Director's Report to the National Advisory Council on Drug Abuse

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Director

National Institute on Drug Abuse

May 11, 2021

NIH National Institute on Drug Abuse
Advancing Addiction Science

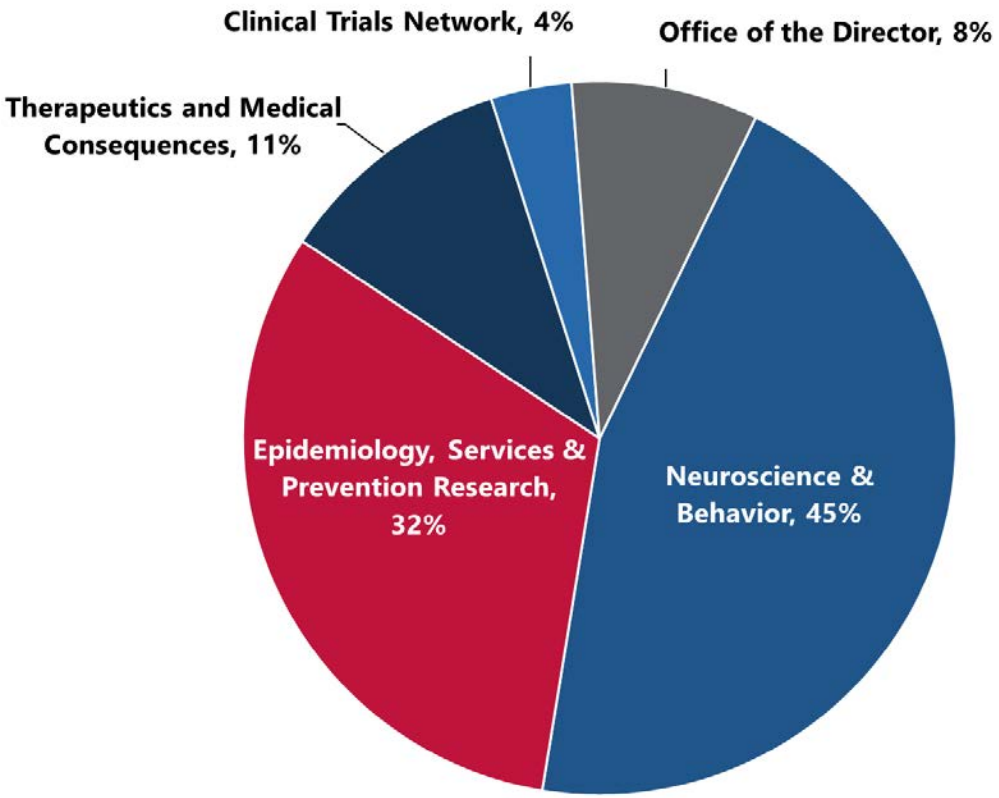
NIDA BUDGET

	FY 2020 ($k)	FY 2021 ($k)	FY 2022 PB ($k)
Base	$1,191,362	$1,210,014	TBD
HEAL	$266,321*	$270,295*	
Total	$1,457,683	$1,480,309	

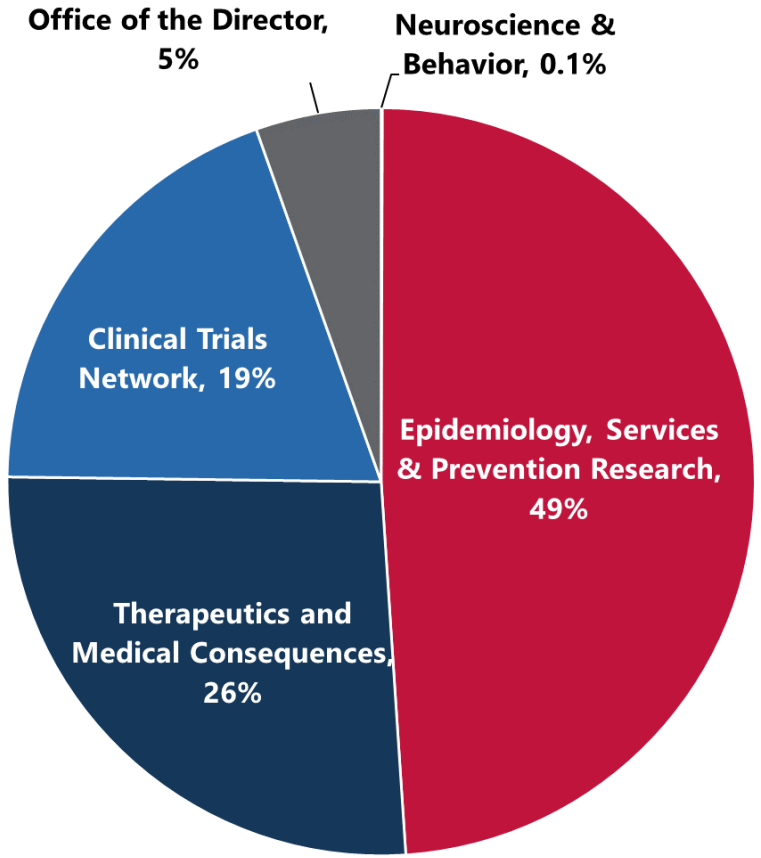
*NIH's total HEAL funding is split evenly between NIDA and NINDS

