ADDICTION SCIENCE & CLINICAL PRACTICE

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CLINICAL PERSPECTIVES

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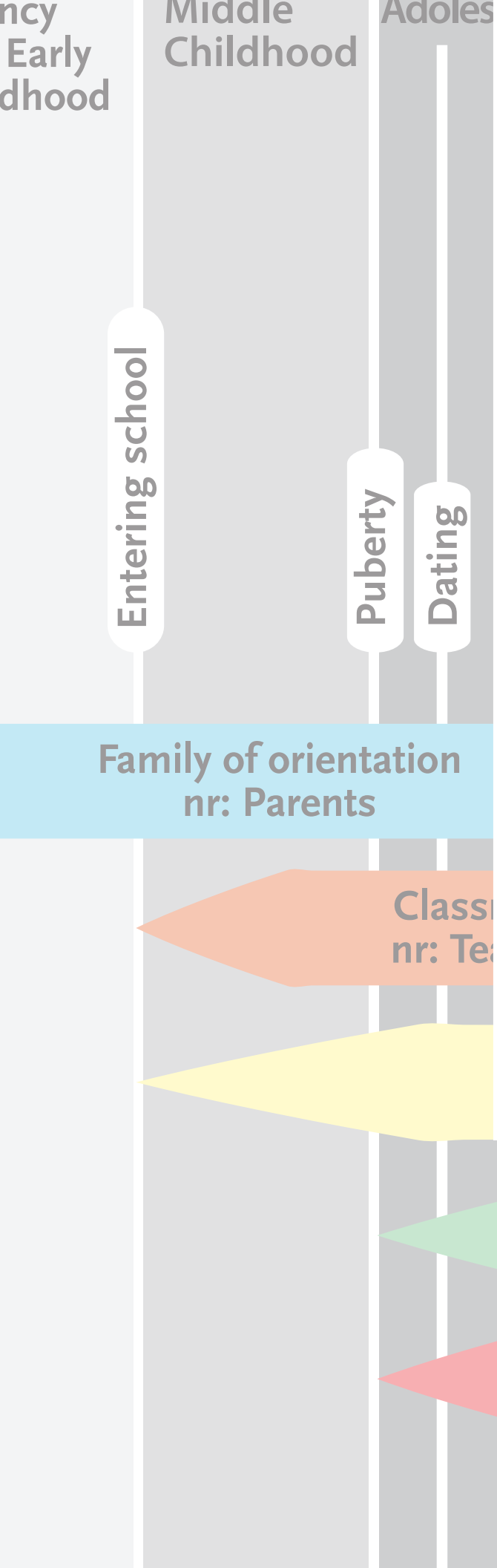

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ADDICTION SCIENCE & CLINICAL PRACTICE

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A Note From NIDA's Director

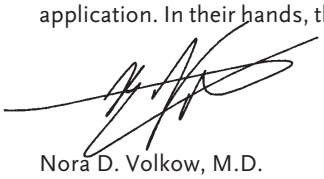
Addiction Science & Clinical Practice (AS&CP) is about to enter a new stage in its development.

After this issue, the journal moves to a new publisher, Biomed Central, and assumes a new format as an open-access, Internet-only publication. Taking over as Editors are Richard Saitz, M.D., M.P.H., and Jeffrey Samet, M.D., M.A., M.P.H., of the Clinical Addiction Research and Education Unit at Boston Medical Center and Boston University School of Medicine and School of Public Health.

AS&CP was launched in 2002 with its original title, *Science & Practice Perspectives*. The journal was a key component of NIDA's response to a challenge issued by the Institute of Medicine (IOM). The IOM had identified a gap between substance abuse research and practice as a major obstacle to progress and called upon the field to close it. NIDA's new peer-reviewed journal set out to foster rich, creative exchanges between researchers and clinicians. That goal informed its every aspect— its diverse editorial board, article selection, additional features, style, design, and layout.

In its 9 years under the outstanding leadership of Founding Editor David Anderson, M.S., *AS&CP* has proved that the field values that mission and product. Top authorities at bench and clinic have welcomed the opportunity and the challenge of imparting their knowledge across the research-practice divide, with special attention to practical implications and constructive advice. Response panels in which clinicians and researchers engage in free give and take in reaction to a particular article have been among the journal's most distinctive and popular features. *AS&CP* has more subscribers than any other addiction journal, and articles have been translated into several languages.

At its new home, AS&CP will be well placed to continue to advance the research-practice interchange. Drs. Saitz and Samet are experienced editors who spend every working day at the interface of the creation of new knowledge and its application. In their hands, the journal has a bright future.



Nora D. Volkow, M.D.
Director
National Institute on Drug Abuse

Editor's Note

Leaving the Banquet

The offerings in this, my last issue as Editor of *Addiction Science & Clinical Practice,* reinforce my feeling of stepping away from a banquet that has many rich courses still to come. In this final issue produced by NIDA:

- Drs. Manoranjan D'Souza and Athina Markou review what researchers have discovered about how nicotine affects brain function to produce dependence, and examine the prospects for medications based on each of the instrumental interactions;
- Dr. Sonia Minnes and colleagues examine the damage that use of tobacco and other drugs by pregnant women inflicts upon their children. Longitudinal studies, now maturing along with their participant cohorts, are starting to reconcile earlier findings and trace the effects of prenatal drug exposure throughout childhood and adolescence;
- Dr. Sheppard Kellam and coauthors ponder the lessons learned from a longitudinal study in which addressing first- and second-graders' aggressive and disruptive behaviors curbed smoking, illicit drug abuse, and violence when they became young adults. These researchers envision a unified system for human development research and practice with universal interventions as the front line of a multitiered system of prevention and treatment;
- Dr. Matthew O. Howard and colleagues summarize the current state of understanding of inhalant abuse—its epidemiology, pharmacology, and consequences. Although most inhalant abusers soon quit, and the problem is infrequently seen in treatment centers, the review makes a strong case that more research on this early-onset, highly dangerous behavior is critically needed;
- Dr. Alexandra E. Shields explores the ethical risks that genetically based research and treatments will bring along with their potential benefits, particularly when they address highly stigmatized diseases such as addiction. This article highlights the need for distributive justice—making sure that genetic advances lessen rather than exacerbate existing health disparities;
- Dr. Alexandre B. Laudet advocates assessing patients' quality of life as a measure of progress and success in substance abuse treatment. She argues that clinicians' goals for their patients should, and usually already do, exceed simple abstinence, and that defining and standardizing criteria for quality of life will facilitate research and full recovery.

As I retire from the editorship of the journal, I have many thanks to bestow. Board members lent their prestige, critiqued issues, suggested topics, and steered us to authors and panelists. Peer reviewers provided invaluable guidance. Authors, many accustomed to writing mainly for peers in their own specialty areas, fashioned state-of-the-art reviews to be grasped and used by a much wider group of colleagues. Panelists brought their experience to bear on the article contents and debated meanings and implications. Readers—I hope—found much to stimulate their thinking and much to use.

Although I will continue to keep abreast of developments in the field as Editor of *NIDA Notes*, I will miss the special engagement with people and issues that editing the journal has made possible. I will continue to follow *AS&CP* in its new home, and I wish the new Editors an experience as fine as I have had.

David Anderson
Editor
National Institute on Drug Abuse

Drug abuse counselors can earn continuing education credits by reading *Addiction Science & Clinical Practice*. See inside back cover for details.

We invite you to join the discussion of the topics addressed in this issue. Visit our Reader Response Page at *www.nida.nih.gov/ascp/feedback/* to make a comment or pose a question to an author.

Neuronal Mechanisms Underlying Development of Nicotine Dependence: Implications for Novel Smoking-Cessation Treatments

Tobacco smoking causes high rates of mortality and morbidity throughout the world. Despite the availability of smoking-cessation medications, maintenance of long-term abstinence is difficult, and most individuals who attempt to quit smoking relapse. Although tobacco smoke contains many substances, researchers and policymakers agree that nicotine is a major cause of tobacco dependence. Understanding the neural substrates of nicotine dependence is essential for the development of more effective antismoking medications than those currently available. This article focuses on the neural substrates, especially nicotinic acetylcholine receptors, that mediate the reinforcing effects of nicotine and the development of nicotine dependence. Neuroadaptations in the function of the neurotransmitters dopamine, glutamate, and gamma-aminobutyric acid (GABA), which have been shown to be critically involved in nicotine dependence, are also reviewed. Finally, the article discusses progress in the discovery and development of smoking-cessation medications.

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Tobacco dependence is a major public health problem that results in significant morbidity, mortality, and health care costs for both smokers and society. The health benefits of smoking cessation are well-known, and nearly 40 percent of smokers in the United States try to quit each year. Nevertheless, only approximately 3 to 6 percent of those who attempt to quit succeed in avoiding smoking for 6 to 12 months, with the majority of quit attempts failing within the first 8 days (Hughes et al., 2004). Professionally administered smoking-cessation therapy improves the odds of a successful quit attempt, but its effectiveness is limited by a lack of highly effective medications. To date, the only smoking-cessation medications approved by the Food and Drug Administration (FDA) are nicotine replacement therapy (NRT), bupropion (Wellbutrin/Zyban), and varenicline (Chantix), along with the second-line agents nortriptyline and clonidine. Of these treatments, varenicline appears to be most effective, yielding abstinence rates of approximately 22 percent at the end of 1 year, compared with 9 percent with placebo (Gonzales et al., 2006). For a comprehensive review of current smoking-cessation medications, see Nides (2008).

An understanding of the neural substrates (structures and processes) that maintain nicotine dependence is essential for the development of effective smoking-cessation medications. Although people probably do not smoke solely to obtain nicotine—some of tobacco's 4,000 other chemical ingredients, as well as sensory

and conditioned effects, may also contribute to the habit—nicotine certainly plays a major role in tobacco dependence (Stolerman and Jarvis, 1995; Rose, 2006). This review discusses: (1) the interaction of nicotine with neuronal pathways in the brain that leads to the initiation and maintenance of the tobacco-smoking habit, (2) the adaptations in several neurotransmitter systems that result from chronic nicotine exposure and lead to continued smoking and the development of nicotine dependence, and (3) the implications of these interactions and neuroadaptations for the design and discovery of novel smoking-cessation treatments.

THREE PHASES OF NICOTINE DEPENDENCE

Nicotine dependence is characterized by three phases:

- *Acquisition and maintenance of nicotine-taking behavior:* In humans, the administration of nicotine through tobacco smoking produces a mild pleasurable rush, mild euphoria, increased arousal, decreased fatigue, and relaxation (Henningfield et al., 1985). These reinforcing effects play an important role in the initiation and maintenance of tobacco smoking (Watkins et al., 2000; Markou, 2008). Several other species, such as rats and nonhuman primates, exhibit behavioral evidence of nicotine reinforcement by reliably self-administering intravenous nicotine (Rose and Corrigall, 1997).
- *Withdrawal symptoms upon cessation of nicotine intake:* Chronic nicotine use induces neuroadaptations in the brain's reward system that result in the development of nicotine dependence. Thus, nicotine-dependent smokers must continue nicotine intake to avoid distressing somatic and affective withdrawal symptoms. Newly abstinent smokers experience symptoms such as depressed mood, anxiety, irritability, difficulty concentrating, craving, bradycardia, insomnia, gastrointestinal discomfort, and weight gain (Shiffman and Jarvik, 1976; Hughes et al., 1991). Experimental animals, such as rats and mice, exhibit a nicotine withdrawal syndrome that, like the human syndrome, includes both somatic signs and a negative affective state (Watkins et al., 2000; Malin et al., 2006). The somatic signs of nicotine withdrawal include rearing, jumping, shakes, abdominal constrictions, chewing, scratching, and facial tremors. The negative affective state of nicotine withdrawal is characterized by decreased responsiveness to previously rewarding stimuli, a state called anhedonia.
- *Vulnerability to relapse:* Abstinent smokers remain prone to relapse for weeks, months, or even years after cessation of tobacco smoking. Resumption of smoking, like relapse to other drugs of abuse, often occurs upon exposure to people, places, objects, or other stimuli that individuals have learned to associate with the positive rewarding effects of the drug (Hughes et al., 2004). Stress and cigarette smoking itself can also precipitate resumption of habitual smoking.

Comprehensive medication therapy for nicotine dependence will have to target all three phases of drug dependence. Whether by a single "magic bullet" or a sequential strategy using multiple medications, such therapy will need to attenuate the reinforcing effects of nicotine, alleviate the negative affective and somatic symptoms of withdrawal, strengthen abstinence behaviors, and block relapse to smoking. To do so, the medication or medications will need to act upon the neurobiological substrates that underlie each of those aspects of nicotine dependence. The remainder of this review focuses on our current knowledge of these substrates and their potential as targets for smoking-cessation medications.

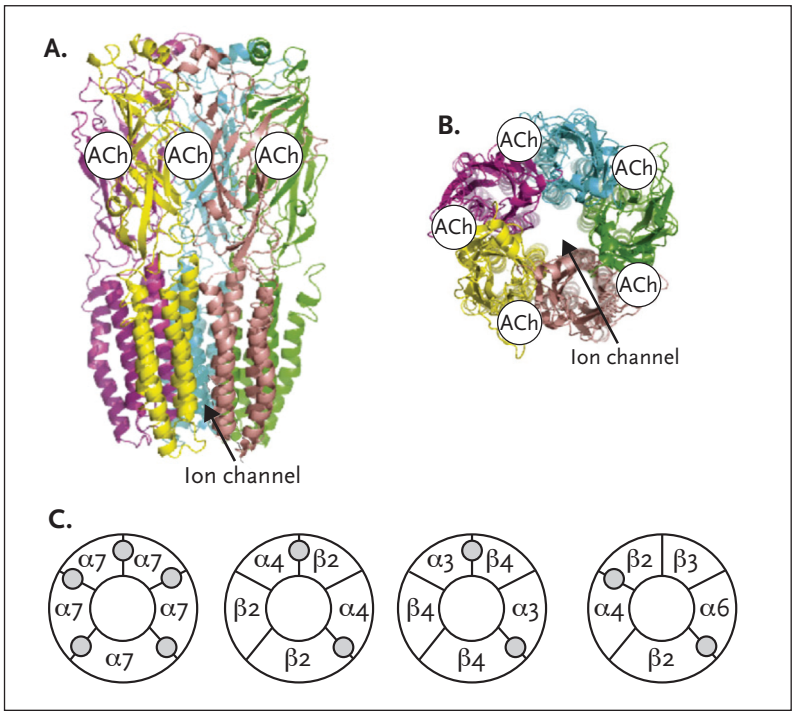
Nicotine influences mood, cognition, and body function by activating nicotinic acetylcholine receptors located on neurons in the brain.

THE ROLE OF NICOTINIC RECEPTORS

Nicotine influences mood, cognition, and body function by binding to and activating nicotinic acetylcholine receptors (nAChRs) located on neurons in the brain (Figures 1 and 2). When activated by either nicotine or the endogenous neurotransmitter acetylcholine, the nAChR opens a channel that allows ions to pass through the neuron's membrane from the exterior to the interior of the cell and trigger changes that activate the cell. In this section, we examine the interactions of nicotine with nAChRs and the possibility of treating nicotine dependence by altering these interactions.

Nicotine produces rewarding effects by interacting with nAChRs on neurons in the brain's mesolimbic reward system. This system comprises dopaminergic neurons that originate in the ventral tegmental area (VTA) and release the neurotransmitter dopamine in regions involved in information processing, memory, and emotions, such as the nucleus accumbens (NAc), hippocampus, amygdala, and prefrontal cortex (PFC). Increases in dopamine levels within the mesolimbic system give rise to rewarding effects. Nicotine directly enhances dopamine levels in the mesolimbic system by interacting with nAChRs on the dopaminergic neurons and causing them to release more of the neurotransmitter (Balfour, 2009; Barrett et al., 2004; Koob and Volkow, 2010). Nicotine also modulates dopamine

FIGURE 1. Nicotine Acetylcholine Receptor



(A) Side view of the α7 nAChR showing binding sites for acetylcholine or nicotine. (B) Top view of the α7 nAChR showing binding sites. (C) Schematic top views of four nAChR subtypes, showing their subunit composition: α7 (homomeric); α4β2 (heteromeric); α3β4 (heteromeric); α4α6β2β3 (heteromeric). Reproduced with permission from Changeux and Taly, 2008.

release indirectly by binding to nAChRs located on excitatory glutamatergic and inhibitory gamma aminobutyric acid (GABAergic) neurons in the VTA. These glutamatergic and GABAergic neurons originate from a number of brain areas, such as the NAc, hippocampus, PFC, amygdala, ventral pallidum, and pedunculopontine tegmental nucleus, and regulate the activity of dopaminergic neurons.

The mix of subunits in each nAChR gives the receptor its distinct pharmacological properties.

In contrast, binding of nicotine to nAChRs located on excitatory glutamatergic terminals results in glutamate release, which in turn stimulates dopaminergic neurons. Binding of nicotine to nAChRs located on inhibitory GABAergic projections leads to the release of gamma aminobutyric acid (GABA), which in turn inhibits dopaminergic neurons. Both glutamate and GABA neurotransmission play important roles in the development of nicotine dependence (for a review, see Markou, 2008). nAChRs are also present on neurons that release other neurotransmitters, including opioids, norepinephrine, serotonin, orexin, and cannabinoids, but the role of these neurotransmitter systems in nicotine dependence has not been extensively studied.

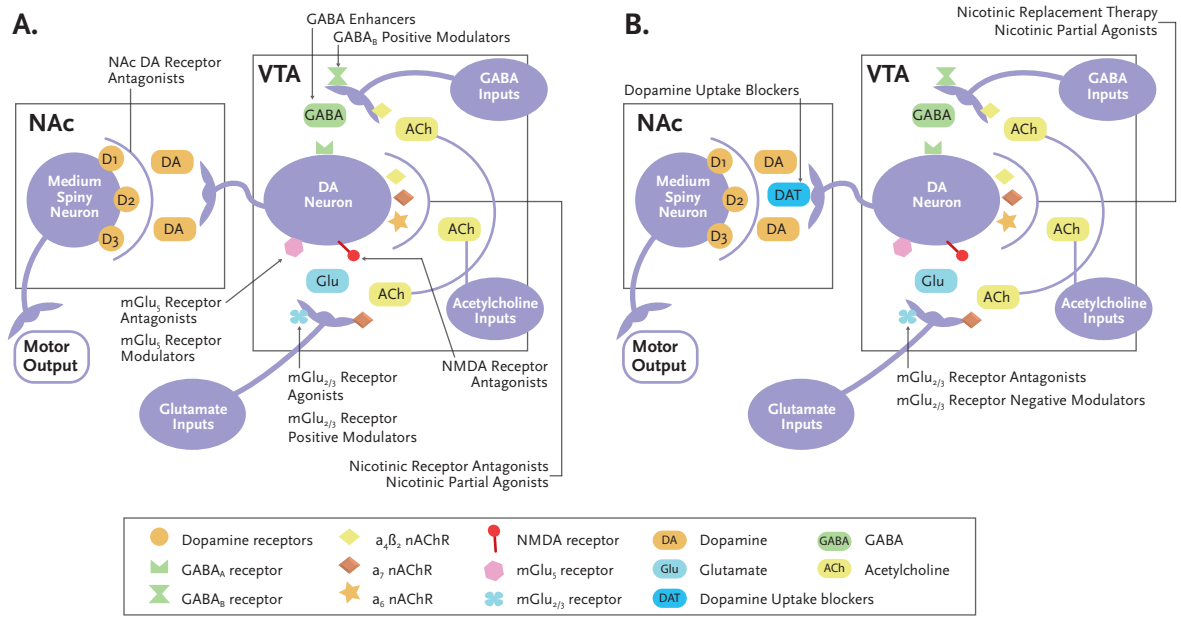
Nicotinic Receptor Subunits and Nicotine Reinforcement

The ability of nicotine to activate a particular nAChR depends on the subunits that make up the receptor. nAChR subunits exist in 12 isoforms (variant forms), labeled α2–α10 and β2–β4 (Figure 1; Dani and Bertrand, 2007). Every nAChR consists of five subunit molecules arranged in a ring around a central channel that opens to admit ions when the receptor is activated. In some nAChRs, called homomeric nAChRs, all five subunits are the same—for example, all are α7. Other nAChRs, called heteromeric, have a mix—for example, two α4 and three β2 subunits. The mix of subunits in each nAChR gives the receptor its distinct pharmacological properties, including its response to nicotine stimulation.

Extensive preclinical evidence suggests that β2-, α4-, α5-, α6-, and α7-containing nAChRs mediate the reinforcing and behavioral effects of nicotine (Fowler et al., 2008; Markou, 2008). Here we briefly summarize this evidence (Figure 2):

- *β2-containing nAChRs:* Mice that lack the β2 nAChR subunit as a result of genetic manipulation, called β2 knockout mice, do not self-administer nicotine (Picciotto et al., 1998). However, β2 knockout mice begin to self-administer nicotine when the missing receptor subunit is introduced into their brains with another genetic manipulation. Furthermore, rats treated with a compound that blocks the action of nicotine at α4β2-containing nAChRs self-administer less nicotine than control animals given an inert vehicle like saline.
- *α5-containing nAChRs:* Mice bred to lack the α5 subunit (i.e., α5 knockout mice) had fewer nicotine-induced seizures and attenuated nicotine-induced locomotor activity compared with wildtype mice. Importantly, α5 knockout mice showed *increased* nicotine self-administration compared with wildtype mice. This work by Fowler and colleagues (2011) suggests that activity of the α5 subunit in the medial habenula-interpeduncular nucleus pathway reduces the aversive effects of high doses of nicotine. Humans who have a single-nucleotide polymorphism (SNP) in the gene for the α5 subunit that decreases the expression of the α5-containing nAChRs are twice as likely as those without this SNP to develop nicotine dependence. Taken together with the animal findings, this pattern of results suggests that agonists of α5-containing nAChRs or other compounds that increase the activity of α5-containing nAChRs may promote smoking ces-

FIGURE 2. Pharmacological Strategies to Attenuate Nicotine Reinforcement and Alleviate Withdrawal



A) Potential targets in the mesolimbic reward system can promote smoking cessation by attenuating the reinforcing effects of nicotine. The reinforcing effects of nicotine are partly mediated by the activation of dopamine neurons in the ventral tegmental area (VTA) and the release of dopamine (DA) in the nucleus accumbens (NAc). The activity of dopamine neurons in the VTA is regulated by glutamatergic and GABAergic inputs from different brain regions. Pharmacological strategies that attenuate the reinforcing effects of nicotine and cue-induced reinstatement of nicotine seeking in animals include compounds that block nicotine and acetylcholine from stimulating nACh receptors on glutamate- and dopamine-releasing neurons, such as nicotinic receptor antagonists and partial agonists; compounds that reduce excitatory glutamatergic neurotransmission in the VTA, such as the presynaptic mGlu2/3 receptor agonists/positive modulators, postsynaptic mGlu5 antagonists/negative modulators, and *N*-methyl-D-aspartate (NMDA) receptor antagonists; and compounds that increase the influence of the inhibitory neurotransmitter GABA at receptors on dopamine neurons such as GABA enhancers and GABAB positive modulators. Compounds that reduce dopaminergic neurotransmission, such as DA receptor antagonists, also attenuate nicotine reinforcement and reinstatement in animal models.

B) Potential targets in the mesolimbic reward system may help to alleviate the negative affective symptoms seen in smokers who quit smoking. Chronic nicotine exposure results in decreased dopamine and glutamate neurotransmission in the VTA and NAc. Pharmacological compounds that facilitate dopamine and/or glutamate release in the VTA and/or NAc alleviate the negative affective effects of nicotine withdrawal in animals. Such compounds/strategies include nicotine replacement therapy, nicotine receptor partial agonists, mGlu2/3 receptor antagonists/negative modulators, and dopamine uptake blockers.

sation by enhancing the aversive effects of nicotine.

- *α6-containing nAChRs:* Compounds that selectively reduce the activity of α6-containing nAChRs dose-dependently decrease nicotine self-administration in rats, suggesting these nAChRs are important in nicotine's reinforcing effects (Dwoskin et al., 2009).
- *α7-containing nAChRs:* Rats self-administered less nicotine after systemic administration of a compound that prevents nicotine from interacting with predominantly homomeric α7-containing nAChRs (Markou and Paterson, 2001). These results suggest a role for α7-containing nAChRs in the reinforcing effects of nicotine.

In summary, activation of nAChRs that contain β2, α4, α6, or α7 subunits appears to promote the reinforcing effects of nicotine. By contrast, α5-containing nAChRs appear to limit nicotine reinforcement, possibly by mediating the drug's aversive effects. An important unanswered question is whether every nAChR that contains one of these subunits contributes to nicotine reinforcement, or whether only subsets of these nAChRs are involved. Ultimately, the complete subunit composition and stoichiometry of nAChRs containing these five subunits needs to be fully understood to develop medications that will block the reinforcing effects of nicotine and promote smoking cessation.

Nicotinic Receptor Subunits and Nicotine Withdrawal

Evidence from rodent models and genetically modified mice suggests that nAChRs and their various subunits mediate the aversive somatic and negative affective

TABLE 1. FDA-Approved and Investigational Smoking-Cessation Medications Targeting Nicotinic Acetylcholine Receptors

MEDICATIONS/ COMPOUNDS	MECHANISM	STATUS	REFERENCE
Nicotine replacement therapies*	Replace nicotine obtained from tobacco smoke through the use of safer options	FDA approved	Nides, 2008
Varenicline	Partial α4β2 nAChR agonist Acts as an antagonist in the presence of nicotine to decrease the reinforcing effects of nicotine Activates nicotinic receptors during abstinence and limits the aversive effects associated with nicotine withdrawal	FDA approved	Gonzales et al., 2006
Mecamylamine	Nonselective nicotinic receptor antagonist	Utility limited due to nonselective action	Schnoll and Lerman, 2006

*Nicotine patch, gum, inhaler, microtab, nasal spray, and lozenge.

Varenicline's dual actions attenuate nicotine's reinforcing effects and reduce withdrawal symptoms.

signs of nicotine withdrawal (for reviews, see Kenny and Markou, 2001; Fowler et al., 2008). For example, nicotine-dependent rats treated with a compound that blocks α4β2-containing nAChRs exhibited a negative affective or depression-like state, during which they were less responsive to electrical stimulation of their reward system but showed no somatic signs of nicotine withdrawal (Epping-Jordan et al., 1998).

By contrast, nicotine- dependent rats treated with a compound that blocks multiple nAChR subtypes, including β4-containing nAChRs, exhibited both a depression-like state and somatic signs of nicotine withdrawal. Importantly, experiments with knockout mice suggest that nAChRs containing α5, α7, and β4 subunits are instrumental in the expression of somatic signs of nicotine withdrawal, whereas β2-containing nAChRs contribute to the nicotine withdrawal-induced negative affective state (Fowler et al., 2008).

Nicotinic Receptor–Based Treatment Strategies

Developers of antismoking medications have long focused on compounds that interact with nAChRs (see Table 1). Varenicline, for example, is a partial agonist at α4β2-containing nAChRs. Varenicline attenuates the reinforcing effects of nicotine by occupying the binding sites on these receptors and blocking nicotine from binding to them. Varenicline and other partial agonists also weakly stimulate α4β2-containing nAChRs, thereby reducing withdrawal symptoms.

On the basis of the preclinical literature discussed above, compounds that act at nAChRs that contain the β2, α5, α7, and β4 subunits have the potential to reduce the negative affective and aversive somatic symptoms of nicotine withdrawal.

Researchers are also exploring the potential for a new generation of smoking-cessation therapies based on allosteric modulation of nAChRs (Yoshimura et al., 2007). Allosteric modulators are compounds that bind to sites on the receptor that are different from the sites where agonists or antagonists bind. Allosteric modulators do not directly stimulate nAChRs, but instead increase or decrease their responsiveness to agonists like nicotine or natural neurotransmitters like acetylcholine. Researchers have identified several allosteric binding

sites on nAChRs. Allosteric compounds acting at these sites may either help to reduce the reinforcing effects of nicotine or may alleviate the aversive effects of nicotine withdrawal, or both, and thus may help prevent relapse (Taly et al., 2009).

Other promising strategies currently under investigation aim to inhibit stimulation of nAChRs by reducing the amount of nicotine that reaches the brain. These include immune-based approaches, such as nicotine vaccines and pharmacokinetic treatments that alter the availability of nicotine by enhancing its peripheral metabolism and clearance (Xi et al., 2009).

NEUROTRANSMITTER SYSTEMS IN NICOTINE ADDICTION

As described above, nicotine initiates the processes leading to nicotine dependence by interacting with nAChRs on dopaminergic, glutamatergic, and GABAergic neurons. Accordingly, as discussed, one set of potential medication strategies for treating nicotine dependence focuses on modulating the nicotine-nAChR interaction. A second group of potential strategies targets the receptors and transporters that mediate the effects of dopamine, glutamate, and GABA after exposure to nicotine.

Dopamine

Dopamine has been strongly implicated in the reinforcing and withdrawal effects of nicotine. The key evidence includes experiments in laboratory animals that show:

- administering nicotine increases dopamine transmission within the mesolimbic reward system; and
- administering compounds that block dopamine binding to its receptors (D1, D2, D3, D4, and D5 receptors) decreases the reinforcing effects of nicotine.

Dopaminergic neurotransmission is decreased during nicotine withdrawal. For example, in nicotine-dependent rats, the induction of nicotine withdrawal by administration of the nAChR antagonist mecamylamine resulted in decreased dopamine levels in the NAc compared with administration of an insert substance (Hildebrand et al., 1998). In addition, the decrease in NAc dopamine correlated well with the somatic and affective signs of nicotine withdrawal. The decrease in NAc dopamine was greater in adult rats compared with adolescent rats (Natividad et al., 2010), possibly indicating a more important role for mesolimbic dopamine in nicotine withdrawal in adult rats compared with adolescent rats. Dopamine-based smoking-cessation medications that are currently available or under development are directed toward either alleviating nicotine withdrawal symptoms, blocking nicotine reinforcement, or both (see box, Treatment Strategies for Nicotine Dependence Based on Dopaminergic Neurotransmission).

TREATMENT STRATEGIES FOR NICOTINE DEPENDENCE BASED ON DOPAMINERGIC NEUROTRANSMISSION

Alleviation of withdrawal symptoms by blockade of dopamine uptake transporter

Bupropion is approved by the Food and Drug Administration (FDA) as a smoking cessation medication. It acts by blocking the uptake of synaptic dopamine via the dopamine transporter (DAT). In addition to blocking dopamine uptake, bupropion has other potentially therapeutic actions, such as blockade of nicotinic acetylcholine receptors and norepinephrine uptake (Paterson, 2009). Clinically, bupropion alleviates negative affective symptoms associated with smoking cessation, such as depression, difficulty in concentrating, and irritability.

Attenuation of the reinforcing effects of nicotine via blockade of dopamine receptors

Blocking the reinforcing effects of nicotine using a dopamine receptor antagonist is another dopamine-based strategy that can be developed for smoking cessation (Figure 2, page 7). Blockade of D1, D2, and D3 dopaminergic receptors decreases nicotine self-administration. There is considerable interest in D3 receptor antagonists because this subtype of dopamine receptors has high affinity for dopamine and is extensively expressed in the mesolimbic dopamine system (Diaz et al., 2000). Another reason for the interest in D3 dopamine receptors is that D1 and D2 receptor antagonists tend to produce adverse effects in humans.

Glutamate

Glutamate, the brain's primary excitatory neurotransmitter, also plays a critical role in the development of nicotine dependence (Liechti and Markou, 2008). Nicotine increases the release of glutamate by binding to excitatory α7-containing nAChRs located on presynaptic terminals of glutamatergic neurons in the VTA, NAc, amygdala, hippocampus, and PFC (Mansvelder and McGehee, 2002). The released glutamate binds to ionotropic and metabotropic glutamate receptors located on neurons in these areas (Figure 2).

Decreases in dopamine in the nucleus accumbens correlate well with symptoms of withdrawal.

Glutamate and nicotine reinforcement

Glutamate released into the VTA after nicotine administration binds to glutamate receptors on dopaminergic neurons. The resulting increased firing of VTA dopaminergic neurons leads to dopamine release in the NAc and, consequently, nicotine reward (Grillner and Svensson, 2000). The rewarding effect of nicotine can be attenuated by administering compounds that reduce glutamate

transmission. For example, animals self-administered less nicotine than control animals when treated with compounds that:

- prevent glutamate from binding to postsynaptic ionotropic or metabotropic glutamate receptors, such as antagonists at postsynaptic *N*-methyl-D-aspartate (NMDA), AMPA receptors, or mGlu5 receptors (Liechti and Markou, 2008).
- activate presynaptic inhibitory mGlu2/3 receptors.

