Substance Use Disorders Therapeutics Development Research Update

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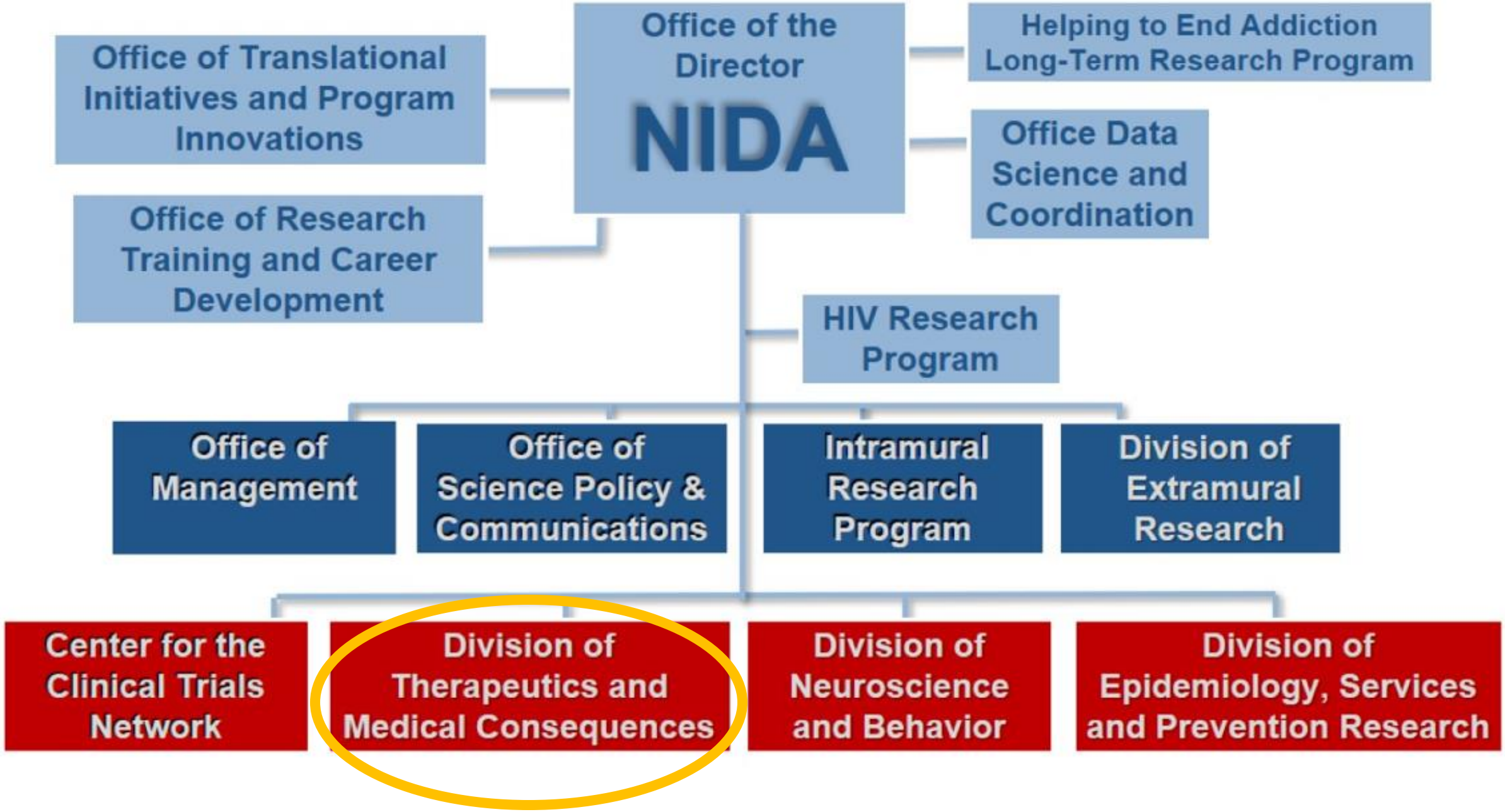
NIDA

Disclosures

- No conflicts of interest to disclose
- No official views of NIDA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Division of Therapeutics and Medical Consequences
Division of Neuroscience and Behavior
Division of Epidemiology, Services and Prevention Research

Division of Therapeutics and Medical Consequences (DTMC)

- In 1989, mandate from U.S. Congress to establish a *Medications Development Program* to combat Cocaine Use Disorder
  - Develop a close working relationship with the pharmaceutical industry
  - Conduct studies to gain approval of new medications
  - Work with the FDA to assure that efficacy of compounds is expeditiously evaluated and approved
- In 1990, NIDA created the *Medications Development Division* (now DTMC) to operationalize those goals

NIDA's Therapeutics Development Program

Current Mission

To use science as a vehicle for improving the management of Substance Use Disorders (SUD) and their medical consequences, including HIV