FY 20 Funding Overview

Non-HEAL Research



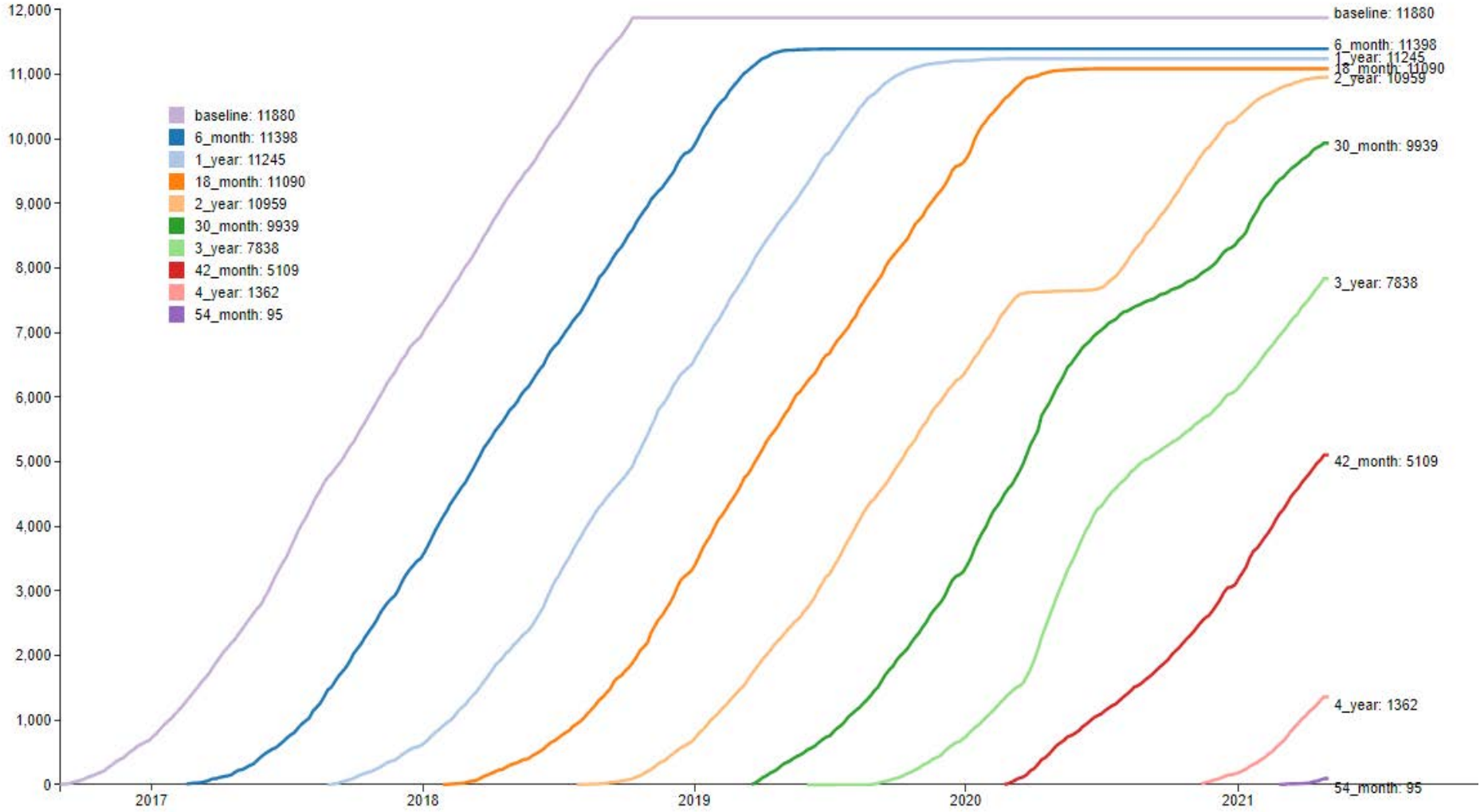
HEAL Research*



*Includes all NIDA HEAL projects regardless of funding source

Adolescent Brain Cognitive Development Study

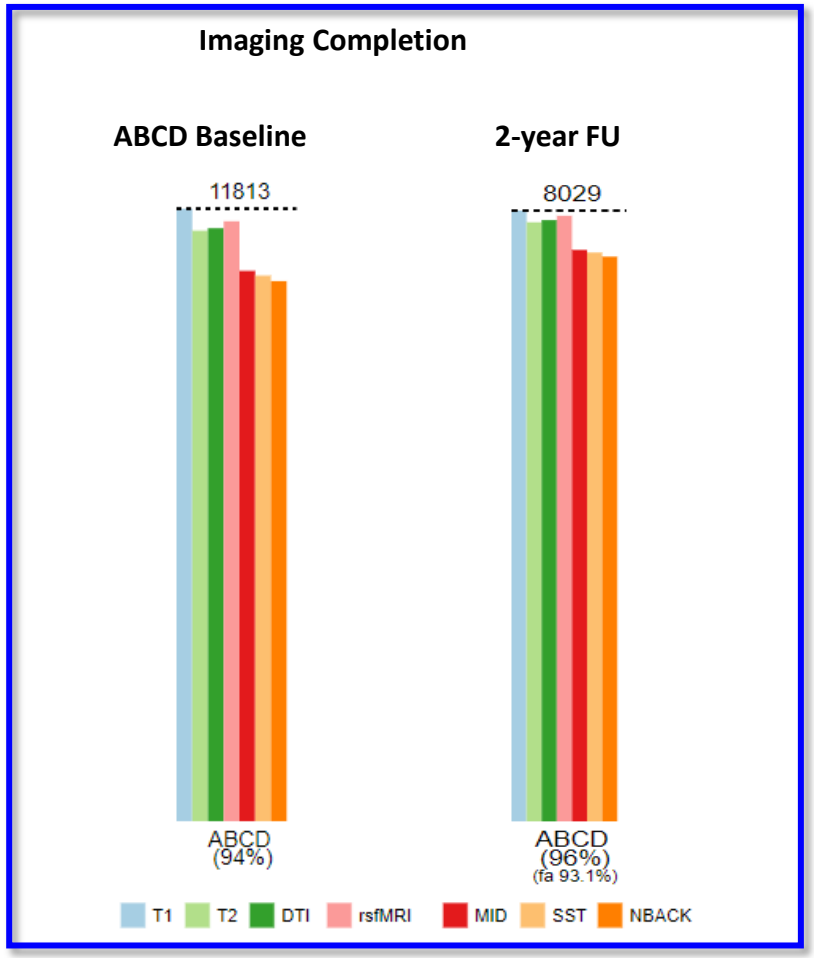
98.5 Percent Retained



As of April 2021

Adolescent Brain Cognitive Development Study (ABCD): Progress up to April 2021

145 papers, half from ABCD, half from non-ABCD investigators

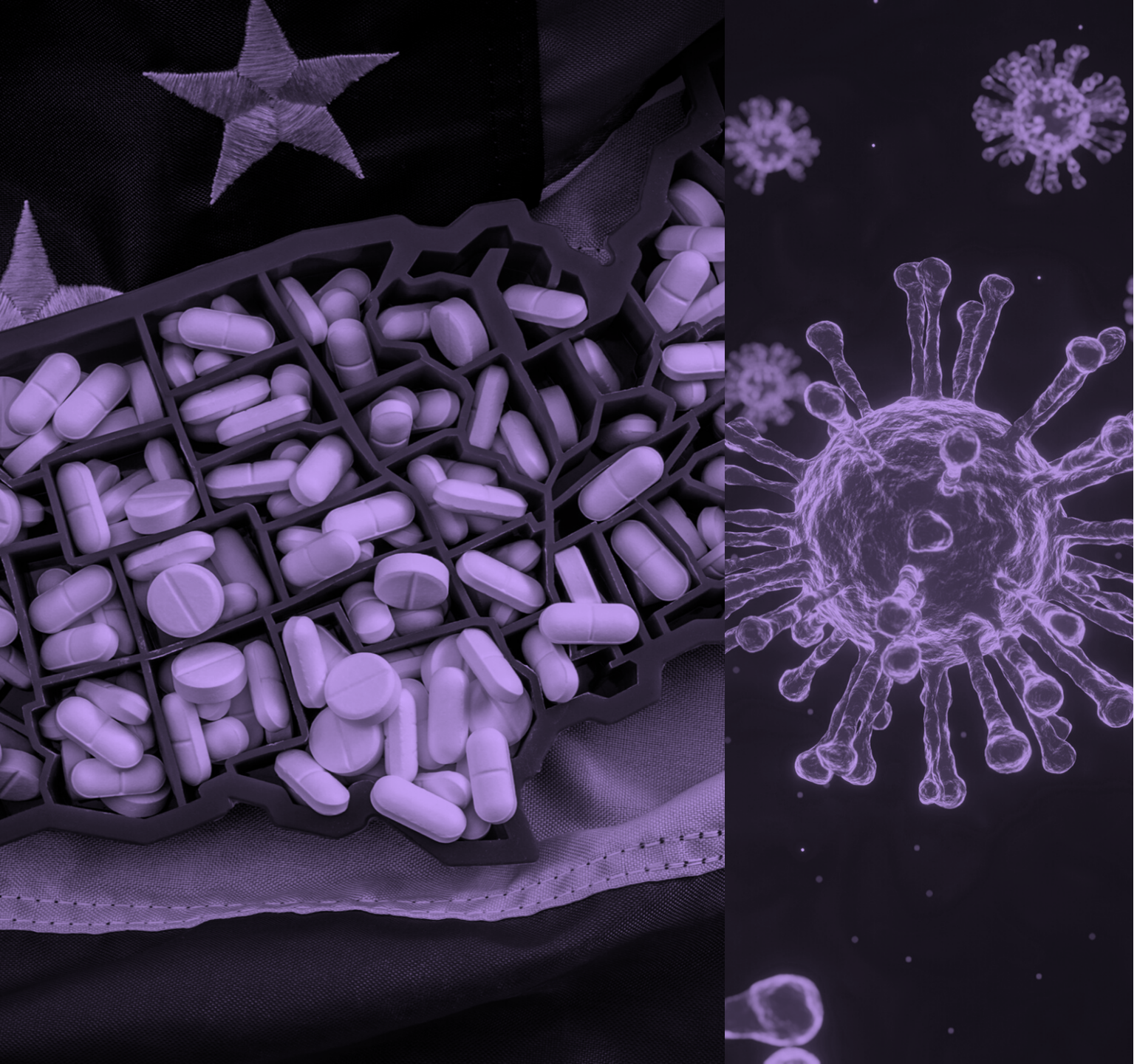


hBCD Study

Longitudinal study to understand normative neurodevelopment from birth to 9-10 years with an emphasis on assessing the impact of *in utero* exposures to drugs and harmful environments

Phase 1 Accomplishments

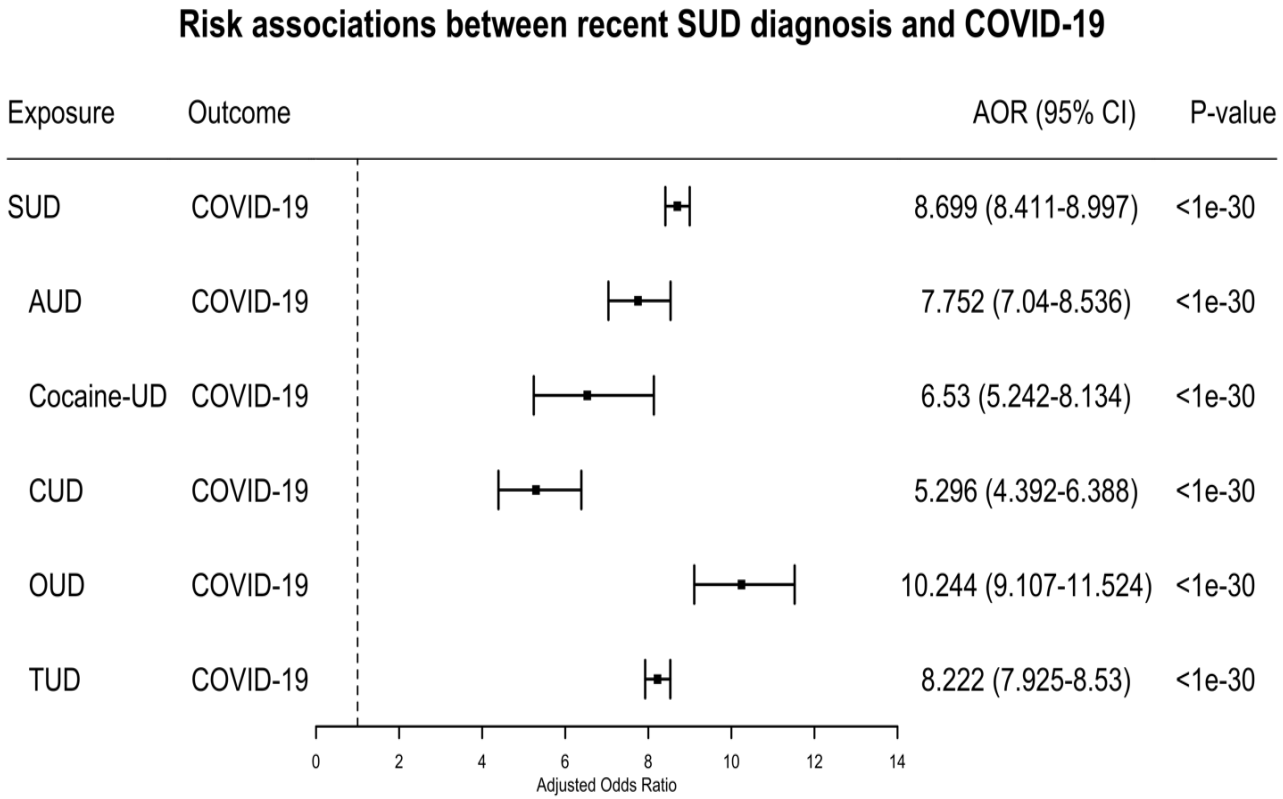
- Training for research coordinators
- **MRI compatible crib** to image newborns and infants
- Summit of families, legal scholars, ethicists, healthcare providers, and relevant agencies to mitigate risk and maximize benefit to women and children enrolled
- **Workshop on bioethics**
- **Motion correction system** developed and tested
- Protocols for remotely collecting saliva and stool
- **Protocols for MRI data collection in infants with neonatal abstinence syndrome (NAS)** created
- Purchased **Sprinter van to demonstrate feasibility of scanning remotely**
- Developed a **multimodal protocol using EEG and MRI** to assess brain structure, function, and connectivity.
- **Conducted extensive literature review of recruitment and retention with vulnerable populations**
- Conducted **state by state assessment of legal and ethical issues related to substance use and pregnancy in research**