Furthermore, rats treated with glutamate receptor antagonists showed reduced nicotine-induced dopamine release compared with rats receiving an inert substance (Fu et al., 2000). These findings suggest that decreasing glutamate transmission can facilitate smoking cessation by decreasing the reinforcing effects of nicotine.

One approach to help smokers maintain abstinence is to weaken and overwrite memories that link stimuli to smoking and the rewarding effects of nicotine.

Glutamate and nicotine withdrawal

Withdrawal after chronic nicotine exposure is characterized by decreased glutamate transmission and compensatory changes in glutamate receptors (Mansvelder et al., 2002). For example, rats exhibited decreased expression of NMDA ionotropic glutamate receptor subunits, as well as decreased functioning of mGlu2/3 receptors in the PFC, during early withdrawal following chronic nicotine self-administration (Kenny et al., 2009; Liechti et al., 2007). Because presynaptic mGlu2/3 receptors reduce glutamate release when activated, the decreased functioning of mGlu2/3 receptors appears to be a compensatory mechanism to offset the reduction in synaptic glutamate levels that occurs during early withdrawal.

Similarly, rats in early withdrawal after chronic nicotine self-administration exhibited downregulation of the glutamate transporter (GLT1) in the NAc and cystine-glutamate transporter (xCT) in the VTA and NAc (Knackstedt et al., 2009). These transport proteins are located on glial cells and have opposite roles in the regulation of synaptic glutamate levels. GLT1 decreases synaptic glutamate by drawing glutamate out of the synapse into the glia; by contrast, xCT extrudes vesicular glutamate from glia in exchange for synaptic cystine. The downregulation of GLT1 and xCT during nicotine withdrawal are therefore examples of compensatory mechanisms in response to synaptic glutamate depletion that occurs after chronic nicotine exposure.

In summary, preclinical data suggest that withdrawal from chronic nicotine exposure is characterized by decreased glutamatergic transmission. Thus, medications that increase synaptic glutamate levels may help to alleviate withdrawal symptoms in abstinent smokers.

Glutamate and cue-induced relapse

As described above, memory associations that link certain people, places, and things with the rewarding effects of smoking can trigger intense cravings that lead to relapse in abstinent smokers. In animals, exposure to cues previously associated with nicotine can enhance mesolimbic glutamatergic neurotransmission, resulting in the resumption of drug-seeking behavior (Kalivas and O'Brien, 2008). Treating animals with compounds that block glutamatergic neurotransmission suppresses this effect (Liechti and Markou, 2008). Accordingly, one strategy to prevent relapse in humans is to administer compounds that block glutamatergic neurotransmission.

Unfortunately, learned associations that induce craving cannot be easily erased. Therefore one approach to help smokers maintain abstinence is to replace memories that link stimuli to smoking and the reward effects of nicotine with new memories that will not induce craving or raise the risk of relapse (Taylor et al., 2009). This type of learning, which decreases the reward value of stimuli previously associated with smoking, is called extinction learning (Myers et al., 2011). Interestingly, increasing glutamate transmission facilitates extinction learning. Therefore, another strategy to prevent relapse in abstinent smokers is to aid extinction learning via administration of compounds that increase glutamatergic neurotransmission.

Glutamate-based treatment strategies

Table 2 lists specific glutamate-based strategies that target the different glutamatergic receptors and transporters for the treatment of nicotine dependence (see also Figure 2). Major preclinical findings that involve glutamatergic substrates are described below (for a more detailed review, see Liechti and Markou, 2008):

mGlu2/3 receptors

Administration of an mGlu2/3 receptor agonist in rats decreases nicotine self-administration. Furthermore, such administration decreased reinstatement of nicotine-seeking behavior upon exposure to cues previously associated with the effects of nicotine (Liechti et al., 2007). These findings suggest that mGluR2/3 receptor agonists may help promote smoking cessation and prevent relapse in humans.

However, the attenuating effects of mGlu2/3 receptor agonists on nicotine self-administration in rats waned after repeated administration. This loss of effectiveness suggests the development of tolerance that may

TABLE 2. Potential Therapeutic Utility of Glutamatergic Drugs Based on Preclinical Evidence

	POTENTIAL THERAPEUTIC UTILITY	GLUTAMATE RECEPTOR	COMPOUND(S)/ LIGAND(S)
1	Promote smoking cessation by blocking the reinforcing effects of nicotine	mGlu2/3 receptor	mGlu2/3 receptor agonists mGlu2/3 receptor positive allosteric modulators
		mGlu5 receptor	mGlu5 receptor antagonists mGlu5 receptor negative allosteric modulators
		NMDA receptor	Glycine-site partial agonists
		Cystine-glutamate exchanger	Cystine-glutamate activators, such as N-acetylcysteine
2	Prevent relapse by decreasing the aversive effects associated with abstinence from nicotine	AMPA receptor	AMPA receptor positive modulators
		mGlu2/3 receptor	mGlu2/3 receptor antagonists mGlu2/3 receptor negative modulators
3	Prevent relapse by enhancing extinction of nicotine-seeking behavior	NMDA receptor	NMDA receptor co-agonists, such as D-cycloserine
		mGlu5 receptor	mGlu5 receptor agonists mGlu5 receptor allosteric positive modulators
4	Prevent relapse by blocking reinstatement of nicotine-seeking behavior	mGlu2/3 receptor	mGlu2/3 receptor agonists mGlu2/3 receptor allosteric positive modulators
		mGlu5 receptor	mGlu5 receptor antagonists mGlu5 receptor allosteric negative modulators
		Cystine-glutamate exchanger	Cystine-glutamate activator, such as N-acetylcysteine
		Glutamate transporter	Inhibitors of glutamate transporters, such as ceftriaxone

limit the therapeutic utility of full agonists at mGlu2/3 receptors. Currently, positive allosteric modulators for mGlu2/3 receptors are available and are being evaluated clinically for other indications, including treatment of schizophrenia. mGlu2/3 receptor positive allosteric modulators may prove to be more suitable than the full mGlu2/3 receptor agonists. However, the utility of these compounds as potential antismoking medications still needs to be determined both preclinically and clinically.

As described above, animals exhibit a depression-like state upon withdrawal from chronic nicotine exposure. That state is attributed to a decrease in glutamatergic neurotransmission. In animal studies, administration of compounds that increase glutamatergic neurotransmission by blocking presynaptically located inhibitory mGlu2/3 receptors reversed the depression-like state associated with nicotine withdrawal. Thus, mGluR2/3 antagonists may be useful for treating the negative affec-

tive symptoms resulting from smoking abstinence in humans.

mGlu5 receptors

Administration of compounds that block the mGlu5 receptors decrease the self-administration of nicotine and attenuate the reward-enhancing effects of nicotine in rats (Kenny et al., 2003; Paterson et al., 2003), suggesting that mGlu5 receptor antagonists decrease the reinforcing effects of nicotine. Administration of mGlu5 receptor antagonists in rats also blocked the reinstatement of nicotine-seeking behavior in response to cues previously associated with nicotine, suggesting that these compounds may help prevent relapse in humans (Markou, 2008).

Smokers given D-cycloserine had fewer cravings on exposure to smoking-related cues.

However, administration of mGlu5 receptor antagonists aggravated the depression-like state and somatic signs associated with nicotine withdrawal in rats. Furthermore, at the highest tested dose, mGlu5 receptor antagonists on their own induced a depression-like state in nicotine-naïve rats. Thus, these compounds may have negative affective effects in humans. Taken together, these data suggest that, in humans, mGlu5 receptor antagonists may promote smoking cessation and prevent relapse after a period of abstinence but may worsen the symptoms of early nicotine withdrawal.

Negative allosteric modulators of the mGlu5 receptor may prove to be better smoking-cessation aids than full antagonists. Compounds of this type are currently being clinically evaluated for indications including gastroesophageal reflux disease, migraine, and pain. Evaluation for potential use as a treatment for nicotine dependence is highly warranted.

NMDA receptors

In animals, administration of compounds that reduce glutamate neurotransmission by blocking the NMDA receptors decreased nicotine self-administration, suggesting that NMDA receptor antagonists can decrease the reinforcing effects of nicotine (Kenny et al., 2009). In a small study, memantine, a low-affinity NMDA receptor antagonist that also blocks some nAChRs, did not reduce cigarette smoking or craving in smokers. Unfortunately, high-affinity NMDA receptor antagonists are known to produce severe adverse neurotoxic and psychogenic effects in humans and therefore are unlikely to be developed into medications for human use.

The structure of the NMDA receptor is quite complex, and its activation requires the binding of both glutamate and a co-agonist, such as glycine. Therefore glutamate neurotransmission can also be decreased with compounds that block the binding of glycine to the NMDA receptor. In mice, administration of such a compound blocked both the acquisition and expression of preference for a nicotine-associated environment in a conditioned place preference (CPP) study. This finding suggests that compounds that occupy the glycine binding site on the NMDA receptor have the potential to decrease the reinforcing effects of nicotine and thus may help people quit smoking.

Interestingly, activation of the NMDA receptor facilitates extinction learning. There is strong preclinical evidence to suggest that administration of D-cycloserine, an NMDA receptor co-agonist that subtly activates the NMDA receptor, facilitates extinction of learned fear responses in animals (Woods and Bouton, 2006). D-cycloserine is currently being evaluated as a treatment for people who suffer from extreme anxiety or fear (phobias) of certain places and situations in their environment (Hofmann et al., 2006). It is hypothesized that D-cycloserine will help these people establish new learned associations that will eventually alleviate their phobias. In rats, administration of D-cycloserine facilitates extinction of cocaine seeking and cocaine-induced CPP behavior (Myers et al., 2011). Importantly, in a small preliminary study, smokers who were given D-cycloserine had fewer cravings when exposed to smoking-related cues than smokers given a placebo (Santa Ana et al., 2009). However, these data are very preliminary and further investigations are required to examine whether D-cycloserine facilitates extinction of nicotine-seeking behavior.

AMPA receptors

As described previously, cessation of smoking in humans can result in negative affective symptoms, including irritability, changes in mood, and depression. These effects cause many abstinent smokers to restart the smoking habit. In nicotine-dependent rats, inhibition of glutamatergic transmission by a compound that blocks AMPA receptors decreased responsiveness to previously rewarding stimuli, resulting in the development of a depression-like state resembling nicotine withdrawal (Kenny, Gasparini, and Markou, 2003). This finding suggests that antagonists at the AMPA receptor will worsen the negative affective symptoms that result from smoking cessation in humans. Thus, conversely, medications that stimulate AMPA receptors, such as AMPA receptor agonists or AMPA

receptor positive modulators, may alleviate these negative symptoms. Interestingly, AMPA receptor positive modulators have produced antidepressant-like effects in animal models of depression (Paul and Skolnick, 2003). Such compounds need to be evaluated clinically before conclusions can be reached about their potential utility as treatments for nicotine dependence.

Glutamate transporters

On the basis of preclinical evidence, it is hypothesized that the hypoglutamatergic state resulting from the cessation of tobacco smoking promotes nicotine-seeking behavior (Markou, 2007). Therefore, restoring normal glutamatergic neurotransmission through manipulation of glutamate transporters, such as xCT and GLT1, may help smokers maintain abstinence. Consistent with these hypotheses, smokers in a small pilot study smoked fewer cigarettes when given a compound such as N-acetylcysteine compared with smokers who received a placebo; alcohol consumption was taken into consideration. N-acetylcysteine binds to xCT and releases glutamate into the synapse from intracellular stores in exchange for synaptic cystine (Knackstedt et al., 2009). However, further clinical work is required to determine if this strategy will be effective in promoting smoking cessation and preventing relapse in all smokers.

In summary, the function of the neurotransmitter glutamate has considerable promise as a target for smoking-cessation medications. In addition, compared with ionotropic glutamate receptors, metabotropic glutamate receptors are potentially excellent targets for medication development because they are slow-acting, populate brain areas involved in reward and emotion, subtly modulate glutamate transmission, and are less likely to produce undesirable side effects seen with manipulation of fast-acting ionotropic receptors (Markou, 2007). Furthermore, allosteric modulators that subtly modulate the endogenous glutamatergic system, and thus produce fewer undesirable effects compared with full glutamate receptor agonists and antagonists, appear to have a good chance of proving useful in humans (Rudd and McCauley, 2005). Although currently there are no FDA-approved glutamate-based smoking-cessation agents, several of these compounds are being evaluated clinically for treatment of psychiatric disorders that are associated with high rates of smoking, such as depression and schizophrenia (Conn and Jones, 2009). These studies may shed light on whether these compounds may also have effects on cigarette smoking.

Gamma-Aminobutyric Acid

GABA is the major inhibitory neurotransmitter in the mammalian nervous system. An increase in GABA levels in the VTA limits reward and reinforcement by reducing the activity of mesolimbic dopaminergic neurons. GABA is released in the VTA by neurons that originate in several brain areas, such as the pedunculopontine tegmental nucleus, ventral pallidum, and NAc, as well as interneurons located within the VTA itself (Kalivas and O'Brien, 2008). Endogenous GABA acts via ionotropic $GABA_A$ and $GABA_C$ receptors and metabotropic $GABA_B$ receptors.

Role of GABA in nicotine reinforcement, withdrawal, and relapse

In nicotine-naïve animals, acute nicotine exposure increases GABA release by activating excitatory 4 2-containing nAChRs that are located on GABAergic neurons in the VTA. Thus initially, nicotine-induced GABA release limits the rewarding effects of nicotine. By contrast, chronic nicotine exposure desensitizes 4 2-containing nAChRs on GABAergic receptors (Mansvelder and McGehee, 2002). Hypothetically, this desensitization will decrease nicotine-induced GABA release, leading to decreased inhibition of VTA dopaminergic neurons and increased dopamine release in the NAc —and so facilitate the reinforcing effects of nicotine. Administration of compounds that increase GABAergic neurotransmission decreases both the reinforcing effects of nicotine and reinstatement of cue-induced nicotine-seeking behavior in rats (Markou, 2008; Vlachou et al., 2011). Thus, treatments that enhance GABA transmission may prevent relapse to tobacco smoking.

Restoring normal glutamate transmission may help smokers maintain abstinence.

GABA-based treatment strategies

GABA-based drug discovery for smoking cessation has focused on increasing GABAergic transmission, either by inhibiting the breakdown of GABA or by activating GABAergic receptors (Markou, 2008; Figure 2).

Inhibition of GABA breakdown

The levels of GABA can be increased irreversibly by inhibiting GABA transaminase, the primary enzyme involved in GABA metabolism. In animal studies, administration of gamma-vinyl GABA (GVG; also referred to as vigabatrin), a compound that inhibits GABA transaminase, decreased nicotine self-administration and blocked both the acquisition and expression of nicotine-induced CPP (Dewey et al., 1999). These findings suggest that

GVG reduces the reinforcing effects of nicotine. In addition, GVG dose-dependently lowered nicotine-induced increases in NAc dopamine in both nicotine-naïve and nicotine-treated rats. On the basis of these findings, it appears that GVG may help smokers quit. GVG is approved by the FDA for the treatment of infantile spasms and is currently used to treat epilepsy in many countries. However, its use is associated with serious adverse events, such as visual field defects, that may limit its utility as a smoking-cessation aid.

$GABA_B$ receptor activation

Administration of compounds that activate $GABA_B$ receptors, such as $GABA_B$ receptor agonists, decreased nicotine self-administration in rats. Importantly, the reduction in nicotine self-administration persisted even after repeated administration of the $GABA_B$ agonist, indicating that little tolerance to its effectiveness had developed (Paterson et al., 2005). In the same study, $GABA_B$ receptor agonists also blocked the reinstatement of nicotine-seeking behavior in rats upon re-exposure to nicotine-associated cues. Together these results suggest that $GABA_B$ receptor agonists may promote smoking cessation. Consistent with the above preclinical evidence, in a small double-blind clinical study, the $GABA_B$ receptor agonist baclofen reduced the number of cigarettes smoked per day as well as craving associated with abstinence (Franklin et al., 2009). However, $GABA_B$ receptor agonist administration in animals also resulted in nonspecific effects, such as decreased responding for nondrug rewards, including food and pleasurable electrical brain stimulation, and undesirable effects such as severe motor impairment. These preclinical findings suggest that $GABA_B$ receptor agonists may have limited utility for use in humans.

Treatments that enhance GABA transmission may prevent relapse to tobacco smoking.

$GABA_B$ receptor positive allosteric modulators

Researchers are investigating the effects of modulators that bind to allosteric sites on the $GABA_B$ receptor and enhance the receptor's responsiveness to GABA. Importantly, these positive allosteric modulators tend to have more subtle effects than full agonists, which bind to the same $GABA_B$ site as GABA (Guery et al., 2007). For example, positive allosteric modulators of $GABA_B$ receptors do not cause the severe motor impairment seen with $GABA_B$ receptor agonists.

Administration of positive allosteric modulators of $GABA_B$ receptors in rats decreased nicotine self-administration at doses that did not affect responding for nondrug rewards such as food (Paterson et al., 2008). Furthermore, positive allosteric modulators of $GABA_B$ receptors also blocked the cue-induced reinstatement of nicotine-seeking behavior in rats (Vlachou et al., 2011). These findings strongly suggest that $GABA_B$ receptor positive allosteric modulators may help promote smoking cessation and prevent relapse in humans. In addition, these allosteric modulators may have better side-effect profiles than full $GABA_B$ receptor agonists.

CONCLUSIONS

Tobacco smoking is a harmful habit that can be targeted to bring down both morbidity and future health care costs. Significant progress has been made over the last 2 decades in understanding the neural substrates involved in nicotine dependence. This article has reviewed our current understanding of nAChRs and the role of nicotinic receptor subtypes in nicotine reinforcement and dependence. Preclinical work that evaluates the role of non-nAChR substrates, such as dopamine, glutamate, and GABA, in nicotine reinforcement and dependence was also reviewed. Both nAChR-based and non-nAChR-based smoking-cessation strategies are under various stages of development. Although several of these strategies need to be clinically validated, there is much ground for hope that the next generation of smoking-cessation agents will provide better medications than those currently available.

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Response: A Quest and a Wager

Rick Bevins, Ph.D., Paul Kenny, Ph.D., and Jed Rose, Ph.D.

Paul Kenny: Dr. Markou's paper is a good overview of where we are in the quest for new pharmacological treatments for smoking addiction. The field is focusing mainly on the nicotinic receptors and the glutamate and GABA neurotransmitter systems. The nicotinic receptors regulate the effects of nicotine, and through these receptors, nicotine brings both glutamate and GABA into play.

Jed Rose: I think we are far from exploiting the full potential of nicotine itself as a replacement for smoking. At present, fewer than 10 percent of people using nicotine replacement therapy (NRT) achieve long-term smoking cessation. I think the success rate is low because we haven't yet learned to administer nicotine in a way that reproduces the full effect of nicotine obtained from smoking. Along with acute reinforcement, stress reduction, and cognitive enhancement, we also need to address the habit component—the constellation of sensory cues that develop around inhaling smoke.

Kenny: Do you believe that it's a viable strategy to consider medications that bypass the nicotinic receptor and instead work on other systems, like GABA and glutamate, that underlie the habitual aspects of smoking behavior?

Rose: Trying to modulate those downstream systems is an important strategy. However, I think it will likely be best used in combination with improved nicotine replacement. The difficulty of having a large impact on smoking without doing anything at the nicotine receptor should not be underestimated.

Rick Bevins: Combining pharmacological treatments with behavioral approaches is a must. There may be a place for combining medications, for example, targeting reinforcing effects with one and craving with another, or using one medication to alleviate the side effects of another. Such strategies are hinted at in the article but not addressed directly in a way that might encourage this approach.

Kenny: It seems very logical to give people the safest therapeutic that we know works, which right now would be NRT. And then, it seems like a good idea to have as many tools as possible to try to help those people for whom NRT is less effective. So that's where many of the compounds that the authors discuss come in, such as metabotropic glutamate receptor agonists or $GABA_B$ receptor agonists.

Bevins: The nicotine vaccine is another tool. One wouldn't use it with NRT, of course, because it prevents nicotine from getting to the brain, but it makes a nice adjunct to non-nicotine treatments. It doesn't have any central nervous system effects, so what you're hoping it will do, at least in my mind, is just to catch people who slip and get them back on the abstinence track.

Rose: I wouldn't totally rule out the idea that there might be creative combinations of NRT and nicotine vaccine, perhaps in a sequence where we use the former to wean

someone away from the smoking habit and then the latter to prevent its reestablishment. In general, however, the nicotine vaccine and other treatments that prevent nicotine from activating nicotinic receptors can help people partway, but not all the way, to long-term quitting. The reason is that these treatments don't replace the nicotine effects that motivate most people to smoke—stress relief, enhanced pleasure, weight control, cognitive enhancement, and so forth.

Bevins: A conundrum in treatment is that you want to reduce nicotine's impact on glutamate and dopamine neurotransmission enough to block the drug's motivating effects, but sustain enough neurotransmission to ward off symptoms of withdrawal. This is why it's important to learn exactly what each compound does at the various nicotinic receptor subtypes. For example, varenicline (Chantix) seems to be effective because it stimulates some subtypes strongly but others in only a limited way.

Kenny: Right. It's all about balance. The therapeutic window you want to reach is the one in which you can control the person's urge to smoke, but avoid the precipitation of withdrawal symptoms.

The dosage of a compound can affect which receptor populations it strikes, and we have shown that this is true of nicotine as well. Nicotine at low doses activates the high-affinity $\alpha4\beta2$ and other receptor subtypes that are responsible for many of its pleasurable and other effects. At higher doses, the drug begins to hit $\alpha5$-containing receptors in the habenula, which underlie aversive effects such as inhibition of reward systems.

Rose: That observation has tremendous treatment potential. It suggests that one could get a very strong combination effect with a dual-action compound that activated the $\alpha4\beta2$ receptors and also allosterically modulated the $\alpha5$-containing receptors. The first action would relieve withdrawal and supply some of nicotine's desirable effects, and the second action would trigger aversive effects if the individual smoked.

Kenny: Yes. While nicotine's effects on the nicotinic receptors and consequently on various neurotransmitter systems make sense as first places to look for an understanding of nicotine addiction, the drug also produces a large constellation of intracellular effects on signaling molecules and pathways. For example, nicotine can turn various kinases, phosphatases, and acetylases on or off. Hence, there are many other potential targets for therapeutic development within neurons. A further example of the potential of non-neurotransmitter, nonreceptor targets are the findings of George Uhl and other geneticists who are producing evidence that molecular processes classically thought to be involved in brain development are also implicated in addiction.

As the field progresses in coming years, we will likely be looking for answers in domains of neuroscience that currently are not typically considered relevant to addiction.

A wager

AS&CP: If you had $1,000 to bet on which strategy is going to bring the next large incremental advance in smoking control, what would it be?

Rose: I would put my money on the user-friendly form of inhaled nicotine that we have been developing in my laboratory. We have shown that people can self-administer nicotine in a particle form that produces more satisfaction, less irritation, and more rapid rises in blood levels than they get from the currently available nicotine vapor system. I think the impact on smoking rates will be dramatic. People will still be self-administering nicotine, but most authorities believe that nicotine constitutes less than 10 percent of the danger of smoking. I want to disclose a financial interest, because Philip Morris International just bought the patent rights to the approach.

Bevins: I'm going to bet on policy changes. For example, how about providing everyone easy and inexpensive access to whatever antismoking intervention they want? The health care savings that we would gain by making the whole range of smoking cessation interventions highly affordable and available would easily pay back the taxpayers.

Kenny: I'm going to split my money into three $333 bets. First, I agree with Jed that nicotine and nicotine-like compounds have untapped promise. My own bias in this respect is for compounds that modulate the $\alpha5$-containing receptors.

Second, there are other regulatory pathways that might produce breakthroughs. The authors discuss the GABA and glutamate pathways, but there are others. For example, Bill Corrigall has shown that the hypocretin pathway has very profound effects on nicotine-seeking behavior in rodents.

Finally, there are entirely new directions that we might go in. Some medications that are already available for treating cancer, cardiovascular disease, or diabetes may be effective for smoking. Some of these influence systems that there is currently no reason to believe might play a role in smoking, yet they may be central to the process.

We may already have a great compound out there. We just don't know it yet.

Rose: That raises an excellent point. We could potentially learn a great deal from clinical trials that are conducted on a wide range of conditions if they were to collect information on smoking. It has been especially frustrating when clinical trials that test compounds for conditions that are highly associated with smoking, such as cocaine abuse, don't measure the impact on smoking. After all, bupropion was developed because of the observation that people treated for depression reported changes in their smoking.

Inhalant Use and Inhalant Use Disorders in the United States

More than 22 million Americans age 12 and older have used inhalants, and every year more than 750,000 use inhalants for the first time. Despite the substantial prevalence and serious toxicities of inhalant use, it has been termed "the forgotten epidemic." Inhalant abuse remains the least-studied form of substance abuse, although research on its epidemiology, neurobiology, treatment, and prevention has accelerated in recent years. This review examines current findings in these areas, identifies gaps in the research and clinical literatures pertaining to inhalant use, and discusses future directions for inhalant-related research and practice efforts.

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Inhalant abuse refers to the intentional inhalation of vapors from commercial products or specific chemical agents to achieve intoxication. Abusers may inhale vapors directly from a container, from a bag into which a substance has been placed, or from a rag soaked with a substance and then placed over the mouth or nose (American Psychiatric Association [APA], 2000). Intoxication occurs rapidly and is short-lived, although some abusers repeatedly or continuously self-administer inhalants to maintain a preferred level of intoxication.

Inhalant abuse and dependence criteria parallel the generic substance abuse and dependence diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV; APA, 2000). The criteria do not include withdrawal symptoms, although some evidence suggests a characteristic withdrawal syndrome (Perron et al., 2009a). Amyl nitrate, other nitrite vasodilators, and nitrous oxide are sometimes abused by inhalation, but the criteria specifically exclude them from the list of substances considered.

Glue, shoe polish, toluene, spray paints, gasoline, and lighter fluid are among the inhalants most commonly abused by young people (Substance Abuse and Mental Health Services Administration [SAMHSA], 2008b). However, hundreds of products containing single substances or mixtures that can produce intoxication if inhaled are commercially available (Table 1). The huge variety of products that emit psychoactive vapors poses difficulties for classification. The current approach of grouping inhalants by form, product type, or intended use has conceptual and heuristic limitations. Classification into groups that share pharmacological properties and distinctive patterns of abuse may be more useful, but is unavailable at present because little is known about the pharmacologic effects of many abused vapors.

TABLE 1. Commonly Abused Inhalant Products and Their Constituents

GLUES AND ADHESIVES	
Airplane glue	Toluene, ethyl acetate
Other glues and cements	Hexane, toluene, methyl chloride, acetone, methyl ethyl ketone, methyl butyl ketone, benzene, xylene, trichloroethylene, tetrachloroethylene, chloroform
Spray paint	Butane, propane (U.S.), fluorocarbons, toluene, hydrocarbons, xylene
Hair spray	Butane, propane (U.S.), chlorofluorocarbons
Deodorant; air freshener	Butane, propane (U.S.), chlorofluorocarbons
Analgesic spray	Chlorofluorocarbons
Asthma spray	Chlorofluorocarbons
Fabric spray	Butane, trichloroethane
PC cleaner	Dimethyl ether, hydrofluorocarbons
Video head cleaner	Ethyl chloride
Gaseous	Nitrous oxide
Liquid	Halothane, enflurane, desflurane, isoflurane
Local	Ethyl chloride
Dry cleaning	Tetrachloroethylene, trichloroethane
Spot remover	Xylene, petroleum distillates, chlorohydrocarbons
Degreaser	Tetrachloroethylene, trichloroethane, trichloroethylene
Lacquer; thinners	Acetone, methanol, ethyl acetate, methyl chloride, toluene
Nail polish remover	Acetone, ethyl acetate, toluene (rarely)
Paint remover	Toluene, methylene chloride, methanol, acetone, ethyl acetate
Paint thinner	Petroleum distillates, esters, acetone
Correction fluid and thinner	Trichloroethylene, trichloroethane, isoparaffins
Fuel gas	Butane, isopropane
Lighter fluid	Butane, isopropane
Fire extinguisher	Bromochlorodifluoromethane
Gasoline	Benzene, n-hexane, toluene, xylene

Modified from Sharp and Rosenberg (2005).

Inhalant use disproportionately afflicts the poor, mentally ill, and juvenile- and criminal-justice involved.

Although inhalant abuse is common and associated with harmful outcomes that may rival or exceed those of other psychoactive drugs (Dinwiddie, 1994; 1998; Sharp and Rosenberg, 2005), inhalants remain the least-studied class of psychoactive agents (Balster, 1996). There are no clearly effective treatment interventions reported in the clinical research literature. Here we discuss the consequences of inhalant abuse and review potential treatments under investigation and harm reduction measures that appear to be effective.

EPIDEMIOLOGY OF INHALANT USE

The most informative surveys of inhalant use are the Monitoring the Future (MTF) survey, the Youth Risk

Behavior Survey (YRBS), and the National Survey on Drug Use and Health (NSDUH) (Table 2). They reveal:

- An estimated 9 percent of the U.S. population age 12 and older—22.5 million people—has used an inhalant for its psychoactive properties at least once (NSDUH);
- Inhalant use tends to start early, with 58 percent of users reporting first use by the end of ninth grade (MTF);
- Thirteen percent of students in grades 9 through 12 reported having ever used an inhalant on the 2007 YRBS;
- Fewer students in older grades than in younger grades (15.7 percent in 9th grade, 9.9 percent in 12th grade) reported having ever used an inhalant on the 2008 MTF, suggesting that many who start using inhalants early drop out of school;
- Most inhalant users initiate the behavior quite young, and most discontinue it quickly (Crocetti, 2008; d'Abbs and MacLean, 2008; SAMHSA, 2008b; Siqueira and Crandall, 2006). For example, the 2006 MTF indicated that on average, half of 8th, 10th, and 12th graders who had ever used inhalants had not done so during the past year (Johnston et al., 2007). However, as noted above, young people who drop out of school appear to continue using inhalants at higher rates than those who stay;
- White and Hispanic students reported lifetime use rates (14.4 percent) that were about twice those of African Americans (8.5 percent; YRBS);
- Important risk factors for inhalant use among middle and high school students include low levels of parental education and a lack of intention to complete 4 years of college (MTF);
- More than half of eighth graders saw the regular use of inhalants as a "great risk," but only a third attributed the same amount of danger to using an inhalant once or twice (MTF).

Studies have produced a range of estimates of inhalant users' risk of developing an inhalant use disorder.

The MTF and NSDUH have produced conflicting findings regarding whether gender influences adolescent inhalant use. The 2006 MTF indicated that more 8th- and 10th-grade girls than boys, and more 12th-grade boys than girls, had used an inhalant (Johnston et al., 2007). In contrast, the NSDUH and its predecessor, the National Household Survey on Drug Abuse (NHSDA), have consistently shown equal use rates among boys and girls (Neumark, Delva, and Anthony, 1998; SAMHSA, 2006; Wu, Pilowsky, and Schlenger, 2004).

Inhalant, use disproportionately afflicts subpopulations including the poor, mentally ill, and juvenile- and criminal-justice involved (Howard et al., 1999). For example, studies have documented inhalant use rates of:

- 34.3 percent among 475 juvenile probationers surveyed in Utah (Howard and Jenson, 1999). The earlier that individuals had initiated use and the more frequently they used, the higher the likelihood that use was associated with significant psychosocial dysfunction;
- 36.9 percent of 723 Missouri youth surveyed in a residential treatment center for antisocial behavior (Howard et al., 2008);
- approximately 18 percent of 847 adolescents referred to a treatment program for substance abuse or behavioral problems (Sakai et al., 2004). In addition, 10 percent of adult substance abusers surveyed in a treatment center had used inhalants more than five times (Compton et al., 1994).

Efforts have been made to identify subtypes of inhalant users, which could facilitate the identification of at-risk individuals, assessment, and treatment planning (Perron, Vaughn, and Howard, 2007; Vaughn, Perron, and Howard, 2007). These studies have found elevated inhalant use rates among youths who experienced a recent major depressive episode (SAMHSA, 2008a) and a subgroup of adolescents who used inhalants to "self-medicate" for unhappiness and anxiety (Perron, Vaughn, and Howard, 2007). These latter youths exhibited significantly more polydrug use, psychiatric comorbidity, and antisocial behavior than did two other classes of adolescent inhalant users.

