academy of Sciences with the goals of actively taking on the challenge of exploring brain development and identifying the signatures of mental illness and markers of treatment response. <http://www.drugabuse.gov/news-events/news-releases/2014/07/new-brain-imaging-dataset-now-available-to-enhance-reliability-reproducibility>

**July 15, 2014:** *Passive e-cigarette exposure may urge young adults to smoke.* A NIDA-funded study shows that being around someone who is using (vaping) an e-cigarette can trigger a desire for tobacco cigarettes in young adults who regularly smoke. This passive exposure to e-cigarette use also increased desire for an e-cigarette. These results highlight the need for more research into the

effects of exposure to e-cigarettes in order to help prevent smoking in young adults.

<http://www.drugabuse.gov/news-events/news-releases/2014/07/passive-e-cigarette-exposure-may-urge-young-adults-to-smoke>

**July 30, 2014** – *Regular marijuana users may have impaired brain reward centers.* New research shows that regular marijuana users show impairments in the brain’s ability to respond to dopamine – a brain chemical that is involved in reward, among other functions. Although this research can’t determine if regular marijuana use causes deficits in brain reward centers – or if users take marijuana to compensate for less reactive dopamine systems – these results could help explain why regular marijuana users are more prone towards depression, anxiety, irritability, and increased sensitivity to stress. <http://www.drugabuse.gov/news-events/news-releases/2014/07/regular-marijuana-users-may-have-impaired-brain-reward-centers>

**August 20, 2014** – *Journal issue explores early interventions to prevent risky sexual behaviors related to HIV/AIDS.* A special issue of the journal *Prevention Science* spotlights six NIDA-funded early interventions (delivered prior to the onset of adolescence) that successfully reduced later health-risking sexual behaviors related to HIV/AIDS. Traditionally, prevention interventions to avert risky sexual behavior and related problem behaviors like drug use have targeted teens and young adults, because these are the ages most directly affected. But research shows interventions during childhood can be effective at heading off those risks, with demonstrable effects that extend into adolescence, and adulthood. <http://www.drugabuse.gov/news-events/news-releases/2014/08/journal-issue-explores-early-interventions-to-prevent-risky-sexual-behaviors-related-to-hiv-aids>

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## **INTERVIEW HIGHLIGHTS: May 2014 - July 2014**

*ABC News* – Dr. Marilyn Huestis was interviewed about drugged driving.

*Alcoholism & Drug Abuse Weekly* – Dr. Lorenzo Leggio was interviewed about the role of baclofen as a new treatment for alcoholism.

*Associated Press* – Dr. Nora Volkow was interviewed about marijuana.

*Bloomberg* (2) – Dr. Volkow was interviewed about heroin and marijuana.

*Cincinnati Enquirer* – Dr. Volkow was interviewed about opioids.

*CBS Radio Network* – Dr. Marilyn Huestis was interviewed about drugged driving.

*FOX News Channel* – Dr. Marilyn Huestis was interviewed about drugged driving.

*Huffington Post* - Dr. Marilyn Huestis was interviewed about drugged driving.

*LiveScience.com* (2) – Dr. Volkow was interviewed about marijuana; Dr. Eugene Kiyatkin was interviewed about MDMA.

*Los Angeles Times* – Dr. Steve Gust was interviewed about marijuana.

*Men’s Health* – Dr. Lorenzo Leggio was interviewed about the role of appetitive hormones in food and alcohol intake and reward.

*MSNBC* – Dr. Wilson Compton was interviewed about marijuana.

*National Journal* – Dr. Compton was interviewed about heroin.

*Nature* – Dr. Compton was interviewed about e-cigarettes.

*Reuters Health* – Dr. Geetha Subramaniam was interviewed about a tool for screening teens for substance abuse.

*Rodale News* – Dr. Volkow was interviewed about marijuana.  
*Science Magazine* - Dr. Huestis was interviewed about marijuana.  
*The Economist* – Dr. Volkow was interviewed about marijuana.  
*The New York Times* (2) – Dr. Volkow was interviewed about compulsive overeating and heroin.  
*The Washington Post* - Dr. Volkow was interviewed about marijuana.  
*Time* – Dr. Volkow was interviewed about marijuana.  
*Time Warner Cable News* - Dr. Compton was interviewed about marijuana.  
*USA Today* (4) – Dr. Volkow was interviewed about marijuana; Dr. Compton was interviewed about elderly prescription drug abuse; Dr. Huestis was interviewed about drugged driving; and Dr. Kiyatkin was interviewed about MDMA.  
*Your Teen Magazine* – Dr. Jack Stein was interviewed about prescription drugs.

## MEETINGS/CONFERENCES

On June 26-27, 2014, the Office of Diversity and Health Disparities, hosted a two-day Research Development Seminar Series Part II Workshop **Mock Grant Review** at NIDA Headquarters in Rockville, Maryland. Chaired by Flair Lindsey, Program Analyst, this workshop convened 14 new early stage investigators, who participated in an initial Research Development Seminar Series Part I Workshop, to submit their “draft” research grant applications for a mock grant review. Led by Scientific Review Officer (SRO) Dr. Jose Ruiz, Office of Extramural Affairs (OEA), NIDA, and consisting of a review panel of NIDA-funded investigators and select NIDA program officials, the mock grant review enabled early stage investigators to experience a first-hand look at an actual Study Section (Scientific Review Group, SRG) review. Participants gained a thorough understanding of reviewers’ evaluations, critiques and outside opinions, as well as scoring. For the sake of this workshop, all applications were discussed. Following the mock grant review, participants received overall feedback and updates on the grants submission process, as well as have individual consultations with assigned reviewers. Through this workshop, ODHD strived to thoroughly evaluate and identify areas of strengthening early stage investigators’ “draft” research grant applications, so that they can be successful and competitive.

NIDA’s African American Researchers and Scholars Workgroup, with support from the Office of Diversity and Health Disparities, convened the **6<sup>th</sup> annual Addiction Research Training Institute (ARTI) at Morehouse School of Medicine** in Atlanta, Georgia, July 14-17, 2014. The four-day workshop provided 13 early stage investigators with mentoring and invaluable grantsmanship tools and technical assistance on grant writing, grant development, NIH application/grant submission, funding mechanisms and opportunities, peer review, scientific writing and research training. Flair Lindsey, Program Analyst, provided 13 early stage substance abuse and addiction research investigators with information on NIDA research priorities and funding opportunities. Flair individually consulted with select early stage investigators to provide guidance on the most appropriate funding mechanisms for their proposed research.

NIDA awarded 20 **Director’s Travel Awards** for the annual meeting of the College on Problems of Drug Dependence (CPDD), June 14-19, 2014, in San Juan, Puerto Rico. Awardees are National Research Service Award (NRSA) trainees and fellows, and Diversity Supplement recipients to present at the CPDD meeting and attend the NIDA Grant-Writing and Career Workshop.

Drs. Mimi Ghim, Ericka Boone, and Michele Rankin, and Ms. Usha Charya, OSPC, coordinated the **NIDA Grant-Writing and Career Workshop** and the **NIDA/CPDD Training Networking Event** at CPDD, June 17 and 16 respectively, in San Juan, Puerto Rico. The Grant-Writing and Career Workshop provided information on NIDA research priorities, program interests and funding opportunities, review procedures, and training on grantsmanship and other career-building skills. Drs. Kevin Walton and Gerald McLaughlin presented some of the core content in this workshop, as well as guest speakers Drs. Linda Cottler (University of Florida) and Frances Levin (Columbia University). The Training Networking Event provided a forum for training directors, trainees, and NIDA staff to learn about the different training programs that NIDA supports and for trainees to find future training and employment opportunities.

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Dr. Albert Avila, Director, Office of Diversity and Health Disparities (ODHD), attended the “Vulnerability to Drug Abuse among Hispanics: Bridging Science and Society” conference in El Paso, Texas on May 29, 2014. Dr. Avila presented an overview of NIDA's research priorities, diversity outreach mission, and research funding opportunities available to early-stage investigators. He also met individually with students and junior faculty providing tailored advice in regards to research proposals, funding opportunities, and application review.

Dr. Mark Swieter, Acting Director, OEA, attended the June, 2014 CPDD in Puerto Rico and co-chaired with Elena Koustova a workshop titled “Irreproducible Research: Is it Relevant to the Addiction Research Community?”

Dr. Gerald McLaughlin, OEA, delivered a presentation entitled, “Understanding NIH Peer Review” to participants in the June, 2014 CPDD Grant Writing and Career Development Workshop.

Dr. Jose Ruiz, OEA, delivered a presentation entitled, “NIH Grant Applications: Submission Process and Peer Review” to participants of the April 10-11, 2014 NIDA Diversity Supplements Workshop organized by the Office of Diversity & Health Disparities.