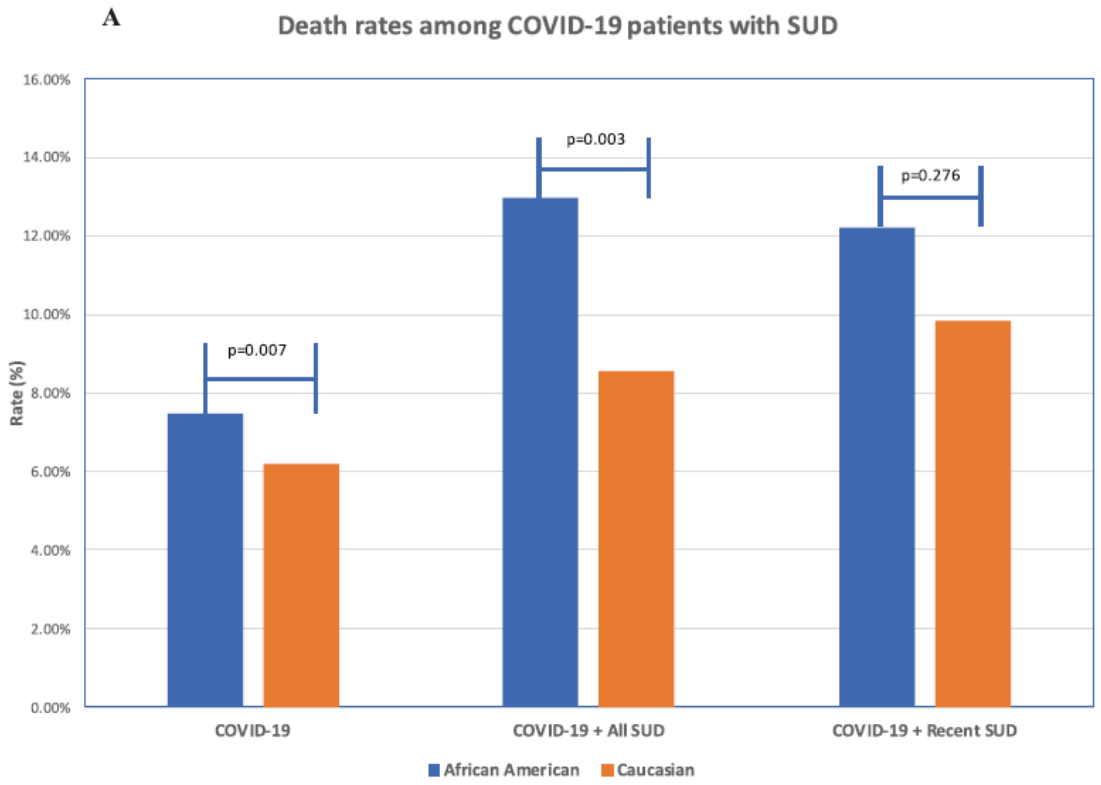


Intersection Between Drug Crisis and COVID-19

COVID-19 risk and outcomes in patients with substance use disorders: analyses from electronic health records in the United States

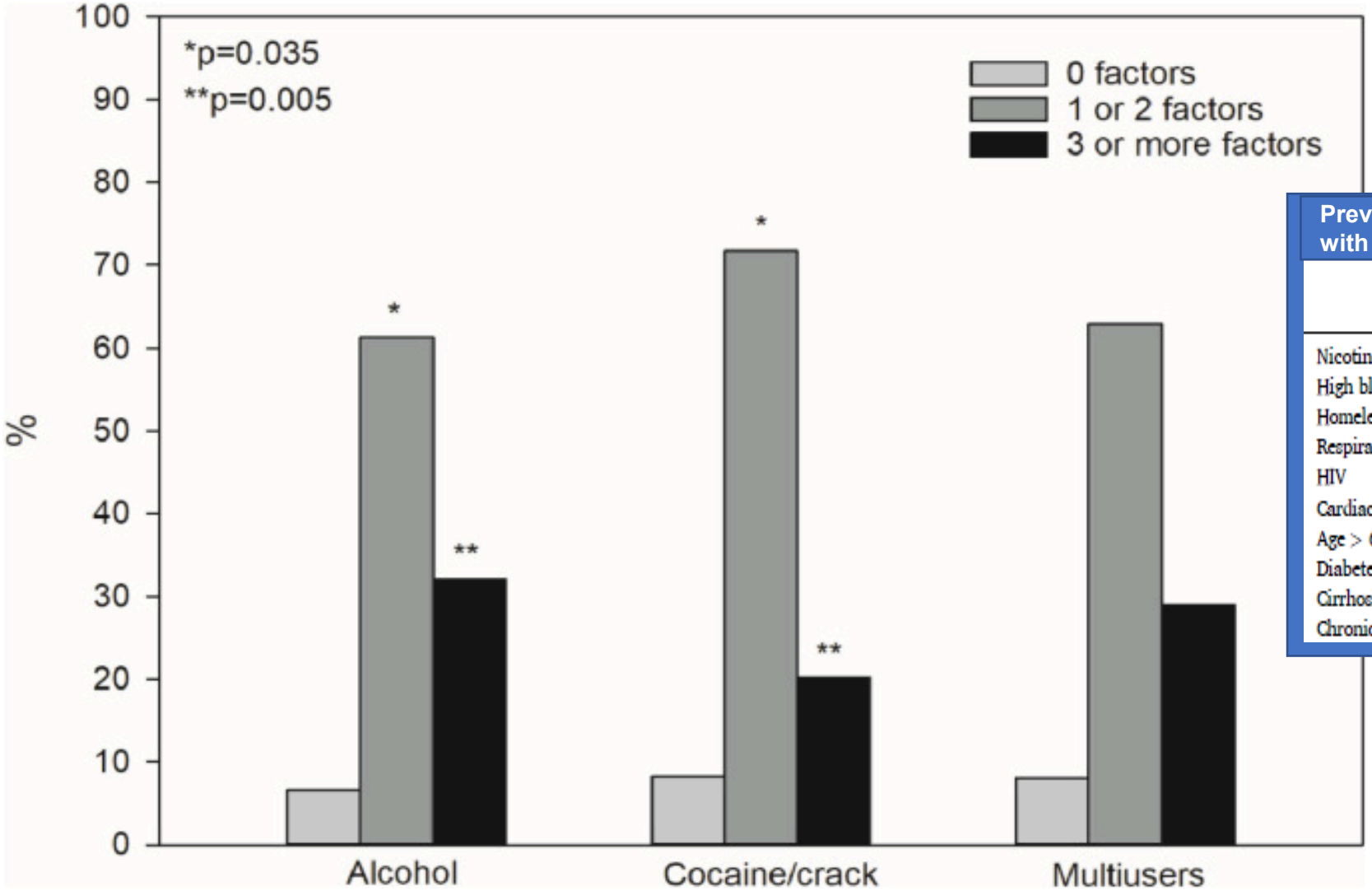
Quan Qiu Wang, David C Kaelber , Rong Xu , Nora D Volkow [4]





Wang et al., Mol Psychiatry 2020

Frequency and Comparison Of Number Of Risk Factors For COVID-19 According To Substance Use