Low monetary cost and ease of access probably contribute to the concentration of inhalant use among younger children and adolescents; low-income and unemployed adults; people living in isolated rural or reservation settings; and people housed in institutions such as psychiatric hospitals, prisons, and residential treatment centers. Inhalants can also be purchased and used without arousing the suspicion of parents, salespeople, school or law enforcement professionals, social service workers, or health care providers (Anderson and Loomis, 2003). Few people, for example, think of butane cigarette lighters, computer air dusters, nail polish, nail polish remover, or paint thinner as items that can be abused for their psychoactive effects; if challenged, young people can often offer plausible benign explanations for having these items.

EPIDEMIOLOGY OF INHALANT USE DISORDERS

Inhalant use disorders are among the least prevalent substance use disorders. In nationally representative

TABLE 2. Nationally Representative Surveys of Inhalant Use

Survey Name	Design, Target Population, and Frequency of Administration	Inhalant Question	Estimates of Lifetime Prevalence of Inhalant Use	Limitations and Strengths of the Surveys
Monitoring the Future	Annual cross-sectional survey since 1975 for 12th-graders and since 1991 for 8th- and 10th-graders	"On how many occasions (if any) have you sniffed glue, or breathed the contents of aerosol spray cans, or inhaled any other gases or sprays in order to get high in your lifetime?" "During the past 12 months?" "During the past 30 days?"	2010, by grade: 8th: 14.5 % 10th: 12.0% 12th: 9.0%	School-based survey misses dropouts and truants. Uses single omnibus item for inhalant use assessment. Provides data on perceived danger and disapproval of inhalants.
Youth Risk Behavior Survey	Semi-annual cross-sectional survey conducted since 1991 for grades 9 through 12	Middle school version: "Have you ever sniffed glue, or breathed the contents of spray cans, or inhaled any paints or sprays to get high?" Response options: Yes/No. High school version: "During your life, how many times have you sniffed glue, breathed the contents of aerosol spray cans, or inhaled any paints or sprays to get high?" Response options: 0 times; 1 or 2 times; 3 to 9 times; 10 to 19 times; 20 to 30 times; 40 or more times.	2009, by grade: 9–12: 11.7% 10th: 12.5% 12th: 9.1%	School-based survey misses dropouts and truants. Provides data on comorbid risk behavior and state-specific findings.
National Survey on Drug Use and Health	Annual cross-sectional survey of U.S. residents 12 and older conducted since 1971	"These next questions are about liquids, sprays, and gases that people sniff or inhale to get high or to make them feel good. Have you ever, even once, inhaled [INHALANT NAME] for kicks or to get high? Response options: Yes/No for the following inhalants: a) amyl nitrite "poppers," locker room odorizers or "rush;" b) correction fluid, degreaser, or cleaning fluid; c) gasoline or lighter fluid; d) glue, shoe polish, or toluene; e) halothane, ether, or other anesthetics; f) lacquer thinner or other paint solvents; g) lighter gases, such as butane or propane; h) nitrous oxide or "whippets; " i) spray paints; j) some other aerosol spray; and k) any other inhalants besides the ones that have been listed.	2007 by grade: 8th: 12.0% 10th: 10.7% 12th: 8.2% 9–12: 10.8% 12 years or older: 9.1% or 22,470,000 U.S. residents.	Household survey that captures dropouts and truants, but misses institutionalized populations and respondents younger than 12. Provides state-specific estimates.

surveys, youths reporting symptoms that would permit a diagnosis of inhalant abuse or dependence have included 0.6 percent of the 15- to 24-year-old participants in the 1992 National Comorbidity Survey (NCS) (Anthony, Warner, and Kessler, 1994), and 0.2 percent of the 12- to 17-year-olds who responded to the 2002–2003 NHSDA (Wu, Pilowsky, and Schlenger, 2004). The past-year prevalence of inhalant use disorder among adult participants in the 2001–2002 National Epidemiologic Survey on Alcohol and Related Conditions was 0.02 percent (Grant et al., 2004).

Motor deficits observed in mice exposed to toluene imply long-lasting brain damage.

Studies have produced a range of estimates of inhalant users' risk of developing an inhalant use disorder. At the lower end, an analysis of NCS data yielded an estimate that 7.9 percent of 15- to 24-year-olds with a history of inhalant use were dependent (Anthony, Warner, and Kessler, 1994). Similarly, Wu, Pilowsky, and Schlenger (2004) found that 6 percent of 12- to 17-year-olds who reported past-year use on the 2000 and 2001 NHSDA surveys met criteria for past-year inhalant abuse, and 4 percent met criteria for past-year dependence. Higher estimates for rates of inhalant use disorders among individuals with histories of inhalant use include:

- 18 percent among adults who participated in the nationally representative National Epidemiologic Survey on Alcohol and Related Conditions (Wu and Howard, 2007b);
- 47 percent among a community sample of 162 young adults in St. Louis, Missouri (Ridenour, Bray, and Cottler, 2007).

The wide divergence in prevalence estimates may reflect the presence of elevated-risk groups in some samples. For example, Howard and Perron (2009) found a 47 percent prevalence of inhalant use disorders among 279 juvenile justice-involved inhalant users in Missouri. In the Wu, Pilowsky, and Schlenger NHSDA-based study (2004), adolescents who had initiated inhalant use before age 15 were five to six times as likely as those who had started later to be diagnosed with inhalant dependence in the year prior to the survey.

CONSEQUENCES OF INHALANT USE

Inhalant use is associated with a large number of adverse effects and psychosocial outcomes.

Acute Effects

Inhalant intoxication produces a syndrome similar to alcohol intoxication, consisting of dizziness, incoordination, slurred speech, euphoria, lethargy, slowed reflexes, slowed thinking and movement, tremor, blurred vision, stupor or coma, generalized muscle weakness, and involuntary eye movement (APA, 2000). Inhalant use can result in chemical and thermal burns (Moreno and Beierle, 2007), withdrawal symptoms (Keriotis and Upadhyaya, 2000), persistent mental illness (Jung, Lee, and Cho, 2004), and catastrophic medical emergencies such as ventricular arrhythmias leading to "sudden sniffing death" (Avella, Wilson, and Lehrer, 2006; Bowen, Daniel, and Balster, 1999). Inhalant intoxication also increases the risk for fatal injuries from motor vehicle or other accidents (Bowen, Daniel, and Balster, 1999).

Neurological and Cognitive Effects

Studies of occupationally exposed workers laid the foundation for much of what we know about inhalant-related cognitive deficits. Morrow and colleagues (1997) found significant learning and memory impairments in journeyman painters relative to controls and evidence that many patients' inhalant-related cognitive problems were slow to resolve (Morrow, Steinhauer, and Condray, 1996; 1998).

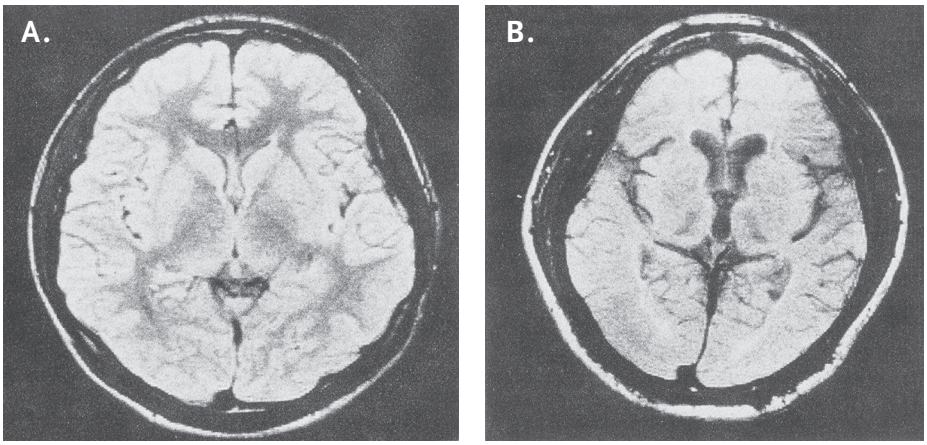
Even a single occupational exposure leading to inhalant intoxication can produce long-term memory problems and processing speed impairments (Stollery, 1996), an ominous finding given that inhalant abuse is characterized by exposures to neurotoxins at much higher levels than those typically incurred in occupational exposures (Bowen, Wiley, and Balster, 1996).

Early research with recreational inhalant users noted that, similar to the findings with occupational exposures, these individuals have memory, attention, and judgment deficits compared with controls and polydrug users (Hormes, Filley, and Rosenberg, 1986; Korman, Trimboli, and Semler, 1980). Maruff and colleagues (1998) found that current inhalant users performed worse than former users and controls in a test of visual-spatial memory that challenges the test taker to remember the location in which a symbol briefly flashed on a computer screen. Tenebein and Pillay (1993) found diminished brain activity in response to visual and auditory events, a possible marker for neurological dysfunction, in 8 of 15 inhalant users 9 to 17 years of age, even though the youths had no clinical evidence of neurological abnormalities.

Subsequent studies have disclosed that recurrent inhalant intoxication can lead to neurological disorders, including Parkinsonism, impaired cognition due to degradation of brain cells (encephalopathy) or loss of brain cells (cerebral atrophy), and loss of muscle strength and

coordination due to damage to the cerebellum (cerebellar ataxia) (e.g., Finch and Lobo, 2005; Gautschi, Cadosch, and Zellweger, 2007). Imaging studies of inhalant abusers have documented thinning of the corpus callosum (the band of nerve fibers joining the cerebral hemispheres) and lesions of the white matter that facilitates communication between brain cells (Finch and Lobo, 2005; Gautschi, Cadosch, and Zellweger, 2007). Regional reductions in cerebral blood flow are observable with functional magnetic resonance imaging (fMRI) after 1 year of inhalant use (Okada et al., 1999; Yamanouchi et al., 1998). Other radiologic abnormalities found in inhalant users include areas of reduced MRI signal strength (hypointensities) in the thalamus and basal ganglia (Lubman, Yücel, and Lawrence, 2008) and irregular uptake of radiolabeled pharmaceuticals in single-photon emission computed tomography (SPECT) studies (Küçük et al., 2000). Lubman and colleagues (2008) reviewed recent clinical and neuroimaging studies of chronic inhalant abusers, documenting significant cognitive deficits, structural abnormalities in specific brain areas (e.g., periventricular, subcortical, and white matter), and reduced brain perfusion and blood flow.

FIGURE 1. Brain Atrophy in a Toulene Abuser



Compared with the brain of an individual with no history of inhalant abuse (A), that of a chronic toluene abuser (B) is smaller and fills less of the space inside the skull (the white outer circle in each image). Courtesy of Neil Rosenberg, M.D., *NIDA Research Report* (NIH 05-3818).

Animal models have been helpful for studying acute and chronic biobehavioral effects of inhalants. They have shown that toluene and other inhalants can have reversible disruptive effects on response rates in behavior modification protocols; most of these effects appear to be greater after binge patterns of exposure than after lower levels of exposure (see Bowen et al., 2006, for review). In one of the few animal studies to examine the impact of binge-pattern exposures on higher cognitive processes, Bowen and McDonald (2009) reported that mice exposed to high concentrations of toluene (3,600 and 6,000 parts per million) for 30 minutes per day for 40 days (similar to the amounts chronic abusers inhale) demonstrated long-lasting motor deficits on a waiting-for-reward task. This result implies the presence of long-term brain damage, possibly resulting from cerebellar insult or cortical cell loss. Further animal trials are needed to identify toluene's impact on cognition so that these toluene-related impairments can be recognized early and measures can be initiated to prevent potentially extensive neurological damage. Additional preclinical studies suggest that toluene and 1,1,1-trichloroethane (TCE) impair learning, memory, and attention (e.g., von Euler et al., 2000).

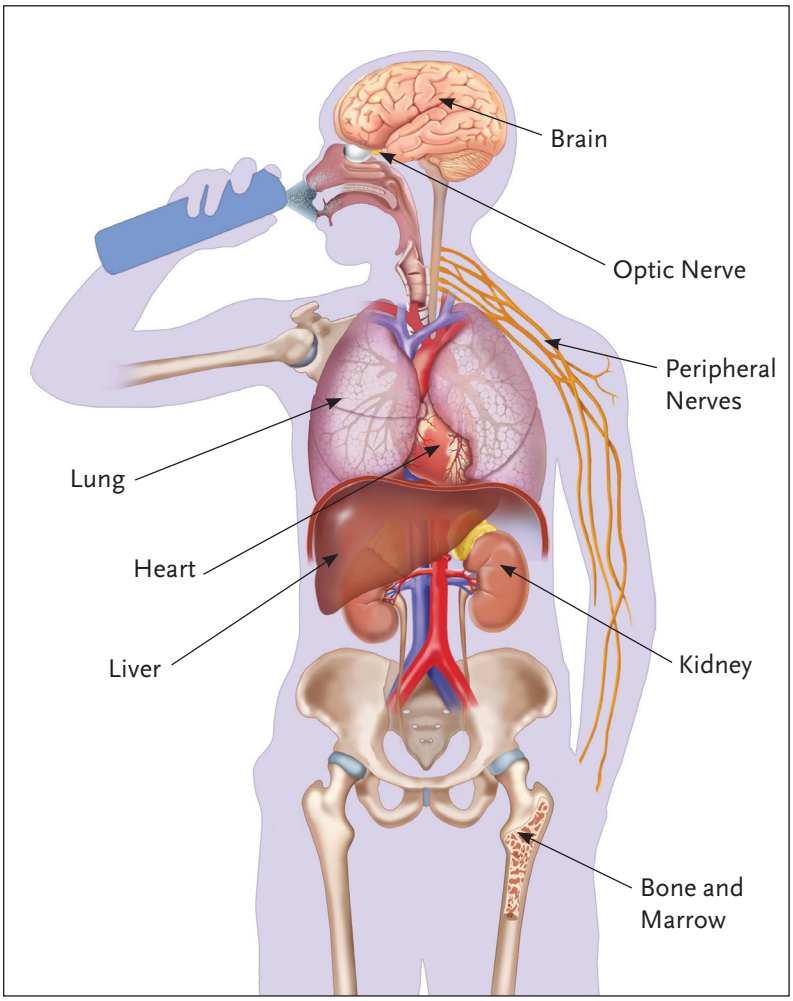
Effects on Organs Other Than the Brain

Evidence is mounting that inhalants can cause chronic medical problems affecting multiple organ systems (Figure 2). Animal studies, case reports, and small clinical investigations have implicated inhalant use in liver, heart, and kidney toxicity; bone demineralization; bone marrow suppression; and reduced immunity (T-cell responsivity) (e.g., Karmakar and Roxburgh, 2008; Takaki et al., 2008). Diminished plasma and red blood cell levels of selenium and zinc have also been noted, potentially impairing immune function and increasing the risk for infectious disease (Zaidi et al., 2007). O'Brien, Yeoman, and Hobby (1971) reported a case of liver and kidney failure in a 19-year-old who had sniffed glue for 3 years, and Wiseman and Banim (1987) diagnosed irreversible congestive heart failure in a 15-year-old patient who had sniffed glue for 2 years. Inhalants can also cause peripheral neuropathy leading to chronic pain and vision-impairing optic nerve damage (e.g., Twardowschy et al., 2008).

Adult inhalant abusers have higher rates of major depression, suicidal ideation and attempts, and anxiety and substance use disorders.

Several recent studies suggest that inhalant abuse is associated with serious pulmonary dysfunction and disease. An epidemiological study of 29,195 adults aged 35 to 49 participating in the NSDUH found that duration of inhalant abuse was significantly positively associated with likelihood of having experienced tuberculosis, bronchitis, asthma, and sinusitis (Han, Gfroerer, and Colliver, 2010). Cayir and colleagues (2011) compared

FIGURE 2. Organs Damaged by Inhalant Exposure



Jackie Heda, CMI

18 volatile solvent abusers with 18 control subjects (all of whom were tobacco smokers), noting that radioisotope pulmonary clearance was significantly accelerated in the solvent abuser group. The authors concluded that alveolo-capillary membrane dysfunction may follow inhalant abuse. A recent death of an 18-year-old man due to bilateral pneumonia following inhalation of a computer keyboard cleaner has also raised concerns about potential pulmonary consequences of inhalant abuse (Schloneger, Stull, and Singer, 2009).

Psychosocial Effects

Workers occupationally exposed to inhalants experience relatively high post-exposure levels of depression and anxiety (Morrow et al., 2000). Condray and colleagues (2000) found that journeyman painters were significantly more likely than controls (41 percent versus 16 percent) to meet lifetime criteria for a mood disorder and that virtually all painters who met criteria for a mood disorder experienced their first episode after starting their painting careers.

Relatively little is known about the natural history of inhalant use, inhalant use disorders, and associated psychiatric and psychosocial comorbidities in the general population. Clinical, criminological, and general population studies have identified robust associations between lifetime inhalant use, other drug use, and mental health disorders or symptoms. For example, SAMHSA (2005) estimated that youths who had used inhalants by ages 12 or 13 were nearly five times as likely than nonusing peers to have used another psychoactive drug. Associations between early-onset inhalant use and risk for later heroin and intravenous drug use (Storr, Westergaard, and Anthony, 2005; Wu and Howard, 2007a), antisocial behavior, and polydrug abuse have also been identified (SAMHSA, 2005).

Studies of adults in substance abuse treatment and in the general population indicate that inhalant users have higher rates of major depression, suicidal ideation and attempts, anxiety disorders, and other substance use disorders than nonusers of inhalants (Howard et al., 2010a; 2010b). Wu and Howard (2007b) and Wu, Howard, and Pilowsky (2008) documented dramatically elevated rates of mood and anxiety disorders, personality disorders, and substance use disorders in a nationally representative sample of U.S. inhalant users. Inhalant use and inhalant use disorders also appear to raise the odds for stressful life events such as having troubles at school or with a boss or co-worker, being fired, or being arrested or sent to jail (Dinwiddie, 1994; 1998).

Some researchers have questioned whether inhalant use contributes directly to subsequent drug use and adverse psychosocial outcomes, arguing instead that it may be a general indicator of a deviant disposition (Howard and Jenson, 1999; 2010a; 2010b). Published reports suggest that childhood and adolescent inhalant use may be a "red flag" signaling membership in a subgroup of antisocial youths that is marked by high levels of psychiatric symptoms, polydrug use, and psychosocial impairment, as well as earlier onset of behavior problems and a wider range of antisocial conduct than are typical of nonusers of inhalants (Howard and Jenson, 1999; Howard et al., 1999; 2008; Freedenthal et al., 2007; Jacobs and Ghodse, 1988; McGarvey, Canterbury, and Waite, 1996). Additional studies are needed to evaluate how inhalant abuse contributes to the etiology of psychiatric disorders and related mental, emotional, and physical disabilities.

Effects on the Fetus

Maternal inhalant use during pregnancy may produce effects in offspring similar to those seen in fetal alcohol syndrome (Jones and Balster, 1998; Bowen and Hannigan, 2006; Hannigan and Bowen, 2010). One study, for example, reported high rates of head and facial deformities, smaller-than-normal head and brain development, low birth weight, developmental delays, and other pregnancy and birth complications in infants born to women who inhaled solvents recreationally (Pearson et al., 1994). Tenebein (1993) described a neonatal withdrawal syndrome potentially attributable to maternal inhalant use. Recent laboratory studies also have demonstrated evidence of growth and developmental aberrations, physical deformities, and other adverse outcomes (e.g., Bowen et al., 2005; 2007; 2009; Bowen, Hannigan, and Cooper, 2009).While discussion of these findings is beyond the scope of this paper, they have been capably reviewed by Bowen and colleagues (2006), Lubman and colleagues (2008), and Hannigan and Bowen (2010).

NEUROBIOLOGY OF INHALANT USE

Much has been learned during the past decade about inhalants' pharmacological properties and effects (Bowen et al., 2006; Lubman, Yücel, and Lawrence, 2008). Although there has been limited research on the reinforcing properties of inhalants, animal studies suggest that several abused inhalants function as reinforcers (see Bowen et al., 2006, p. 643, for a review of findings). For example, in the conditioned place preference reward paradigm, toluene increases rats' tendency to gravitate to a chamber in which they formerly received the drug over one in which they did not (Lee, Schiffer, and Dewey, 2004). Of the few studies that have examined self-administration of inhaled compounds in nonhuman species, one demonstrated that mice will self-administer intravenous toluene and TCE (Blokhina et al., 2004), and another has shown that rats will self-administer ether vapor (Pogorelov and Kovalev, 1999). Other investigations have demonstrated that nonhuman primates will self-administer chloroform, ether, nitrous oxide, and toluene (see Evans and Balster, 1991).

Toluene and TCE appear to produce motor excitation at low concentrations and sedation, anesthesia, coma, and death at higher concentrations (Bowen and Balster, 1998). Benzene and diethyl ether also produce tranquilizing effects (Bowen, Wiley, and Balster, 1996; Paéz-Martinez, Cruz, and López-Rubalcava, 2003). Bowen and colleagues (2006) concluded that "the anxiolytic [anxiety reducing] effects of solvents are not an unexpected finding since these compounds, like other [central nervous system] depressants, act as positive modulators of $GABA_A$ receptors… [W]hat remains unclear is whether other solvents share these anxiolytic properties, the relative potencies to produce these effects, and whether tolerance (or sensitization) develops after chronic binge exposure."

The neuropharmacological effects of these solvents do not appear to be limited to modulation of the GABA receptor. Drug-discrimination studies using laboratory animals (Bowen et al., 1999) have shown that toluene can induce subjective effects similar to those of the psychedelic anesthetic phencyclidine (PCP), suggesting that toluene, like PCP, may block the NMDA receptor. It should be noted, however, that toluene failed to induce subjective effects similar to those of dizocilpine, another selective NMDA receptor blocker, in a similar drug-discrimination study (Shelton and Balster, 2004).

Toluene can induce subjective effects similar to those of phencyclidine (PCP).

In support of these behavioral results, recent *in vitro* studies have demonstrated that several abused inhal-

FUTURE RESEARCH

Inhalant abuse is one of few types of substance abuse for which demonstrably effective treatment interventions are largely absent from the clinical research literature. Specific areas for future research include:

- Ethnographic studies of cross-national patterns of inhalant use, including products (agents) used and consequences of use;
- Longitudinal studies of the trajectory of inhalant use and inhalant use disorders, including factors that predict initiation, escalation, maintenance, and cessation of use (e.g., Perron et al., 2009b);
- Investigations of the clinical manifestations of inhalant use disorders, including the nature and characteristics of tolerance and withdrawal symptoms across a wide range of abused inhalants;
- Studies of acute and long-term consequences of inhalant use;
- Psychometric evaluations of the reliability, validity, and latent structure of DSM-IV inhalant abuse and dependence diagnoses (e.g., Howard et al., 2001; Howard and Perron, 2009);
- Efficacy trials of combined pharmacological and psychosocial interventions for adolescents and adults with inhalant use disorders;
- Taxonomic efforts to identify subtypes of inhalant users and abusers;
- Evaluations of promising inhalant use prevention interventions; and
- Evaluations of product modification, law enforcement, and other supply-side approaches to reducing the availability of abused inhalants in the social and physical environments.

ants act with varying affinity and efficacy at a number of molecular sites. Toluene appears to cause its central nervous system depressant effects in large part by noncompetitively preventing glutamate stimulation of NMDA NR1 and NR2B receptor subtypes (Bale et al., 2005; Cruz et al., 1998), and prolonged exposure to toluene increases levels of brain NMDA receptors (Williams, Stafford, and Steketee, 2005). Other solvents, including benzene, ethylbenzene, propylbenzene, TCE, and xylene, also antagonize the NMDA receptor (Cruz, Balster, and Woodward, 2000; Raines et al., 2004).

A recent study showed that toluene and alcohol exert opposite effects on two channels that mediate the passage of potassium into and out of brain cells (the large-conductance calcium-activated potassium channel and G protein–coupled inwardly rectifying potassium channel). Alcohol excites these channels, but toluene inhibits them, a finding that eliminates them as likely candidates to underlie effects that toluene and alcohol produce in common (Del Re, Dopico, and Woodward, 2006). Exposure to toluene increases dopamine levels in the rat prefrontal cortex and striatum and increases neuronal firing in the ventral tegmental area in a manner similar to other drugs of abuse, effects that could be integral to the rewarding effects of toluene (Riegel and French, 1999; 2002; Riegel et al., 2004; 2007). Gerasimov and colleagues (2002; 2005) demonstrated that radioactively labeled toluene, butane, and acetone were rapidly taken up and cleared from areas such as the striatal and frontal brain regions of nonhuman primates.

An instrument for assessing abuse of 55 products is available without cost.

SCREENING AND ASSESSMENT

Systematic screening and assessment of inhalant use would facilitate earlier and more effective prevention and treatment, but clinicians appear to have a low index of suspicion for inhalant use and related problems (Anderson and Loomis, 2003). A few attempts have been made internationally to develop paper-and-pencil screening assessments of inhalant use, but these instruments are of limited utility for U.S. practitioners (e.g., Ogel et al., 2005). Howard and colleagues (2008) prepared the Volatile Solvent Screening Inventory (VSSI) and Comprehensive Solvent Assessment Interview (CSAI). The VSSI is freely available, requires approximately 20 minutes to complete, and assesses past-year and lifetime frequency of use of 55 inhalant chemicals and products, medical history, demographic characteristics, current psychiatric symptoms, suicidal thoughts and attempts, trauma history, temperamental traits such as impulsivity, and the frequency and nature of antisocial behavior in the prior year. The CSAI is also free, requires 20 to 90 minutes to complete (depending on the extent of the reported history of inhalant use), and assesses reasons for starting and stopping inhalant use; typical modes, locations, contexts and subjective effects of use; adverse acute consequences of inhalant intoxication; perceived risks of inhalant use; estimated likelihood of future use; sibling and friends' inhalant use; and DSM-IV inhalant abuse and dependence criteria. The reader can access these instruments on the Internet: *dx.doi.org/10.1016/j.drugalcdep.2007.08.023* (Howard et al., 2008).

Efforts are under way to improve laboratory diagnosis of inhalant use and abuse (e.g., Chakroun et al., 2008; Thiesen, Noto, and Barros, 2007), but such tests are not yet widely available, nor have they been implemented in routine clinical practice. Findings from the occupational toxicology and inhalant abuse literature suggest that bioassays for hippuric acid, o-cresol levels, and benzylmercapturic acid may eventually be useful urinary markers of toluene abuse (Broussard, 2000; Chakroun et al., 2008; Çök, Dagdelen, and Gökçe, 2003; Inoue et al., 2004; Ukai et al., 2007).

TREATMENT AND PREVENTION

Few studies have examined pharmacological or psychosocial interventions for those who use inhalants or who have inhalant-induced disorders. Reasons for the lack of studies are unclear. Drug abuse researchers may have been slow to recognize the importance of inhalant use disorders, perhaps because of the stigmatized nature of the behavior. Studies may be difficult to execute because of the social disenfranchisement of inhalant users and their frequent residence in locations that are geographically isolated (e.g., rural settings or reservations) or inhospitable to clinical research (e.g., juvenile or criminal justice facilities or psychiatric hospitals). In addition, people who have inhalant use disorders may be difficult to recruit, assess, and follow because they are typically dependent on multiple drugs and afflicted with comorbid mood, anxiety, and personality disorders.

Treatment programs that specialize in inhalant dependence are almost nonexistent in the United States; only one, the Tundra Swan Inhalant Treatment Program of the McCann Treatment Center in Bethel, Alaska, is currently operating. This center is administered by the Yukon-Kuskokwim Health Corporation and serves 15 to 19 youths at a time, who range in age from 10 to 18 years and reside mostly in nearby rural Alaskan

areas. Treatment services include traditional indigenous cultural practices, such as native dancing, crafts, and sweat lodges, and intensive family involvement. No formal evaluations of the Tundra Swan program have been published.

Nevertheless, substance abuse treatment practitioners express a desire for specialized training in inhalant-related assessment and treatment. Beauvais and colleagues (2002) surveyed 550 program directors in the United States: nearly three-quarters (73.9 percent) responded that inhalant abusers were somewhat-to-substantially more difficult to treat compared with abusers of other drugs, and only 15.1 percent thought current training resources were sufficient. A large survey of agencies serving young people in Wisconsin reported similar findings: 40.6 percent of respondents indicated that inhalant abusers exhibit brain impairments and medical, family, and developmental concerns that are more severe than those of other drug abusers (Malesevich and Jadin, 1995). Survey respondents tended to believe that detoxification and treatment stays should be longer for inhalant abusers than for abusers of other psychoactive drugs. Given the substantial prevalence and serious consequences of inhalant abuse and the virtual absence of specialty inhalant treatment programs in the United States, it is important that practitioners become aware of current inhalant screening and treatment approaches.

Pharmacological Interventions

Pharmacologic treatments for inhalant use disorders have rarely been evaluated. A few studies have documented reductions in psychotic symptoms in inhalant abusers, although it is not clear whether the psychoses were due to or simply comorbid with the inhalant abuse:

- Misra, Kofoed, and Fuller (1999) reported successful use of risperidone to treat paranoid psychosis in a 25-year-old Caucasian man who had been inhaling gasoline and carburetor cleaner almost daily for 5 years and who had failed to fully respond to prior trials with thioridazine and divalproex. Risperidone given at a dosage of 0.5 mg twice daily for 4 weeks reduced auditory and visual hallucinations, paranoia, and aggressive behavior. When the dose of risperidone was increased to 1 mg twice daily, craving for inhalants was significantly reduced, paranoid ideation ceased, and continuous abstinence from inhalants was maintained for 12 weeks. The researchers recommended that risperidone be studied further as a treatment for craving in inhalant-dependent people.
- Hernandez-Avila and colleagues (1998) conducted a randomized trial with 40 psychotic men with histories of inhalant abuse who were treated with either haloperidol or carbamazepine. After 5 weeks of treatment, the men in both the carbamazepine and haloperidol groups showed reductions in symptom severity of 48.3 percent and 52.7 percent, respectively, on the Brief Psychiatric Rating Scale. The investigators concluded that approximately half of the patients in each arm of the study responded to treatment, but that carbamazepine caused fewer side effects.

One case report and one preclinical study have reported positive but very preliminary evidence of potentially effective pharmacotherapies for inhalant dependence. Shen (2007) described the successful treatment of a 21-year-old man who had been using inhalants for 4 years but had no history of other substance abuse problems. When treated with 100 mg of lamotrigine daily, the subject reported fewer cravings for inhalants and achieved 6 months of continuous abstinence without significant side effects from the medication. Lee, Schiffer, and Dewey (2004) reported preclinical evidence suggesting that vigabatrin, a selective GABA transaminase inhibitor, could be an effective treatment for inhalant dependence.

Lamotrigine and vigabatrin have shown potential effectiveness for treating inhalant dependence.

Psychosocial Interventions

Few psychosocial interventions have been tested with inhalant users in the United States. Holistic approaches incorporating elements of traditional indigenous cultures have reportedly been used successfully in Canada (Dell, Dell, and Hopkins, 2005; YSAC Annual Report, 2007) and with aboriginal populations in Australia (Preuss and Brown, 2006). Demand-reduction interventions—including community-based approaches, education, youth and recreation programs, clinical management and counseling, and residential programs—were comprehensively evaluated in a recent Australian report (d'Abbs and MacLean, 2008). The relevance of these findings to an American context is uncertain. The recommendation that treatment be broadly focused on the diverse problems of inhalant users is certainly sensible, as are the notions that aftercare and family involvement are crucial.

D'Abbs and MacLean (2008) addressed the highly controversial topic of harm reduction interventions. These interventions have, for example, encouraged inhalant users to avoid covering their heads with plastic bags to prevent accidental asphyxiation; sniff from containers with small surface areas; avoid inhalation in

enclosed places or in hazardous places such as next to busy roadways; inhale under supervision; take precautions to avoid burns, overdose, and aspiration of vomitus; and avoid inhalants such as butane and propane that pose heightened risk for sudden death. Ethnographic studies indicate that some inhalant users take the initiative to minimize risks associated with their inhalant use (Sandover, Houghton, and O'Donoghue, 1997).

Broadly focused biopsychosocial treatment interventions may well be critically important given the manifold problems of inhalant abusers. Outreach to homeless young people and adults, youths who have dropped out of school or who are frequently truant, people in juvenile or adult correctional facilities or psychiatric hospitals, and inhalant abusers who are not actively seeking treatment is critical.

Several promising prevention strategies have been identified in recent years.

Additional treatment research is also critical, because current findings suggest that inhalant abusers may have comparatively poor treatment outcomes (e.g., Sakai, Mikulich-Gilbertson, and Crowley, 2006).