Dr. Jose Ruiz served as the SRO for the Research Development Seminar Series Part II Workshop Mock Grant Review event held on June 26-27, 2014 organized by the Office of Diversity & Health Disparities.

Dr. Jack Stein, Director, OSPC participated in a Webinar entitled “A Multi-Dimensional Look at Mental and/or Substance Use Disorders, their Treatment and Recovery at the Entertainment Industries Council Network & TV Worldwide Studios in Chantilly, Virginia on June 24, 2014.

Dr. Ruben Baler, Science Policy Branch, OSPC, lectured on “Addiction Science – Building Resilience from the Brain Up” at the National Rx Drug Abuse Summit in Atlanta, Georgia on April 24, 2014.

Dr. Baler presented an interactive webinar through the NASADAD State Youth Substance Abuse Coordinators Committee about “The Effect of Youth Drug Use on Brain Development” on June 18, 2014.

Dr. Baler presented at the annual "Breaking the Silence on Youth Violence" Youth Summit at the Friendship Collegiate Academy Public Charter School in Washington, D.C. on June 27, 2014.

Dr. Susan Volman, DBNBR, presented a talk entitled “NIH Funding for Behavioral Research” in a symposium at the Association for Behavioral Analysis International (ABAI) annual meeting in Chicago, IL, May 25, 2014.

Dr. Minda Lynch, DBNBR, presented in an American Psychological Meeting NIDA-supported symposium entitled “Evolving Role of Behavior in Science at the National Institute on Drug Abuse” in August 2014.

Dr. Vishnu Purohit, DBNBR, in collaboration with Dr. Toby K. Eisenstein organized a symposium on CB2 functions in the brain and periphery at the 76th annual CPDD Meeting, San Juan, Puerto Rico, June 14-19, 2014.

Dr. Roger Sorensen, DBNBR, participated in the OER-sponsored Regional Grant Writing Workshop in Baltimore in June 2014.

Dr. Nancy Pilotte, DBNBR, participated in the Special Populations Office mock review.

Drs. Nancy Pilotte and Roger Sorensen spoke with students at the IRP during the IRP Science Presentations in June 2014.

Dr. Jonathan D. Pollock, DBNBR, attended the International Behavioral and Neural Genetics Society Meeting in Chicago, IL, May 10-13, 2014 where he chaired an invited talk session.

Dr. John Satterlee, DBNBR, gave a presentation on “Data Sharing and Publication Policies of Non-clinical Common Fund Programs” at the Common Fund All Hands meeting in Bethesda, MD on July 8, 2014.

Dr. Satterlee co-chaired a scientific session on “Bioinformatic Analyses of Extracellular RNAs” at the Common Fund exRNA Communication Consortium held in Bethesda, MD in May 2014.

Dr. Satterlee organized a Cutting Edge Symposium featuring Dr. Courtney Miller, Scripps Florida who spoke about “Selective, retrieval-independent disruption of methamphetamine-associated memory by actin depolymerization” on July 9, 2014.

Dr. Kristopher Bough, DBNBR, was selected by Dr. Sally Rockey’s Office of Extramural Research to participate on an HHS Program Integrity/Risk Assessment Committee to evaluate the requirements of the SBIR/STTR Reauthorization Act of 2011.

Drs. Mark Caulder, Kris Bough, Jose Ruiz, and Joni Rutter presented a poster at the Portfolio Analysis Poster Meeting, OPA, NIH on July 23, 2014. Programmatic & Strategic Advancement of Science (PASAS): NIDA’s Portfolio Analysis and Visualization Tool.

Drs. Jane B. Acri, Nathan M. Appel, and David A. White, DPMCDA, presented a workshop at CPDD entitled “Go/No-go Decisions in Medication Development: Why some compounds should not go forward, and how do we identify them?” Jane Acri’s presentation was entitled, “Introduction and early stage toxicity testing in drug development: Examples of how predictions of toxicity are evaluated and can be used to guide SAR.” Nate Appel presented “Cardiovascular safety interaction testing and how it may kill a promising target,” and David White presented “Assessing anhedonia in drug development using intracranial self-stimulation: What it might predict and does it matter?”

Dr. David McCann and Bob Walsh, DPMCDA, chaired a mini-symposium on June 15, 2014 at the annual meeting of the College on Problems of Drug Dependence. The symposium was entitled “New Buprenorphine Formulations and Drug Combinations in Clinical Development.” Frank Vocci and Behshad Sheldon (Braeburn Pharmaceuticals) presented on the development of Probuphine subdermal implants, Fredrik Tiberg (Camurus AB) presented on the development of long-acting buprenorphine injection formulations (CAM2038), and Elliot Ehrich (Alkermes) presented on the development of ALKS-5416, a sublingual co-formulation of buprenorphine and a new opioid antagonist, ALKS-33.

Dr. David McCann participated in a “Town Hall” Industry/Academia Forum on June 15, 2014 during the annual meeting of the College on Problems of Drug Dependence. He presented his perspective on the challenges and advantages of using academic medical centers in conducting pharmacotherapy research.

Dr. Jag Khalsa, based on his contributions to the field of viral hepatitis and as a NIH Representative on the HHS Viral Hepatitis Implementation Group, was invited to participate in the World Hepatitis Day event at the White House, July 30, 2014.

On May 15, 2014, Dr. Cheryl Anne Boyce, DCNBR, led a webinar workshop hosted by the New Connections Program of the Robert Wood Johnson Foundation entitled Building a Competitive Research Program: What They Never Told You - But Really Need to Know with participants Drs. Karen Y. Sirocco (NIDA), LeShawndra Price (NIMH), and Kellina Craig-Henderson (NSF). Federal funding opportunities from the National Institutes of Health (NIH) were highlighted as a model for successful grant writing across various levels of career development and institutional/organizational settings.

Dr. Cheryl Anne Boyce presented “Essentials of a Successful Grant (Planning and Review)” as part of the NIMH meeting Developing Diverse Investigators in HIV/AIDS Behavioral Research held in Rockville, MD on May 16, 2014.

On May 16, 2014, Drs. Cheryl Anne Boyce and Karen Y. Sirocco, DCNBR, along with other NIDA colleagues, participated in a technical assistance meeting with NIDA funded American Academy of Child and Adolescent Psychiatry (AACAP) K12 scholars in Rockville, MD as part of their annual retreat.

Dr. Cheryl Anne Boyce attended and presented on NIH research grant priorities and strategies at the NIDA funded R25 UCLA HIV/AIDS Substance Abuse and Trauma Training Program (HA-STTP) Spring 2014 Institute held May 21-23, 2014 in Los Angeles, CA.

Dr. Cheryl Anne Boyce attended The Human Placenta Project Workshop sponsored by NICHD on May 28-29, 2014 at the Bolger Center in Potomac, MD.

Dr. Karen Sirocco attended the workshop Collaborative Research on Addiction at NIH (CRAN) Initiative on Neurodevelopmental Consequences of Substance Use: National Longitudinal Study of Neurodevelopmental Consequences of Substance Use on May 28-29, 2014 in Rockville, MD.

On July 9, 2014 Dr. Cheryl Anne Boyce chaired an invited session “The 2013 Institute of Medicine Report: New Directions in Child Abuse and Neglect Research” for Head Start’s 12th National Research Conference on Early Childhood held in Washington, DC.

On July 15, 2015 Dr. Cheryl Anne Boyce presented a webinar on “Building an Independent Research Program” for the Columbia School of Social Work HIV Intervention Science Training Program (HISTP) at the invitation of Dr. Nabila El-Bassel, Columbia University.

Dr. Cheryl Anne Boyce participated in a discussion hour “Beyond Academe--- Alternative Careers for Experimental Psychologists” held on August 7, 2014, at the 122nd annual meeting of the American Psychological Association in Washington, DC.

Dr. Cheryl Anne Boyce presented “Integrating a Research, Clinical, and Public Health Career” during the symposium “Research in Graduate School---Why and How Should I Get Involved?” at the 122nd annual meeting of the American Psychological Association in Washington, DC on August 7, 2014.

Drs. Karen Y. Sirocco and Cheryl Anne Boyce co-chaired a symposium featuring NIH scientists entitled “Adolescence: Brain Development to Prevention Policy” held on August 8, 2014, at the 122nd annual meeting of the American Psychological Association in Washington, DC.

Dr. Karen Y. Sirocco gave a presentation entitled “Employing Neuroscience to Build Effective Behavioral Interventions for the Prevention and Treatment of Drug Abuse” in a NIDA organized symposium entitled “The Evolving Role of Behavior in Science at the National Institute on Drug Abuse” held on August 9, 2014 at the 122nd annual meeting of the American Psychological Association in Washington, DC.

Dr. Cheryl Anne Boyce chaired a symposium entitled “Innovative Models with Evidence to Reduce Racial/Ethnic Health Disparities and Risk” held on August 9, 2014, at the 122nd annual meeting of the American Psychological Association in Washington, DC.