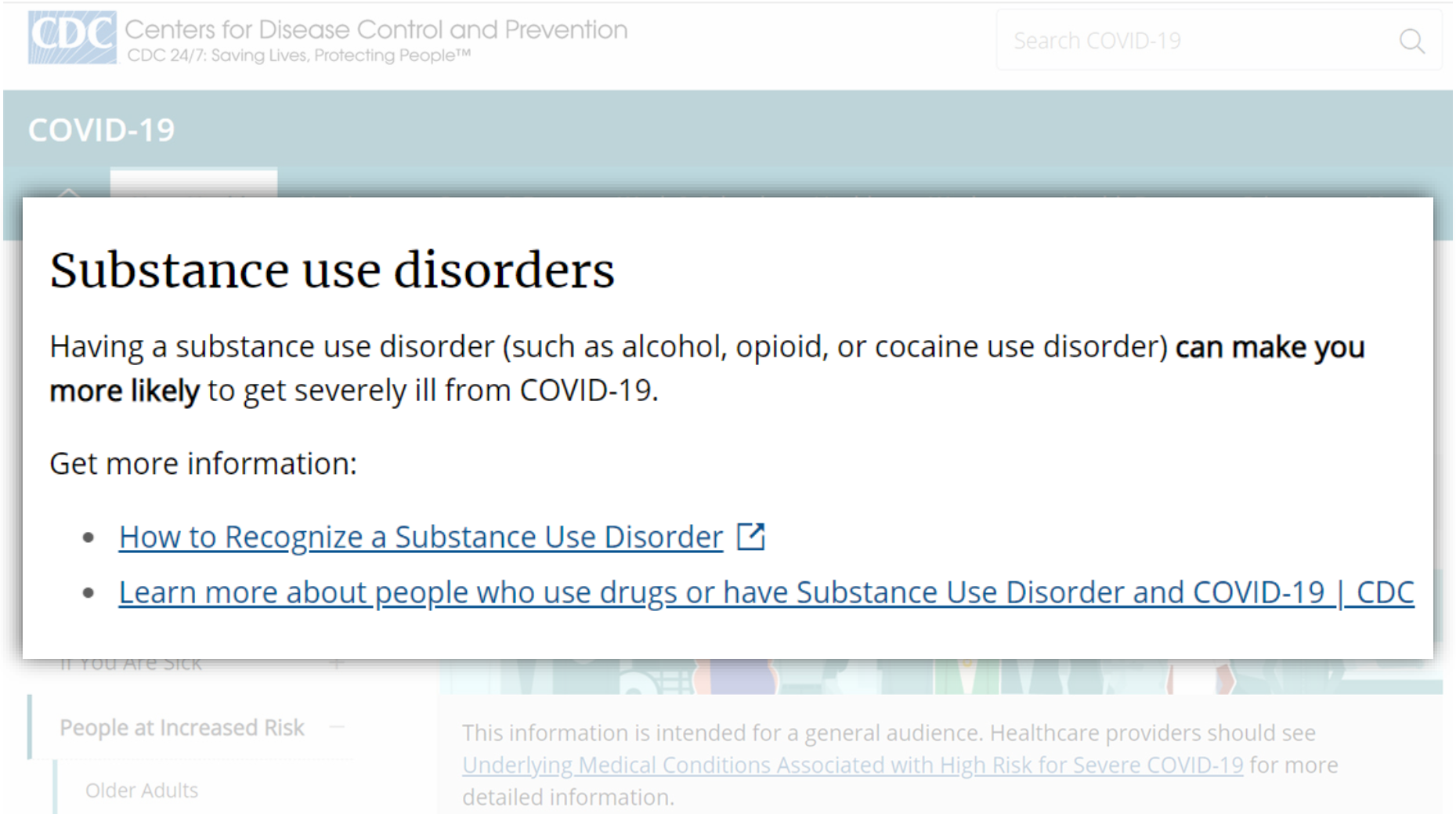


Prevalence of Risk Factors for COVID-19 In Individuals with Substance Use Disorder

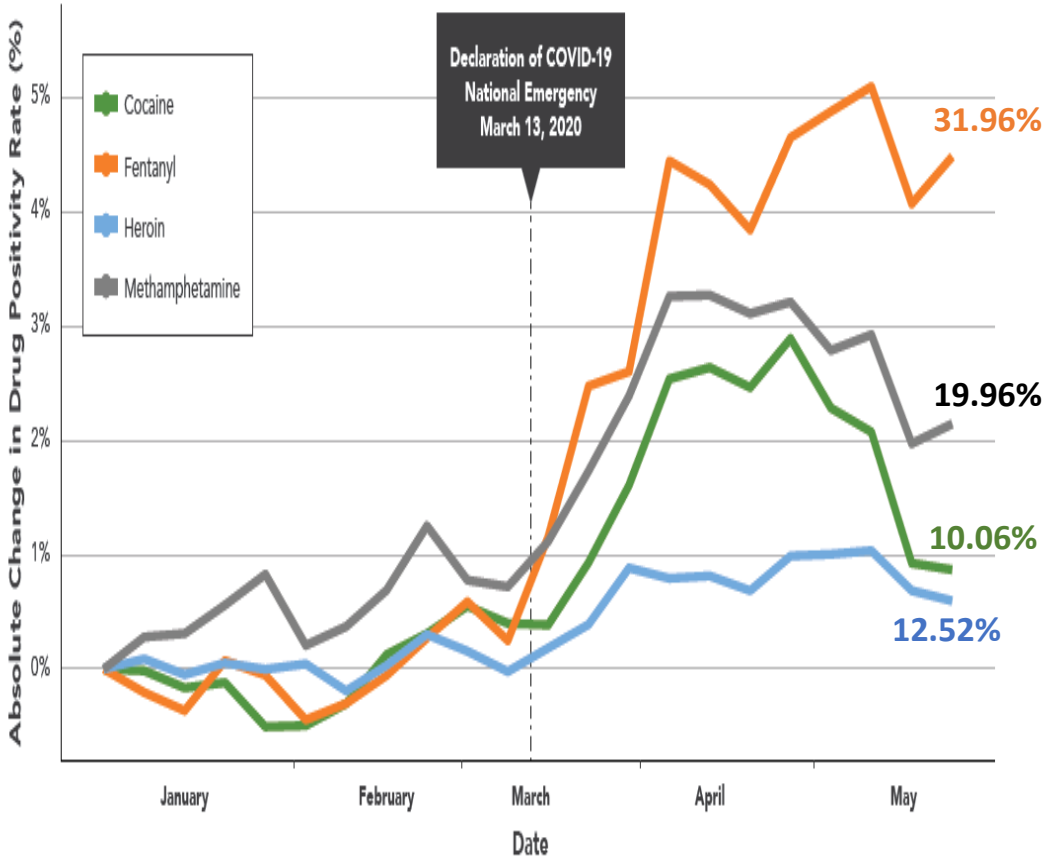
	Total *n*=821	Alcohol *n*=305	Cocaine/Crack *n*=233	Multiusers[1] *n*=283
Nicotine dependence	82.5	80.7	83.7	83.4
High blood pressure	26.6	38.0	12.9	25.4
Homelessness*	25.1	15.4	28.4	32.9
Respiratory*	23.4	23.3	21.2	25.2
HIV	7.3	3.7	7.1	11.4
Cardiac disease*	6.7	11.5	3.9	3.9
Age > 60 years	6.3	15.7	0	1.4
Diabetes	5.7	7.9	3.9	4.9
Cirrhosis	4.4	7.9	0.9	3.5
Chronic kidney disease*	3.6	3.6	2.1	4.6

Benzano D et al., Psychiatry Research 2021 Mar 31;300:113915.