Prevention

Prevention approaches targeted to inhalant use are uncommon and have not always been successful (e.g., Brown et al., 2007; Collins, Johnson, and Becker, 2007; Furr-Holden et al., 2004). However, several promising prevention strategies have been identified in recent years. Schinke and colleagues evaluated correlates of inhalant use among adolescent girls and subsequently reported significantly reduced inhalant use at a 2-year followup in a randomized controlled trial of a gender-specific, computer-delivered prevention intervention for adolescent girls and their mothers (Schinke, Fang, and Cole, 2008; 2009).

An innovative, integrated approach to inhalant use prevention involving community mobilization efforts, environmental strategies, and school-based activities was described by Johnson and colleagues at the Pacific Institute for Research and Evaluation. They describe results of a related feasibility evaluation (Johnson et al., 2007), explain how the environmental component—designed to reduce retailers' sales of inhalants—can be implemented and evaluated (Courser et al., 2007), and present positive findings from a randomized controlled evaluation of the intervention, which was implemented in frontier Alaskan communities (Johnson et al., 2009). These reports and others that present positive findings regarding inhalant prevention (e.g., Spoth et al., 2007) suggest that comprehensive, theory-informed, and gender-specific prevention approaches may be effective methods for inhalant use prevention.

Supply-side interventions have not been widely applied in the United States, but in Australia they have included adding "bittering" agents to frequently abused inhalant products, selling gasoline substitutes such as aviation fuel or Opal gas that are not readily abused, and modifying products so that they are no longer sought out by abusers of inhalants.

CONCLUSIONS

More than 22 million Americans age 12 and older have used inhalants, and more than three-quarters of a million become new users annually. Inhalant use may lead to inhalant abuse or dependence in less than 10 percent to nearly 50 percent of cases, depending on the characteristics of the population studied. There are many acute and long-term consequences of inhalant use and these can be catastrophic, but far more needs to be learned about the full range of maladies associated with use of specific inhalant products and factors that increase vulnerability for these disorders.

Although some inroads have been made in understanding the pharmacology and neurobiology of inhalant abuse during the past decade, more needs to be learned about similarities and differences of specific abused inhalants. Ethnographic reports suggest that many youths abuse inhalants in order to achieve a euphoric state (d'Abbs and MacLean, 2008); survey findings confirm that young people intentionally abuse inhalants to produce intoxication (Howard et al., 2008); and operant conditioning and other laboratory paradigms suggest that inhalants may act as reinforcers in much the same way as other drugs of abuse (Bowen et al., 2006).

Practitioners should maintain a high index of suspicion for inhalant use, screen for inhalant use and inhalant use disorders, and intervene early in the course of the disorder with educational interventions and approaches that have been used in the treatment of other substance use disorders (e.g., motivational enhancement and relapse prevention interventions). This approach seems reasonable until researchers develop and fully evaluate effective evidence-based interventions for inhalant abusers. Given the high prevalence of conduct, substance use, mood, anxiety, and personality disorders among inhalant abusers, it is important that practitioners also avail themselves of evidence-based interventions for these commonly co-occurring conditions (Hepner et al., 2007; Woolgar and Scott, 2005).

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Ethical Concerns Related to Developing Pharmacogenomic Treatment Strategies for Addiction

Pharmacogenomics (PGx) research is poised to enable physicians to identify optimally effective treatments for individual substance abusers based on their genetic profiles. This paper addresses ethical issues related to PGx treatment strategies for addiction, focusing especially on the use of race variables in genomics research and ensuring equitable access to novel PGx treatments. Unless the field addresses the ethical challenges posed by these issues, PGx treatment innovations for addiction threaten to exacerbate already dramatic disparities in the burden of drug dependence for minority and other underserved populations.

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Expectations are high that pharmacogenomics (PGx) research will soon enable physicians to use genetic profiles to identify the safest and most effective treatments for each individual patient. Recent articles have addressed a range of important ethical considerations in translating emerging PGx research into clinical practice (Buchanan et al., 2002; Robertson et al., 2002; Clayton, 2003; van Delden et al., 2004; Corrigan, 2005; Lee, 2005; Ossorio and Duster, 2005; Roden et al., 2006; Marx-Stolting, 2007; Fitzgerald, 2008; Haga and Burke, 2008; Peterson-Iyer, 2008; Fleeman and Dickson, 2009), and a few have addressed issues related to PGx treatment strategies for addiction specifically (Shields et al., 2004; Caron et al., 2005; Munafo et al., 2005; Shields and Lerman, 2008). Largely missing from these analyses has been consideration of distributive justice and health disparities.

Although eliminating health disparities is one of two primary goals of Healthy People 2010 (U.S. Department of Health and Human Services, 2000), the substance abuse field has made far more progress in documenting disparities than in reducing them (Fiscella et al., 2000; Hargraves et al., 2001; Kressin and Petersen, 2001; Fiscella et al., 2002; Institute of Medicine, 2002a; 2002b; Schneider et al., 2002; Saha et al., 2003). Compared with whites, racial and ethnic minorities have a greater need for substance abuse treatment (National Institute on Drug Abuse, 2003) and are less likely to have access to it (Wells et al., 2001). The "treatment gap," defined as the proportion of a population who are in need of drug or alcohol treatment but have not received any in the past year, increased for all nonwhite racial/ethnic groups between 2002 and 2009, with the exception of Asian Americans (Schmidt and Mulia, 2009).

In this paper, I review major ethical issues pertinent to PGx research and its translation into practice, focusing on the context of addiction. Reflecting concerns for distributive justice, I pay particular attention to ways in which PGx research and treatment strategies may exacerbate disparities in the burden of addiction. Powers and Faden (2006) argue that individuals and groups who have been "systematically disadvantaged" by our health care system have a particular claim on public resources and investments.

Following the overview of major issues, I focus on two areas that are critical to ensure that minority and other underserved populations benefit equally from PGx advances in addiction treatment: using race variables in genomics research (Institute of Medicine, 2002a; 2002b) and ensuring equitable access to novel PGx treatments once they become widely available. These two issues have the greatest potential implications for just distribution of the benefits of PGx research on addiction and might be considered essential bookends in the examination of ethical issues related to the long trajectory from PGx research to improved health outcomes. Unless the field proactively addresses the ethical challenges they pose, innovations in addiction treatment will likely widen the existing disparities in treatment outcomes and the burden of drug dependence.

ETHICAL ISSUES IN PHARMACOGENOMICS RESEARCH

Privacy and the Potential for Discrimination

The advent of genomic medicine has raised unprecedented concerns about privacy and confidentiality, two key standards in medical research and practice that reflect the fundamental values of beneficence and the responsibility to do no harm (Beauchamp and Childress, 2001). Genetic information is unique relative to other medical information in at least two respects that increase its sensitivity. First, information about an individual's genome simultaneously provides information about his or her relatives (Buchanan et al., 2002; Robertson et al., 2002; Nuffield Council of Bioethics, 2003). Second, many genetic variants are pleiotropic—that is, they have clinical relevance for more than one condition. A classic example of pleiotropy is a variant of the apolipoprotein (APOE) gene that influences both cardiac care and the risk of late onset Alzheimer's disease (Hayden, 2008). Accordingly, some medical professionals and ethicists have worried that genetic research could usher in new forms of stigmatization and discrimination by health insurers or employers against individuals who are identified as having increased risk of specific conditions or being nonresponders to medication.

These concerns may be amplified in the context of addiction. Substance abusers, especially those who are poor, are among the most stigmatized individuals in society (Room, 2005). The process of matching substance abusers to optimal PGx treatments could potentially expose them to still further devaluation, depending on the genetic variants used to match them to the optimal choice of medication. Gene variants implicated in nicotine dependence, for example, have been associated with increased risk of becoming addicted to cocaine and alcohol, and with psychiatric conditions, including Tourette's syndrome, post-traumatic stress disorder, attention-deficit hyperactivity disorder, obsessive-compulsive disorder, anxiety, paranoia, depression, and suicide (Shields et al., 2005).

The advent of genomic medicine has raised unprecedented concerns about patient privacy and confidentiality.

Although some concerns have been allayed by the passage of the Genetic Information Nondiscrimination Act (H.R. 493, 110th Cong., 2nd Sess., 2008) and the Patient Protection and Affordable Care Act (H.R. 3590, 111th Cong., 2nd Sess., 2010), many analysts still consider privacy and genetic discrimination protections to be inadequate (Hudson et al., 2008; Slaughter, 2008; McGuire and Majumder, 2009). Health care reform may soon address concerns that individuals will be denied insurance coverage or charged higher premiums based on genetic status, but more diffuse manifestations of social stigma or discrimination may be harder to curtail.

Data Storage and Use

The sensitive nature of genetic information highlights the need for responsible storage in biobanks and medical records and poses challenges for informed consent procedures (Nuffield Council of Bioethics, 2003; Corrigan, 2005; Peterson-Iyer, 2008). Large banks of genetic data are indispensable for PGx studies that explore how genes interact with each other and the environment to produce health effects, but the storage and use of such data raise concerns (Clayton, 2005; Corrigan, 2005; Haga and Burke, 2008). One challenge has been clarifying whether the scope and intent of participants' informed consent for participation in a past study permits the use of their genetic data in new studies that may not have been envisioned at the time the consent was provided. The U.S. Department of Health and Human Services has advanced policy recommendations intended to minimize harm to and

respect the informed wishes of study participants while facilitating the aggregation of diverse data sets needed to advance science (U.S. Department of Health and Human Services, 2008). Consumers have expressed a preference for tiered consent schemas that allow individuals to specify the level of data sharing permitted with respect to their genomes (McGuire et al., 2008; Peterson-Iyer, 2008).

Beyond research, as more patients undergo genetic testing in clinical settings, there is growing concern about the storage and use of genetic test results (Buchanan et al., 2002; Robertson et al., 2002; Nuffield Council of Bioethics, 2003; Schubert, 2004; Corrigan, 2005; Munafo et al., 2005; Marx-Stolting, 2007; Haga and Burke, 2008; Henrikson et al., 2008; Peterson-Iyer, 2008). Who should have access to individuals' genetic information, and how can it be protected against unauthorized access, particularly as electronic health records (EHRs) become more widespread? The EHR concept aims to make relevant patient information readily available to all treating clinicians to increase the coordination of health care, reduce harm and waste, and increase quality and efficiency.

However, the question of how much of patients' genetic status data should be included in EHRs, and under what restrictions, has not yet been systematically addressed. I have argued elsewhere (Shields et al., 2005) that the sensitive nature of addiction-related phenotypes warrants increased scrutiny regarding processes for storing and communicating information about patients' genetic status and that prudent policies should be based on the most potentially stigmatizing information generated by a given genetic test.

Merely describing a new test as "genetic" reduced physicians' willingness to offer it to patients.

Answers to these questions will become increasingly urgent and financial incentives aimed at increasing EHR use within the U.S. health care system promise to accelerate widespread adoption of EHR systems nationally. (Currently only 13 percent of physicians [DesRoches et al., 2008] and 8 percent of hospitals (Jha et al., 2007; 2008) have EHR systems in place.)

Beyond the clinic, the proliferation of "home-brew" genetic tests (manufactured with noncommercial reagents and not approved by the U.S. Food and Drug Administration) (Buchanan et al., 2002) and the accumulation of genetic information by private companies that market genetic tests directly to consumers (Wolfberg, 2006; Hudson et al., 2007; Hogarth et al., 2008) pose further challenges to ensuring against irresponsible use of genetic test results.

Provider Readiness to Use PGx Treatments

Although genetically guided treatment has been incorporated into routine practice in some specialties for many years (e.g., oncology), the fact that addiction is most often first treated in primary care settings will pose substantial challenges for clinical integration, with practices serving poor and minority patients likely to face greater challenges than others (Bach, 2004). Few primary care physicians (PCPs) have formal training in genetics, which constitutes a barrier to clinical integration of novel PGx treatment strategies. Nationally, only 4 percent of PCPs report feeling very prepared to counsel patients considering genetic testing, and 5 percent feel very confident in interpreting genetic test results (Shields et al., 2005). In studies addressing challenges to incorporating genetically tailored smoking-cessation treatment, merely describing a new test to tailor smoking-cessation treatment as "genetic" (vs. "nongenetic") reduced physicians' willingness to offer it to their patients (Shields et al., 2005). Informing physicians that the same genotypes that likely would be used to match patients to optimal treatment were also associated with increased risk of becoming addicted to substances besides tobacco markedly dampened their enthusiasm for testing (Levy et al., 2007).

Understanding the genetics of complex behaviors such as addiction will place particular demands on physicians. Future PGx approaches to identify treatment responders and nonresponders will likely involve assessing multiple genes in multiple interacting neurobiological pathways that mediate a medication's pharmacodynamic effects, as well as genetic variants in drug metabolizing enzymes (Munafo et al., 2005; Rutter, 2006). PGx practitioners will need to evaluate not only the relative importance of multiple gene variants, but also potential interactions of these polymorphisms with other drugs and environmental exposures. Clear and accessible guidelines will be essential to assist PCPs and allied health professionals with addiction treatment decisions (Freedman et al., 2003), as will decision support available through EHR systems.

Minorities with substance dependence are more likely than whites to be treated in primary care settings rather than specialty alcohol or drug treatment programs (Schmidt et al., 2007). Therefore, preparing PCPs to implement new PGx treatments for addiction will have a direct bearing on disparities. To achieve this preparation, infrastructure and capacity will need strengthening. Small primary care practices, which currently make up 50 percent of all practices nationally (Burt et al., 2005), are

especially in need of infrastructure development. They consistently lag behind in adoption of new technologies, such as health information technology (DesRoches et al., 2008). Ensuring that PCPs have access to EHR systems that have the decision support platforms they need will be essential to guarantee that future PGx treatment strategies for addiction reach underserved patients in need of substance abuse treatment.

Patients' Willingness to Undergo Genetic Testing

Ultimately, patients will benefit from PGx treatment strategies only if they are willing to undergo genetic testing. Therefore, it is critical to understand how patients' knowledge, attitudes, and experiences may affect their willingness to participate in PGx-based medicine. Several studies have documented a general lack of awareness, knowledge, and understanding of genetic testing (Bluman et al., 1999; Donovan and Tucker, 2000; Kinney et al., 2000; Singer et al., 2004), especially among low-socioeconomic status (SES) and minority communities (Hughes et al., 1997; Mogilner et al., 1998; Lipkus et al., 1999; Kinney et al., 2001; Armstrong et al., 2002; Peters et al., 2004; Singer et al., 2004; Bates et al., 2005; Murphy et al., 2009; Suther and Kiros, 2009). Individuals' interest in genetic testing rises with educational level (Andrykowski et al., 1996; Mogilner et al., 1998; Lerman et al., 1999; Peters et al., 2004), and those with higher levels of education express fewer concerns about possible misuse of genetic information (Suther and Kiros, 2009).

Mistrust is a major factor affecting patients' willingness to undergo genetic testing, especially within minority communities that have historically experienced discrimination. Although some studies have found no racial differences in willingness to undergo genetic testing (Lacour et al., 2008), several have shown that African Americans are more likely than other groups to believe that genetic test results will be misused (Singer et al., 2004; Suther and Kiros, 2009), be used to label their racial/ethnic group as inferior (Thompson et al., 2003; Peters et al., 2004), or lead to racial discrimination (Zimmerman et al., 2006). African Americans are far more likely than other groups to see racism as a significant problem in health care (Lillie-Blanton et al., 2000) and consistently report racial discrimination in obtaining medical care (Henry J. Kaiser Family Foundation, 1999; Klassen et al., 2002; Smedley et al., 2003). The legacy of the Tuskegee syphilis study (Gamble, 1997) and of insurance and employment discrimination based on the results of sickle cell screening (Bowman and Murray, 1990; King, 1992a; 1992b) remain salient within the African American community. African Americans tend to have negative views about participation in medical research and to be skeptical that their community will share in any positive benefits of genetic research (Corbie-Smith et al., 1999). Latinos also have expressed mistrust about genetic testing. In a national survey of 1,724 individuals, African Americans were 66 percent and Latinos were 58 percent more likely than whites to have concerns about potential misuse of genetic information (Suther and Kiros, 2009).

Religious orientation also shapes attitudes toward genetic testing. Regular church attendance and reliance on God in health care decisionmaking correlate negatively with perceived benefits and acceptance of genetic testing, and are traits more common among African Americans than whites (Singer et al., 2004). Catholics are less likely to endorse positive views of genetic testing, and Latinos are more likely to be Catholic (Singer et al., 2004). In summary, outreach and communication strategies tailored to the needs, preferences, and cultures of minority and low-SES communities will be necessary to ensure that new PGx treatment strategies for addiction are translated into practice in ways that improve treatment outcomes for all patients and do not exacerbate existing racial and SES disparities.

African Americans are more likely to believe that genetic testing will be misused.

THE USE OF RACE VARIABLES IN PGx RESEARCH

While the majority of ethical analyses of PGx have focused on the ethical imperative to do no harm at the level of the individual patient, two key issues have particular salience for the notion of distributive justice and the potential of PGx research to translate into harm or benefit for minority communities. The first relates to how race variables are used, interpreted, and communicated in PGx research. Numerous articles and editorials have debated the implications of using race variables in the design of genetic research studies, data interpretation, results communication, and impact on broader societal concerns (Osborne and Feit, 1992; Bhopal, 1997; Kaufman and Cooper, 2001; Lee et al., 2001; Schwartz, 2001; Wood, 2001; Burchard et al., 2003; Cooper et al., 2003; Haga and Venter, 2003; Kaplan and Bennett, 2003; Stevens, 2003; Cooper, 2004; Shields et al., 2005). There are three major drawbacks to using self-identified racial variables in PGx research on addiction:

- self-identified race is an inadequate proxy for human genetic heterogeneity;

- focus on race obscures understanding the role of environmental influences; and
- the use of race variables increases the potential for discrimination.

PGx research on addiction can help to disentangle the genetic, social, and environmental influences underlying "racial" differences in drug dependence and treatment response.

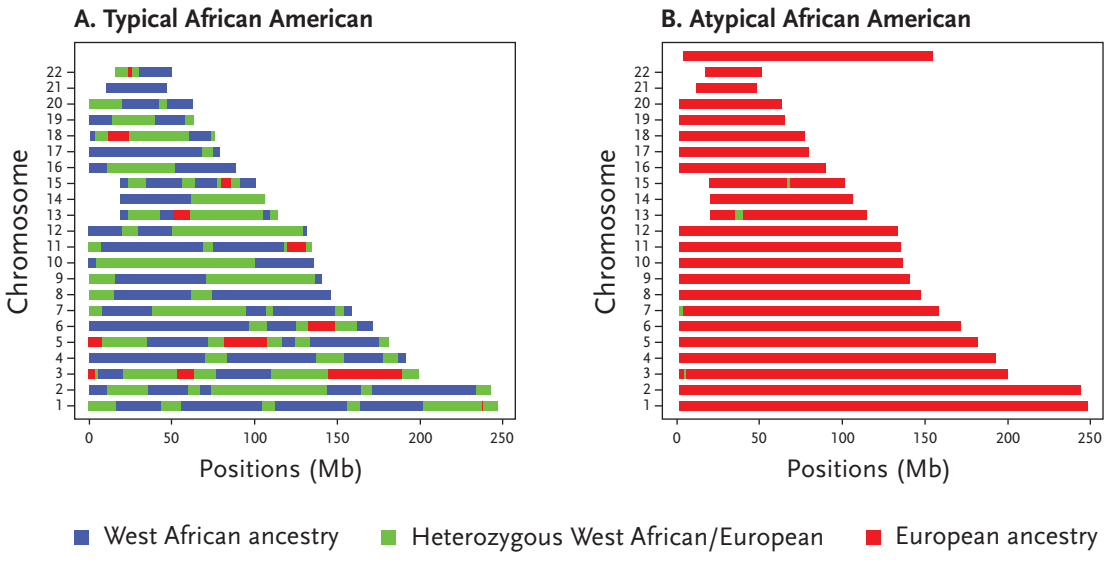
Race Versus Genetic Heterogeneity

Racial categories mask genetic diversity, so that PGx treatments based on research using racial categories could be ineffective or even harmful for many individuals. Self-identified racial categories such as those set forth by the Office of Management and Budget (OMB Directive 15, National Institutes of Health, 2001) and used in the federal census are a rough and poorly characterized proxy for defining an amalgam of influences related to social identity, geographical ancestry, and social status (Shields et al., 2005). More scientifically precise methods are available for measuring population structure (Novembre et al., 2008; Bryc et al., 2010) and should be used.

The limited usefulness of self-identified racial categories is perhaps most clearly illustrated by the term "African American," since genetic heterogeneity is greater among self-identified African Americans than among most other self-identified groups. For example, Bryc and colleagues (2010) analyzed fine-scale population structure among 146 individuals representing 11 different populations in West and South Africa; 57 Yorubas genotyped as part of the International HapMap project; 365 self-identified African Americans from throughout the U.S.; and 400 individuals in Europe. The researchers used fine-scale genetic mapping to infer the mix of African ancestries in the African Americans and to identify West African populations closest to the ancestral populations of African Americans. Although the African Americans as a group averaged 77 percent West African ancestry, individual African Americans ranged from less than 1 percent to more than 99 percent West African ancestry (Figure 1; Bryc et al., 2010). Such diversity compels extreme caution in prescribing clinical guidelines or developing warnings for adverse drug responses for "African Americans."

Fine-scale mapping of European cohorts has identified genetically distinct subpopulations (Lao et al., 2008; Novembre et al., 2008; McEvoy et al., 2009) that would be missed if the general terms "European" or "white" were used in analyses. For example, using genotype data from 197,146 loci from 1,387 individuals of European ancestry from the Population Reference Sample, Novembre and colleagues (2008) were able to identify genetically

FIGURE 1. African and European Ancestry in African Americans



A representative individual among 365 self-identified African Americans had 73.5 percent West African ancestry, as revealed by genomic analysis (A). West African ancestry ranged from less than 1 percent in one individual (B) to over 99 percent. Blue bands = West African ancestry in both maternal and paternal chromosomes; green = West African ancestry in one chromosome and European ancestry in the other; red = European ancestry in both maternal and paternal chromosomes.

distinct subpopulations among French-, German-, and Italian-speaking groups in Switzerland.

With new technologies (e.g., the Affymetrix 500k SNP chip) now widely available to identify nuanced differences in population structure, the use of gross racial/ethnic categories in PGx studies or treatment guidelines becomes ethically problematic. Although technical limitations or resource constraints sometimes will limit a research team's ability to do such fine-scale mapping, its availability raises the bar for all genomics researchers.

Race, Genes, and Environmental Exposures

The use of self-identified race as a proxy for human genetic heterogeneity in PGx studies of addiction is especially problematic when studies do not measure other social and physical environmental exposures that track with race in America. First, such analyses increase the likelihood that the self-identified race variable will be statistically significant and thus reify self-identified race as the most relevant frame for understanding differences in response to addiction treatment. Second, such research designs miss the opportunity to disentangle complex genetic, social, and environmental interactions (Hernandez and Blazer, 2006) or epigenetic effects (Olden et al., 2011) that affect the progression to addiction, response to treatment, or a drug's kinetic effects.

Potential for Worsening Discrimination

The poor specificity of racial/ethnic variables in PGx research is often compounded by failure to measure social and environmental exposures that track with self-identified race in America, thereby masking important gene-environment effects. Missing these effects means missing an opportunity to disentangle the complex social, environmental, behavioral, and genetic factors that interact to create disease and determine treatment outcomes. PGx studies of addiction would likely be far more informative if population structures were finely mapped and if other social and environmental exposures that often track with "race" were measured independently. Such research would also be more likely to yield insights useful for addressing disparities. Low-SES and minority patients' experiences subject them to a distinct confluence of social and environmental exposures that likely interact with clinically relevant genotypes.

PGx analyses that frame new knowledge in terms of "racial differences" in allele frequencies relevant to disease risk or drug response continue a long and painful history of comparative racial science in the U.S. Such science leads to headlines such as "Blacks more likely to have gene X associated with addiction," and has almost always been used to allege that African Americans are inferior (King, 1992a; 1992b). When "racial" differences intersect with socially charged phenotypes, such as those related to addiction or mental illness, physicians shy away from genetic testing for fear that results may lead to discrimination against their patients (Levy et al., 2007).

The reporting of higher frequencies of genotypes associated with addiction to nicotine, cocaine, and other substances among African Americans relative to whites has a particularly problematic intersection with existing racial stereotypes. For example, several studies have documented physicians' inadequate prescribing of pain medications for African American patients relative to white patients with similar conditions and illness severity, noting physician concerns about potential drug abuse by minority patients (Cleeland et al., 1997; Todd et al., 2000). It is not surprising, therefore, that African Americans tend to be more concerned than other groups that genetic test results will be used to discriminate against them or their community.

ACCESS TO NOVEL PGx ADDICTION TREATMENTS

The second "bookend" of the PGx research trajectory that has important implications for distributive justice is ensuring equal access to new PGx applications once they are validated and available to be used in clinical settings. To the extent that novel PGx treatments for addiction improve outcomes by an order of magnitude over previous regimens, it will be especially important to ensure equal access to these markedly improved treatments; otherwise, these advances will merely widen the existing disparities gap in substance abuse treatment.

A successful strategy for ensuring equal access to PGx information and treatments must engage patients, providers, and policymakers.

Disparate access to new technologies and treatments is certainly not a new issue; widespread and persistent gaps have been documented (Smedley et al., 2003). A successful strategy for ensuring equal access to PGx information and treatments must engage patients, providers, and policymakers. The benefits of individualized treatment must be communicated to minority and low- SES patients in ways that are culturally competent, accessible, and appropriate, and that mitigate concerns about genetic testing (Betancourt, 2004). Modes of dissemination must be carefully considered. The recent Health Information National Trends Survey indicated that media saturation on a given topic reaches similar percentages of people in all socioeconomic position

(SEP) classifications; in the absence of media saturation, however, people in higher SEP groups have better access to other sources of information, such as physicians or informed friends (Viswanath et al., 2006). Diffusing information about genomic medicine is challenging in any context. Even with the establishment of high-risk guidelines for hereditary breast and ovarian cancer in the 1990s (American Society of Clinical Oncology, 1996; Daly, 1999) and the development of *BRCA1/2* testing to assess hereditary breast cancer risk, only 10.7 percent of women who were appropriate candidates for genetic testing according to national guidelines had ever even discussed the possibility of genetic testing with their doctor or another health professional (Levy et al., 2009).

Ensuring that new PGx treatments reach minority and low-SES patients will require investment in the infrastructure and clinical capacity of the providers who serve them. One potential strategy for reaching minority patients is to concentrate on minority-serving providers. Approximately 22 percent of physicians, for instance, care for 80 percent of all black Medicare beneficiaries in the U.S. (Bach et al., 2004). Focusing on minority-serving providers may be an especially effective strategy in the context of substance abuse treatment, given that minorities with substance dependence are more likely than whites to be treated in primary care settings rather than specialty alcohol or drug treatment programs (Schmidt et al., 2007).

The more effective PGx treatments for addiction are, the more important it will be to ensure that minority and underserved populations share in their benefits.

The challenges related to physicians' preparedness to incorporate PGx treatments into practice will be especially keen in these settings that disproportionately serve poor and minority patients. In a national survey of PCPs, those who served the highest proportions of minority patients (i.e., ranking in the top 20 percent of the national distribution) were significantly less likely to have ever ordered a genetic test to assess risk for breast cancer (18 percent vs. 29 percent; $P = 0.01$), colon cancer (11 percent vs. 18 percent, $P = 0.05$), or Huntington disease (6 percent vs. 18 percent; $P < 0.001$) compared with those serving fewer minority patients (Shields et al., 2008). Among community health centers (CHCs), which serve 1 in 4 poor, 1 in 7 uninsured, and 1 in 10 minority patients (National Association of Community Health Centers, 2005), only 4.3 percent have the capacity to deliver genomics services (Shields et al., unpublished data). These findings are consistent with several studies documenting safety net providers' difficulty accessing specialty care for their patients (Felt-Lisk et al., 2002; Felland et al., 2003).

Targeted financial support is also likely to be needed. The current average CHC operating margin is less than 1 percent (McAlearney, 2002; National Association of Community Health Centers, 2005), leaving scarce resources to expand genetics services. Safety net hospitals and clinics that disproportionately serve minority patients are similarly strapped (Lewin and Altman, 2000; Varkey et al., 2009). Increased fiscal pressures have decimated many state Medicaid programs, the primary source of health insurance for low-income families, and many of these programs have restricted prescription drug benefits (Crowley et al., 2005; Kaiser Commission on Medicaid and the Uninsured, 2010). Low-income Americans will not have equal access to PGx treatments if Medicaid does not provide the same coverage for these services as private insurers.

The over-representation of minorities dependent on substances among the uninsured also threatens to exacerbate disparities. According to data from the National Alcohol Survey, for example, 28 percent of African Americans and 41 percent of Hispanics with a current substance dependence diagnosis are uninsured, compared with only 19 percent of whites with such a diagnosis (Schmidt and Mulia, 2009). Uninsured adults have tremendous difficulty accessing care for alcohol, drug abuse, and mental health problems (Wells et al., 2002). Uninsured adults and those on Medicaid have the greatest unmet need and delays in care (Wells et al., 2002). While health care reform may reduce some of these barriers, many will surely remain. Targeted supplemental reimbursement will most likely be needed to enable safety net providers to ensure access to new PGx treatments for addiction.

CONCLUSION

PGx research is making remarkable progress in identifying genetic variants associated with increased vulnerability to drug dependence and variable response to substance abuse treatment. The next generation of studies, now just beginning, will tackle measurement of gene-gene and gene-environment interactions that affect susceptibility and treatment responses. The sensitive and stigmatized nature of addiction phenotypes, in concert with pleiotropic associations of key genotypes with other socially stigmatized conditions, warrants great care in the handling of reporting and use of PGx test results. It is hard to overstate the importance of finding ways to communicate the complex and continuous nature of human genetic variation to the general public and

USE OF RACE VARIABLES IN PGx RESEARCH ON ADDICTION

Traditional racial categories are ill-suited to pharmacogenomics (PGx) research, especially in studies that examine sensitive phenotypes such as drug abuse and addiction. From this viewpoint, I assessed the use of race variables in all 2007–2010 PGx addiction publications included in a recent comprehensive review conducted by Mroziewicz and Tyndale (2010).

All 32 human studies used self-reported race/ethnicity variables for participant recruitment. Two required a more stringent self-reported definition: Berrettini and colleagues (2008) enrolled only participants "for whom the four grandparents were of European origin," and Le Marchand and colleagues (2008) enrolled only those "having both parents of Japanese or European ethnicity, or of any amount of Native Hawaiian ancestry."

The thorny issues related to successfully recruiting a diverse study population and resolving the tensions between self-identified race and population structure have led many researchers to sidestep the issue completely by studying only "European" or other samples assumed to be genetically homogeneous. Eighteen of the 32 studies took this route by recruiting all participants from "single" populations. Ten studies included only "European" or "Caucasian" subjects, with no further information given (Audrain-McGovern et al., 2007; Bierut et al., 2007; Lee, et al., 2007; Vanyukovet al., 2007; Amoset al., 2008; Berrettini et al., 2008; Conti et al., 2008; Uhl et al., 2008; Oroszi et al., 2009; Pillai et al., 2009). Six other studies were conducted with "Europeans" or "Caucasians" from specified locations (e.g., Northern Poland [Sieminska,et al., 2008]; Croatia [Mokrovic et al., 2008]; and Finland [Arias et al., 2008]); and persons of "European descent" from St. Louis, Detroit, Minneapolis, and Australia (Saccone et al., 2007). Other "single" population studies included Koreans (Kim et al., 2009) and Han Chinese from Taiwan (Huang et al., 2007). The most common rationale provided for limiting analyses to a "single" population was to "minimize the potential bias resulting from ethnic admixture" (Audrain-McGovern et al., 2007; Huang et al., 2007; Lee et al., 2007; Amos et al., 2008; Berrettini et al., 2008; Conti et al., 2008; Hung et al., 2008; Lerman et al., 2010).

Of the 32 studies in our sample, only seven (one multiethnic and six "single" population) conducted additional analyses to assess population structure and admixture using ancestry-informative markers (AIMs). For example, a multi-ethnic study used 207 AIMs to "verify self-reported ancestry and assess admixture within racial groups," using an inclusion threshold of at least 80 percent ethnic identity (Sherva et al., 2008). Saccone and colleagues (2007) similarly analyzed "289 high performance" single nucleotide polymorphisms (SNPs) to test for population admixture among their "European" cohort of participants from St. Louis, Detroit, Minneapolis, and Australia, but found no evidence of population structure. In all these cases, if the investigators found no evidence of population structure using AIMs, they assumed there was none. These results, however, contrast dramatically with the fine-scale mapping of Europeans by Novembre and colleagues (2008) that found identifiable population structure within very narrow geographical areas, emphasizing the high threshold for identifying population structure embedded in the STRUCTURE software program typically used. AIMs are only as robust as the reference population samples used to identify a set of given SNPs as indicative of membership in one ancestral group versus another. Using Yorubas to stand in for all persons of African ancestry (Tishkoff et al., 2009; Bryc et al., 2009) is faulty from the start, as recent research has shown.