Drs. LeShawndra Price, NIMH, and Cheryl Anne Boyce co-chaired an invited plenary session entitled “Two of a Kind? Understanding RDoC and DSM-V” with presentations by Dr. Bruce Cuthbert (NIMH) and Dr. Michael First (Columbia University) held on August 9, 2014, at the 122nd annual meeting of the American Psychological Association in Washington, DC.

Dr. Cheryl Anne Boyce chaired an invited plenary address “Standing at the Crossroads: Will the Affordable Care Act Eliminate Health Inequities?” presented by Dr. Brian Smedley of The Joint Policy Center held on August 9, 2014, at the 122nd annual meeting of the American Psychological Association in Washington, DC.

Dr. Lisa Onken, DCNBR, chaired a symposium entitled: “Programs of Excellence and the Delaware Project on Clinical Science Training” held on May 22, 2014, at the 26th Annual Meeting of the Association for Psychological Science in San Francisco, CA.

Dr. Harold Gordon, DCNBR, attended (by formal invitation) the meeting of the Sleep Research Network (funded by a CDC contract to develop sleep research) in Minneapolis, MN on May 31, 2014.

Dr. Yu (Woody) Lin, DCNBR, organized and presented at a symposium entitled “AAPI-ACTION: Advancing Clinical Translation, Innovations, Opportunities and Networks.” It was a session of NIDA International Forum, a pre-meeting event of the 2014 CPDD Annual Meeting that was co-sponsored with NIDA AAPI Workgroup, International Office and AIDS Office, held at San Juan, Puerto Rico on June 14, 2014.

Dr. Steven Grant, DCNBR, gave a talk entitled “What Needs to be Translated in Substance Abuse Research” at the 2014 CPDD Annual Meeting held at San Juan, Puerto Rico on June 14 - 18, 2014.

Drs. Cora Lee Wetherington, DCNBR, and Ivan Montoya, DPMCDA, co-chaired the symposium, “Medications for Drug Addictions: Sex Differences in Outcomes in Animal and Human Laboratory Studies and in Clinical Trials,” at the 2014 College on Problems of Drug Dependence Annual Meeting, June 14-19, 2014, San Juan, Puerto Rico. The speakers presented their data funded via the ORWH/NIDA Specialized Centers of Research (SCOR) on Sex Differences: Yann Mineur (Yale), Sherry McKee (Yale), Marilyn Carroll (Minn), and Kathleen Brady (MUSC). Discussant: Ivan Montoya.

Dr. Cora Lee Wetherington hosted the roundtable, “NIDA International Funding Opportunities on Women and Gender,” at the annual InWomen (International Women: A subgroup of the NIDA International Program), at the CPDD Satellite Conference, June 13, 2014, San Juan, Puerto Rico.

Dr. Cora Lee Wetherington co-chaired the symposium, “Cognitive and Affective Factors in Substance Use in Men and Women,” at the 122<sup>nd</sup> American Psychological Association Annual Convention, Washington, DC, August 7-10, 2014.

Dr. Dave Thomas, DCNBR, chaired a session at the 19th Annual CyberPsychology, CyberTherapy & Social Networking Conference, titled “U.S. & European Funding Programs,” June 19th, 2014, Washington DC

Dr. Dave Thomas chaired a session at the 19th Annual CyberPsychology, CyberTherapy & Social Networking Conference, titled “Opportunities and Strategies for Funding the Development and Testing of Cyber Technologies to Reduce Pain,” June 19th, 2014, Washington DC.

Dr. Dave Thomas, made a presentation at the 2014 Kenneth L. Artiss Symposium – Psychiatry And Pain Management, titled “Pain Treatments and Prescription Opioid Abuse. Challenges and Solutions,” Walter Reed National Intrepid Center of Excellence, June 4th, 2014, Bethesda, MD.

Dr. Dave Thomas participated in FDA/Pharma public meeting on post-market safety studies of opioids. May 17-18, 2014, White Oak, MD.

Dr. Dave Thomas participated in a workshop at the 33rd Annual Scientific Meeting of the American Pain Society, titled “NIH Workshop on Successful Grant Writing and Funding Opportunities in Pain Research” May 2nd, 2014, Tampa, FL.

Dr. Dave Thomas chaired a session at the 33rd Annual Scientific Meeting of the American Pain Society, titled “State of the Science and Practice of Interprofessional Pain Education” May 3rd, 2014, Tampa, FL.

Dr. Dave Thomas made a presentation to the Pain Care Forum, titled “NIDA Participation in Major NIH Pain Consortium Initiatives” May 8th, 2014, Washington, DC.

Dr. Dave Thomas served as a content expert at the DHHS Conference “Advancing Policy and Practice: A 50-State Working Meeting to Prevent Opioid-Related Overdose,” July 17-18, 2014, Crystal City, VA.

Dr. Dave Thomas is participating in the National Pain Strategy (NPS) in developing a comprehensive population-based plan to improve pain treatment in America. This initiative is in response to recommendations from the IOM report, "Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research." Recommendations from the NPS will go to DHHS leadership for consideration of implementation.

Dr. Joe Frascella, Director, DCNBR, participated in and gave an introductory presentation at the annual meeting of the Interdisciplinary Research Training Institute Scientific Conference, June 4-7, 2014 in Coral Gables, Florida.

Dr. Joe Frascella participated in 2<sup>nd</sup> Annual Open House for the Morgan State University Patuxet Environmental and Aquatic Research Laboratory (PEARL), June 20, 2014 in St. Leonard, MD.

Dr. Redonna K. Chandler, Acting Director, DESPR, presented a plenary entitled, Effective Substance Abuse Treatment in the Criminal Justice System at the Addiction and Criminal Justice Forum sponsored by Senator Sheldon Whitehouse and Senator Robert Portman, Washington, DC, April 29, 2014.

Dr. Redonna Chandler presented Using Medication to Address Drug Abuse in Criminal Justice Settings at the Second Chance Act National Conference, Washington, DC, May 14, 2014.

Dr. Redonna Chandler presented Evidence Based Approaches to Adolescent Substance Use Disorders at the Annual Meeting of the National Association of State Alcohol Drug Abuse Directors, Omaha, NE, June 5, 2014.

Dr. Redonna Chandler presented a plenary entitled, The Neurobiology of Addiction and Effective Treatment at the 3rd Residential Substance Abuse Treatment Technical Assistance Conference, Chicago, IL, July 18, 2014.

Dr. Redonna Chandler presented a Poster titled Studies of Medications for Addiction Treatment in Correctional Settings Research Collaborative at The College on Problems of Drug Dependence 76th Annual Scientific Meeting, San Juan, PR, June 17, 2014.

On April 12, 2014, Dr. Harold Perl, DESPR, co-taught a clinical skills workshop titled, "Motivational Interviewing: Skills to Engage Patients and Initiate the Discussion of Substance Abuse in Internal Medicine", at the 2014 Scientific Meeting of the American College of Physicians in Orlando, FL.

On May 29, 2014, Dr. Harold Perl organized and chaired a Roundtable session titled, "NIDA Prevention Research in an Era of Fiscal Constraints" at the 22nd Annual Meeting of the Society for Prevention Research on in Washington, DC. Other NIDA staff speaking at the session included Wilson Compton, M.D., Jack Stein, Ph.D., Redonna Chandler, Ph.D. and Jacqueline Lloyd, Ph.D.

On May 28, 2014, Dr. Harold Perl organized and co-led a Special Interest Group meeting titled, "Prevention Research Under Healthcare Reform" at the 22nd Annual Meeting of the Society for Prevention Research on in Washington, DC.

Dr. Dionne Jones, DESPR, gave a presentation on “Grant writing and Development Opportunities at NIH” to DIDARP grantees and junior investigators at the 76th Annual Meeting of the College on Problems of Drug Dependence on June 14-19 2014.

Dr. Dionne Jones presented on ‘Health Services Research at NIDA’ by telephone conferencing to participants in the Early Career Stage Investigator Mentoring Initiative of the National Hispanic Science Network through Michigan State University on May 20, 2014.

Dr. Dionne Jones presented on “Health Disparities: Addressing Special Population Needs” at the 7th Academic & Health Policy Conference on Correctional Health, Houston, TX, on March 20-21, 2014.

On June 13, 2014, Dr. Dionne Jones was discussant for a panel “Global Perspectives on Women and Addiction” at the 2014 International Women’s and Children’s Health and Gender Group Conference, a satellite of the 76th Annual Meeting of the College on Problems of Drug Dependence.