The CDC Recognizes Substance Use Disorders as an Underlying Medical Condition Associated with High Risk for Severe COVID-19

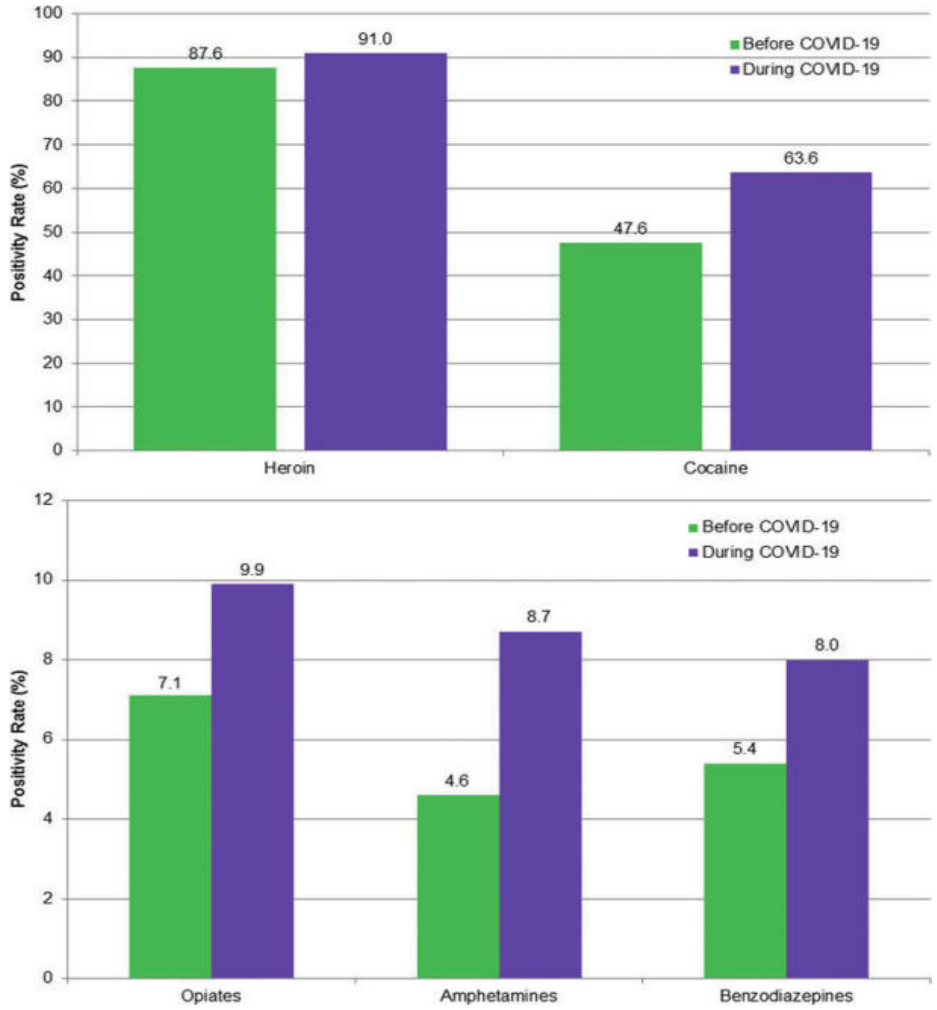


Drug Use Increase During COVID



Millennium Health Signals Report™ COVID-19 Special Edition: Significant Changes in Drug Use During the Pandemic Volume 2.1 Published July 2020

Fentanyl Positivity with Other Drugs Before and During COVID



Niles JK et al., Population Health Management, 2020.

Overdose Deaths Increased Again in 2019 (and 2020*)

	ALL DRUGS	HEROIN	NAT & SEMI – SYNTHETIC	METHADONE	SYNTHETIC OPIOIDS	COCAINE	OTHER PSYCHO-STIMULANTS (mainly meth)
September 2019 *	70,036	14,548	12,136	2,832	34,758	15,389	15,600
March 2020*	75,687	14,145	12,349	2,837	40,756	17,465	18,033
September 2020*	90, 237	14,201	13,649	3,501	53,877	19,952	22,791
Year end September 2019-September 2020 Change	**+28.8%**	**-2.4%**	**+12.5%**	**+23.6%**	**+55.0%**	**+30.0%**	**+46.0%**

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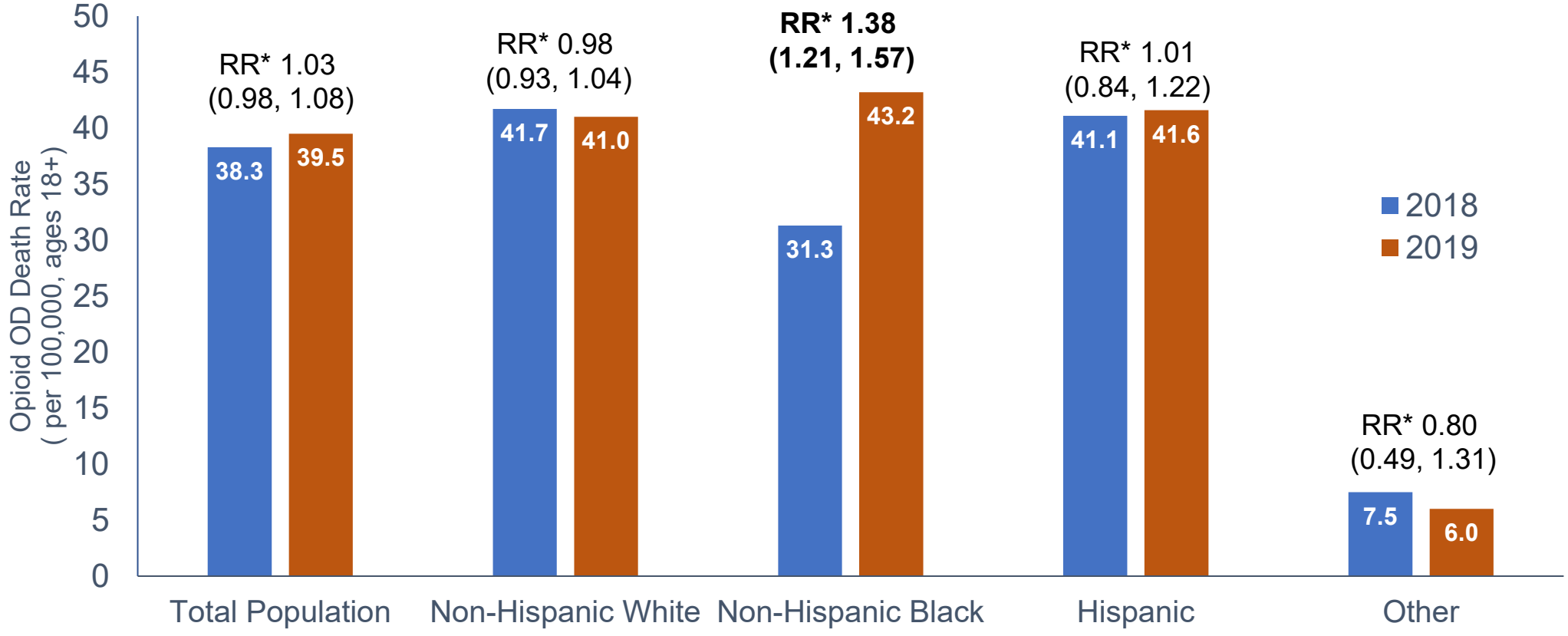
NCHS Provisional Drug Overdose Death Counts:** ***https://www.cdc.gov/nchs/nvss/vsrr/drug-overdose-data.htm