These research practices have important ramifications for determining who will benefit from PGx research on addiction. First, the extent to which PGx study results are generalizable to all persons of "European" ancestry is questionable, let alone persons of more distant geographical heritage. What genetic effects might reach the threshold of significance if populations were defined with greater specificity and studies were adequately powered to capture genetic effects among these identifiable subpopulations? An important challenge for PGx research will be to determine which levels of genetic heterogeneity are important to measure for clinical purposes, a calculation that may differ according to phenotype. In the case of PGx research, the importance of identifying individuals at risk of adverse drug events, and the consequences of not identifying such individuals, demands a more fine-grained approach to defining clinically relevant subpopulations than is typically used in current practice.

to discover new ways of framing genetic information about differential risk of illness or response to treatment in ways that transcend the very harmful blunt instrument of traditional racial/ethnic categories. While these categories continue to be a useful bureaucratic tool for tracking health disparities, they are no longer appropriate for use in biomedical research aimed at understanding the etiology of complex diseases such as addiction or factors affecting treatment response.

There is great hope that PGx research will change the landscape of addiction in America by enabling physicians to match individual patients to the substance abuse treatment that will work best for them based on their genetic profile and other information. For this to happen, however, patients must be willing to undergo genetic assessment, physicians must have the capacity and willingness to refer their patients for genetic assessment and execute the tailoring of treatment recommendations, and health insurers must be willing to cover the costs of such services. The more effective PGx treatment strategies are

relative to current strategies, the more important it will be to ensure that minority and underserved populations are able to access them. Otherwise, PGx treatments for addiction will exacerbate already dramatic disparities in the burden of addiction and its impact on individuals' and families' health and horizons of opportunity.

Ensuring that research designs are adequately powered to identify clinically relevant subpopulations in terms of both genetic structure and environmental exposures will be essential to maximizing the benefits and minimizing the harms of PGx research. At the other end of the translational spectrum, once efficacious new treatment strategies for addiction are ready for widespread use, the challenge will be to find creative ways to overcome the disparities in access and quality of care that have forever plagued our health care system. Addiction is a debilitating disease and one that affects not only individuals, but also families and generations to come. Commitment to reaching those communities in greatest need with improved treatments for addiction could go a long way toward addressing these disparities.

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The Case for Considering Quality of Life in Addiction Research and Clinical Practice

Substance use disorders are increasingly viewed as chronic conditions, and addiction treatment services are beginning to adopt models that were developed to address other chronic conditions. These models address the impact of disease and services on the patient's overall well-being. From this perspective, treatment for addiction aims for the broad goal of recovery, which is defined as abstinence plus improved quality of life. However, the addiction field has come late to the chronic disease perspective, and the concept of quality of life in addiction is relatively undeveloped. This article reviews the evidence for the relevance of quality of life in substance use disorder treatment and recovery and discusses the importance of incorporating quality-of-life indices into research and services.

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Substance use disorders (SUDs) are characterized as "maladaptive patterns of substance use leading to clinically severe impairment or distress" potentially affecting physical or psychological functioning; personal safety; social relations, roles, and obligations; work; and other areas (American Psychiatric Association, 1994). Substance abusers seek help quitting drugs not as an end in itself, but as a means to escape these negative consequences and to gain a better life. Accordingly, while substance abuse treatment seeks to promote abstinence or at least significant reductions in substance use, its ultimate aim is to improve the patient's quality of life (QOL). In this paper, I present current concepts of QOL and tools used to measure it, summarize recent paradigmatic shifts in the SUD field that are leading to an emerging interest in QOL, and review the evidence bearing on QOL in the treatment of addiction. Finally, I present the implications of incorporating QOL concepts into clinical practice and research.

CURRENT CONCEPTS OF QUALITY OF LIFE

QOL describes clients' experiences in aspects of functioning that are important to them but are not captured by traditional symptom assessments such as the Addiction Severity Index (ASI) (Donovan et al., 2005). To date, there is no universally accepted biomedical definition of QOL, but there is consensus that it incorporates the individual's subjective view of a broad range of clinical, functional, and personal variables (Bonomi et al., 2000a).

Researchers have conceptualized two types of QOL (Table 1). The first, health-related QOL (HRQOL), is a patient's perception of how his or her health

status affects physical, psychological, and social functioning and well-being (Leidy, Revicki, and Geneste, 1999). HRQOL is assessed using instruments such as the Short Form 36 Health Survey (SF-36) or the abbreviated SF-12, with questions such as "Does your health problem prevent you from walking one block?" (Stewart and Ware, 1989). In its focus on limitations caused by disease and treatment, HRQOL aligns with traditional pathology-focused care.

In contrast, generic or overall QOL (OQOL) encompasses the patient's satisfaction with life in general, not solely in relation to disease-related limitations on functioning. One influential definition of OQOL, drafted by the World Health Organization (WHO), is "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (WHOQOL Group, 1995). The gold standards for measuring OQOL are the World Health Organization Quality of Life (WHOQOL) instrument and its shorter version, the WHOQOL-BREF (WHOQOL Group, 1998), which assess the patient's perception of how he or she is functioning objectively (e.g., "how is your memory?") and how he or she feels about it (e.g., "how satisfied are you with your memory?"). These and other OQOL assessments cover not only the three domains of functioning included in HRQOL but also, for example, environment, safety, finances, access to transportation and health services, and opportunities for recreation and leisure. Reporting on the U.S. validation of the WHOQOL instrument, Bonomi and colleagues (2000b) noted that "these additional factors … have been found important to individuals, groups and society, and are integral in describing overall QOL."

THE WORLD HEALTH ORGANIZATION QUALITY OF LIFE BREF INSTRUMENT (WHOQOL-BREF)

The WHOQOL-BREF assesses individuals' quality of life overall, not only in relation to health problems. The scope of the inquiry may be suggested by the following questions, selected from among a total of 26. Patients are instructed to keep in mind their "standards, hopes, pleasures and concerns" as they respond to each with a rating of 1 to 5.

- To what extent do you feel your life to be meaningful?
- How well are you able to concentrate?
- Have you enough money to meet your needs?
- To what extent do you have the opportunity for leisure activities?
- How well are you able to get around?
- How satisfied are you with your capacity for work?
- How satisfied are you with your personal relationships?
- How satisfied are you with your access to health services?

The full WHOQOL-BREF is posted at *www.who.int/substance_abuse/research_tools/whoqolbref/en/*.

TABLE 1. Summary of Prevalent Concepts and Measurements of Quality of Life

	HEALTH RELATED QUALITY OF LIFE (HRQOL)	OVERALL QUALITY OF LIFE (OQOL)
Definition	An individual's perception of the effects of illness on the physical, mental, and social dimensions of his/her well-being	An individual's perception of his/her position in life in the context of the culture and value systems in which he/she lives and as related to his/her goals, expectations, standards, and concerns
Paradigm	Symptoms, pathology	Wellness
Instrument	SF-36, SF-12	WHOQOL-100, WHOQOL-BREF
Domains	Physical, mental, social health	Physical, mental (including spiritual), and social health, and living environment (e.g., housing, finances, safety, access to care)
What is assessed	Limitations in functioning due to disease	Objective functioning and satisfaction with functioning
Treatment focus	Symptom reduction	Maximized overall functioning and life satisfaction

Clinical Relevance

The subjective views elicited by QOL measures are important because they offer a complementary perspective to that of clinicians. Clinicians tend to focus on symptoms, whereas for clients, symptom management is a means to an end: optimal well-being ("recovery" in the substance abuse field). As a result, clinicians and clients often differ in their ratings of quality of care. In general, patients' views provide unique information and insights into both the humanity and the effectiveness of health care (Black and Jenkinson, 2009).

Clinicians tend to focus on symptoms, whereas for clients, symptom management is a means to an end.

QOL assessments serve as both evaluation and diagnostic tools (Rudolf and Watts, 2002). They coincide with the treatment goal of enhanced client functioning and predict treatment adherence (Smith and Larson, 2003). Moreover, some evidence suggests that QOL has prognostic value in treatment settings; for example, higher pretreatment QOL predicts better outcomes in inpatient psychiatric units, independent of baseline psychiatric status and other relevant factors (Smith and Larson, 2003). Finally, as will be discussed, QOL may influence the odds of symptom reduction.

QOL measures can greatly assist clinicians in selecting and assessing the effectiveness of a specific course of treatment. Their use is in keeping with a growing interest throughout the health field in models that engage patients as partners in their own care (Black and Jenkinson, 2009; Rudolf and Priebe, 2002). The WHO defines health as "a state of complete physical, mental, and social well-being, not merely the absence of disease" (World Health Organization, 1985). QOL takes on its full importance as a diagnostic and outcome measure when health is thought of in this way. Indications of a growing recognition of the critical value of patients' reports on their own health include the recent launch of the National Institutes of Health (NIH) Patient-Reported Outcomes Measurement Information System (PROMIS) initiative to "address the pressing need to better quantify clinically important patient-reported symptoms and aspects of health-related QOL across chronic conditions" and recent Food and Drug Administration (FDA) guidelines in which QOL outcomes count as key evidence to support claims in medical product labeling *(www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf).*

Increasing QOL and longevity were two of the goals of NIH's Healthy People 2010 (U.S. Department of Health and Human Services, 2000) and remain central goals in Healthy People 2020 *(www.healthypeople.gov/2020/default.aspx).* Biomedical research is gradually shifting from the traditional paradigm of evaluating interventions by assessing disease-specific outcomes to a new paradigm that incorporates or is complemented by QOL outcomes. Large-scale biomedical clinical trials now routinely include QOL as, at least, a secondary endpoint and often as a primary outcome; more than 7,000 articles were listed in *Index Medicus* under the keyword "quality of life" in 2003 (Donovan et al., 2005). Whereas, in 1990, QOL could be called "the missing measurement in health" (Fallowfield, 1990), today virtually no area of medicine is without published studies on QOL.

RELEVANCE OF QUALITY OF LIFE IN SUBSTANCE ABUSE TREATMENT

The nature of SUD makes consideration of QOL, particularly OQOL, highly relevant. First, active substance abuse affects nearly all areas of functioning—vocational, social/familial, physical and mental health, residential status, and access to services (American Psychiatric Association, 1994). Commenting on findings from a study of individuals' reasons for seeking treatment for alcohol abuse, researchers noted that "the most striking aspect … was the sheer number of problems that people were experiencing" (Orford et al., 2006, p. 167).

Individuals want SUD services to address the full range of problems that prevent them from living fully and are more likely to drop out if such help is not forthcoming. When my colleagues and I examined polydrug abusers' reasons for dropping out of outpatient treatment, 33 percent said they might have stayed if the program had done something differently; of these, 54 percent cited unmet social service needs, especially vocational/educational and housing (Laudet, Stanick, and Sands, 2009).

The relevance of broad QOL domains, as measured by the WHOQOL instruments, to the recovery experience is bolstered by findings of a recent study of recovery priorities among community-based persons in recovery for periods ranging from 1 month to more than 10 years. We found that, in addition to concern about remaining abstinent, participants at all stages of recovery expressed concerns about multiple areas of functioning—most notably, employment, education and training, and housing (Laudet and White, 2009).

Widely used measures, such as the ASI, evaluate patients' experiences in key domains that are found to be problematic for many. However, QOL instruments are more comprehensive and are also likely more

relevant to persons in long-term recovery who are no longer receiving services but continue to struggle with addiction-related sequelae.

SUD is a chronic condition for most affected individuals, and QOL improvement is a particularly important goal in treating conditions that cannot be cured. QOL measurement in a chronic illness framework intends to capture the full impact of a medical condition and recommended treatment on an individual (WHOQOL Group, 1995). As a commonly used outcome measure in chronic illnesses, QOL provides an empirical assessment of how patients experience functioning and the burden of disease after treatment (Mendlowicz and Stein, 2000), which is useful information for public health evaluations and for service development and evaluation.

In accord with the growing medical recognition that patients require improved function in broad areas, the SUD field has been revising the concept of recovery. Although abstinence from drugs and alcohol was traditionally considered a proxy for good function in other areas, that assumption no longer holds (McLellan, Chalk, and Bartlett, 2007). To the contrary, abstinence rarely brings instant relief from all other problems in life (Vaillant, 1995), and it is common to see reductions in drug use without concurrent improvement elsewhere, especially early on (Dennis, Foss, and Scott, 2007). A consensus is emerging that recovery—the common goal of clinicians, clients and their families, funders, policymakers, and society at large—is best conceptualized as abstinence plus improvements in global functioning or, in other words, improved QOL. Thus, the Substance Abuse and Mental Health Services Administration (SAMHSA) defines recovery as "a process of change through which an individual achieves abstinence and improved health, wellness, and quality of life" (Center for Substance Abuse Treatment, 2006). Similarly, but more colloquially, former SAMHSA Director Charles Curie has said, "Recovery is when patients are not just free of symptoms—they have a life" (Curie, 2005). Consistent with this stance, QOL domains are central to SAMHSA's National Outcome Measures (NOMs) (Substance Abuse and Mental Health Services Administration, 2004), which are used to evaluate all publicly funded services *(integratedrecovery.org/wp-content/uploads/2010/08/SAMHSA-National-Outcome-Measures.pdf)* and are a key part of NIH's PROMIS initiative *(www.nihpromis.org/default.aspx).*

These changes in the understanding of SUDs have given rise to a new service model that relies on patients' experiences, especially their reports of well-being or QOL, to guide and evaluate service provision. Called "recovery-oriented systems of care" (ROSC; *www.pfr.samhsa.gov/rosc.html),* the model offers person-centered, strength-based continuity of care for individuals, families, and communities to take responsibility for their health, wellness, and recovery from alcohol and drug problems (Clark, 2008). In line with calls from the Institute of Medicine and leading addiction researchers for a shift in SUD treatment from the acute care model to one more akin to the model used in other chronic conditions (Institute of Medicine, 2005; McLellan et al., 2000; White et al., 2005), the recommended range of services is intended to respond to clients' changing needs across their lifespan. ROSC offers a comprehensive menu of services and supports that can be coordinated and integrated to meet the individual's needs and chosen path to improved function and a better life. Clients may receive help with education and job training, housing, child care, transportation to and from treatment and work, case management, as well as SUD-related services (e.g., relapse prevention, recovery support, SUD education for family members, peer-to-peer services and coaching, self-help, and support groups) (Kaplan, 2008).

QOL improvement is a particularly important goal in treating conditions that cannot be cured.

THE IMPACT OF SUBSTANCE ABUSE ON QUALITY OF LIFE

The addiction field lags far behind other mental health and biomedical disciplines in embracing QOL as an essential outcome, especially in the United States (Morgan et al., 2003). Systematic use of QOL indicators to monitor outcomes has been scarce, despite the wide-ranging effects of SUD on patients, families, and society (Dawson et al., 2009; Préau et al., 2007). Fewer than 100 studies of QOL among SUD populations have been published in English in the past 20 years (e.g., Donovan et al., 2005; Morgan et al., 2003; Rudolf and Watts, 2002; Smith and Larson, 2003), and almost all of them involve alcohol-dependent subjects. Most QOL studies of drug-abusing populations have been conducted outside of the United States and involved dually diagnosed persons (those with mental illness and SUD) and/or opiate abusers (Bizzarri et al., 2005; Millson et al., 2006; Puigdollers et al., 2004; Villeneuve et al., 2006). Aside from our own work, we found only one QOL study of crack/cocaine-dependent individuals (Havassy and Arns, 1998). Some studies have yielded information on QOL without using the term; for example, many have used the ASI, which assesses clients' level of functioning in

some QOL areas. Even so, only 38 percent of multigroup studies published between 1990 and 1998 reported on psychological functioning, the non-substance-abuse outcome most frequently examined. Moreover, studies focusing on QOL have almost all looked at HRQOL rather than OQOL, even though the latter relates more directly to recovery goals.

What follows is a summary of the current state of knowledge on well-being/QOL in substance-abusing populations. Because of the dearth of studies among drug-dependent populations, evidence among both alcohol- and drug-abusing individuals is reviewed.

QOL Among Active Substance Abusers and Treatment Seekers

QOL is poorer among substance-dependent individuals and SUD treatment seekers than among cohorts without SUD (Donovan et al., 2005; Rudolf and Watts, 2002; Smith and Larson, 2003). This finding is consistent across comparisons with clinical and nonclinical cohorts, primary care patients, groups with chronic physical or mental health conditions, and healthy nonabusers (Foster, Peters, and Marshall, 2000; Kraemer et al., 2002; Smith and Larson, 2003). For example, on the SF-36 indices of physical and mental functioning, clients in SUD treatment score significantly lower than the general population, as low as or lower than patients with lung disease and diabetes, and significantly lower than patients awaiting cardiac surgery (Smith and Larson, 2003).

Greater number and severity of alcohol or drug problems each consistently associates with poorer functioning in nearly all QOL domains.

While the evidence is equivocal regarding negative impacts of SUD on physical functioning (Morgan et al., 2003; Stein et al., 1998), SUD is clearly associated with severe impairments across several other functional domains. Mental functioning is particularly affected (Preau et al., 2007; Smith and Larson, 2003; Volk et al., 1997), as are social and physical role function (daily activities, work), general health perception, employment, and leisure activities (Hubbard, Craddock, and Anderson, 2003; Smith and Larson, 2003).

A large study of methamphetamine-dependent patients enrolled in treatment found that at intake, participants' health status, as measured by the SF-36, was substantially lower than that of the normative U.S. population. Their lowest scores were in overall mental health and mental health subscales, including vitality, social functioning, and emotional well-being (Gonzales et al., 2009). They also reported poorer general health and more physical role limitations than the population as a whole, although there were no differences in overall physical health status.

Correlates of QOL in SUD Populations

Sociodemographic and clinical variables have been studied most as predictors of QOL in SUD populations. The findings are somewhat inconsistent and difficult to interpret because of differences in methodologies, instruments, domains, and populations (Morgan, Landron, and Lehert, 2004). Overall, however, younger age, higher education, male gender, and being employed are consistently associated with better functioning on all HRQOL dimensions, when other covariates are held constant (Donovan et al., 2005; Foster et al., 2000; Youssef, Moubarak, and Kamel, 2005). Comorbid psychiatric and physical conditions, including HIV and/or hepatitis C infection, are linked to greater impairment of functioning (Millson et al., 2006; Morgan et al., 2003; Puigdollers et al., 2004).

In general, the greater the number of chronic conditions a person has, the higher the risk for functional impairment in all QOL dimensions (Thommasen and Zhang, 2006). As expected, physical and mental comorbidity associate most strongly with impairments in physical and mental functioning, respectively (Gunther et al., 2007); however, either raises the odds of impairments in almost all life domains (Bizzarri et al., 2005; Fassino et al., 2004; Villeneuve et al., 2006). Nevertheless, across studies, the combined influence of known demographic and clinical variables has accounted for only 2 to 7 percent of the variance in HRQOL among SUD treatment seekers (Stein et al., 1998), suggesting that other factors are at play and additional research is needed.

An important question and an emerging area of research is the extent to which substance abuse affects QOL in itself, independently of other factors. Greater number and severity of alcohol or drug problems each consistently associates with poorer functioning in nearly all QOL domains (McKenna et al., 1996; Volk et al., 1997), but other commonly used dependence indices, such as age at onset of drug use, duration of dependence, drinking pattern, prior withdrawal distress, and number of prior treatments, are not reliably predictive of QOL (Millson et al., 2006). Drug abuse may impair functioning more than alcohol abuse (Smith and Larson, 2003), and this may be especially true of cocaine and polysubstance abuse (Havassy and Arns, 1998; Puigdollers et al., 2004).

SUD Symptom Remission and QOL

Intuitively, one might expect reduced SUD symptoms and abstinence to be accompanied by significant improvements in QOL, and there is evidence that QOL improves with abstinence and deteriorates in relapse (Kraemer et al., 2002; Villeneuve et al., 2006). Studies most consistently link reduced drug and alcohol abuse and abstinence with improved mental functioning (Foster et al., 2000). For example, the most methodologically sophisticated investigation of SUD's influence on QOL found that individuals in a general population sample whose drinking patterns fluctuated—between no drinking, controlled drinking, alcohol abuse, and alcohol dependence—during a 3-year followup were more likely to experience related changes in their mental than in their physical functioning (Dawson et al., 2009). Participants who developed an alcohol use disorder or progressed from abuse to dependence experienced substantial declines in mental functioning, whereas all forms of remission were independently associated with substantially improved mental functioning. Increases associated with abstinent and nonabstinent remission were about twice as large as those seen with partial remission (i.e., not meeting criteria for dependence but having one or more symptoms of abuse or dependence).

Consistent with the view that reduced substance abuse is not in itself an adequate criterion for recovery, its impact on mental functioning appears to be small. For example, Morgan and colleagues (2003) studied 252 adults in an outpatient randomized clinical trial and estimated that reduced drug abuse accounted for 4.8 percent of variance in mental functioning at the 3-month followup. Moreover, studies have not consistently shown that reducing substance abuse affects domains of QOL other than mental functioning. For example, among dually diagnosed clients, researchers found no correlation between the extent of reduction in substance abuse 3 years post-intake and changes in general life satisfaction, social and family contact, or satisfaction with contacts (McHugo et al., 1999).

As with other positive treatment outcomes, a critical question is whether gains in QOL resulting from reductions in substance abuse endure. Very little research has addressed this issue, and the relationship between duration of abstinence and QOL remains unclear (Rudolf and Watts, 2002). Mann and colleagues followed a cohort of alcoholics for 6 years; at the final assessment, 65 percent of the group had been abstinent for 4 years or more, and these individuals had markedly superior physical, psychological, social, and everyday life functioning compared with those still drinking (Mann, Morlock, and Mezger, 1997). The positive relationship between abstinence duration and QOL has been described as linear in short-term studies (McKenna et al., 1996); however, a handful of cross-sectional studies suggest that QOL increases may peak after 1 or 2 years of abstinence (Amodeo, Kurtz, and Cutter, 1992). In one, for example, participants with 12 to 42 months of abstinence scored better on QOL assessments than participants with either 3 to 12 months or 43 to 108 months of abstinence, and scores tailed off as the length of abstinence increased (Chaturvedi, Kirthana, and Desai, 1997).

My colleagues and I examined the association between abstinence duration and QOL satisfaction in two studies with formerly polydrug-dependent persons (Table 2) (Laudet, Morgen, and White, 2006; Laudet and White, 2008). At recruitment, participants were abstinent for 1 month to more than 10 years. In cross-sectional analyses, overall QOL satisfaction increased gradually from about 6 months to more than 3 years of abstinence—the latter a duration that is often considered stable remission. Abstinence duration correlated significantly and positively with QOL satisfaction over the entire cohort and accounted for 9 percent of the variance in QOL satisfaction. In prospective analyses, after controlling for baseline levels of QOL satisfaction, longer abstinence duration at baseline significantly predicted higher levels of QOL satisfaction 1 year later. We also recently reported that the level of QOL satisfaction at the end of outpatient treatment is a significant predictor of commitment to abstinence, which in turn is a strong predictor of sustained abstinence (Laudet and Stanick, 2010).

TABLE 2. Quality-of-Life Satisfaction as a Function of Abstinence Duration

Abstinence Duration at Baseline	Mean QOL	Standard Deviation	*N*
Less than 6 months	6.75	1.97	99
6 to 18 months	7.51	2.05	92
18 to 36 months	8.13	1.64	71
More than 36 months	8.05	1.79	92

Participants (*N* = 354) responded to the question: Overall, how satisfied are you with your life? 0 = not at all; 10 = completely (Laudet, Morgen, and White, 2006).

There is evidence that QOL improves with abstinence and deteriorates in relapse .

The longest study of QOL components among individuals with SUD reassessed alcoholics 2 and 10 years after their initial treatment episode (Moos, Finney, and Cronkite, 1990). At both followups, participants whose drinking remitted (49 percent at 2 years and 57 percent at 10 years) had significantly higher levels of physical, mental, social, and occupational functioning than did the relapsed group. Moreover, compared with a matched community-based sample with no dependence history, the stably remitted group exhibited few deficits at the 2-year followup in physical and mental health and functioned equally well at the 10-year followup.

SUD Treatment and QOL

Whereas SUD treatment primarily targets substance abuse, it also provides services and referrals aimed at alleviating SUD-related problems in areas such as education, employment, physical and mental health, family functioning, and housing. A growing number of studies are examining the impact of treatment per se on QOL, including but not limited to any impact on substance abuse itself. The investigations completed to date have reported treatment-related improvements in most or all key QOL areas of functioning, including occupational status, overall life satisfaction, employment, and psychosocial functioning, among both alcohol- and drug-dependent samples (Fassino et al., 2004; Foster, Marshall, and Peters, 2000; Hubbard et al., 2003; Morgan et al., 2003; Villeneuve et al., 2006).

Does an addicted individual's QOL satisfaction predict his or her chances for remission?

Recently, Gonzalez and colleagues (2009) measured changes in HRQOL as a function of treatment completion and continued service exposure over a 1-year period among methamphetamine abusers. Significant improvements in mental and, to a lesser degree, physical health status were observed at followup relative to baseline. To explore the role of treatment and aftercare on QOL, the researchers modeled the change trajectories in SF-36 scores in four groups of patients: (1) treatment completers who engaged in some type of continuing care for SUD problems, (2) treatment completers who did not engage in continuing care, (3) noncompleters who engaged in continuing care, and (4) noncompleters who did not engage in continuing care. After controlling for other relevant variables, the researchers found that clients who received the greatest number of services (those in group 1) during the followup year experienced the most improvement in mental health functioning (gains of 9.6 points, based on normative calculation from the U.S. general population ranging from 0 [worst possible health status], to 100 [best possible health status]), whereas those who got the fewest services experienced the least improvement (2.2 points). The authors noted that "this 7.4 point difference is substantial, showing the importance of both successful treatment adherence (i.e., treatment completion) and subsequent continued care." There was no association between levels of service utilization and physical health status.

QOL as a Promoter of SUD Symptom Reduction

Research on QOL among those with chronic conditions has focused thus far on the unidirectional effect of symptom management on QOL—that is, whether symptom reduction leads to improved QOL. Another potentially important question is whether the relationship between SUD symptoms and QOL may be bidirectional so that improvement or deterioration of either can cause a similar change in the other. A few researchers have suggested that this is the case in chronic diseases other than SUD. For example, one group noted that "uncontrolled blood pressure alters hypertensive patients' QOL through anxiety and depressive reactions, and poor QOL hampers blood pressure control even with a therapeutic regimen" (Youssef et al., 2005). By extension, one may ask: Does an addicted individual's QOL satisfaction predict his or her subsequent remission?

Behavioral economics and behavior choice theory provide useful concepts for framing this question. Drug dependence can be understood as a choice, and behaviorists ask the question: What factors result in the choice of drug over other reinforcers (Bickel and DeGrandpre, 1996)? A relevant basic principle of choice theory is demand law, whereby consumption decreases as "price" increases (Allison, 1983). For a former drug abuser, the prospect of losing QOL improvements and positive experiences that accumulate in drug-free periods raises the price of reverting to drug use and reinforces motivation for continued abstinence. In this context, Blomqvist noted that among remitted substance abusers, "stability/improvements in several life areas contributed to sustaining … [their] resolution [to remain abstinent]" (Blomqvist, 2002). Among alcoholic women, higher satisfaction with life at treatment intake predicted higher subsequent abstinence rates (Rudolf and Priebe, 2002). Conversely, low QOL heightened the risk of relapse (Foster, Marshall, and Peters, 1998).

Based on demand law, we tested the hypotheses that QOL predicts sustained abstinence and that motivational constructs mediate the association (Laudet et al.,

2009). We found that, in a prospective cohort study of formerly polysubstance-dependent individuals abstinent for 1 month to more than 10 years, controlling for other relevant variables, baseline QOL satisfaction predicted continuous abstinence (biologically corroborated) 1 and 2 years later. As we had hypothesized, the association was partially mediated by a measure of motivation: commitment to abstinence.

IMPLICATIONS FOR CLINICAL PRACTICE AND RESEARCH

We have argued that QOL is highly relevant to SUD and recovery and that emerging changes in the SUD service field will require the incorporation of QOL indices in service development and research. Although the knowledge base is small and suffers from several methodological limitations, available evidence suggests that QOL is generally poor among active substance abusers and treatment seekers, and that reductions in substance abuse, including abstinence and participation in professional treatment, are associated with QOL improvements. To date, only physical and psychological health outcomes have been examined systematically, and little is known about other important domains of functioning. Here we present some suggestions for promoting QOL in SUD clinical practice and research questions that will need to be addressed to inform SUD service development, monitoring, and evaluation.

Implications for Clinical Practice

As discussed above, improvements in the functioning domains that constitute QOL are critical components of recovery, and thus impairments in these areas must be considered in clinical practice. As noted by McLellan and colleagues (2005), "Typically, the immediate goal of reducing alcohol and drug use is necessary but rarely sufficient for the achievement of the longer-term goals of improved personal health and social function and reduced threats to public health and safety—i.e., recovery."

In terms of service development and funding, the ideal scenario is the adoption of an integrated, multisystem, recovery-oriented model that meets all service needs. The emerging ROSC model, an example of such an approach, appears to have great potential to address not only substance abuse issues but also related service needs, and to possibly improve QOL in areas where impairments develop, and often endure, after abstinence has been achieved. Although the current fiscal austerity affecting most States may delay widespread adoption of ROSC, some states (e.g., New York) are moving forward, while other States and cities, most notably Connecticut (White, 2008b) and Philadelphia (White, 2008a), have well-established recovery-oriented systems.

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The current model of SUD services also harbors opportunities to consider and promote QOL. Treatment programs routinely assess clients' functioning in QOL-related areas such as housing, employment, and family functioning using SAMHSA's Government Performance and Results Act (GPRA) Client Outcome Measures. As well, many programs offer non-SUD services onsite or refer patients to outside agencies for needed services.

Regrettably, the outcome measurement model that currently prevails is ill-suited to monitor the impact of services on client functioning or identify QOL-related service needs. For example, for adult clients, SAMHSA

requires that the GPRA be administered at intake, discharge, and 6 months after intake. With this schedule, in contrast to standard practice with other chronic conditions, most assessments of patient functioning occur after services have ended. McLellan and colleagues (2005) have proposed an alternative model, concurrent recovery monitoring (CRM), to help clinicians pinpoint areas of impairment and newly arising issues on an ongoing basis throughout treatment. In CRM, clinicians would monitor substance abuse, personal health, social function, and behaviors that constitute threats to public health and safety at regular intervals during treatment (McLellan et al., 2005). A suggested CRM frequency would be weekly in intensive outpatient settings and monthly in standard outpatient settings, with each data collection requiring no more than 5 minutes per patient.

Clinical and recovery-oriented services must include improvements in key QOL domains among the goals of treatment.

If CRM were to be adopted, it might be useful to include a single OQOL item in CRM assessments, such as one taken from the OQOL subscale of the WHOQOL: "Overall, how satisfied are you with your life?" Although of limited usefulness for research purposes, a response to this question is considered an adequate and reliable indicator of how a person feels (U.S. Department of Health and Human Services, 2000); it has been found useful for identifying persons at increased risk for adverse health outcomes (Ried et al., 2006); and it predicts subsequent sustained abstinence among substance abusers (Laudet, Becker, and White, 2009). Adding this question to CRM assessments would not substantially add to clinicians' time burden and would promote a dialogue with individual clients to identify unmet service needs.

We hold that QOL is critical to the goal of recovery, and clinical and recovery-oriented services must include improvements in key QOL domains among the goals of treatment. The ideal service model for addressing QOL is likely to be one that integrates a variety of services and provides a continuum of care.