On April 10-11, 2014, Drs. Dionne Jones, Shoshana Kahana, and Tisha Wiley, DESPR, provided technical assistance to participants in the NIDA Diversity Supplements Workshop sponsored by the Office of Diversity and Health Disparities held in Bethesda, MD,

On May 27-30, 2014, Dr. Jacqueline Lloyd, DESPR, organized and chaired a session titled, “High Risk Girls in High Risk Settings: What Have We Learned? What’s Next?” at the 2014 Society for Prevention Research 22nd Annual Meeting in Washington DC., Titled: The Discussant was Dr. John Landsverk. The presenters were Dr. Patricia Chamberlain, Dr. Leslie Leve, Dr. Lisa Saldana, and Attorney Francine Sherman.

On May 27-30, 2014, Dr. Jacqueline Lloyd organized and chaired a session titled “Trans country Cultural and Contextual Adaptation of Prevention Interventions: The Role of Partnerships in Grounding Adaptation”. The Discussant was Dr. Felipe Castro. The presenters were Dr. Lillian Gelberg, Guillermina Natera, Dr. Gil Botvin, and Dr. Veronica Velasco.

On May 27-30, 2014, Dr. Jacqueline Lloyd co-chaired with Dr. Michael Bardo a paper symposium titled “Emotional Self-Regulation and Drug Abuse Vulnerability: Connecting Biology and Prevention Science” at the 2014 Society for Prevention Research 22nd Annual meeting in Washington DC. The Discussant was Dr. Anthony Biglan. The presenters were Dr. Yi-Yuan Tang, Dr. Thomas Wills, and Dr. Michael Bardo.

On May 27-30, 2014, Dr. Jacqueline Lloyd was the Discussant for a paper symposium titled “Context and Populations: HIV Across the Care Continuum in the United States” at the 2014 Society for Prevention Research 22nd Annual meeting in Washington DC. The Chair was Dr. Amanda Tanner. The presenters were Dr. Guillermo Prado, Dr. Amanda Tanner, and Dr. Enbal Shacham.

On May 27-30, 2014, Dr. Jacqueline Lloyd was a panelist for a roundtable titled “NIDA Prevention Research in an Era of Fiscal Constraints” at the 2014 Society for Prevention Research 22nd Annual meeting in Washington DC. The Chair was Dr. Harold Perl. Panelist also included Dr. Redonna Chandler, Dr. Wilson Compton, and Dr. Jack Stein.

On May 4, 2014, Dr. Naimah Weinberg DESPR, organized and chaired a symposium titled “The role of substance use in violence against self and others: How research can inform clinical understanding of risk“, at the annual meeting of the American Psychiatric Association, held in New York City, NY.

On June 19, 2014, Dr. Naimah Weinberg organized and chaired a symposium titled “Addressing the challenges of GxExD research: Application to Substance Abuse” at the annual meeting of the Behavior Genetics Association, held in Charlottesville, VA.

Drs. Belinda Sims and Eve Reider, DESPR presented on NIDA’s early childhood prevention portfolio to Drs. Jeff Levi and Laura Segal, Trust for America’s Health (TFAH). TFAH is a non-profit, non-partisan organization dedicated to saving lives by protecting the health of every community and working to make disease prevention a national priority. The presentation took place on June 25, 2014 at TFAH in Washington, D.C.

Dr. Eve Reider was invited to present on Prevention Science at a Head Quarters Marine Corps Behavioral Health Executive Course (BHEC) being held the week of August 18, 2014, Quantico, VA. The four-day BHEC is an executive level course being given to all Installation Behavioral Health Branch Heads, Marine and Family Programs Division, Marine Corps.

On May 28, 2014, Dr. Eve Reider and Ms. Ashley Fisher, Department of Defense, co-chaired a symposium that was held at the 22<sup>nd</sup> Annual 2014 Society for Prevention Research Meeting in Washington, D.C. The symposium was titled “Adapting Evidence-Based Interventions for Military Families.” The presenters were Drs. Amy Smith Slep, New York University, Abigail Gewirtz, University of Minnesota, Marion Forgatch, Oregon Social Learning Center, Robert Bray, Research Triangle Institute, and Richard Spoth, Iowa State University. Dr. Stephen Cozzo, Uniformed Services University of the Health Sciences, led the discussion.

On May 28, 2014, Dr. Eve Reider and Dr. Katherine Nassauer, Military Operational Medicine Research Program US Army Medical Research and Materiel Command, held a “Brown Bag” Special Interest Group on “Funding Opportunities for Prevention Research with Military Personnel, Veterans and Their Families” on at the 22<sup>nd</sup> Annual 2014 Society for Prevention Research (SPR) Meeting in Washington, D.C. This special interest group provided an opportunity for SPR attendees to network, learn about federal funding opportunities for prevention research with military personnel, veterans and their families and discuss issues relevant to moving the science forward for this population.

On August 8, 2014, Dr. Eve Reider participated in a panel titled “Show Me the Money--- Research Funding in Child and Family Psychology” that was held at the 122<sup>nd</sup> American Psychological Association Annual Meeting in Washington, D.C. The panel was chaired by Dr. Galena Rhoades, University of Denver, and the other presenters included Drs. Layla Esposito, NICHD, and Melissa Gerald, NIA.

On May 28, 2014, Dr. Belinda Sims was the discussant for a Symposium at the 22<sup>nd</sup> Annual Society for Prevention Research annual meeting entitled “Innovative Research in Implementation Science from the Next Generation of Prevention Scientists and Methodologists” held in Washington, D.C.

On May 28, 2014, Drs. Abigail Fagan and Belinda Sims, DESPR, co-chaired a Special Interest Group Brown Bag at the 22nd annual Society for Prevention Research entitled “Ensuring High Quality and Dynamic Presentations at Future SPR Annual Meetings: Possibilities to Consider and Pitfalls to Avoid”, held in Washington, D.C.

On May 29, 2014, Dr. Belinda Sims was the discussant on a Research Roundtable at the 22nd Annual Society for Prevention Research annual meeting entitled “Variation in Intervention Response as a Function of Variation in Participation: Applying What We Know to Translate Efficacious Preventive Interventions to Real-World Delivery Settings”, held in Washington, D.C.

Dr. Richard Jenkins, DESPR, chaired the committee responsible for the Invited Symposium, HIV/AIDS Prevention: Intersecting Identities and Intersecting Epidemics” and Invited Plenary, ”Integrated HIV/AIDS Prevention: Policy, Practice, and Research Perspectives” for 22nd Annual Society for Prevention Research annual meeting on May 29 and May 30, 2014 in Washington, DC. Dr. Jenkins moderated the invited Plenary and co-moderated the accompanying Roundtable Discussion.

On May 27, 2014, Drs. Eve Reider and Dr. Richard Jenkins along with NIDA International Program were responsible for organizing the NIDA International Poster Session and Reception at the 22nd Annual Society for Prevention Research annual meeting held in Washington, DC.

On May 29, 2014, Dr. Augusto Diana DESPR, organized, moderated and was the discussant for a Symposium at the 22nd Annual Society for Prevention Research annual meeting entitled “Designing Messages to Promote Health: Media, Branding and Social Influence Strategies,”, held in Washington, D.C.

On May 28, 2014, Dr. Aria Crump was the discussant for a Society Prevention Research Annual Meeting Organized Poster Forum on Interventions for Health Promotion and Disease Prevention in Native American Populations held in Washington, D.C.

On May 28, 2014, Drs. Elizabeth Robertson, Belinda Sims, and Aria Crump co-organized a symposium entitled “21st Century Family-Based Prevention: Connecting Theory to Etiology to Intervention Content” for the annual meeting of the Society for Prevention Research held in Washington, D.C.

On May 29, 2014, Drs. Belinda Sims and Aria Crump co-chaired a session for investigators interested in seeking federal research funding entitled, “Avoiding Common Barriers and Pitfalls in the Federal Application and Funding Process” at the annual meeting of the Society for Prevention Research. Federal Staff participating in the session included Dr. Hiromi Ono from NIDA and Ms. Wilma Peterman-Cross from the NIH Office of Disease Prevention along with federal personnel from CDC, ACF.

On May 28, 2014, Drs. Aria Crump and Marcia Scott (NIAAA) co-chaired a Special Interest Group meeting entitled “Genetics and the Prevention of Behavioral Disorders: Moving the Science Forward.” Dr. Erica Spotts from the NIH Office of Behavioral and Social Sciences offered remarks at this session.

Dr. Eve Reider was an organizer and theme reviewer for the 7<sup>th</sup> Annual NIDA International Poster Session, which was held at the 22<sup>nd</sup> Annual Society for Prevention Research Annual Meeting held in May 2014 in Washington, D.C.

Dr. Amy Newman, IRP, gave Grand Rounds at St. Elizabeth's Hospital, Department of Psychiatry, Washington D.C. in May 2014.

Dr. Lorenzo Leggio, IRP, served as member of the Program Committee for the 2014 RSA/ISBRA meeting and was appointed as a member of the ISBRA Membership Committee for 2014 – 2016.