HEALing Communities Study:
Opioid Overdose Death Rate Trends

All Study Communities By Race/Ethnicity, 2018-2019



* Rate Ratio for 2019 vs 2018 with 95% Confidence Interval

Under review, Am. J. Public Health

Treating Fentanyl OUD and Overdoses

Limited data on efficacy of MOUD to treat fentanyl OUD

- Methadone is effective in fentanyl OUD.
  - **Methadone protected against death, but relapse rates were high (Stone, et al., 2018, Stone, et al. 2020).**
- Buprenorphine is effective in fentanyl OUD **(Wakeman, et al., 2019).**
  - Harder to initiate patients on buprenorphine
- Naltrexone no published data

Deaths from fentanyl are increasing despite naloxone (Torralva and Janowsky, 2019).

- OD from fentanyl require multiple naloxone doses **(Schumann et al., 2007, Somerville et al., 2017)**
  - Shorter duration of naloxone ($t_{1/2}$ 1.3–2.4 h) than fentanyl ($t_{1/2}$ 7-8 h)
  - Slower clearance of fentanyl in frequent users
- Chest wall rigidity from fentanyl

Treating Psychostimulant Use Disorder and Overdoses

- No FDA approved medications. Though promising results from combinations (Naltrexone + Buproprion, Naltrexone + Buprenorphine)
- Behavioral therapies: Most effective intervention is **contingency management** (uses rewards for evidence of abstinence) **combined with a community reinforcement approach** (uses recreational, familial, social, and vocational reinforcers, to make non-drug-using lifestyle more rewarding than substance use) (De Crescenzo et al., 2018).
- No overdoses reversal medications currently available

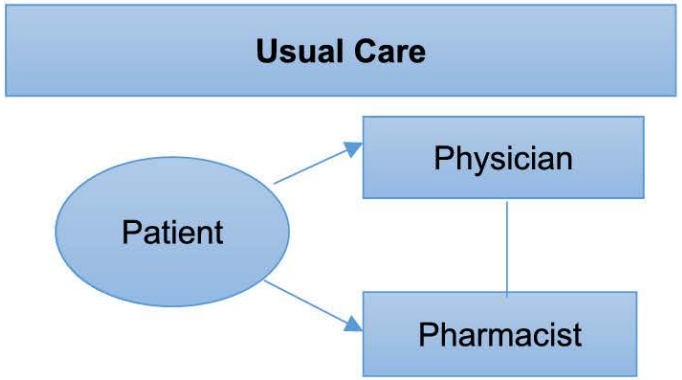
Treating Polysubstance Use Disorders

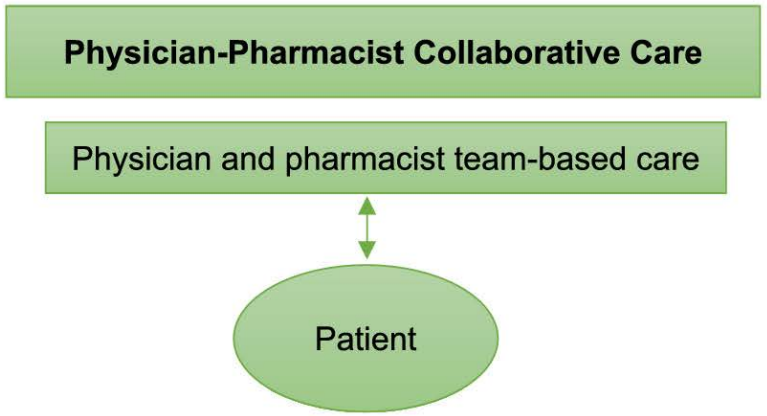
Reverting Polysubstance Overdoses

How Do We Address the Failure To Implement Evidence Based Treatments?

- Develop and promote sustainable models of care (use of pharmacies)
- Economic research (costs of not intervening; cost of relapse; Averted cost with extended-release formulations)
- Integrated healthcare interventions
- Telehealth

Buprenorphine Physician–Pharmacist Collaboration for OUD Management





Usual Care	Physician-Pharmacist Collaborative Care
▪ *Role:* Physician evaluates patient, prescribes buprenorphine, determines dosage, and monitors drug use and treatment safety. Pharmacist checks PDMP* and dispenses buprenorphine. ▪ *Visit:* Patient sees physician monthly and as needed. Patient sees pharmacist for prescription refill. ▪ *Communication:* Physician and pharmacist communicate about the prescription as needed.	▪ *Role:* Physician and pharmacist collaborate on patient's care. Physician provides clinical guidance and/or coaching to pharmacist. Physician prescribes buprenorphine and determines dosage. Pharmacist conducts dose reconciliation and patient education, and monitors drug use, treatment safety and adverse events. Pharmacist checks PDMP* and dispenses buprenorphine. Pharmacist provides feedback to physician. • *Visit:* Patient sees pharmacist monthly and as needed. Patient sees physician as needed. ▪ *Communication:* Physician and pharmacist communicate monthly or more frequently about patient's progress.

*PDMP: Prescription Drug Monitoring Program

Conclusions

A collaborative care model for people with OUD that involves buprenorphine-waivered physicians and community pharmacists appears to be feasible in the US and has high acceptability to patients

Wu L-T et al., Addiction 11 January 2021

HHS Releases New Buprenorphine Guidelines

The Practice Guidelines for the Administration of Buprenorphine for Treating Opioid Use Disorder provide an exemption from certain certification requirements under 21 U.S.C. § 823(g)(2)(B)(i)-(ii) of the Controlled Substances Act (CSA). Specifically, the *Practice Guidelines* provide that:

- … **buprenorphine,** practitioners, defined as physicians, physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists, and certified nurse midwives, who are licensed under state law, and who possesses a valid DEA registration, **may be exempt from the certification requirements related to training, counseling and other ancillary services**.
- Practitioners utilizing the exemption are limited to treating no more than 30 patients at any one time.
- HHS press release: https://www.hhs.gov/about/news/2021/04/27/hhs-releases-new-buprenorphine-practice-guidelines-expanding-access-to-treatment-for-opioid-use-disorder.html `