Key Research Questions

The preceding sections indicate that there are many more questions than answers with regard to QOL in the addictions. Therefore the first implication of this review for researchers is the urgent need to broaden the scope of outcome evaluations to include standardized QOL measures (Cisler et al., 2005). QOL must be embraced as a bona fide outcome in SUD research in the same way it is in other areas of the mental health and biomedical fields. Second, as is often the case in an emerging field, the QOL knowledge base suffers from several limitations that restrict the generalizability of findings (Cisler et al., 2005; Dawson et al., 2009; Donovan et al., 2005; Laudet et al., 2009). Future studies need to overcome key limitations pertaining to the following methods:

- *Sampling:* Most QOL studies have used samples of convenience, typically treatment-enrolled individuals, precluding generalization to the active abusers who are out of treatment and persons in recovery who are no longer enrolled in services. Moreover, most QOL studies have examined abuse or dependence on alcohol, but not other drugs. Given the emerging evidence that abuse of other drugs may impair QOL more severely than alcohol, more research among current and former drug abusers is critically needed;
- *Design:* The majority of QOL studies of SUD populations are cross-sectional, especially those conducted in the United States, precluding causal inference. Prospective studies have used very short followups (3 months to 1 year) that are inadequate to capture the full scope of change in either substance abuse or QOL or the longitudinal association between the two domains;
- *Measurement:* Overall, there has been a lack of uniformity in the instruments used to measure QOL and in the way scores are reported, making cross-study comparisons difficult. More importantly, studies have almost exclusively used indices of HRQOL, principally the SF-series instruments, that fail to capture functioning in domains—especially social functioning and living environment—that are important to SUD-affected populations and to the recovery experience. The WHOQOL instruments offer a very promising alternative (Betty Ford Institute Consensus Panel, 2007), yielding scores in physical, psychological, and social functioning; living environment; and an overall satisfaction score. The 26-item WHOQOL-BREF is used increasingly in biomedical research and practice worldwide and is slowly being adopted by SUD researchers abroad (Bizzarri et al., 2005; Gunther et al., 2007) and in the United States—for example, in the multisite COMBINE trial funded by the National Institute on Alcohol Abuse and Alcoholism (Cisler et al., 2005).

The full list of research questions to be addressed regarding QOL is beyond the scope of this paper. Key areas where investigation is critically needed to guide service development and policy, and to augment our knowledge of the full impact of addiction and full benefits of recovery, include the following:

- Identification of all the functional domains that are impaired by active SUD and where improvements occur as a function of remission. This research is likely to benefit from the inclusion of qualitative methods.
- Thorough assessment of the extent of impairments in all key areas of functioning among all segments of the SUD-affected population, including out-of-treatment active abusers, clients in treatment, and persons in successive stages of recovery. This knowledge will help pinpoint service and funding needs in primary care, specialty care, and recovery-oriented services. It will also inform prevention and education efforts.
- Elucidation of longitudinal changes in each QOL domain as a function of service and recovery supports as well as changes in substance abuse. These studies will require long-term followups, similar to that recently published by Dawson and colleagues (2009). The results will inform service development and funding decisions.
- Specification of correlates and predictors of patterns of QOL change beyond fixed characteristics, such as demographics and clinical variables, that explain but a fraction of the variance in QOL outcomes. For instance, research needs to determine the role of positive and negative recovery capital (Cloud and Granfield, 2008), participation in self-help support groups, and other forms of recovery support.
- Exploration of the possibility that QOL prospectively influences the odds of abstinence.
- Consideration of possible subgroup differences, such as gender, ethnicity/culture, age, and primary substances abused.

In sum, the investigation of QOL in the addiction field is in its infancy. Much remains to be done to inform service development and policy, guide clinical practice, and give substance abusers and all other stakeholder groups realistic, empirically based expectations. Fortunately, researchers studying QOL in SUD can draw questions and methodologies from a large body of work that has been conducted in the mental health and other biomedical fields. Together with the many researchers and clinicians who have contributed to developing the QOL concept and instruments, I hope that QOL will become a bona fide outcome in SUD clinical practice and research. Its current relative absence from the field represents a notable gap in the knowledge needed to promote stable recovery.

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Response: Toward Better Lives

Danny Hall, Ph.D., Dave Ross, Ph.D., and Lucy Zammarelli, M.A., N.C.A.C. II, C.A.D.C. III

Lucy Zammarelli: I like the way the article pulls substance abuse treatment into a standardized medical perspective. Quality of life is typically a goal in treating many diseases other than substance abuse. In the drug abuse field, it provides a broader, more encompassing gauge of success than just whether the client used a drug or how much.

Dave Ross: The issue is extremely important. Quality of life doesn't mean just that somebody is now sober. It's much more than that, and it takes a multidimensional program with some longevity to truly address it.

Zammarelli: The quality-of-life concept gives us a way to talk to patients about their situation that doesn't play into the shame that surrounds this disease. Instead of pathologizing their behavior, we can say, "Our goal is to help you succeed in your life."

Danny Hall: I practice patient-centered care. My perspective is that if you're truly doing patient-centered care, your outcome is quality of life. And if you're doing a good job, quality of life will improve.

Instruments and relationships

Zammarelli: I would like to become more familiar with the WHOQOL form that's mentioned in the article. We don't use anything like that in our program.

Hall: In our program at the VA, we don't objectively measure quality of life. We use an assessment called the Brief Addiction Measure, which covers quality-of-life issues very broadly with questions about mental and physical health; cravings; work, school and volunteer activities; and religion and spirituality. I think that ultimately it will be a very useful instrument, but so far we don't have norms on it.

Ross: At Catholic Charities, we give patients a form that has check-off boxes for mental and addiction issues, general and sexual health, chronic medical problems, food, clothing, shelter, and so on. Patients fill it out at intake and again when they exit the program to measure their progress. Most importantly, we use it as a clinical tool.

Interestingly, we initially designed the form using seven-point Likert scales, but that turned out to be too complex for some folks at intake. We shortened the form to three-point scales, and that has been much more successful.

Zammarelli: Our field has much to gain from adopting standardized instruments like the WHOQOL. We have such eclectic working methods; it'll be good for everyone when we can develop a standardized vocabulary. Quantifiable empirical data on quality of life will also be very useful.

Hall: Right. Our program just had a visit from a tracer for the Joint Committee on the Accreditation of Healthcare Organizations (JCAHO). She told us that we're going to have to show JCAHO that we are using data to guide our decisions about changes to the program. They won't be satisfied with us just telling them why we thought something was a good idea. We're going to have to show them the data that we generated to help us choose between option A and option B.

Zammarelli: A broadly used instrument like the WHOQOL can also relieve stigma. We can say to patients, "We're going to give you a screener that's like one that's used in heart disease and diabetes to help us determine our goals in treatment."

Ross: In my experience, much of the quality-of-life material that researchers develop tends to be top-down. The instruments assess what researchers think counts toward quality of life. So there will be items on food, clothing, shelter, abstinence, and so on. At Catholic Charities, we think it's also important to ask clients about quality of life in their own frame of reference. For example, have they reconnected with their friends, taken up a hobby or a sport or something else that they used to do?

Zammarelli: Relationships are a key aspect of quality of life. Many, many clients have had a terrible lack of caring, loving relationships in their lives. Their empathic

relationships with their counselors are the main factor in their continuing in treatment. The caring social connections that they form with others who are battling the same disease often are also critical.

Ross: I think some patients, particularly homeless people who enter treatment reluctantly, grieve over the people they knew on the street. They've become very attached to those people—who looked after them, protected them, and probably stole money and drugs from them, too. The patients have lost their primary social group, and often there's no one else left who has much empathy for them. I mean, on the way to becoming a full-blown addict, you trash a lot of people. It's hard to go back and say, "Okay, I need your help now."

Treatment goals

Hall: I was concerned that the author defined recovery as "abstinence plus quality of life." Throughout the article, the assumption seems to be that all therapy should aim to produce abstinence. That way of thinking overlooks the field of harm reduction therapy. It doesn't speak to the fact that people can be in multiple stages of change for each substance they use.

Ross: I noticed that, too. Our program serves three counties, and one of them, San Francisco, requires us to use harm reduction models. However, I just assumed that harm reduction wasn't a focus of this particular article.

Hall: For example, someone may come in and say, "I've got an abstinence goal for alcohol, a harm reduction goal for cocaine, and I don't want you to touch my cigarettes." If we are practicing patient-centered medicine, we have to accept that and work with it. Of course, somewhere during the course of therapy, we're going to show the patient that his use of all these drugs is related. The lighter that lights cigarettes also lights other things, and cigarettes are a trigger for cocaine use.

Zammarelli: We would not call ours a harm reduction program. I think that in general, people who are spending money on treatment expect abstinence to be a primary outcome. Insurance companies and drug courts certainly do.

A main reason that abstinence is a gold standard is that many people are aware that they can maintain recovery if they maintain abstinence. They know that if they chip away at a substance, have a few tokes or a couple of drinks, they can slide back down into the progressive nature of the disease.

At the same time, addiction is an episodic condition, and people go in and out of using. For that reason, broadening the idea of treatment and patient success is good, and it fits with the harm reduction model.

Ross: I like that clarification.

Hall: Yes. The "abstinence *eventually*" mindset makes a lot of sense to me.

Zammarelli: There is a question as to how much we can improve a patient's quality of life in the course of a treatment episode. With a mandated patient who has a co-occurring disorder, achieving initial stabilization and at least attempting abstinence can easily take 45 days. Then beginning to comprehend the quality-of-life issue and getting on track to deal with it can take up another 45 days. Now we are at the end of our 90-day treatment, and we've just started to help someone look at real quality-of-life issues like education and caring relationships.

Hall: I don't want to be Pollyanna-ish about it and say there's no limit to what we can achieve. However, I think putting limitations on goals for patients is problematic. Some research has shown that therapists' negative perceptions about patients' prospects for recovery can become self-fulfilling prophecies.

I let patients decide how we'll improve their quality of life. I often say, "You are the captain of your own boat. I have a couple of maps. So what do you want to do about your quality of life?"

Ross: To follow up on that idea, I encourage my clinicians to ask patients if they're feeling better. Sometimes the answers are surprising. The clinician might assess the person objectively and think he or she is still angry in group therpy, or see some other sign that progress isn't being made, but the patient might say, "Things are terrific compared with where I was."

This goes back to the patient's frame of reference. Once a patient came to me and said, "Dr. Ross, I really made it." I said, "What happened?" He had a new housing situation. He had moved from sleeping in an alley into an abandoned car. So he had created a home, with a roof that kept him dry, and for him that was a terrific advance in quality of life.

Zammarelli: Substance abusers sometimes have a frame of reference that makes them think they need to achieve magnificent goals before they can feel good about themselves. Their drug use leaves them with a weird mix of disempowerment and narcissism, shame, and feelings that they are unique and amazing. We try to help our patients see that it's all right to just be a person who has a house to live in and a job to work at and meaningful relationships. The quality-of- life perspective helps with this. It says, "It's enough to be average; you don't have to be so special or win any awards."

Prenatal Tobacco, Marijuana, Stimulant, and Opiate Exposure: Outcomes and Practice Implications

Abuse of drugs by pregnant women both in the United States and worldwide has raised many questions regarding the effects of prenatal drug exposure on the developing fetus and subsequent child outcomes. Studies using the neurobehavioral teratology model have been undertaken to determine specific prenatal drug effects on cognitive and behavioral development. Here we summarize the findings of studies that have investigated the developmental effects of prenatal exposure to tobacco, marijuana, stimulants, and opiates. These studies consider the timing and amount of prenatal exposure; other drug exposures; maternal characteristics; and other health, nutritional, and environmental factors. We review treatment options for pregnant, substance-dependent women and therapeutic interventions for exposed children.

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Several well-designed and methodologically sound studies have described long-term effects of specific prenatal drug exposures on children's health and development. Some longitudinal studies now extend into late adolescence and early adulthood and assess vulnerability to substance abuse and dependence.

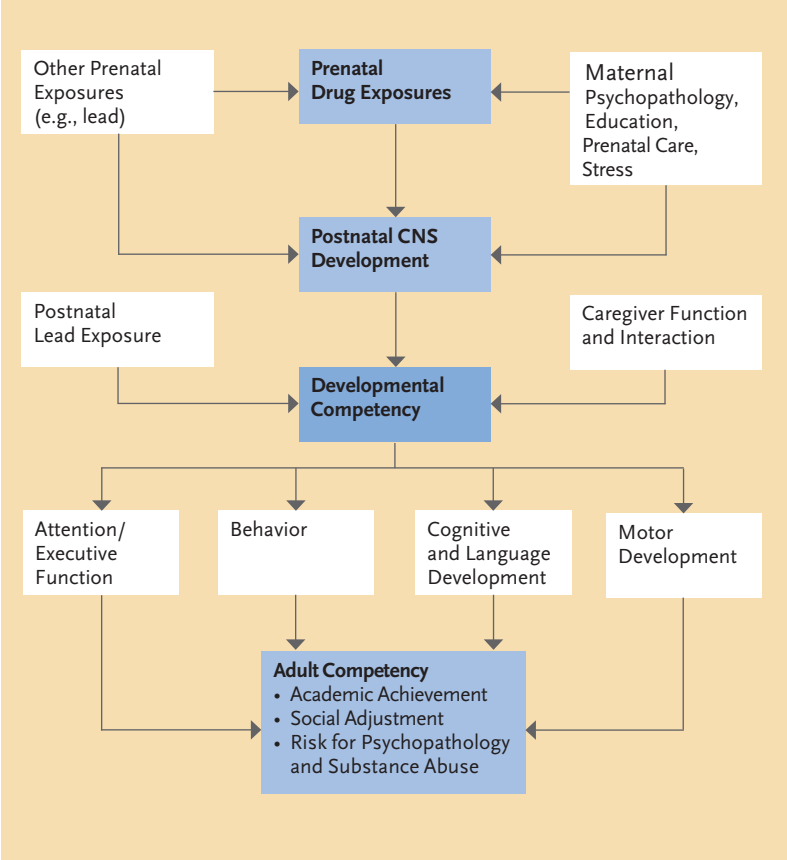
The psychoactive substances widely used by women of childbearing age include alcohol, tobacco, marijuana, stimulants, and opioids. Here we summarize current knowledge of the effects of prenatal exposure to each of these drugs, except alcohol. The extensive research on prenatal alcohol exposure has been reviewed elsewhere (Manji et al., 2009; O'Connor and Paley, 2009; Paley and O'Connor, 2009). We also discuss promising findings from trials of interventions to help pregnant and postpartum substance-abusing women and prenatally drug-exposed children.

A MODEL FOR INVESTIGATION: NEUROBEHAVIORAL TERATOLOGY

The conceptual framework used to study prenatal drug exposure is neurobehavioral teratology, which addresses the impact of prenatal exposure to a foreign agent on a child's central nervous system (CNS) and behavior. An important principle of teratology is that the harm caused by a toxic agent is a function of several factors, including the individual's genetic makeup, the fetal and postnatal environment, the dose of the agent, and the developmental stage of the fetus at the time of exposure. Vorhees (1989) has added two specific neurobehavioral tenets:

- Damage to the CNS during the prenatal period continues to have effects through fetal, neonatal, infant, and childhood development; and

FIGURE 1. Model to Study Effects of Prenatal Drug Exposure on Developmental Outcomes



Adapted from Mayes, 2002.

Drug metabolites interact with an individual's genetic makeup to influence cognitive development and behavior.

• CNS injury may result in behavioral impairments rather than physical birth defects.

Mayes (2002) developed a model for neurobehavioral teratology research that highlights the direct and indirect effects of prenatal drug exposure and the ongoing reciprocal influences of CNS disruption, maternal characteristics, and environmental factors (Figure 1).

Women often abuse more than one drug, so a child's problems frequently reflect the combined impact of multiple exposures. Substance-abusing women often also have other characteristics that can result in fetal harm, including high stress, lack of prenatal care, sexually transmitted infections, and high-risk behaviors such as drug-trade activities that expose them to violence. Once the child is born, influences that may come into play include low maternal IQ and verbal abilities, maternal psychopathology and chaotic lifestyle, exposure to lead or other toxins, and placement in institutional or foster care. The child's CNS disruption can hinder his or her odds of reaching full developmental and academic potential directly and in combination with parental and environmental factors. For example, a parent's poor functioning in the caregiver role may compound the limiting impact that a child's drug-related irritability and reduced self-regulatory abilities have on opportunities for regular, language-rich dyadic exchange. A child's drug-related cognitive and learning disabilities may derail social and vocational adjustment, and both may increase the odds of substance abuse, psychopathology, and involvement with the criminal justice system.

Because of this merging of effects, research to evaluate the specific effects of prenatal exposure to a particular drug must include assessment of key covariates known to affect the developmental and behavioral outcomes under study (Table 1). Studies must generally include an adequate number of subjects to achieve statistical power, and longitudinal studies must retain most subjects over many years. A sufficiently large control group of similar sex, race, and socioeconomic status (SES) is essential. Recently, investigators have begun to apply new technologies to relate behavioral findings of prenatally drug-exposed children to brain structure and function and genetics.

DRUG ACTION IN THE DEVELOPING FETUS

Although the placenta was once thought to protect the fetus against exposure to toxins, it is now known that metabolites of drugs, including cocaine, opiates, amphetamines, marijuana, and tobacco, enter the fetal bloodstream. Active metabolites can penetrate the fetal blood-brain barrier and interfere with early neuronal cell development or cause neuronal death (Lee et al., 2008). Researchers hypothesize that drug metabolites interact with an individual's genetic makeup to influence cognitive development and behavior. Thus, for example, some individuals may be genetically more susceptible than others to cocaine's deleterious effects on development.

Maternal drug abuse also affects the fetus indirectly. For example, crack cocaine, heroin, tobacco, and marijuana cause vasoconstriction that restricts the fetal oxygen supply. As well, substance abuse often conflicts with healthy maternal practices—such as eating a nutrient-rich diet and accessing prenatal care—that reduce pregnancy complications such as diabetes, preeclampsia, and preterm labor. Conditions that commonly co-occur with drug abuse, including sexually transmitted infections, depression, post-traumatic stress disorder, and exposure to chronic stress and violence, also may lead to fetal injury. Neonatal abstinence syndrome (NAS), which

occurs after opiate use during pregnancy, puts the infant under physiological stress that increases the risk of health and possibly developmental problems.

Neuroimaging studies have revealed evidence of physiological brain changes in prenatally drug-exposed children, some of which correlated with the results of behavioral assessments. However, the studies need to be replicated, because they had small sample sizes and some lacked controls for possible confounding factors.

TOBACCO

Despite wide awareness that smoking is bad for both mother and developing fetus, in 2007, an estimated 16.4 percent of pregnant American women were current tobacco smokers (SAMHSA, 2008). Although pregnant women overall had lower smoking rates than nonpregnant women, pregnant 15- to 17-year-olds had higher smoking rates than their nonpregnant age mates.

Smoking increases a woman's risk of ectopic pregnancy and placenta previa, both of which increase the odds of maternal mortality. Women who smoke during pregnancy are somewhat less likely to develop preeclampsia than those who do not smoke; however, among pregnant women who develop preeclampsia, smoking seems to increase mortality (Cnattingius, 2004).

Tobacco use has also been linked to low birth weight and pregnancy complications, including prematurity, placental abruption, and intrauterine death. Low birth weight suggests that the fetus has not obtained important nutrients and oxygen, which are important for optimal brain growth and neuronal development. Some evidence indicates that maternal tobacco use during pregnancy doubles the likelihood of sudden infant death syndrome (Salihu and Wilson, 2007; Table 2).

Neonates who were exposed to tobacco prenatally are more excitable, have greater muscle tension, require more handling to be calmed, and show more signs of CNS stress (e.g., abnormal sucking, excessive gas, gaze aversion) than unexposed infants (Law et al., 2003). Dose-response relationships have been established between maternal tobacco use, as measured by levels of salivary cotinine (the active metabolite of nicotine) or self-report, and signs of physiological stress.

Infant CNS functional abnormalities related to prenatal tobacco exposure include deficits in self-regulation (the infant's ability to soothe or quiet itself) (Table 3). At 2 to 4 weeks and at 7 months of age, prenatally tobacco-exposed infants exhibited, compared with unexposed infants, more negative affect and manifestations of sadness, distress in response to limitations, decreased soothability, and fear during a test used to assess emotional self-regulation (Schuetze and Eiden, 2007; Schuetze, Eiden, and Coles, 2007). Low birth weight and reduced head growth may underlie these disturbances.

In 2007, an estimated 16.4 percent of pregnant American women were current tobacco smokers.

Prenatal tobacco exposure has been consistently associated with lower IQ throughout childhood (Fried, 2002; Herrmann, King, and Weitzman, 2008). In one study, children of women who smoked more than 16 cigarettes a day while pregnant had a mean IQ in the average range, but 8 points lower than those of unexposed children (Fried, Watkinson, and Gray, 2003). Children prenatally exposed to tobacco are also at increased risk for attention problems during the early elementary school years (Cornelius et al., 2007; Langley et al., 2005; Linnet et al., 2003).

Conduct disorder can be an adverse outcome of prenatal tobacco exposure. In one study, adolescent children of mothers whose blood cotinine levels during pregnancy had been in the top 20 percent of those tested were twice as likely as the 20 percent of children with the least exposure to develop a conduct disorder (Braun et al., 2008). Postnatal exposure to secondhand smoke may also contribute substantially to diagnoses of conduct disorder in U.S. children (Braun et al., 2008). Recent data suggest that prenatal tobacco exposure may promote later conduct disorders by inhibiting the brain enzyme monoamine oxidase (MAO) during fetal development

TABLE 1. Maternal and Caregiver Covariates to Be Considered in Prenatal Substance Exposure Research

Prenatal drug use
Socioeconomic status
Marital status
Parity
Prenatal care
Psychological distress
Quality of home environment
Race
Cognitive ability
Years of education

TABLE 2. Prenatal Drug Exposure: Potential Effects on Birth and Pregnancy Outcomes

TOBACCO	MARIJUANA	STIMULANTS	HEROIN/OPIOIDS
Pregnancy complications	No fetal growth effects	**Cocaine**	Stillbirth
Prematurity	No physical abnormalities	Prematurity	Prematurity
Decreased birth weight		Decreased birth weight	Decreased birth weight
Decreased birth length		Decreased birth length	Decreased birth length
Decreased birth head circumference		Decreased birth head circumference	Decreased birth head circumference
Sudden infant death syndrome (SIDS)		Intraventricular hemorrhage	Fetal and neonatal abstinence syndrome
Increased infant mortality rate		**Methamphetamine**	Sudden infant death syndrome (SIDS)
		Small for gestational age	
		Decreased birth weight	

(Baler et al., 2008). MAO participates in the regulation of the levels of monoaminergic neurotransmitters that are critical for fetal forebrain development.

Prenatal tobacco exposure has also been implicated in depression and anxiety in early childhood through late adolescence (Robinson et al., 2008). However, these internalizing symptoms have not received as much attention as conduct disorder, perhaps because they are less disruptive to families and classrooms.

Prenatal tobacco exposure appears to increase the likelihood of tobacco use in childhood and early adolescence. In one study, the risk differential of exposed and unexposed children at age 10 was more than fivefold after controlling for environmental factors, other prenatal exposures, current maternal smoking, and child and maternal psychological covariates (Cornelius et al., 2005). However, when the children in this study were 14, prenatal tobacco exposure was no longer a significant predictor of their tobacco use when factors such as peer smoking were taken into account.

A magnetic resonance imaging (MRI) study of children aged 10 to 14 found reductions in cortical gray matter and parenchyma volumes, as well as head circumference, in those whose mothers had smoked while pregnant (Rivkin et al., 2008). Some researchers have suggested that prenatal tobacco exposure accelerates puberty among males (Fried, James, and Watkinson, 2001).

Behavioral interventions are recommended as the first treatment options to help pregnant women stop smoking.

Treatment Recommendations

Behavioral interventions are recommended as the first treatment options to help pregnant women stop smoking (Oncken and Kranzler, 2009; Slotkin, 1998). Several studies have demonstrated that contingency management (CM), a strategy that dispenses cash or other tangible prizes as incentives for achieving treatment goals, helps pregnant smokers maintain abstinence (Donatelle et al., 2000; Heil, Scott, and Higgins, 2009; Higgins et al., 2004). CM may be more effective with low-income pregnant smokers (Donatelle et al., 2004), whose quit rates with CM have ranged from 19 to 40 percent, compared with 6.6 to 20.5 percent with other behavioral interventions. On its own, cognitive-behavioral therapy (CBT) yields only modest reductions in smoking-cessation rates among pregnant women. Combined treatment with CBT and nicotine replacement therapy (NRT) is more effective than CBT alone for pregnant moderate to heavy smokers (Osadchy, Kazmin, and Koren, 2009).

Although NRT is widely used and effective in the general population, there are concerns regarding its effectiveness for pregnant smokers and safety for the fetus. At issue is whether the risks for both mother and child outweigh the harmful effects of cigarette smoking on the fetus. Some researchers endorse the use of NRT under a physician's close supervision in combination with behavioral interventions for moderate to heavy

smokers (Osadchy, Kazmin, and Koren, 2009). For heavy smokers, the benefits of NRT likely outweigh the risks of smoking during pregnancy because NRT (1) usually delivers a dose of nicotine less than or the same as what the person gets from smoking, (2) may eliminate fetal exposure to other toxins in cigarette smoke, and (3) may reduce the overall dose and duration of nicotine exposure (Oncken and Kranzler, 2003). When used, NRT therapy should begin as early in the pregnancy as possible, because a fetus may be especially sensitive to the adverse effects of nicotine exposure after the first trimester (Slotkin, 1998). The safety and efficacy of bupropion, another medication that is effective for smokers in the general population, has not been established for pregnant smokers (Oncken and Kranzler, 2003).

Abstinence from smoking during the first 2 weeks of a quit attempt is critical to long-term success (Higgins et al., 2006). It is therefore important to closely monitor early abstinence and adjust treatment as needed. Clinicians should continue to encourage women to quit even if they initially fail, because quitting at any time before childbirth reduces the risk of complications for both the mother and child.

MARIJUANA

The Ottawa Prenatal Prospective Study (OPPS), the Maternal Health Practices and Child Development (MHPCD) study, and other well-controlled studies have not implicated *in utero* marijuana exposure in any major fetal growth or physical abnormalities (Day et al., 1992; Fried and Smith, 2001; Table 2). The OPPS study did find a 1-week-shorter gestation period and two abnormalities associated with the visual system: true ocular hypertelorism (widely spaced eyes) and severe epicanthus (skin folds at the corners of the upper eyelids) among infants whose mothers smoked more than five joints per week while pregnant (Fried and Smith, 2001). However, the study authors concluded that the visual abnormalities were likely related to prenatal alcohol exposure rather than directly to marijuana exposure.

Studies of neonatal neurobehavioral outcomes of prenatal marijuana exposure have observed mild withdrawal symptoms and poor autonomic control, particularly of state regulation (the ability to adjust one's level of alertness as required for a task). Autonomic control was normal, however, when assessed at 6 months or 1 year of age (Fried, 1995; Table 3).

The OPPS and MHPCD study examined the relationship between marijuana exposure and developmental problems throughout childhood. Children of women who smoked one or more marijuana joints a day during the first trimesters were more likely than controls to exhibit deficits in school achievement, particularly in reading and spelling (Goldschmidt et al., 2004). Prenatal marijuana exposure had persistent negative effects through age 16 on higher-order thinking, including problem solving, memory, planning, impulsivity, and attention (Fried, 2002; Fried, Watkinson, and Gray, 2003; Goldschmidt et al., 2008; Richardson, Goldschmidt, and Larkby, 2007). Researchers did not find overall suppression of IQ.

Abstinence from smoking during the first 2 weeks of a quit attempt is critical to long-term success.

Prenatal marijuana exposure may have long-term emotional and behavioral consequences. At age 10, children who had been exposed to the drug during their first and third trimester of gestation reported more depressive symptoms than did unexposed controls (Gray, 2005). Among 16- to 21-year-olds, prenatal exposure to marijuana at least doubled the risk of both tobacco and marijuana use (Day, Goldschmidt, and Thomas, 2006; Porath and Fried, 2005). Adolescents with histories of daily prenatal marijuana exposure were 1.3 times as likely as those with less or no exposure to be high-frequency users of the drug, even after extensive control for other factors known to increase the risk of adolescent substance abuse (Day, Goldschmidt, and Thomas, 2006).

A recent functional MRI study of 18- to 22-year-olds linked prenatal marijuana exposure to altered neural functioning during a psychological test that involves remembering the placement of images that flash on a screen. Compared with a control group, the exposed group showed greater activation of neurons in the inferior and middle frontal gyri and superior temporal gyri (Smith et al., 2006).

Treatment Recommendations

Although they have not been studied specifically with pregnant users, CBT, motivational enhancement, and CM therapies have been demonstrated to be effective for reducing marijuana use (McRae, Budney, and Brady, 2003). Controlled studies of pharmacotherapies for marijuana dependence are still needed, as is intervention research specifically targeting pregnant marijuana users.

COCAINE AND OTHER STIMULANTS

Several recent prospective studies have examined the consequences of prenatal cocaine exposure. Relatively few, in contrast, have addressed prenatal exposure to methamphetamine, ecstasy, or methylphenidate (Ritalin

TABLE 3. Prenatal Drug Exposure: Potential Effects on Central Nervous System Development, Cognitive Function, and Behavior*

TOBACCO	MARIJUANA	STIMULANTS	OPIATES
Disturbed maternal-infant interaction Excitability Hypertonia Stress abstinence signs Conduct disorder Reduced IQ Aggression Antisocial behavior Impulsivity ADHD Tobacco use and dependence	Mild withdrawal symptoms Delayed state regulation Reading, spelling difficulty Executive function impairment Early tobacco and marijuana use	**Cocaine** *Neonatal/Infancy* Early neurobehavioral deficits: Orientation, state regulation, autonomic stability, attention,sensory and motor asymmetry, jitteriness Poor clarity of infant cues during feeding interaction Delayed information processing General cognitive delay *Childhood* Lower nonverbal perceptual reasoning Lower weight for height Lower weight curve trajectories Attention problems Disruptive behaviors by self-report and caregiver report	Neonatal abstinence syndrome Less rhythmic swallowing Strabismus Possible delay in general cognitive function Anxiety Aggression Feelings of rejection Disruptive/inattentive behavior
		Methamphetamine Poor movement quality (3rd trimester exposure) Lower arousal Increased lethargy Increased physiological stress No mental or motor delay (infant/toddler)	

*Effects may be subtle and transient.

or Concerta) or other stimulant medications used to treat attention-deficit/hyperactivity disorder (ADHD).

Cocaine

At the height of the most recent crack-cocaine epidemic, in the late 1980s and the first half of the 1990s, an estimated 100,000 prenatally exposed children were born yearly in the United States. As many as 18 percent of live births were affected in some urban, primarily low-SES areas (Kandel, Warner, and Kessler, 1998; Ostrea et al., 1992; SAMHSA, 2000). Nearly 2 million Americans living today were prenatally exposed to cocaine, many of whom are now adolescents or young adults. Currently, an estimated 50,000 infants are born in the Nation each year having been prenatally exposed to cocaine.

Impact on neonatal and infant development

A majority of studies have reported that infants with histories of prenatal cocaine exposure have reduced weight, head circumference, and/or length at birth (Bada et al., 2005; Eyler et al., 1998; Singer et al., 2002b; Zuckerman et al., 1989). A meta-analysis of 33 studies conducted between 1989 and 1997 attempted to distinguish the direct effects of cocaine, as opposed to other risks commonly associated with cocaine abuse (e.g., abuse of other drugs, poor prenatal care) on these and other neonatal features and on pregnancy complications. The

results confirmed two problems as directly attributable to cocaine-related physiological stress in the prenatal environment: amniotic sac rupture more than 1 hour before labor begins and separation of the placenta from the uterus prior to delivery (Addis et al., 2001).

Considerable evidence implicates prenatal cocaine exposure in subtle CNS abnormalities. When assessed with the Brazelton Neonatal Behavioral Assessment Scale, exposed infants showed deficits—albeit with much variability—in orientation, habituation, state regulation, autonomic stability, reflexes, tone, motor performance, irritability, alertness, and excitability (Singer et al., 2000). Compared with infants of mothers with similarly low SES who used other drugs during pregnancy, cocaine-exposed infants showed higher rates of sensory and motor asymmetry, poor muscle tone, jitteriness (Singer et al., 2000), and reduced novelty preference (Singer et al., 1999). Both of these studies correlated greater prenatal cocaine exposure with poorer assessment scores in nonverbal reasoning (Table 3).

Studies of the impact of prenatal cocaine exposure on development during the first 3 years of life have produced inconsistent results. For example, among low-SES children who may also have been prenatally exposed to alcohol, tobacco, and marijuana, Richardson and colleagues reported an association between cocaine exposure during the second and third trimester of gestation and decrements in motor but not in mental abilities, as measured by the Bayley Scales of Infant Development (BSID) (Richardson, Goldschimdt, and Willford, 2008). In contrast, Frank and colleagues (2002) reported no correlation between cocaine exposure and either mental or motor scores on the same instrument. Singer and colleagues (2002a) used the BSID mental development index to compare prenatally cocaine-exposed and non-cocaine-exposed 2-year-olds; the cocaine-exposed group scored 6 points lower and were twice as likely to have significant mental delay. Other research suggests that cocaine has an indirect effect on mental development through reduced head size (Behnke et al., 2006a).