Dr. Lorenzo Leggio, IRP, chaired a session and served as a discussant at the 2014 joint meeting of the Research Society on Alcoholism (RSA) and the International Society for Biomedical Research on Alcoholism (ISBRA) in Bellevue, WA.

Dr. Bruce Hope, IRP, gave an invited lecture at the Icahn School of Medicine at Mount Sinai in New York, NY in May 2014.

Dr. Jean Lud Cadet, IRP, presented a talk on dopamine systems as part of the Neuroscience Lecture series for summer students on June 19, 2014 at the NIH Biomedical Research Center.

Dr. Jean Lud Cadet presented a talk entitled "Epigenetics and transcriptional effects of repeated methamphetamine injections" to summer students as part of the Summer Seminar Series on July 2, 2014 at the NIH Biomedical Research Center.

Dr. Kenner Rice, IRP, delivered the 2014 John Daly Lecture sponsored by the National Institute of Diabetes, Digestive, and Kidney Diseases, National Institutes of Health, June, 2014. Dr. Rice's topic was Medicinal Chemistry as an Enabling Art in Biomedicine.

Dr. George Uhl, IRP, recently presented an invited talk at Johns Hopkins University.

Dr. George Uhl recently presented an invited talk at Johns Hopkins University School of Nursing.

Dr. George Uhl recently presented an invited talk at the University of New Mexico.

Dr. George Uhl, IRP, recently presented an invited talk at the NIDA Genetics Consortium Meeting.

Dr. George Uhl, IRP, recently presented an invited talk for the NIDA Medications Development Program.

Dr. George Uhl, IRP, recently presented an invited talk at the NIDA IRP.

Major Marisol S. Castaneto, a CDM pre-doctoral IRTA, gave an invited lecture at the 2014 Tri-Service Forensic Drug Testing Meeting, Department of Defense, June 9-11, 2014, Great Lakes, MI. Her presentation entitled, "Synthetic Cannabinoid Testing in Military Urine Samples," is part of her dissertation and CDM's interagency research agreement with the Department of Defense.

Dr. Michael Baumann, IRP, gave a talk at the Annual Meeting of the Community Epidemiology Work Group (CEWG) in Phoenix AZ on June 5, 2014.

Dr. Yavin Shaham, IRP, recently gave an invited lecture at the University of Mississippi.

Dr. Yavin Shaham gave an invited lecture at the 2014 CPDD meeting.

Dr. Geetha Subramaniam, CCTN, served as chair and moderator of a symposium titled “Cannabis Use and Youth: Risk Assessment and Implications for Clinical Practice.” at the American Psychiatric Association (APA) 167th Annual meeting held May 3-7, 2014.

Carmen Rosa, CCTN, organized, chaired and presented a pre-meeting workshop titled “Incorporating New Media Tools in the Design and Conduct of Clinical Trials.” at the 35th Annual Meeting of the Society for Clinical Trials held May 18-21, 2014 in Philadelphia, PA. In addition, Ms. Rosa organized, co-chaired and presented an invited session titled “Implementation of Risk-Based Monitoring: From Guidance to Practice.”

Carmen Rosa organized, chaired and presented a session during the NIDA International Forum, titled “Substance Use Treatments: Secondary Analyses Using the CTN Datashare.”

On July 31, 2014, Dr. Udi Ghitza, CCTN, organized and chaired a workshop titled “Clinical Quality Measures and Electronic Health Record Systems for Substance Use Disorders (SUD): Where We Stand and Future Directions.

NIDA’s Blending Initiative provided support for a session titled “Addiction Treatment Research vs. Usual Care: What are the Foreseeable Risks?” at The College on Problems of Drug Dependence (CPDD) 76<sup>th</sup> Annual Meeting June 14-19, 2014 in San Juan, Puerto Rico.

## **PLANNED MEETINGS**

\* (*Pending approval*)

### **Society for Neuroscience Frontiers in Addiction Research Mini-convention – Washington D.C., November 14, 2014**

NIDA will present its annual Frontiers in Addiction Research Mini-convention as a satellite event of the Society for Neuroscience Annual meeting on November 14, 2014 in Natcher auditorium. The mini-convention provides a forum for presentations on contemporary topics in the areas of neuroscience and addiction research. The NIDA Mini-convention includes: four scientific symposia, keynote presentations by the 2013 and 2014 winners of the SfN Jacob P. Waletzky Award which recognizes excellence in research in the area of substance abuse and the brain and nervous system, and a poster session showcasing the work of early career investigators. The symposia this year are:

- Emerging and Novel Aspects of Neuronal Transmission
- Extracellular RNAs in Neuroscience: Biology, Biomarkers, and Therapeutics
- Advances in High Resolutions and Large Scale Imaging of Brain Networks and Circuits
- The Effects of Drug-, Stress-, and Pain-induced Neuroinflammation on Glymphatics and Sleep

**So You Want to Be a Scientist...and Get Paid Along the Way: A NIH Grant Workshop for Early Career Investigators – Washington D.C., Sunday November 16, 2014**

NIDA will once again present an Early Career Workshop at the Society for Neuroscience annual meeting. The focus of this year's workshop is on the individual Ruth L. Kirschstein National Research Service Award (NRSA) grant applications for predoctoral and dual degree candidates, and postdoctoral fellows. This workshop offers the opportunity for graduate students and postdoctoral fellows to have their questions answered concerning their role in working on research projects and in preparing NRSA fellowship applications.

**NIH Funding Opportunity: Longitudinal Study of Neurodevelopmental Consequences of Substance Use – Washington D.C., Monday, November 17, 2014**

The Collaborative Research on Addiction at NIH (CRAN), comprising NIDA, the National Institute on Alcohol Abuse and Alcoholism (NIAAA), and the Division of Cancer Control and Population Sciences at the National Cancer Institute (NCI), in partnership with the Eunice Kennedy Shriver National Institute of Clinical Health and Human Development (NICHD) are hosting a workshop to solicit input for a large-scale prospective cohort study to assess developmental effects of substance use from early adolescence into young adulthood in human subjects. The study goals are to understand the impact of various patterns and trajectories of substance exposure on brain structure and function; future substance use disorders or other psychopathology; and functional outcomes, including academic achievement, social development and other behaviors of public health importance.

**Novel RNA Modifications in the Nervous System: Form and Function – Washington D.C., Date TBD.**

NIDA will hold a satellite symposium at the Annual Society for Neuroscience meeting in November 2014. Modified RNA molecules have recently been shown to regulate nervous system functions. This mini-symposium will provide an overview of the types and known functions of novel modified RNAs in the nervous system, include (1) methylated RNAs in intellectual disability and dopamine neuron function, (2) circular RNAs in microRNA regulation and specification of neuron fate; and (3) the consequences of adenosine-to-inosine RNA editing in neurological diseases and substance abuse.

**Bath Salts, Spice, and Related Designer Drugs: The Science Behind the Headlines – Washington D.C., Date TBD**

NIDA will hold a satellite symposium at the Annual Society for Neuroscience meeting in November 2014. Recently, there has been an alarming increase in the nonmedical use of novel psychoactive substances known as “designer drugs.” Synthetic cathinones and synthetic cannabinoids are two of the most widely abused classes of designer drugs. This mini-symposium will present the most up-to-date information about the molecular sites of action, pharmacokinetics and metabolism, and in vivo neurobiology of synthetic cathinones and cannabinoids.

## **STAFF HIGHLIGHTS**

### **Staff Awards**

#### **2014 NIH DIRECTOR'S AWARDS**

**Dr. Steven Grant**, DCNBR, received a NIH Director's Team Award for his participation in the BRAIN Initiative.

**Dr. Michael Baumann**, IRP, received an NIH Director's Award for "significant and timely contributions to the NIH mission by serving as an ambassador for educating the public about the dangers of designer drugs".

The **Collaborative Research on Addictions at NIH (CRAN) Coordination Committee** received an NIH Director's Award for "outstanding work implementing the first round of funding announcements in the new CRAN (Collaborative Research on Addictions at NIH) program". NIDA Staff receiving this award were: **Kevin P. Conway**, **Matthew S. Finger**, **Denise A. Pintello** (now with NIMH), **David Shurtleff** (now with NCCAM) and **Susan R. Weiss**.

The **NIDA/NIH SPIRES Automated Publication Carts Team** received an NIH Director's Award "in recognition of NIDA/NIH's new SPIRES real-time and continuous publication carts to enhance portfolio review activities. NIDA Staff receiving this award were: **Augusto Diana**, **Matthew S. Finger**, **Marsha F. Lopez**, **Genevieve C. Vullo**, and **Tisha R. Wiley**.

#### **2014 NIDA DIRECTOR'S AWARDS**

##### **CENTER FOR THE CLINICAL TRIALS NETWORK**

**David Liu** -- In recognition of scientific expertise, unselfish sharing of his wisdom with colleagues, and willingness to assume ever increasing challenges contributing to the accomplishment of NIDA's mission.