Stimulant (Cocaine and Methamphetamine) Use Disorder Medication Pipeline

Early Preclinical T2L: (> 12 years)	Late Preclinical (10 – 12 years)	Phase I (6 – 10 years)	Phase Ib (5 – 9 years)	Phase II (4 – 6 years)	Phase III (3 – 5 years)
◉ SBI-0069330 / SBI-0801315 mGluR2 PAM	○ IXT-m200 Long-duration anti-meth mAb	● dAdGNE Anti-cocaine vaccine	○ Mirtazapine NE/5HT antagonist	● NS2359* DAT/NET/SERT inhibitor	
● NOP/Kappa/Mu ligands	○ Methamphetamine conjugate vaccine	● Cocaine hydrolase gene therapy	○ Duloxetine & Methylphenidate NET/SERT inhibitor & CNS stimulant	○ IXT-m200 Anti-meth mAb	
◉ PTPRD ligands	○ IXT-v100 Methamphetamine vaccine	● h2E2 Anti-cocaine mAb	○ Pomaglumetad methionil mGluR2/3 agonist prodrug	● Bupropion DAT/NET inhibitor	
● Peptidic KOR agonists			● Clavulanic acid GLT-1 activator	● Mavoglurant* mGluR5 non-competitive antagonist	
● GLT-1 up-regulator			● Ketamine NMDA antagonist	● EMB-001 Metyrapone & oxazepam GC synth inhibitor & benzodiazepine	
○ Methamphetamine vaccine			● Pioglitazone PPAR-γ agonist	● Guanfacine α2A agonist	
● Cocaine catabolic enzyme				○ Naltrexone SR injection & oral Bupropion Mu antagonist & DAT/NET inhibitor	
○ VMAT-2 inhibitor					

KEY:
● – NME ● – New Indication ● – Biologic ● – Gene Therapy | ● – cocaine ○ – meth ◉ – both cocaine and meth

2/24/21 KR

* Not currently supported by NIDA

NIDA Supported Opioid Use Disorder Medication Pipeline

(potential novel treatment options for OUD/overdose patients) updated: 16Mar21

Early Preclinical Time to Launch: >12 yrs		Late Preclinical 10-12 yrs		Phase I 6-10 yrs	Phase Ib 5-9 yrs	Phase II 4-6 yrs	Phase III 3-5 yrs	New Formulation <3 yrs	
D24M MOR/DOR het antagonist	SBI-553 NT-1 biased PAM	R-methadone prodrug	PF5190457 GHS1aR antag	INDV-2000 OX-1 antagonist	Ketamine NMDA antagonist	Pregab + Lofex VDCC inh/a2 agonist		Olani 6 mo naltr implant	LAAM Oral, re-intro
Oxy/Fentanyl nano-vaccine	NAN/NAQ MOR modulator	NRS-033 Nalmefene prodrug	NYX-783 NMDA modulator	Liraglutide/ Semiglutide GLP-1R agonist	Suvorexant OX-1/2 antagonist			BICX102 3 mo naltr implant	Naltrexone 1 yr implant
Fentanyl vaccine	GPR151 antagonist	KNX100 Unknown mech	NP10697 GluN2B antagonist	Cannabidiol (CBD)	ASP8062 GABA-B PAM			OPNT003 Nasal nalmefene	Nalmefene implant
Carfentanyl mAb	AT-121 NOP/MOR partial agonist	BTRX-246040 NOPr antag	Tezampanel AMPA antag	Oxycodone vaccine	Cannabidiol (CBD)			Bupren/Nalox Oral, long acting	LYN-014 Long-acting methadone
	PTPRD inhibitor	P1A4 Fen mAb	Heroin Vaccine	ITI-333 MOR PA/5HT2a antagonist	Lemborexant OX-1/2 antagonist			Naltrexone 2 mo injection	AP007 XR nalmafene
		Metho-cinnamox MOR antag	Brexpiprazole D2/5HT1A par. ago.		CVL-936 D3/D2 antag			Naltrexone 6 mo implant	
		PZM21 MOR biased agonist	Mitragynine analogs		Guanfacine a2 adr. agonist				

Key: Red – Non-MOR Black – MOR Blue – Biologic

HCS and COVID Impact

- OD fatalities increased in 2020
- Virtual platforms deployed to work with coalitions and communities
- Telehealth focus:
  - Provide training to communities to facilitate telehealth
  - Distributed cell phones for patient use
  - Worked with communities to enhance broadband and other access issues
  - Greater emphasis on peer services and remote virtual outreach
  - Develop phone apps for overdose training
- Expanded data collection to include COVID-19
- Increased Health communications campaigns on social media
- Adapted study design and timeline
  - Fast-tracked OD education and naloxone before other EBPs to respond to releases from jail and prison
  - **Extended intervention period for Wave 1 communities due to delays in healthcare and justice settings**

JCOIN -- COVID Impacts

- **Relationships with practitioners** gave us real-time understanding of how the field was responding to the pandemic
  - Opportunities & challenges re: telehealth & MOUD initiation/continuation
- Most **clinical trials delayed by ~1 year in launch**
  - 9 of 13 now underway; 2 pilot testing; 2 imminent
- Investigators were able to **adapt protocols and explore interesting questions around COVID impacts** (e.g., OD associated with rapid decarceration in 2020)
- **RADX-UP:** funded 3 new studies of COVID-19 testing in CJ populations
- Shifted resources to develop **on-line training resources** that can be used post-pandemic

Tisha Wiley, Ph.D., Chief, Services Research Branch, tisha.wiley@nih.gov

Notice of Information:

Establishment of a Standard THC Unit to be Used in Research

https://grants.nih.gov/grants/guide/notice-files/NOT-DA-21-049.html

Notice Number: NOT-DA-21-049

Key Dates:

Release Date: May 7, 2021

Issued by: National Institute on Drug Abuse (NIDA); National Heart. Lung and Blood Institute (NHLBI); National Institute of Mental Health (NIMH); National Cancer Institute (NCI)

Purpose:

…. Inconsistency in the measurement and reporting of THC exposure has been a major limitation in studies of cannabis use, making it difficult to compare findings among studies. A standardized measure of THC in cannabis products is necessary to advance research by providing greater comparability across studies of both its adverse effects and potential medical uses. …this Notice informs research applicants of a new requirement to measure and report results using a standard THC unit in all *applicable* human subjects' research, beginning May 7, 2021. A standard THC unit is defined **as any formulation of cannabis plant material or extract that contains 5 milligrams of THC.**

NIDA Racial Equity Initiative Research Priorities

- Develop interventions to improve health disparities (HD) by addressing structural racism
- Assess vulnerabilities & progression of substance use and addiction in HD populations
- Develop and test targeted efficacious and scalable, culturally-specific interventions
- Assess and address stigma and discrimination in the context of SUD and treatment
- Conduct HD research in the CJS, with focus on linkage to SUD & HIV treatments
- Build partnerships with state/local agencies and private health systems to develop models to eliminate barriers to addiction care
- Advance basic science to understand racial disparities

THANK YOU!