Because cocaine targets the monoaminergic (dopamine, norepinephrine, epinephrine, and serotonin) neurotransmitter systems, which are known to regulate attention, researchers have been interested in the drug's impact on children's capacity for attention. Studies indicate that prenatal cocaine exposure can impair visual attention, visual processing speed, and visual memory in infancy and throughout the first year of life (Jacobson et al., 1996; Singer et al., 1999; 2005).

How cocaine effects measured in infancy will play out in later childhood, adolescence, and adulthood is unclear. Early CNS abnormalities are considered potential early warning signs of underlying damage that may manifest later as self-regulatory problems. However, psychological assessments made before age 4 are generally weak predictors of how a child will perform later, although reduced novelty preference has been correlated with subsequent low IQ.

Impact on children 4 years and up

No childhood physical abnormalities have been definitively attributed to prenatal cocaine exposure (Minnes et al., 2006). However, some evidence points to enduring growth consequences with lower weight-to-height ratios at 6 years of age (Minnes et al., 2006) and slower head circumference and weight trajectories from 1 to 10 years (Richardson, Goldschmidt, and Larkby, 2007).

As children grow older, psychological assessments become more stable. Subtle negative effects involving perceptual reasoning have been associated with prenatal cocaine exposure in children 4 to 9 years of age (Singer et al., 2004; 2008). Perceptual reasoning refers to one's ability to envision solutions to nonverbal problems, such as recreating a spatial design with 3D colored blocks.

Considerable evidence implicates prenatal cocaine exposure in subtle CNS abnormalities.

Problems of attention are particularly worrisome because they relate to poor school achievement and behavior problems. Prenatally cocaine-exposed 4- to 7-year-olds performed below standard norms on tests that measure sustained attention (Bandstra et al., 2001) and selective attention (Noland et al., 2005). On the tests, which require subjects to watch a computer screen and respond appropriately each time a particular image or stimulus appears, they made more than the average number of incorrect responses, indicating impulsivity, and omitted more correct responses (Accornero et al., 2007), indicating general inattention.

Rule breaking, aggression, and other externalizing behaviors are associated with prenatal cocaine exposure and are attributed to a lack of self-regulation. Ratings completed by teachers, experimenters, and caregivers indicate that being prenatally cocaine-exposed, being male, and living in a high-risk environment are each independently predictive of aggressive behavior (Bendersky, Bennett, and Lewis, 2006). Linares and colleagues (2006) reported that among prenatally cocaine-exposed 6-year-olds:

- 17 percent reported symptoms of oppositional defiant disorder, compared with 9 percent of unexposed age mates; and

- 12 percent reported clinically elevated levels of ADHD symptoms, compared with 7 percent of unexposed peers.

At 10 years, boys with histories of prenatal cocaine exposure were more likely than unexposed boys to report high-risk traits, including aggression, substance use, and disregard for safety, on the Youth Risk Behavior Survey (Bennett, Bendersky, and Lewis, 2007). Teachers attribute high rates of behavioral problems, particularly hyperactivity, to prenatally cocaine-exposed boys (Delaney-Black et al., 2004). One longitudinal study associated clinically elevated delinquent behavior with prenatal cocaine exposure in girls (Minnes et al., 2010). Some studies have found that recent caregiver drug use and psychological symptoms, but not prenatal cocaine exposure, predicted behavioral problems (Accornero et al., 2002; 2006; Sheinkopf et al., 2006; Warner et al., 2006b). Overall, however, the evidence suggests that children with prenatal cocaine exposure should be routinely screened for behavioral problems.

There are growing concerns regarding the widespread use of stimulant medications for ADHD by women of childbearing age.

Imaging studies

Several researchers have deployed brain imaging to study the effects of prenatal cocaine exposure. These studies documented:

- reduced gray matter in the right parietal and left occipital lobes and corpus callosum of 7- to 8-year-olds (Dow-Edwards et al., 2006; Singer et al., 2006) and the caudate in a group averaging 14 years of age (Avants et al., 2007);
- higher diffusion in white matter frontal projections at ages 10 to 11 (Warner et al., 2006a);
- decreased volume of the right anterior cerebellum at 11 years of age (Dow-Edwards et al., 2006; Behnke et al., 2006b);
- significantly smaller caudate in adolescents (Avants et al., 2007); and
- also in adolescents, more functional connectivity in the default mode network (related to arousal regulation) and a greater signal increase when shown emotionally arousing stimuli (Li et al., 2011).

Methamphetamine

In the only large-scale, well-controlled study of the effects of prenatal methamphetamine exposure—the Infant Development, Environment, and Lifestyle Study—exposed infants were 3.5 times as likely as controls to be small for gestational age and had a lower average birth weight (Smith et al., 2006). By using the Neonatal Intensive Care Unit Network Neurobehavioral Scale, prenatal methamphetamine exposure has been associated with lower arousal from sleep, lack of energy, and physiological symptoms indicating withdrawal. Preliminary findings indicate no impact on scores on the BSID at age 1, 2, or 3 (Lester and Lagasse, 2010). Additional followup of this cohort at later ages is needed to evaluate more subtle learning and behavioral problems.

Stimulant Medications for ADHD

There are growing concerns regarding the widespread use of stimulant medications for ADHD by women of childbearing age. To date, research has uncovered no clear pattern of negative effects on pregnancy or offspring when the medications are taken at therapeutic doses (Humphreys et al., 2007). However, no well-controlled prospective studies have been completed.

Treatment Recommendations

All stimulant drugs, including prescribed medications, should be avoided during pregnancy. Women who wish to use prescribed stimulants during pregnancy should be assessed to determine whether the potential benefits to the mother outweigh any risk to the fetus (Goodman and Quinn, 2002).

CM is a reliably effective treatment for cocaine dependence in the general population, and the use of voucher-based incentives has demonstrated promising results with pregnant women (Higgins, Alessi, and Dantona, 2002). CM used in conjunction with behaviorally based substance abuse treatment can reinforce both cocaine abstinence and compliance with prenatal care in terms of weekly attendance at prenatal clinic visits (Elk et al., 1995; 1998). In one study, CM did not greatly reduce dropout from residential treatment participation, but improved outpatient treatment retention during the transition from residential care (Svikis et al., 2007).

Methamphetamine and cocaine abusers often respond similarly to treatment (Cretzmeyer et al., 2003). Although they have not been investigated with pregnant women, CBT, CM, and the Matrix Model may be the most effective treatment approaches for stimulant abuse and dependence (Winslow, Voorhees, and Pehl, 2007).

OPIATES

Rates of prenatal opiate exposure are difficult to obtain and vary widely from less than 1 percent to 21 percent, depending on the risk status of those screened and the time period (Ostrea, 1992; Yonkers et al., 2010). A U.S. multicenter study investigating the rates of prenatal

drug use by meconium analyses and maternal self-report indicated that 10.7 percent of 8,527 infants screened were exposed to cocaine or opiates (Lester et al., 2001). Although today more people abuse prescription pain relievers than illegal opiates, most research on opiates has involved subjects who are addicted to heroin or receiving opioid agonist therapy.

Fluctuations in an expectant mother's daily heroin use due to voluntary abstinence or lack of access to the drug affect the fetus as well. If abrupt, these changes can precipitate fetal abstinence syndrome, which increases the risk of premature delivery, low birth weight, stillbirth, and sudden infant death syndrome (Joseph, Stancliff, and Langrod, 2000; Table 2). NAS occurs when birth abruptly deprives an infant of opiates it received via the placenta during gestation. NAS can manifest with serious but usually not persistent CNS symptoms, such as seizures, in 2 to 11 percent of neonates (Bandstra et al., 2010).

Heroin exposure decreases birth weight, birth length, and head circumference, but has not been associated with congenital malformations. Prenatal opiate exposure has greater adverse impact than prenatal cocaine exposure on the infant CNS and autonomic nervous system (Das, Poole, and Bada, 2004), with effects that include abnormally high muscle tone, inconsolability, irritability, sneezing, stuffiness, excessive sucking, poor sucking ability, and high-pitched cry (Table 3). The high-pitched cry signifies a CNS abnormality that can result from increased cranial pressure or a congenital malformation. Infants who were exposed to both opiates and cocaine had louder and higher-pitched cries than infants exposed to either drug alone (Lester et al., 2002).

Followup studies of children prenatally exposed to opiates have had sample sizes too small to control for important covariates. Some have found evidence of delayed general cognitive function at 3 years (Wilson et al., 1979), lower verbal ability, and impaired reading and arithmetic skills (Ornoy et al., 2001); others found no cognitive delay at 6 to 13 years of age (deCubas and Field, 1993). Prenatal opiate exposure has frequently been associated with behavioral problems in childhood. One small study indicated that opiate-exposed children were more likely to have ADHD or other disruptive behavior diagnoses at 10 years of age (Hans, 1989).

In summary, studies of prenatal opiate exposure and infants' early cognitive development have yielded mixed results, but there seems to be a pattern linking the exposure to behavioral problems, including increases in ADHD and other disruptive behaviors.

Treatment Recommendations

Since the late 1970s, it has been widely recognized that pregnant women addicted to heroin benefit from opioid agonist therapy with methadone. By stabilizing opiate withdrawal symptoms, such treatment reduces the use of illegal heroin and increases attendance in prenatal care, healthy diet, and other positive maternal health behaviors (SAMHSA, 2005; 2006). Methadone maintenance therapy stabilizes a mother's opiate dose at a low level and reduces physiological withdrawal effects for the fetus. Heroin-addicted women who receive such therapy have infants with higher birth weights and lower rates of intrauterine growth retardation than those who are untreated. However, newborns whose mothers are maintained on methadone have a high incidence of NAS (SAMHSA, 2005; 2006). It is recommended that NAS be treated by giving a very low dose of opiate to the infant and then slowly tapering the dose (O'Grady, Hopewell, and White, 2009).

A prenatally drug-exposed infant's high-pitched cry may be due to a CNS abnormality that results from increased cranial pressure.

Studies that have evaluated whether treating expectant mothers with methadone maintenance affects child development are difficult to compare because they have used different methodologies and measurements (Jones et al., 2008). A current NIDA-funded study called MOTHER is designed to address questions left open because of these methodological concerns. MOTHER will also seek to clarify whether methadone or buprenorphine is the superior pharmacotherapy for opioid-dependent pregnant women and their children (Jones et al., 2008). Buprenorphine, an alternative to methadone in opioid agonist therapy, is currently not FDA-approved for use during pregnancy because of a lack of adequate well-controlled studies with pregnant women.

Critical to the success of opioid agonist therapy is the use of supportive services, including behavioral therapy and assistance with domestic violence issues, employment, housing, food, and educational needs. Psychological interventions are indicated to address disruptions in the mother-child relationship, guilt, depression, low self-esteem and victimization, and past trauma.

INTERVENTIONS FOR DRUG-EXPOSED CHILDREN

Most research on intervention services for drug-exposed infants has evaluated intensive home-based services provided to substance-abusing mothers by community nurses. These services are designed to educate and support mothers to improve the home environment, parenting skills, and child development. Strengthen-

ing maternal functioning has been the goal, because most studies of prenatal drug exposure have found that mothers' level of psychological distress consistently predicts prenatally exposed children's cognitive and behavioral outcomes (Minnes et al., 2010). Few studies have examined interventions that are drug-specific or directed to the infants themselves (Barnard and McKeganey, 2004).

Several studies demonstrate that early intervention services improve the home environment and mothers' parenting behavior. In one, nurses visited substance-abusing mothers and their infants every other week during the first 18 months of the child's life (Black et al., 1994). The nurses guided the women through a curriculum about normal child development, child care, and safety; modeled parent-child activities that promote child development; addressed mothers' concerns, such as relationship problems, affordable housing, and financial issues; and provided information about community resources and advocacy. The mothers who received the intervention were marginally more likely than a control group to be drug-free, keep primary health care appointments, be more emotionally responsive, provide a stimulating home environment, and score lower on a measure of child-abuse potential at the end of the 18-month study period.

Studies demonstrate that early intervention services improve the home environment and mothers' parenting behavior.

As part of the Seattle Birth to 3 Program, paraprofessional advocates visited substance-abusing women and their children weekly for the first 6 weeks after birth, then at least biweekly, depending on need, for 3 years. The advocates worked to establish trusting relationships with the mothers and motivate them to identify and work toward personal goals. They made and monitored followup on community referrals for drug treatment and other services for mother and child, and offered guidance and supervision to ensure that the child was in a safe environment and received appropriate care. At 36 months postpartum, 69 percent of the children receiving the intervention service were in what the research team considered to be an appropriate custody situation relative to their mother's current use of alcohol/drugs (i.e., with mother in recovery for at least 6 months or not with mother unable to maintain abstinence), compared with 29 percent of children in a control group (Ernst et al., 1999).

Butz and colleagues (2001) found that mothers participating in another intensive home nurse intervention program reported a trend toward less parenting stress.

Child Development

Findings regarding the impact of intervention services on child development have been mixed, perhaps because the services usually consist of family case management rather than interventions directed specifically toward the children. Of note, even when children appeared to benefit from an intervention, exposed children in the comparison group who did not receive it usually performed within normal limits on developmental assessments.

Kilbride and colleagues (2000) followed a group of cocaine-exposed infants and their mothers for 3 years, providing intensive family case management, enriched nursery care, and regular evaluations, and found no differences in mean cognitive, psychomotor, or language quotients compared with a group of exposed infants who received only routine followup and a group of unexposed infants. However, at 36 months, verbal scores of the cocaine-exposed infants who received case management were significantly higher than those of the routinely managed children, suggesting that "early intervention may have offset detrimental effects of the crack cocaine environment on verbal development."

In another study, infants who participated in an intensive home intervention program had significantly higher mental and psychomotor development scores compared with control infants (Schuler, Nair, and Kettinger, 2003).

In contrast, Black and colleagues (1994) reported that children receiving home-based intervention services had somewhat higher cognitive scores relative to controls at 6 months of age, but not at 12 and 18 months. Ernst and colleagues (1999) found that the cognitive development of children of substance-abusing mothers who received in-home advocacy services was equivalent at 36 months to that of children whose mothers did not receive the services.

Impact of Child Placement

Drug-exposed infants are often placed outside of the mother's home in kinship, foster, or adoptive care to prevent child abuse or neglect. Researchers have investigated the possibility that such placement might avoid the ill effects of an unstable environment on children's development, but studies show inconsistent results. For example:

- Tyler and colleagues (1997) found that drug-exposed infants who remained with their biological mothers demonstrated better cognitive development at 6 months of age compared with infants placed in the

care of other relatives. In another study by Frank and colleagues (2002), infants in kinship care scored lower on mental development than infants in the care of their biological mothers or in foster care at 6 and 24 months of age (Frank et al., 2002). In the latter study, children in foster care lagged behind children in their biological mothers' care at 6 months, but surpassed them at 24 months.

- Brown and colleagues (2004) observed more positive social-emotional development in 24-month-old cocaine-exposed children placed in nonparental care compared with those in parental care. Within the nonparental care group, those with nonkin caregivers scored higher in mental development, communicative gestures, and positive interactions during feeding than those in the care of relatives.
- Singer and colleagues (2004; 2008) consistently found that over time, cocaine-exposed children fared better in cognitive and language development when placed in non-kin foster care or adoptive homes than when raised in a relative's care or their birth mother's custody. These children experienced better home environments and had more educated, less depressed caregivers than children who remained with their mothers or with relatives (Lewis et al., 2004; Singer et al., 2004; 2008).
- Bada and colleagues (2008) found that instability in living arrangements, such as multiple moves, changes in caregivers, and prolonged involvement with child protection services, predicted negative behavioral outcomes during the first 3 years of life in a cohort of prenatally drug-exposed children. Total behavior problem scores on the Child Behavior Checklist increased 2.3 and 1.3 points, respectively, with each move per year and each year of child protective services involvement.

A Comprehensive Approach

Bandstra and colleagues (2010) have proposed a prevention and intervention model for substance-abusing mothers and their infants that addresses the complex, multiple risk factors associated with maternal drug use. The model proposes the delivery of medical and behavioral health and parenting services to the mother, health and development services to the child, and care coordination and family support to reduce the barriers to accessing services.

Intervention services for this population need to extend beyond infancy and the toddler years, since problems in cognitive, language, and behavioral functioning may persist throughout childhood. Developmental assessment and intervention should continue during the preschool and school years, when children may benefit from enriched educational programs and screening for special education services. Problems can compound when cognitive demands increase during the early school years. Other critical transitional periods occur in the first, fourth, and sixth or seventh grades, when subtle learning or behavior problems may become more evident and lead to functional impairments (Weitzman et al., 2002). Externalizing behavior problems and inattention in particular should not be ignored, as they are known to interfere with school achievement, school completion, and the development of healthy relationships.

Intervention services for substance-abusing mothers and their children need to extend beyond infancy and the toddler years.

Parents should be trained in the skills necessary to address behavior problems throughout childhood to prevent more serious disruptive and risky behaviors in adolescence and young adulthood. Moreover, birth mothers are likely to need ongoing intervention to maintain sobriety and to address mental health symptoms and parenting. As the effects of prenatal drug exposure and their relationships with environmental factors become more clearly understood, more specific early intervention programs for drug-exposed children targeting areas of development that are known to be at risk should be developed and rigorously evaluated (Table 4).

TABLE 4. Suggested Interventions Following Prenatal Drug Exposure

MATERNAL/CAREGIVER	CHILD
Intensive home-based services • Mental health screening • Parenting skills training • Support for substance abstinence	Specific individual therapy • Speech and language • Occupational • Behavioral
Mental health treatment	Early intervention/enrichment
Substance use treatment	Ongoing cognitive and behavioral assessment

CONCLUSION

Substance use during pregnancy can affect the developing fetus both directly, through passage of the drug through the placenta, and indirectly, through poor maternal health habits and environmental conditions. Numerous well-designed studies indicate that specific learning and behavior problems may result from prenatal exposure to tobacco and illicit drugs in combination with negative environmental conditions postpartum. Longitudinal studies indicate that some of the negative effects of

cocaine, tobacco, and marijuana exposure persist into later childhood and adolescence. Although some early CNS symptoms remit over the first year of life, they may be precursors to later developmental outcomes.

Developmental outcomes of prenatally drug-exposed children are determined by factors including the specific drug or drugs, dosage, and timing of prenatal exposure as well as pre- and postnatal environmental conditions, including continued caregiver drug use, psychological symptoms, quality of the home environment, postnatal exposures to lead and other toxins, caregiver stability, and type of caregiver. The effects of negative environmental conditions associated with low SES may sometimes overshadow the effects of prenatal drug exposure.

Pregnancy is a unique time when a woman may seek treatment out of concern for the health and well-being of her child.

Pregnancy is a unique time when a woman may seek treatment out of concern for the health and well-being of her child. To prevent postpartum substance abuse relapse, interventions should focus on cessation rather than temporary abstinence. The ongoing consequences of parental substance abuse on child growth and development should be emphasized, and followup should continue into the postpartum period (Muhuri and Gfroerer, 2009). Interventions that reduce substance abuse in the general population are now being investigated in pregnant substance abusers with promising results. The use of CM appears to increase treatment retention and prolong abstinence in pregnant women with cocaine, opiate, and nicotine dependence. Some medications used to treat addiction, such as methadone, can be relatively safe for pregnant women and their babies. However, the safety and effectiveness of NRT for pregnant smokers requires further investigation.

Additional research is needed on the development of specific interventions for drug-exposed infants and children. Each child must be individually assessed for his or her cumulative risk factors, domain of developmental difficulty, and the quality of the caregiving environment. Developmental outcomes may be optimized by interventions that occur early in life, are tailored for specific problem areas, and target caregivers' level of stress, mental health functioning, continued substance abuse, and parenting interactions.

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Response: How to Use a Window of Opportunity

Margaret S. Chisolm, Ph.D., and Victoria H. Coleman-Cowger, Ph.D.

Margaret Chisolm: It's accepted that pregnancy is a window of opportunity when women are highly motivated to make behavioral changes. There's a higher spontaneous quit rate among pregnant smokers than in the general population of smokers.

Most of the women in our program are extremely motivated for treatment. In part, primarily, they are concerned about the fetus. Those who are abusing illegal substances also know that they might lose custody of their child if they continue to do so during their pregnancy.

Victoria Coleman-Cowger: I understand why some States want to protect children from the lifestyles of drug-abusing parents. At the same time, the policy becomes a barrier to women getting treatment and receiving other needed services as well as to participating in research studies focused on this population. Women are less likely to disclose drug abuse if they know it means that their children might be taken away.

Chisolm: Most of the women we treat at the Johns Hopkins Center for Addiction and Pregnancy use illicit opioids. When I arrived, I was struck by how many of them smoked. That raised questions for me. What was the relative risk of smoking versus the other dependencies we were treating? Did smoking make it more difficult for them to stop using other substances? Conversely, would smoking cessation jeopardize their recovery?

Coleman-Cowger: As a Research Scientist at Chestnut Health Systems, I recognize how difficult it is to study these issues. For longitudinal studies, researchers need to recruit large numbers of mothers and children so that they can control for all the potential influences on outcomes. Then they need to follow the participants for years or decades to see what outcomes occur.

Both requirements are harder when you're talking about illegal substances and lives that may be chaotic. We know more about prenatal tobacco and alcohol exposure than about other prenatal exposures in part because women don't face legal consequences if they acknowledge that they smoke or drink.

Chisolm: It's because of those difficulties that I'm not yet convinced that prenatal exposures cause all the behavioral problems with which studies associate them. For example, a high percentage of women in our program had ADHD diagnosed when they were children themselves. To me, that suggests that genes, rather than drugs, may be at least part of the reason why their children tend to have behavioral problems. The challenge of establishing causal relationships with prenatal exposures increases as children get older and accumulate more environmental exposures and begin to express genetic vulnerabilities that might influence their behavior.

So we tell women that it's better not to smoke or use other drugs during pregnancy. We know that avoiding substances will give them better birth outcomes, because the evidence is conclusive that drug exposures cause pregnancy complications and neonatal morbidity and mortality. But we don't say that smoking is going to increase their children's risk of ADHD or anything like that. I think the evidence is less compelling for those more distal outcomes.

Treatment motivation and interventions

Coleman-Cowger: Contingency management (CM) has been shown to very effectively reduce drug use. I'm planning to use it with pregnant and postpartum smokers in a pilot study of postpartum continuing care, giving Babies R Us gift cards in escalating amounts for each successive negative urine test.

Chisolm: There is a lot of potential with CM to improve outcomes and to save health costs. CM economics probably work best for comprehensive health systems. Although the CM vouchers cost their substance abuse treatment components, their other components save by having to treat fewer or less serious health consequences of abuse. A stand-alone substance abuse program, however, might lay out for the vouchers but not get any savings down the line.

Coleman-Cowger: I don't believe there have been many studies of CM with long-term followup. I've seen studies in which some effects have been sustained after

3 months, but none looking at outcomes for longer periods of time.

Chisolm: I don't consider myself an expert in CM, but the evidence suggests that as soon as you stop the reinforcement, the behavior reverts to what it was before. For example, a study here at Johns Hopkins gave contingency rewards to promote abstinence among postpartum women who had been heavy users of cocaine during their pregnancies. The women maintained close to 80 percent abstinence throughout the 18 months that the rewards were being given, but the rate fell to around 20 percent within a few months after the rewards were stopped.

We have just finished a study in which we measured drug-dependent mothers' carbon monoxide levels on breathalyzer tests. We are looking to see whether giving these mothers feedback on these results might be a powerful reinforcer for reducing smoking, as it is in non-drug-dependent pregnant women. If so, that would be a good low-cost approach to promote abstinence during pregnancy in this population, too.

Coleman-Cowger: Dr. Minnes' endorsement of nicotine replacement therapy (NRT) for pregnant women who are heavy smokers is in line with the recommendation of the American College of Obstetricians and Gynecologists that pharmacological agents be considered when a pregnant woman is otherwise unable to quit smoking. The efficacy studies that have been completed so far haven't proved that NRT makes a difference in cessation rates for pregnant women. However, the results have been mixed and more favorable with respect to reducing use.

Chisolm: That's right. One of the studies that was halted because cessation rates didn't improve actually showed reductions in the number of cigarettes per day. Neonatal outcomes improved as well.

NRT helps nonpregnant women quit smoking. Pregnant women might require higher doses than were used in these trials, since they metabolize the drug twice as fast. However, nobody really wants to give pregnant women higher doses of nicotine since it's a known neuroteratogen.

As Dr. Minnes notes, bupropion is a category C drug, meaning that it has produced some evidence of fetal harm in animal studies and may pose a risk in humans. However, I've talked to many obstetricians and providers who use bupropion off-label as an alternative to NRT for their pregnant patients. This medication has proven efficacy for smoking cessation and as an antidepressant, and perhaps could be the medication of choice for depressed pregnant women who smoke. Certainly, more investigation is warranted.

Coleman-Cowger: Postpartum continuing care is important. Having a newborn is a very high stress time and one of the biggest times of risk for use of any substance. Without continuing to support women as intensively as they were supported during pregnancy, interventions would be very unlikely to have a sustained effect.

Some 80 percent of women who quit smoking during pregnancy relapse within the first year after they've given birth. That's unfortunate for both the woman and her infant, because nicotine is transmitted indirectly at very high rates in mothers' milk, and directly through second-hand smoke, producing adverse outcomes.

Chisolm: Substance-using pregnant women have a high incidence of comorbid mood and anxiety disorders. Up to 50 percent of the women in our program have a DSM-diagnosable mood and/or anxiety disorder. Unless they get intensive treatment for these disorders postpartum, they are ripe for relapse.

Coleman-Cowger: Partner interventions are an important component of care with a substance-using population, particularly with smokers, due to the likelihood that the partner may also be engaging in substance use or other enabling behaviors that could trigger relapse. The lack of focus on partners in the existing literature might be one reason why the interventions Dr. Minnes reports weren't more efficacious.

Chisolm: Pregnant women's smoking is still not usually a targeted problem in drug abuse treatment, even though the links to significant adverse consequences for the mother and child are very clear. It's not unusual for staff to be less interested in addressing tobacco use among their patients because a number of staff may be in recovery and smoke themselves, or are sympathetic to smoking. This is a situation in which we really need to address staff attitudes.

The Good Behavior Game and the Future of Prevention and Treatment

The Good Behavior Game (GBG), a universal classroom behavior management method, was tested in first- and second-grade classrooms in Baltimore beginning in the 1985–1986 school year. Followup at ages 19–21 found significantly lower rates of drug and alcohol use disorders, regular smoking, antisocial personality disorder, delinquency and incarceration for violent crimes, suicide ideation, and use of school-based services among students who had played the GBG. Several replications with shorter followup periods have provided similar early results. We discuss the role of the GBG and possibly other universal prevention programs in the design of more effective systems for promoting children's development and problem prevention and treatment services.

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Drug, alcohol, and tobacco abuse and dependence disorders; antisocial personality disorder; violence; high-risk sexual behavior; and other disorders and problem behaviors impose huge personal, social, and economic costs on individuals, families, schools, and communities. The burden is borne also by institutions that treat or attempt to rehabilitate such problem behaviors and disorders.

Disruptive and aggressive behavior in classrooms as early as the first grade has repeatedly been identified as a risk factor for this spectrum of problems later in life (Kellam et al., 2008). The Good Behavior Game (GBG) is a classroom-wide, teacher-implemented intervention that aims to improve classroom behavior and introduce young children to the role of being a student and a member of the classroom community.

In 1985, in close partnership with the Baltimore City Public School System (BCPSS), we initiated a large-scale, developmental field trial of the GBG that was epidemiologically based and randomized. The trial was implemented in 41 first- and second-grade classrooms within 19 elementary schools with two consecutive cohorts of first graders. The results in young adulthood were reported in a supplemental issue of *Drug and Alcohol Dependence* in June 2008. Here we summarize the theoretical basis, design, and results of the trial, which together lead to three conclusions:

- Aggressive and disruptive behaviors in childhood play a causal role in a spectrum of social, behavioral, and psychiatric problems;
- Introducing the GBG in first- and second-grade classrooms reduces the risk of

A classroom playing the Good Behavior Game in Denver.

some of these problems later in the life course;

- The effectiveness of the GBG supports a role for universal prevention interventions in a redesigned system for child development and problem prevention and treatment.

We also briefly review the findings to date of ongoing replication trials and address the implications of this work for researchers, practitioners, advocates, and policymakers. We believe that the underlying theory, data, and analyses support the development of a newly designed human development services system that integrates prevention and treatment and is closely interrelated with schools and classrooms.

The GBG was developed to help teachers manage classrooms without having to respond on an individual basis each time a student disrupted class.

THE GOOD BEHAVIOR GAME

The GBG was developed to help teachers manage classrooms without having to respond on an individual basis each time a student disrupted class. As designed by University of Kansas researchers Harriet Barrish, Muriel Saunders, and Montrose Wolf, the GBG increases a teacher's precision and consistency in instructing elementary school students in appropriate classroom behavior. In documenting the effectiveness of the approach, an early observer noted reduced "talking out of turn" and "out of seat" behavior during times when the class played the GBG (Barrish, Saunders, and Wolf, 1969).

Our first-generation, large-scale randomized field trials of the GBG in Baltimore began in the 1985–1986 school year. By that time, the positive results reported by Barrish and colleagues had been replicated in more than 20 small observational, nonrandomized studies that showed short-term improvement in student classroom behavior.

How the Game Was Played

Teachers used a manual to ensure precision in the implementation of the GBG and to support fidelity over time and replicability in other trial sites. Early in the first-grade year, teachers displayed a large poster that listed the rules of proper student behavior—for example, sitting still, talking in turn, and paying attention. Toward the end of the first quarter of the school year, when classroom membership had stabilized, teachers divided their students into three teams that were balanced as to gender, aggressive and disruptive behavior, and shy or isolated behavior.

Initially, the GBG was played for designated periods of 10 minutes, three times a week. Each team was rewarded when all of its members behaved well during that interval, but not when the team had more than four rule infractions. In this way, the team's rewards were contingent on each member behaving well.

As the year continued, the GBG was played for increasing lengths of time and when students were working individually. In this way, the GBG facilitated learning without competing for instructional time. As the school year progressed, the rewards changed from tangible and immediate (e.g., stickers, erasers) to more abstract and deferred (e.g., gold stars, more time to do enjoyable activities).

Why the Teacher and Classroom?

The GBG treats the classroom as a community. The teacher is central to the GBG, because he or she sets the rules for becoming a successful student and member of the community and also determines whether each child succeeds or fails. The GBG improves the precision with which the teacher conveys and the child receives these rules, and by doing so improves the teacher-child interaction and the child's chances for success. In addition, in GBG trials, the better behaved children were observed to influence and socially integrate the children who behaved less appropriately.

Why the First Grade?

Two considerations recommend the first grade as a setting for preventive interventions:

- Beginning first grade is a major transition for both the child and his or her family;
- First grade is generally the first place where all children—that is, those at all levels of risk of school and behavior problems—can be found. All States in the United States require parents to register their children for first grade with the school district; in many States, this is the first required contact between children and any official system subsequent to birth registration.

The first-grade classroom is well-suited for interventions, such as the GBG, that focus on inculcating the role of students in classrooms. First grade is the first setting outside the home where many children learn the social and behavioral skills they will need to succeed in school. Although some children attend Head Start, kindergarten, or other preschool programs, the length and content of these programs vary.

The first grade is also a particularly appropriate setting in which to provide teachers with tools, as the GBG does, for effective classroom behavioral management. Early in this school year, teachers must organize the classroom, manage children's behavior, and teach rules, but these skills are not intuitive. For example, children in our GBG trial were assigned to first-grade classrooms in a manner that ensured that the classrooms were equivalent with regard to behavior at the start of the school year. However, by the end of the first quarter, when we examined the behavior in the classrooms that had not participated in the GBG, we found that about half were doing relatively well in regard to aggressive and disruptive behavior, while the other half appeared markedly chaotic (Kellam et al., 1998a) (see box).

THE THEORY GUIDING THE TRIAL

Prevention trials yield the most insight when they are based on a research-backed theory about causes. For the past 4 decades, life course/social field theory has been a foundation for our research on early developmental risk factors and associated adult problem outcomes and their prevention (Kellam et al., 1976). The theory has pointed to what we needed to measure and what interventions might be effective.

Life course/social field theory provides a dual-faceted view of mental health. In this perspective, adaptation has a social dimension and an individual, psychological dimension.

The social dimension focuses on how an individual is viewed by society, both overall and within specific social contexts. At each stage of life, there are a few main social fields where individuals face social task demands.

Social task demands in the classroom include an expectation that children will pay attention, obey rules, learn, and socialize appropriately with their peers and teachers.