##### **The CCTN Clinical Trials Implementation Steering Group**

**Carol Cushing**, **Ronald Dobbins** and **Carmen Rosa**

In recognition of extraordinary efforts in continuous acquiring new knowledge and skills in meeting the ever-evolving clinical research advancement in furtherance of NIDA's mission

##### **DIVISION OF BASIC NEUROSCIENCE AND BEHAVIORAL RESEARCH**

**Susan Volman** -- In recognition of leading NIDA's CEBRA, EUREKA and CRCNS programs and coordinating the poster award program for junior investigators at the NIDA Frontiers in Neuroscience SfN meeting

**DBNBR Portfolio Coding & Analysis Team**

**Paul Hillery, Minda Lynch, Nancy Pilotte, Jonathan Pollock, Dena Procaccini, Vishnudutt Purohit, Rao Rapaka, Jose Ruiz, John Satterlee, Roger Sorensen, Hari Singh, and Da-Yu Wu**  
In recognition of dedication, contributions, and support to meet the mission of NIDA

**NIH BRAIN Initiative Teams and Coordinators**

**James Bjork, Gayathri Dowling, Melissa Ghim, Steven Grant, Jonathan Pollock, Joni Rutter, Catherine Sasek, Roger Sorensen, Susan Volman, Susan Weiss, and Da-Yu Wu**  
In recognition of exceptional dedication to promote an interdisciplinary effort of extraordinary scope to advance Brain Research through Advancing Innovative Neurotechnologies

**DIVISION OF CLINICAL NEUROSCIENCE & BEHAVIORAL RESEARCH**

**Will Aklin** -- In recognition of leadership on neurobehavioral targets for behavioral treatments for drug abuse

**Cheryl Boyce** -- In recognition of public dissemination of neuroscience and child maltreatment research

**Samia Noursi** -- In recognition of exceptional leadership contributions to the success of the trans-HHS symposium on Intimate Partner Violence Screening and Counseling, December 9, 2013

**NIDA Pain Leadership Group**

**Richard Denisco and David Thomas**

In recognition of dedication and longstanding contributions to the field of pain research and treatment. This sustained work has contributed significantly to the mission of NIDA

**DIVISION OF EPIDEMIOLOGY, SERVICES AND PREVENTION RESEARCH**

**Peter Hartsock** -- In recognition of support of NIDA research addressing the HCV epidemic among injection drug users

**American Indian/Alaska Native Research Development Group**

**Will Aklin, Albert Avila, Aria Crump, Augusto Diana, Kathleen Etz and Carmen Rosa**

In recognition of efforts to develop and facilitate research programs conducted by AI/AN investigator that address issues of the AI/AN population.

**DIVISION OF PHARMACOTHERAPIES AND MEDICAL CONSEQUENCES OF DRUG ABUSE**

**Aidan Hampson** -- In recognition of leadership to support NIDA's mission of improving clinical trials by developing novel medication adherence markers

## **INTRAMURAL RESEARCH PROGRAM**

**Mariena Mattson** -- In recognition of your dedication, contributions, and support to meet the mission of NIDA

### **NIDA IRP Office of Education and Career Development**

**Stephen Heishman, Mary Pfeiffer and Rolanda Morris**

In recognition of exceptional leadership and vision to further the training and development of career skills of trainees at NIDA IRP

## **NIDA OFFICE OF THE DIRECTOR**

**Pamela Goodlow** -- In recognition of dedication, contributions, and commitment to NIDA and the Diversity Supplement Program

### **NIDA Consortium on Diversity Workgroup**

**Will Aklin, Debra Battle-Dudley, Dionne Jones, Guifang Lao, Yu Lin, Vishnudutt Purohit, Belinda Sims, Kevin Walton and Ericka Wells**

In recognition of dedication, contributions, and commitment to NIDA Diversity Supplement Program

## **OFFICE OF EXTRAMURAL AFFAIRS**

### **OEA Contract Review Handbook Team**

**Jayson Hill, Minna Liang and Jose Ruiz**

In recognition for creating the OEA Contract Review Handbook, a guide aimed at increasing efficiencies and improvements in service to NIDA and external research community

## **OFFICE OF MANAGEMENT**

### **Financial Management Branch**

**Donna Jones, Stacy Gardner, Sharon Goon, Yvonne Moskal and Nakia Walters**

In recognition of your ability to develop innovative solutions in order to meet fiscal challenges and for significant contributions in efficiently managing NIDA's budget under extraordinary circumstances

## **OFFICE OF SCIENCE POLICY AND COMMUNICATIONS**

### **“Principles of Adolescent Substance Use Disorder Treatment” Publication Team**

**Ericka Boone, Cheryl Boyce, Redonna Chandler, Jessica Cotto, Elisabeth Davis, Gayathri Dowling, Bennett Fletcher, Mark Fleming, Carol Krause, Ivan Montoya, Stephanie Older, Geetha Subramaniam, Isabelle Thibau and Eric Wargo**

In recognition of efforts to develop and disseminate resources to help parents, health care providers, and treatment specialist address substance use disorders among adolescents.

## **2014 NIDA DIRECTOR'S AWARD FOR EEO, DIVERSITY AND QUALITY OF WORKLIFE**

### **Minority Scholars Team**

**Nadine Rogers and Jose Ruiz**

In recognition of efforts to provide training and guidance in NIH grants administration in the areas of drug abuse and addiction to young minority scientists.

## **NIDA DIRECTOR'S INNOVATOR AWARD**

### **Portfolio Analysis Team**

**Kristopher Bough and Mark Caulder**

In recognition of collegiality, diligence, focus, and creativity for developing a new portfolio analysis tool to help the advancement of science within NIDA

### **NIDA TV Team**

**Josie Anderson and Janet Linton**

In recognition of creativity and innovativeness in developing a portal for cataloging and viewing NIDA-related videos to enhance their dissemination

## **30 YEARS OF GOVERNMENT SERVICE AWARDS**

**Joan Deckow, Peter Hartsock, Andrea McGee, Rosanne Ogoh, Hari Singh and Susan Weiss**

## **40 YEARS OF GOVERNMENT SERVICE AWARD**

**Debra Haynes, Donna Jones and Mark Lombardi**

## **Other Staff Honors and Awards**

**Dr. Elizabeth Robertson**, DESPR, was named a fellow of the Society for Prevention Research on May 29, 2014. The SPR Fellows Program, in its second year, is an honor SPR bestows upon a small and select group of members who have a particularly distinguished record of contributions in the field of prevention science.

**Flair Lindsey**, ODHD, received "The Exemplary Leadership Award" from the African American Researchers and Scholars Work Group for leadership in Office of Diversity and Health Disparities programs, including the Research Development Seminar Series.

**Dr. Amy Newman**, IRP, received the 2014 Marian W. Fischman Lectureship Award from the College on Problems of Drug Dependence (CPDD). The award was presented to her at the 76th Annual Scientific meeting of the CPDD where she presented a lecture entitled "What's a Nice Girl Like You Doing in a Field Like This?"

**Dr. Irina Krasnova**, IRP, received a mentoring award on May 14, 2014 from the Office of Education and Training. Dr. Krasnova was one of three recipients honored for mentoring students from diverse and under-represented populations.

**Dr. Mary Pfeiffer**, IRP, received a Special Act Award for her work on the IRP's Animal Care and Use Committee.

**Dr. Michael Baumann**, IRP received a Staff Scientist Mentoring Award from the NIDA IRP.

**Dr. Suchankova Karlsson**, IRP, was the recipient of a 2014 RSA Junior Investigator Travel Award.

**Dr. Petra Suchankova Karlsson's** work on GLP-1 conducted in Dr. Leggio's section was selected as a finalist for the Young Investigator Award at the SCNP Meeting (Copenhagen, Denmark), and was selected as a finalist at the 2014 joint RSA/ISBRA meeting (Bellevue, WA) for both the Enoch Gordis Postdoctoral Award and the ISBRA President Award.

**Dr. Dong Wang**, IRP, received a \$1,000 travel award as a winner of NIH Fellows Award for Research Excellence 2014 competition.

**Dr. Satoshi Ikemoto**, IRP, received a NIDA-IRP Investigator Mentoring Award.

**Dr. Lorenzo Leggio**, IRP, was recently appointed as Editor-in-Chief for North America for 'Alcohol and Alcoholism' (Oxford University Press), the official Journal of the European Society for Biomedical Research on Alcoholism (ESBRA) and the Medical Council on Alcohol (MCA).

**Dr. Vivek Kumar**, IRP, won a 2014 NIH FARE Travel Award.

**Dr. Leslie Whitaker**, IRP, received a 2014 NIH FARE award.

**Dr. Javier Rubio**, IRP, received a 2014 NIH FARE award.

**Dr. Jana Drgonova**, IRP, was approved for appointment as a Staff Scientist.

**Dr. William Kowalczyk**, IRP, received the Intramural AIDS Research Fellowship and the 2015 FARE award.

**Dr. Melody Furnari**, IRP, received a 2015 NIH FARE Award.

## **Staff Changes**

### **New Employees**

**Dr. Maureen Boyle** joined NIDA in June 2014, as the Chief of the Science Policy Branch (SPB) in the Office of Science Policy and Communications (OSPC). Prior to joining NIDA, Dr. Boyle was a Lead Public Health Advisor for Health Information Technology (HIT) at the Substance Abuse and Mental Health Services Administration (SAMHSA) where she coordinated efforts to promote the

use of technology to improve the delivery of substance abuse treatment. Prior to joining SAMHSA, Dr. Boyle was an American Association for the Advancement of Science (AAAS) Science and Technology Policy Fellow serving at the National Institutes of Health, Office of Behavioral and Social Sciences Research (OBSSR). In this role she led multiple initiatives to improve data collection and clinical quality measurement within behavioral health. Dr. Boyle received her Ph.D. in neuroscience from Washington University in St. Louis where she studied the genetic and molecular basis of depression and anxiety-related behaviors. She completed a postdoctoral fellowship at the Allen Institute for Brain Science where she investigated neuropathological, molecular, and genetic abnormalities in Autistic children and animal models of autism.

**Amy Bucheimer** recently joined NIDA's Grants Management Branch. Amy comes to NIDA from NCI, where she worked as a grants specialist for close to seven years. She has a B.S. in Psychology from Pennsylvania State University and a M.Ed. in Special Education from Millersville University, PA.

**Sara Crocoll** joined the Public Information and Liaison Branch (PILB), Office of Science Policy and Communications (OSPC), in May 2014, filling NIDA's newest position as Social Media Strategist. She manages NIDA's social media initiatives to enable dissemination of NIDA's scientific findings in language that is accessible to the general public. She oversees all NIDA social media platforms in order to promote a strategic, proactive social media presence that is well integrated with NIDA's traditional media outreach, Web content and design, and other dissemination mechanisms. Prior to NIDA, Sara was a Presidential Management Fellow with the National Institute of Allergy and Infectious Diseases and completed rotations with various federal communications offices over two years. She served in the United States Air Force (USAF) for four years as a Logistics Readiness Officer, and she is currently a Captain in the USAF Reserves, serving as a Public Health Officer. Sara holds a Masters in Public Health in Leadership from the University of North Carolina-Chapel Hill.

**Dr. Philip Krieter** joined DPMCD's Chemistry and Pharmaceutics Branch as a Health Scientist Administrator on July 27, 2014. Dr. Keieter has 30 years of experience working in the area of drug disposition in the pharmaceutical industry at various companies before he joined NIDA in 2014. He has done both discovery and development preclinical ADME studies and also designed and conducted clinical pharmacology studies. He received his doctorate at the Department of Pharmacology and Toxicology at the University of Iowa with postdoctoral positions at the Mayo Clinic and the University of Texas at Austin. At NIDA, he oversees bioanalytical aspects of studies and contributes pharmacokinetic expertise to Phase 1 studies.

**Dr. Roger Little** has been selected as Deputy Director of NIDA's Division of Neuroscience and Behavioral Research (DBNBR). Roger has over 16 years of post-graduate research in Neuroscience, including 10 years devoted to work at NIH. Most recently, Roger was a Senior Advisor at the National Institute of Mental Health (2006-2014). He also served as a liaison and coordinator for the NIH Common Fund, the NIH Blueprint for Neuroscience, and for Public Private Partnerships, coordinated involvement of NIMH staff in these activities, and is a program co-lead for NIMH for the Common Fund Genes, Tissue, and Expression initiative (<https://commonfund.nih.gov/GTE/index>). He led a trans-NIH workgroup to develop a new model for brain banking at NIH which is called the Neurobiobank (<https://neurobiobank.nih.gov/>) and is now funding via contract 6 brain banks and an IT system to federate them and facilitate access for researchers and provide information to the public. He also served as the NIMH Appeals Officer and helped develop

institute policies. His areas of focus since coming to the NIMH in 2004 have been psychiatric and molecular genetics. Prior to NIH, he was a post-doc at the CDC-NIOSH where he conducted basic molecular neurobiology research focused on the neural signaling pathways related to astroglial activation in response to brain injury. Dr. Little has been recognized with over 25 awards since he began at the NIMH and serves on the Science Advisory Committee of the National Disease Research Interchange. Dr. Little received his B.S. in Biology and English from the University of Vermont and his M.S. in Neurotoxicology and Ph.D. in Molecular Neurobiology from New York University. His doctoral work involved cloning and characterizing a novel G-coupled protein receptor (the calcium-independent receptor of alpha-Latrotoxin or Latrophilin) which was identified because it is a specific receptor for one of the toxins in black widow spider venom. His Masters work involved the signaling mechanisms involved in astroglial activation following brain injury.

**Sussana Morales**, the latest addition to NIDA's Management Analysis Branch, has been at the NIH since 2001. Most recently she was a Management Analyst at the National Institute of Nursing Research where she specialized in continuity of operations planning, emergency response, and risk management. At NIDA, Ms. Morales will be leading our Risk Management Efforts as well as managing the composition and retention of OM's policies and procedures.

**Dr. Thomas Radman** joined DBNBR as a Health Scientist Administrator on June 15, 2014. Dr. Radman earned his doctorate from the City College of New York conducting research on the electrical stimulation of neural tissue in the lab of Dr. Marom Bikson. Following graduate school he conducted post-doctoral research pertaining to cognitive neuroscience, attention, multi-electrode implantable recording, current source density and signal processing at the New York University Medical Center, with co-mentoring by Dr. Charlie Schroeder and Dr. Helen Scharfman. Dr. Radman served for 3 years as lead reviewer and expert scientific reviewer in the subject areas of electrical stimulation and diagnostics, in the Division of Ophthalmic, Neurological and Ear, Nose and Throat Devices in the Center for Devices and Radiological Health, FDA. At the FDA, Dr. Radman reviewed wide-ranging indications for ophthalmic and neurological devices for therapy and diagnosis and assembled center-wide internal curriculum to disseminate the current thinking on the safety and effectiveness for the electrical stimulation of neural tissue. Most recently, Dr. Radman has spent 2 years in Algorithm Development at medical device start-up BrainScope where he has created cutting edge machine learning tools to provide a diagnosis of traumatic brain injury utilizing EEG recordings. Tom is now leading our efforts in Big Data and helping grow our presence in computational neuroscience.

**Dr. Tanya Ramey** recently joined DPMCD as a Medical Officer. Dr. Ramey is a psychiatrist with 18 years of clinical experience, and a physician-scientist with a 15-year- career in the pharmaceutical industry in clinical drug development, translational medicine, and medical affairs at Eli Lilly and Pfizer. She was an executive director and psychiatry lead in Pfizer's neuroscience research unit in Cambridge, MA, before joining NIDA in 2014. Dr. Ramey received her U.S. training in psychiatry at Vanderbilt University. She was previously an assistant professor of psychiatry at the Moscow State University of Medicine and Dentistry (MSUMD). Her Ph.D. is in psychiatric genetics. Her areas of expertise are in addictions, depression, anxiety, psychoses and cognition. She has an extensive experience in all phases of drug development. At NIDA she provides medical and safety monitoring for clinical trials, design and development of clinical trials protocols, and is involved in other pertinent aspects of drug development.

**Jennifer Schermerhorn** joined NIDA's Grants Management Branch in May 2014 as a Grants Management Specialist. Jen joins us from NIAID, where she was a grants management specialist for a little over 6 years. She is from Salisbury, Maryland and has a B.S. in Psychology from Salisbury University.

**Dr. Shelley Su** recently joined DBNBR's Behavioral and Cognitive Science Research Branch. Dr. Su received her Bachelor's degree from the University of North Carolina/Chapel Hill, where she studied memory reconsolidation, cue-induced drug seeking and relapse in animal models of drug abuse, working with Dr. Rita Fuchs. She then completed her graduate training at the University of California, Santa Barbara with a long-standing NIDA grantee Dr. Aaron Ettenberg, where she conducted research on the neurobiology of positive and aversive effects induced by drugs of abuse, the influence of extended access or escalation, the role of conditioned cue-associations, and sex differences. Her post-doctoral training was with Dr. Stan Floresco at the University of British Columbia, where she developed models for decision making and ways to understand cognitive flexibility during the addictive process. Dr. Su has vast experience in animal behavioral paradigms used to investigate diverse features of abuse and addiction, neurobiological techniques and approaches, and a sophisticated understanding of contemporary issues and problems falling within NIDA's priority research areas. She will be a great asset to DBNBR's program areas and the future of integrating behavioral approaches for studying substance use disorders.