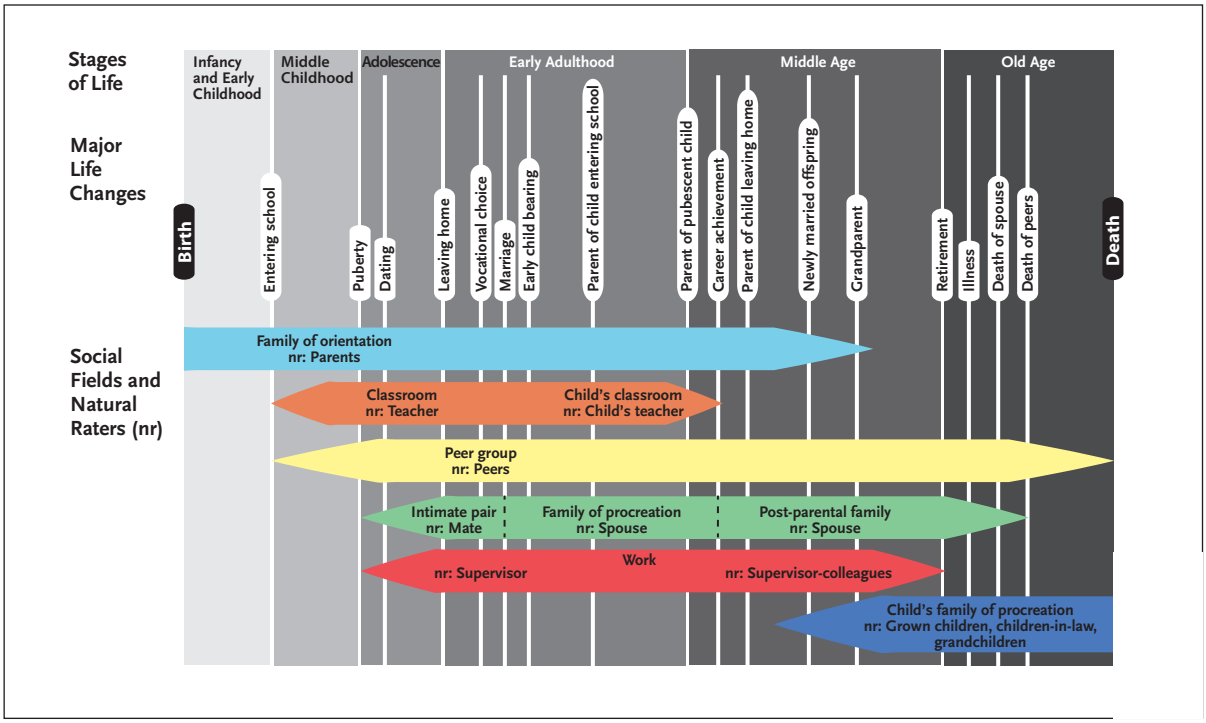
TOOLS THAT TEACHERS NEED

School teachers very often report having received little training in tested methods of classroom behavior management. Pre-service teacher training does not emphasize this area, nor does the National Council for Accreditation of Teacher Education (NCATE) require proof of proficiency in this area for schools to be accredited (NCATE, 2008).

Teachers—especially new (National Commission on Teaching and America's Future, 1997) and elementary school teachers (Walter, Gouze, and Lim, 2006)—rate such training as a pressing need. A lack of effective tools to socialize children into the role of student hampers their instruction. The challenge posed by aggressive and disruptive behavior overwhelms many teachers, leading to burnout and resignation from the profession.

The 1985 Baltimore GBG trial provided further evidence that the quality of classroom behavioral management in early grades has far-reaching consequences. Analysis of the data on children who attended standard program (i.e., non-GBG) first-grade classrooms showed a marked influence on the risk of severe aggressive behavior by middle school. Among children in well-managed classrooms, those rated in the top 25 percent for aggressive and disruptive behaviors were up to 2.7 times as likely as the average child to exhibit severe aggressive behavior by middle school. In contrast, in poorly managed classrooms, the risk differential was up to 59 times.

FIGURE 1. Life Course/Social Field Concept



For children, the classroom is such a field, where social task demands include an expectation that they will pay attention, obey rules, learn, and socialize appropriately with their peers and teachers. In each social field, the person's ability to meet task demands is assessed or rated by individuals we call natural raters. Teachers and student peers are natural raters in classrooms.

Sometimes this rating process is formal, as in the case of teachers giving grades. At other times, it is informal, as when peers respond to a student. Even when ratings are less formal, however, outcomes such as rejection from the peer group can be very powerful. We call this process of demand and response "social adaptation" and the resulting outcome, "social adaptational status."

An individual may be rated as maladapted for reasons that originate with himself or herself, with the rater, or in the process of demand and response between the two. A first-grader, for example, may behave inappropriately due to a developmental lag in ability to sit still and attend, because the teacher lacks effective methods to socialize students to behave appropriately, or because previous persistent bad behavior has created tension between the teacher and the student.

According to life course/social field theory, improving the way teachers socialize children in the classrooms will result in improved social adaptation of the children in the classroom social field. The theory also predicts that this early improved social adaptation will lead to better adaptation to other social fields over the life course (Figure 1). It is this hypothesis that supports using an intervention like the GBG in first and second grade.

The second dimension in life course/social field theory is the individual's internal condition, or psychological well-being. Depression, anxiety, and thought disorder are examples of poor psychological well-being. Psychological well-being and social adaptational status can reciprocally influence each other over the course of development. For example, receiving poor grades may make a child feel depressed, and depression may make a child more likely to get poor grades. Although the GBG's effects on psychological well-being are beyond the scope of this paper, we have reported on its impact on suicidal thoughts and attempts, and we continue to study this dimension (Kellam et al., 2008; Wilcox et al., 2008).

RESEARCH DESIGN

The trial in the BCPSS tested two classroom interventions. The GBG focused on aggressive and disruptive behavior and is the subject of this paper. An enhanced reading intervention that aimed to improve classroom performance was also tested, but is only mentioned here to provide a complete picture of the study design.

TABLE 1. Young Adult Outcomes in GBG and Standard Classrooms

OUTCOMES	GROUP	GBG CLASSROOM	STANDARD CLASSROOM
Drug abuse and dependence disorders	All males	19 percent	38 percent
	Highly aggressive males	29 percent	83 percent
Regular smoking	All males	6 percent	19 percent
	Highly aggressive males	0 percent	40 percent
Alcohol abuse and dependence disorders	All males and females	13 percent	20 percent
Antisocial personality disorder (ASPD)	Highly aggressive males	40 percent	100 percent
Violent and criminal behavior (and ASPD)	Highly agressive males	34 percent	50 percent
Service use for problems with behavior, emotions, drugs, or alcohol	All males	25 percent	42 percent
Suicidal thoughts	All females	9 percent	19 percent
	All males	11 percent	24 percent

Altogether, 41 classes in 19 schools in five sociodemographically distinct areas of Baltimore participated in the trial. All the students were of low to lower middle socioeconomic status, and 70 percent were African-Americans.

Assignment of Intervention Conditions

Within each urban area, three or four schools were matched and randomly assigned to deliver the GBG, the enhanced reading curriculum program, or no intervention. All students in all schools received the standard first-grade educational program.

Within each intervention school, the principal sequentially assigned students to a first-grade classroom by using an alphabetized list. The research staff then checked and in a few cases adjusted the class rosters with the principal to provide an equivalent distribution of children across classrooms with respect to gender, kindergarten records of behavior, socioeconomic status, and other criteria. Then, within the GBG intervention schools, each first-grade classroom with its teacher was randomly assigned to be a GBG classroom or a standard-program classroom.

This design created three types of control classrooms to compare with the GBG classrooms: (1) standard program classrooms within the schools where the GBG was tested; (2) standard program classrooms within the schools where the enhanced reading curriculum program was tested; and (3) all classrooms within the schools where no intervention was tested. These three controls allowed for extensive analyses that strengthened our confidence in the results. For example, when comparing intervention and standard program classrooms within the GBG schools, we eliminated school and community variation as potential explanations for any differences. Our comparisons of GBG classrooms and standard program classrooms in other schools allowed us to rule out intervention "leakage" into control classrooms within the GBG schools. Using the three kinds of controls, we were also able to collect more information about school- and individual-level variation and compare the consistency of the results across schools and urban areas.

The trial included two consecutive cohorts of children. The first cohort began first grade in 1985. The teachers who had been randomly assigned to deliver the GBG intervention received 40 hours of training in GBG implementation, followed by supportive mentoring and monitoring during the school year. When the students in

the GBG classrooms advanced to second grade the next fall, their new teachers received the same training and support as their first-grade teachers and implemented the intervention again.

Also in the fall of 1986, the second cohort began first grade. The same first-grade teachers who had implemented the GBG in 1985 did so again with their new students. They received little retraining, because we assumed that they would continue implementing the GBG with fidelity.

The resources invested in an intervention can have an effect on outcomes independent of the intervention. To minimize differences due to such effects, we provided all teachers in standard-program classrooms with activities comparable in extent to GBG training and support. The focus of these activities—for example, meetings of teachers from different schools and trips with the children—was not on classroom behavior management.

Teacher ratings have considerable predictive power concerning children's outcomes well into adulthood.

Behavior Measurement

Our primary outcome measures were teachers' ratings of children's social adaptation. A teacher's judgment about how a student is responding to classroom social demands is vitally important, because the teacher strongly influences whether the child continues to the next grade. The teacher is not only a predictor but also a participant in the child's successes or failures. Teacher ratings have considerable predictive power regarding children's outcomes well into adulthood.

The teachers rated the children on the Teacher Observation of Classroom Adaptation–Revised (TOCA–R) scale (Kellam et al., 1976; Werthamer-Larsson, Kellam, and Wheeler, 1991). Ratings were obtained in the fall and spring of grades 1 and 2 and thereafter in the spring of grades 3 through 7.

Each time, a trained interviewer established a relationship of trust with the teacher in a quiet room in the school and then recorded ratings of each child, taking care to spend equal time on each child. Aggressive and disruptive behaviors were specified as: breaks rules, breaks things, fights, harms others, harms property, lies, teases classmates, takes others' property, and yells at others. The teachers' data were validated with other measures, such as classroom peer ratings and observation by independent observers.

Collection of Young Adult Data

When students reached ages 19–21, they were contacted to participate in a 90-minute telephone interview about their social adaptational status within their original family, school, work, intimate relationships, marital family (if any), and peer social fields. They also were asked about any use of services for problems with behavior, emotions, or drugs or alcohol, and about their developmental, behavioral, psychological, and psychiatric status. The Composite International Diagnostic Interview–University of Michigan (CIDI–UM) was used to determine psychiatric diagnoses based on the *Diagnostic and Statistical Manual of Mental Disorders–IV* (DSM–IV) criteria (American Psychiatric Association, 1994; Kessler et al., 1994). Information was also obtained from school and juvenile court and adult incarceration records. A second interview at ages 20–23 was conducted in person to inquire about suicidal thoughts and attempts.

The interviewers did not know which participants had experienced the GBG. Of the students present in the fall of first grade in 1985, 75 percent were interviewed at the young adult followup by telephone or in person. No differences in rates of attrition were found between young adults who were in the GBG classrooms and those in the standard classrooms.

RESULTS

The GBG significantly reduced aggressive and disruptive behavior in primary school classrooms. In the first through sixth grades, students in GBG classrooms, especially the males, exhibited less aggressive and disruptive behavior than those in control classrooms (Dolan et al., 1993). By the spring of sixth grade, males in GBG classrooms who had initially been rated above median levels for aggressive and disruptive behavior had significantly reduced these behaviors (Kellam et al., 1994).

Among females, the levels of aggressive behavior were far lower than for males at the beginning of school and through seventh grade. The intervention did not appear to strongly influence such behavior among females (Kellam et al., 1994; 1998a; 1998b).

Outcomes in Young Adulthood

Male students who had played the GBG in first grade reported significantly fewer problem outcomes at ages 19–21 than their peers who received the standard program. The results were particularly striking for those who had higher levels of aggressive and disruptive behaviors in first grade (Table 1).

Female participants had much lower rates of aggressive and disruptive behaviors in first grade and lower rates

of problem outcomes at ages 19–21. The GBG had little or no statistically significant effect on female outcomes except for suicidal thoughts and, to some extent, alcohol abuse and dependence disorders.

The effectiveness of the GBG was clearest for the most illicit behaviors and disorders—for example, drug abuse and dependence disorders, antisocial personality disorder, and incarceration for violence.

Results for the second cohort, first-graders in 1986, were similar, but there was some reduction of impact. The GBG still appeared to reduce drug abuse and dependence disorders, but instead of the higher risk children benefitting most, the benefit was more general. No significant benefit was seen for alcohol abuse and dependence disorders, regular smoking, or suicidal thoughts or attempts.

RESULTS FROM OTHER GBG TRIALS

Large-scale population-based randomized field trials of the GBG have been completed in three locations and are under way in three others (Mackenzie, Lurye, and Kellam, 2008).

Baltimore, 1990s

A second trial in Baltimore in the early 1990s coupled the GBG with an enhanced curriculum and instruction program. The goal was to improve both behavior and achievement, possibly producing synergism and enhancing and expanding impact. By the end of the first and second grades, the combined intervention had significant positive effects on aggressive and disruptive behavior and achievement (Ialongo et al., 1999). By the end of sixth grade, significant reductions occurred in teacher-rated conduct problems, diagnoses of conduct disorder, school suspensions, use of mental health services, and smoking (Ialongo et al., 2001; Storr et al., 2002; Furr-Holden et al., 2004; Petras, Masyn, and Ialongo, in press).

The GBG significantly reduced aggressive and disruptive behavior in primary school classrooms.

Oregon

The GBG was replicated as a component of a population-based trial designed to target early antecedents of later problem outcomes through a multilevel preventive intervention in the first and fifth grades. The trial, called LIFT (Linking the Interests of Families and Teachers), significantly reduced student aggression during the

intervention period and physical aggression following the intervention (Reid et al., 1999; Stoolmiller, Eddy, and Reid, 2000). Followup analyses 3 years later showed reduced severity of attention deficit disorder behaviors in first-graders and, among fifth-graders, delayed time of first police arrest, association with misbehaving peers, and time to first patterned alcohol and marijuana use (Eddy et al., 2003; 2005; Reid and Eddy, 2002). Further followup of fifth-graders until the end of high school showed significantly reduced overall use of tobacco, alcohol, and illicit drugs (DeGarmo et al., 2009).

Netherlands

The GBG was implemented in the first and second grades in the Netherlands. The results showed that the intervention reduced attention deficit hyperactivity problems. Among the initially more disruptive students, a reduction in conduct problems was seen by the end of third grade (van Lier et al., 2004). By age 10, large reductions were documented in antisocial behavior, and these reductions were associated with lower levels of peer rejection and increased affiliation with nondeviant peers (van Lier, Vuijk, and Crijnen, 2005; Witvliet et al., 2009; van Lier et al., 2011). The GBG also reduced physical and relational victimization at age 10 and major depressive disorder, generalized anxiety disorder, and panic disorder/agoraphobia by age 13 (Vuijk et al., 2007). Further analysis revealed that these reductions in depression and anxiety were mediated by the reductions in relational victimization for girls and physical victimization for boys (Vuijk et al., 2007). Use of tobacco, but not alcohol, between ages 10 and 13 was also reduced among children in GBG classrooms (van Lier, Huizink, and Crijnen, 2009). Later replications of the GBG implemented in the Netherlands showed similar benefits.

Maladapting to the classroom social task demands as early as first grade markedly increases the risk of later serious problems.

Belgium

In an epidemiologically based trial of the GBG in Belgium, Leflot and colleagues reported significant reductions in aggressive and disruptive behavior, increases in on-task behavior, decreases in talking-out behavior, and decreases in the development of oppositional behavior. These results were mediated by decreases in negative teacher remarks (Leflot et al., 2010).

LESSONS LEARNED

The main lesson learned from the GBG trials is that a classroom behavior management intervention directed at aggressive and disruptive behavior in first and second grade can improve children's long-term outcomes. The results of these trials show that such behaviors are malleable to effective universal methods applied with fidelity and consistency.

The improved young adult outcomes of male children who played the GBG point strongly to the conclusion that first-grade classrooms are extremely important to children's development. As many previous studies have reported, maladapting to the classroom social task demands as early as first grade markedly increases the risk of later serious problems. For example, Ensminger and Slusarcick (1992) reported that males' first-grade aggressive behavior coupled with poor academic achievement predicted future school dropout, drug abuse, and criminal behavior. The effect size achieved by the GBG is not surprising when we consider that a child's success or failure in learning to read in the first grade makes a substantial difference to his or her future success in school and beyond.

The impact of the GBG among highly aggressive and disruptive male first-graders—the group most at risk for antisocial and criminal outcomes—adds dramatically to our understanding of such children. The results are consistent with the inference that these behaviors play an etiological role in the development of substance use, antisocial and violent criminal behavior, suicide, and other damaging outcomes.

The minimal impact of the GBG among females calls loudly for further study. Girls' aggressive and disruptive behavior does not appear to have the same importance as boys': It is less prevalent, is less enduring from early to later schooling, and appears less salient for females' long-term development. There is an urgent need for developmental epidemiological studies to understand females' developmental pathways and provide a basis for designing interventions for them.

The Need for Partnerships

Prevention research and programming can succeed only when they are accepted by the community's cultural, social, and political structure (Kellam, 2000). The GBG trials have been possible because their aims have accorded with the mission of the communities in which they were conducted. For example, the BCPSS was willing to commit its resources and expose its students to the research out of deep concern over the problem of socializing young children to be successful students. An equally critical condition for success was that the BCPSS and community exercised oversight over the adaptation of

the GBG for their schools and the design and implementation of the trial. Community oversight can necessitate intense working through of issues, but without it the chances are slim that a prevention program will be adopted, even if it proves effective in trials. In the GBG trial, for example, the families challenged the researchers to show that the randomized design was consistent with the researchers' commitment to carry out the study in accord with the community's values. Ultimately, after intensive discussions and trust building, the families came to see randomization as creating an "even playing field," where every child had the same odds of receiving the GBG or standard program. Moreover, everyone would benefit if the GBG performed as hoped and was accordingly adopted into the curriculum.

This model of partnership for research and later implementation represents the foundation of the next generation of public health, public education, and prevention and treatment research. Researchers will need to understand the mission and vision of local community and institutional leaders, such as ministers and block club leaders, school superintendents, and clinic and other service providers. To ensure that prevention research and programming are conducted and administered with fidelity and continuity over time, researchers will need to integrate "silos," bringing together political and agency leaders at the federal, regional, state, city/county, and local levels. Unfortunately, the formation of such partnerships is still not well-taught in graduate schools.

Networks for Replication

The GBG has now been tested in many pre-post and short-term studies and three large-scale population-based randomized field trials, and further trials are under way in Colorado; Houston, Texas; and Oxfordshire, England. To accelerate these and future replications, and to maximize the information learned from them, we are in the early stage of planning, with NIDA support, a GBG International Network of researchers and their policymaking and institutional partners.

The development of such networks is just beginning in the drug abuse field. However, they are essential for efficiently assessing the effectiveness of prevention interventions through replications on a progressively larger scale and in diverse contexts—to find out what works, for whom, and under what cultural and institutional conditions. Researchers, policymakers, and practitioners will benefit from sharing experiences related to theory, measures, analyses, and obstacles to moving interventions beyond effectiveness trials and into implementation and stages of going to scale. Networks can expedite implementation and expansion into practice by including policymakers and practitioners on the same teams as the researchers.

Integrating Replication and Implementation

Moving the GBG from observational studies to systematic population-based randomized field trials and their long-term outcomes and replication in other sites has taken more than 25 years. For a prevention model developed today, this would be an unacceptably long time. Better theory and new designs and statistical methods make possible more rapid advances from research into practice.

An important new strategy combines replication with expanding previously tested programs system-wide or moving them into new community sites. The first stage of moving a program into new sites or into practice is developing a partnership among community advocates, policymakers, service providers, and the research team that carried out the effectiveness trials. The second stage involves training a cadre of implementers to lead the training of additional implementers. As training proceeds, criteria and instruments used during the effectiveness trial can be streamlined and used to measure the effectiveness of the newly trained implementers. Such a strategy can include the designation of waves of trainees such that some would receive training while others awaited the next wave. Trainees could be randomized if their numbers reached levels that required wait-listing (Brown et al., 2006).

By creating representative stratified samples of schools within a new school district and randomly assigning the trial intervention and control conditions to schools at each stratum, researchers could test training and effectiveness at each stratum in the district. Moving on, the next tier of the stratified sample of schools could be covered in a successive randomized roll-out or "dynamic wait list" design (Brown et al., 2006; 2009). With such designs and methods, the next generation of research, policy, and programming for fostering human development holds great promise.

Now is the time to think developmentally and epidemiologically about how an improved health system fits into a broader more functional child development system.

TOWARD A NEW HUMAN SERVICES SYSTEM

The reform of our health system is at the forefront of our national political and social discourse. Now is the time to think developmentally and epidemiologically, particularly at the community level, about how an improved

health system fits into a broader, more functional child development system. On the basis of our experience with the GBG, we suggest that the potential for such a system depends on expanded school information systems and implementation of staged intervention systems.

The Role of School Information Systems

The GBG trial represents a step toward a long-overdue integration of education research and public health prevention research. Further steps in this direction will be greatly facilitated by expansion of school information systems. As we consider the role of school information systems and community and researcher partnerships, the report entitled *Community-Monitoring Systems: Tracking and Improving the Well-Being of America's Children and Adolescents* (Mrazek, Biglan, and Hawkins, 2004; NIDA, 2007) gives important background information.

The universal strategy is the front line of a system of services that optimizes human development as well as physical health.

Most school information systems primarily monitor academic progress and problems and disciplinary actions. An ideal system would also record each child's progress in emotional and behavioral development, including his or her special needs. The added parameters would inform educators, researchers, and clinicians concerning the child's early risk factors for outcomes such as those measured in the GBG trial as well as family needs and other data. They would support more salient planning for—and responses to—the needs of the individual child, the classroom, and the school.

The No Child Left Behind (NCLB) law presents a unique opportunity to specify both educational and public health needs at the level of demographic epidemiology. NCLB establishes a national, state, and local repository of information that can be analyzed at levels from the national to the community and school district. Depending on the parameters included in NCLB assessments, they can furnish the data for epidemiological studies that show the broad distribution of educational and health-related problems and conditions related to them. These then can be used to plan and implement multilevel community partnerships that include service providers, community advocates, and research teams for testing and implementing effective programs. Communities That Care is one example of a program moving in this direction (Hawkins et al., 2008a; 2008b).

Proper safeguards for confidentiality are possible, as they in fact already exist in a myriad of places where personal data are gathered, such as income taxes, medical records, and mail. Systems of restricted access are needed but should not block the integration of school and social services of other kinds, such as foster care placement, juvenile justice, and child welfare.

The Importance of Staged Interventions

The GBG is a universal intervention; it addresses the entire classroom population, not just those who are at higher risk. In public health, universal programs are usually the strategic first line of defense: Chlorine in drinking water, fluoride in toothpaste, and vaccines against influenza are examples.

Like most universal interventions, the GBG reduced some individuals' risk and averted some adverse outcomes, but not everyone's. In general, children who do not respond well to a universal intervention are candidates for selective prevention (based on persistent risk factors alone), indicated prevention (based on actual symptoms of incipient problems), or treatment.

A coordinated system of staged interventions, consisting of a tested universal intervention backed up by empirically proven group and individual interventions, meets the needs of individuals at all risk levels and stages of problem development. It yields efficiency and economy by differentiating lower risk individuals and higher risk responders from those who need more invasive and costly help. The GBG demonstrated another advantage of universal interventions: It does not single out, and thereby risk stigmatizing, children who manifest aggressive and disruptive behavior. Those who do not respond to universal programs can be reliably identified by their specific needs and enrolled in progressively more selective interventions.

The universal strategy is the front line of a system of services that optimizes human development as well as physical health and is central to the next-stage design of human development services we propose. The most logical place to start building this system is in schools and the agencies that are mandated to serve children with special needs. Pre- and perinatal parental interventions can be important prior prevention services. Once school starts and children become part of the information system, family prevention interventions, developed and tested largely as selective interventions, can be closely integrated as back-up to school-based universal interventions. Partnerships will have to be developed radiating out to community leaders and a broad range of agencies and institutions. The formation of the system and the system itself must be responsive to community values and aspirations, safeguard confidentiality, and ensure proper oversight by appropriate stakeholders.

SUMMARY

The GBG, a universal intervention to manage classroom behavior, reduces schoolchildren's aggressive and disruptive behavior and prevents drug abuse and dependence disorders, violent crime, and other adverse outcomes in young adulthood. Findings from completed and ongoing large-scale GBG trials support the hypothesis that aggressive and disruptive behavior as early as first and second grade plays an etiological role in these adverse outcomes. They also endorse the vision of a national, state, and local human services system, founded in schools, that integrates education and health research and employs a strategy of first-line universal and second-line selective and indicated prevention interventions, backed up by specific treatment programs. The initial work to get this system started has already been done.

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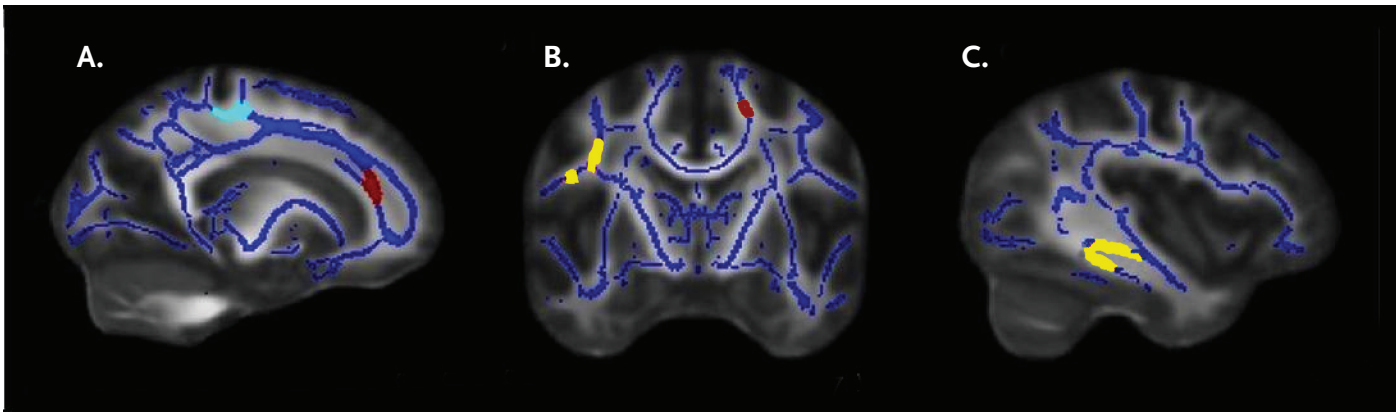
Graphic Evidence

MATURING BRAIN: HIS AND HERS



A 12-year-old brain possesses almost all of the neurons that it will ever have, but still has some maturing to do. Throughout the rest of adolescence and into adulthood, this organ will refine its white matter tracts. These bundles of axon fibers function as the wires in the circuits that connect the neurons in the brain's many regions. Their carrying capacity and speed determine the degree of coordination between the brain's diverse specialty areas, so are essential in shaping our capabilities and behavior.

NIDA-funded researcher Dr. Susan F. Tapert led a diffusion tensor imaging study of white matter in 29 boys and 29 girls, all of whom were healthy and aged 12 to 14. The above images are three different views of the participants' composited white matter tracts. Together, they provide a snapshot of normal white matter development in early adolescence. They point to some contrasting abilities and behaviors of boys and girls at this stage of life.

The girls' fibers showed evidence of being more mature than the boys' in corticospinal tracts (cyan in A and C), which promote motor and verbal skills. The boys' fibers appeared to be of higher caliber than the girls' in the frontal cortex forceps minor (red in A and B) and the longitudinal fasciculus (yellow in B and C), tracts that support rational decision-making and avoidance of risky choices. Tracts shown in navy did not differ significantly between the two genders.

Dr. Tapert and colleagues conducted the study at the University of California and the Veterans Medical Research Foundation in San Diego. Studies that elucidate normal brain maturation will help researchers identify white matter deviations that result from disorders such as substance abuse or lead to disorders such as depression and schizophrenia.

Source: Bava, S., et al., 2011. Sex differences in adolescent white matter architecture. *Brain Research* 1375(13):41–48.

Continuing Education Quiz for Counselors

Substance abuse counselors can earn two nationally certified continuing education (CE) hours by reading the indicated articles and completing the multiple-choice quiz below. This is an open-book exam. Complete the quiz by circling one of the multiple-choice answers. Be sure to answer all questions; unanswered questions will be scored as incorrect. You must score at least 70 percent to earn CE hours. Please note that we must receive your quiz by September 15, 2011.

The Case for Considering Quality of Life in Addiction Research and Clinical Practice—Page 44

1. **Quality of life is an important concern in substance use disorder (SUD) care because:**
   a. SUD is a chronic condition for most affected individuals;
   b. many of those who drop out of treatment programs cite unmet social service needs;
   c. reduction in drug use is always accompanied by concurrent improvements elsewhere;
   d. a and b.

2. **Patients with SUDs report quality of life:**
   a. equal to those of patients awaiting cardiac surgery;
   b. as low or lower than those of patients with lung disease;
   c. better than those with diabetes;
   d. all of the above.

3. **Reductions in substance use have the following effects on quality of life:**
   a. improved mental functioning;
   b. decreased social and emotional problems;
   c. improved physical abilities;
   d. all of the above.

Prenatal Tobacco, Marijuana, Stimulant, and Opiate Exposure: Outcomes and Practice Implications—Page 57

1. **Metabolites of drugs can affect a developing fetus in the following manner:**
   a. they penetrate the fetal blood-brain barrier;
   b. they enter the fetal bloodstream via the umbilical cord;
   c. a and b;
   d. they cannot harm the fetus, because the placenta protects it from harmful drug metabolites.

2. **Prenatal tobacco exposure is associated with:**
   a. higher birth weight;
   b. greater muscle tension in infants;
   c. increased head circumference;
   d. decreased likelihood of tobacco use in adolescence.

3. **Heroin-addicted pregnant women who receive methadone maintenance therapy, compared to those who do not receive that therapy:**
   a. attend more prenatal care sessions,;
   b. are more likely to use heroin after giving birth;
   c. have infants with higher birth weights;
   d. a and c.

The Good Behavior Game and the Future of Prevention and Treatment—Page 73

1. **The aim of the Good Behavior Game (GBG) is to:**
   a. help teachers write challenging curricula;
   b. show researchers how to work with children;
   c. improve classroom behavior and introduce young children to the role of being a student and a member of the classroom community;
   d. instruct parents on how to help their children with homework.

2. **Males who played the GBG in first grade:**
   a had significantly reduced levels of aggressive and disruptive behavior in sixth grade;
   b. had fewer drug use disorders as young adults;
   c. were less likely to be incarcerated for violence;
   d. all of the above.

3. **The GBG is a "universal intervention," which means:**
   a. all children in the classroom showed improvements in behavior;
   b. it addresses the entire classroom population, not just those who are at higher risk;
   c. all schools were made to participate;
   d. all of the children selected for the intervention were at high risk.

This issue of *Addiction Science & Clinical Practice* has the following objectives for drug abuse treatment providers and researchers:

- to consider how to integrate quality-of-life issues into addiction research and the treatment of people with substance use disorders;
- to review current knowledge of prenatal effects of drugs on the developing fetus and child and to evaluate treatment options for pregnant women who use drugs;
- to describe a method for classroom behavior management in the early grades, report how it reduces problems among the young adults who experienced it, and examine how these findings can be used to design other universal prevention programs.

Please rate the following on a 1 to 5 scale, by circling the appropriate number:

1. To what extent did these articles accomplish these learning objectives?

Completely		Adequately		Not at All
1	2	3	4	5

2. To what extent did you learn something useful to your profession?

Completely		Adequately		Not at All
1	2	3	4	5

3. Was the information well presented?

Completely		Adequately		Not at All
1	2	3	4	5

Please print legibly, copy page, and mail with your $25 payment to: AS&CP CE Quiz, RTI International, 6110 Executive Boulevard, Suite 902, Rockville, MD 20852. Quiz and payment must be received by September 15, 2011.

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Make checks payable to RTI International. In about 6 weeks you will receive notification of the results and, if you score 70 percent or higher, a certificate of completion. The National Institute on Drug Abuse, publisher of *Addiction Science & Clinical Practice,* is a NAADAC-approved provider of continuing education home study.

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