**Yvonne Smith Walker** joined the OEA as a program specialist and will be the NIDA Guide Liaison responsible for coordinating the Funding Opportunity Announcement process. Before coming to NIDA/OEA, Yvonne Walker was a Program Specialist at the National Cancer Institute at Frederick. She was responsible for developing and implementing comprehensive plans and strategies for internal and external integration of day to day and long range projects, actions, and managing the education outreach program and other administrative functions within the Office of Scientific Operations. Prior to NCI, Yvonne worked for the Emergency Management Institute and National Fire Academy which is a part of DHS/FEMA located in Emmitsburg. She provided programmatic and administrative support for training specialists and branch chiefs developed and maintained briefing and training materials, also maintained numerous computerized databases. Yvonne is a veteran of the United States Air Force, serving from 2001 to 2009 as an Information Manager. She was responsible for the overall administration, management and life cycle of information and control of information resources as well as supervising a team of airmen and providing workgroup management support. Ms. Walker has a bachelors' degree in Management Studies from University of Maryland University College.

### **Departures**

**Lisa Coleman** left the NIDA COAC as the COAC's Deputy Director on August 9, 2014 to return to the National Cancer Institute (NCI) where she will assume an Operational Contracting Officer position at the NCI's FFRDC Facility in Frederick MD. Amy Siller has assumed some of the Deputy functions while NIDA is recruiting to fill this vacancy.

**Dr. Augie Diana** left NIDA on June 24, 2014. Dr. Diana was a Health Scientist Administrator in the Prevention Research Branch from 2006 through 2014. Dr. Diana oversaw the SBIR program in DESPR, was an active member of the NIDA Worklife Advisory Committee, took the lead on a number of physical activity initiatives, and also was a member of NIDA TOADS. Dr. Diana's new

position is Health Scientist Administrator in the Office of Extramural Science Programs in the Division of Extramural Science Programs at the NIH National Institute of Nursing Research. Dr. Diana's role will include overseeing the SBIR program at NINR.

## **Retirements**

**Loretta Beuchert** retired after 32 years at NIH. She started in 1982 at the Neurology Institute back in a time when the Collaborative Perinatal Project was coming to a close, working under Dr. Martha Denckla, Chief of the section of autism and related disorders. Loretta spent many years in at NINDS but has also worked in the Office of Director, National Heart, Lung, and Blood Institute, and in the Training Office in Building 1. The NIH Training Activities Committee (TAC) was established at that time and she wrote the newsletter for this trans-NIH committee. Loretta came to NIDA in January 2000 and has worked in the Office of Extramural Affairs ever since. At first managing I/START reviews and writing Council minutes among a myriad of other responsibilities before becoming the NIDA Guide Liaison. She considered this position her most challenging but at the same time the most interesting of all the various positions she's held at NIH, mainly because it gave her the opportunity to work with so many different people not only at NIDA but across the institutes.

**Deborah S. Wertz** of the Grants Management Branch, Office of Management retired from Federal service on June 28, 2014. Debbie's Federal career began 41 years ago when she was recruited directly from high school to work at Division of Research Grants/DRG (now Center for Scientific Review/CSR). She has also worked at the FDA, NCI, Center for Nursing Research (now NINR), and Agency for Health Care Policy and Research (AHCPR). Debbie was hired to work at NIDA 24 years ago by Jack Manischewitz (NIDA was under Alcohol, Drug Abuse and Mental Health Administration/ADAMHA at that time). She has administered many complex grant programs at NIDA including NIDA's Clinical Trials Network. We will miss Debbie and are very grateful for her outstanding service and commitment to GMB.

## **GRANTEE HONORS**

**Dr. Michael Bardo** received the 2014 CPDD Mentorship Award in June 2014 during the 2014 College on Drug Problems of Dependence 76th Annual Meeting which took place in San Juan, Puerto Rico. This award is given annually to a member of CPDD who has been an exemplary mentor to developing researchers in the field of drug abuse dependence.

**Drs. C. Hendricks Brown**, Northwestern University; **Dr. William B. Hansen**, Tanglewood Research; and **Dr. Helene R. White**, Rutgers University NIDA grantees were selected for the 2<sup>nd</sup> cohort of Fellows of the Society for Prevention Research (SPR), during the 22<sup>nd</sup> annual meeting, on May 29, 2014. The SPR Fellows Program, in its second year, is an honor SPR bestows upon a small and select group of members who have a particularly distinguished record of contributions in the field of prevention science.

**Brian K. Bumbarger, MEd**, received the Translational Science Award during the 22<sup>nd</sup> annual meeting of the Society for Prevention Research, on May 29, 2014. This award recognizes contributions to the field of prevention science in the area of Type 1 or Type 2 translational research.

**Dr. Donna Coffman** received the ECPN John B. Reid Early Career Award during the 22<sup>nd</sup> annual meeting of the Society for Prevention Research, on May 29, 2014. The award is presented to a person early in their career in prevention who has shown a commitment to prevention science through outstanding contributions to research, policy or practice.

**Dr. Benjamin Cravatt** of The Scripps Research Institute in La Jolla, CA, was the winner of the American Society for Biochemistry and Molecular Biology/Merck Award.

**Dr. Elizabeth D'Amico**, RAND, received the 2014 Medal Award June 2014, RAND's highest honor for recognizing individuals for inspiring contributions for developing innovative methods, tools, approaches to policy, or process as well as furthering RAND's mission and impact and advancing the business strategy. Dr. D'Amico received the award for extending the reach and impact of research findings on stemming teen alcohol and drug use in an innovative manner. Dr. D'Amico oversaw the launch of a website (<http://groupmiforteens.org>) that provides support for Group MI for teens, an intervention developed by Dr. D'Amico and that has been shown through her research to reduce teen drug and alcohol use. Dr D'Amico's success in making an effective intervention freely available to the public was recognized as exceptional.

**Dr. Brian Hicks**, University of Michigan, received the J. L. Fuller & J. P. Scott memorial award for outstanding scientific accomplishments by a member early in their career at the 2014 annual meeting of the Behavior Genetics Association.

**Dr. Stephanie Lanza** received the Friend of ECPN (Early Career Preventionist Network) award during the 22<sup>nd</sup> annual meeting of the Society for Prevention Research, on May 29, 2014. The Friend of ECPN award is presented to a mid-career or senior preventionist who has supported and encouraged early career prevention scientists or issues.

**Dr. Steffanie Strathdee**'s profile will appear in a forthcoming issue of the Lancet in which she will also serve as guest Editor of a new Lancet Series on HIV prevention in sex workers. Dr. Strathdee is widely considered a leader in the field of drug abuse and infectious disease research and prevention, both domestically and internationally, and effectively disseminates the evidence from her research to policy makers, local law enforcement and other community non-government groups. Among her numerous NIDA awards she currently holds a MERIT (R37 DA019829) examining the impacts of Mexico's 2010 change in drug possession laws, decriminalizing "personal" possession of heroin, cocaine, methamphetamine and marijuana.

#### **NIDA CTN Florida Node Alliance**

**Dr. Carlos del Rio** received the 2014 Thomas Jefferson Award, Emory University's highest award for distinguished service to the University. Dr. del Rio is the Hubert Professor and Chair of the Hubert Department of Global Health and Professor of Epidemiology at Rollins School of Public Health, as well as a professor of medicine at Emory School of Medicine and chief of the infectious disease service at Emory University Hospital. He is also the director for clinical sciences and international research of the Emory Center for AIDS Research (CFAR) and directs the Emory AIDS International Training and Research Program. Dr. del Rio has spent his career as a clinician and researcher, working to prevent, treat, and improve patient outcomes for infectious diseases locally and globally. He has focused his work on HIV/AIDS prevention and early diagnosis, access to care and compliance with anti-retrovirals in hard-to-reach populations, including substance abusers.

#### **NIDA CTN Pacific Northwest Node**

**Dr. Dennis Donovan** was appointed to the National Academy of Sciences' Institute of Medicine (IOM) Committee to Evaluate the Department of Veterans Affairs Mental Health Services. The 17-member committee will comprehensively assess the quality, capacity, and access to mental health care services, including treatment of substance use disorders, for veterans who served in the Armed Forces during Operation Enduring Freedom, Operation Iraqi Freedom, or Operation New Dawn. This IOM committee will assess the spectrum of mental health services available across the entire Department of Veterans Affairs. It will determine the extent to which veterans are afforded treatment choices, as well as the extent to which Iraq and Afghanistan war veterans are being offered a full range of necessary mental health services in the VA. The scope of the Committee's assessment will also include barriers faced by patients in utilizing the services offered. In addition to providing expertise in substance use disorder treatment to the committee, Dr. Donovan also brings his experience working within the VA system for nearly 20 years prior to assuming his role at the UW Alcohol & Drug Abuse Institute.