Emphasis

Identification, evaluation, and development of safe and effective medications, biologics, devices, digital therapeutics, and behavioral therapies for SUDs

Overarching Goal

Advance the development of safe and effective treatments for SUD to reduce the public health burden of SUD

Specific Goals

- Determine the safety and efficacy of new therapeutics
- Obtain FDA approval of new medications
- Obtain FDA clearance and approval of therapeutic devices and digital therapeutics
- Improve the treatment outcomes of patients with SUDs

Notable DTMC-Supported Achievements

- LAAM
- Buprenorphine
- Buprenorphine + Naloxone
- Buprenorphine implant
- Naltrexone
- Depot Naltrexone
- Lofexidine
- Intranasal Naloxone
- Intranasal Nalmefene
- RESET/RESET-O
- Contingency Management, CBT, MET

Presentation Outline

- Opioid Use Disorder and Overdose
- Stimulant Use Disorder and Overdose
- Cannabis Use Disorder
- Tobacco Use Disorder
- Therapeutic Devices
- Digital Therapeutics
- Behavioral Therapies

NIH National Institute on Drug Abuse

Opioid Use Disorder and Overdose

Early Preclinical	Late Preclinical	Phase I Clinical Trials	Phase II Clinical Trials	New Formulation
NTR1 modulator	BTRX-246040	Cannabidiol	Cannabidiol	Naltrexone 2-month injection
5HT2R agonist	PF5190457	Lemborexant	Guanfacine	BICX104 Naltrexone 3-month implant
HBS087/HBS093	AT-121	Lofexidine	Pregabalin + Lofexidine	OLANI (Naltrexone 6-month implant)
PN6041/PN6047	TRN-228	Dexmedetomidine	Suvorexant	DLP-160 (Naltrexone 6-month implant)
D-CYSee	NaV1.8 inhibitor	Dextromethorphan/Bupropion	Pramipexole	BIOPIN 6 (Naltrexone 6-month implant)
SBI-0801315/SBI-0799220	CS-1103	CVL-354	Olanzapine	Novel Naltrexone transdermal patch (NNTP)
Opioid biased agonist	Methocinnamox	INDV-2000	Ketamine	LAAM
MOR Selective agonist	Mitragynine analogs	AZD4041	Ketamine	LYN-014
Oxy/Fentanyl nano-vaccine	R-methadone prodrug	KNX100	Semaglutide	LYN-013
Fentanyl/heroin vaccine	MOR modulator	NYX-783	Buprenorphine + Naltrexone	Nalmefene implant
GDNF gene therapy	GM-3009 (Oxa-iboga analog)	EC5026		Nanoparticle-based ADF
	CSX-1004 (Fentanyl mAb)	SBS-1000		PF614-MPAR (Nafamostat/Oxycodone ADF)
	Heroin vaccine	Kindolor		NaxSwab (Pocket Naloxone Corp)
	M-KLH (Heroin Vaccine)	MEB-1170		Buprenorphine
	Fentanyl vaccine	NRS-033		
	mAb Fentanyl	ITI-333		
		EPD-2520		
		Oxycodone vaccine		

OUD/Overdose – Preclinical

Early Preclinical	Late Preclinical	Phase I Clinical Trials	Phase II Clinical Trials	New Formulation
NTR1 modulator	BTRX-246040			
5HT2R agonist	PF5190457			
HBS087/HBS093	AT-121			
PN6041/PN6047	TRN-228			
D-CYSee	**NaV1.8 inhibitor**			
SBI-0801315/SBI-0799220	CS-1103			
Opioid biased agonist	Methocinnamox			
MOR Selective agonist	Mitragynine analogs			
Oxy/Fentanyl nano-vaccine	R-methadone prodrug			
Fentanyl/heroin vaccine	MOR modulator			
GDNF gene therapy	GM-3009 (Oxa-iboga analog)			
	CSX-1004 (Fentanyl mAb)			
	Heroin vaccine			
	M-KLH (Heroin Vaccine)			
	Fentanyl vaccine			
	mAb Fentanyl			

NaV1.8 inhibitor: Opioid-sparing analgesic development

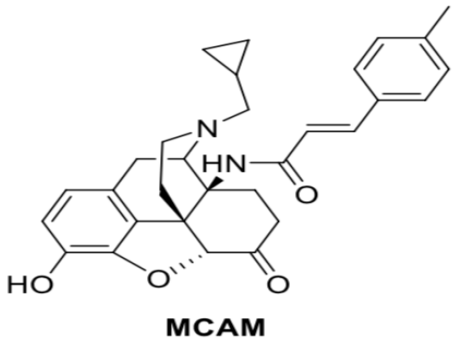
- NaV1.8 voltage gated sodium channels are located in pain pathways but are highly restricted to the dorsal root ganglia and trigeminal neurons
- Rodents treated with antisense oligonucleotides targeting NaV1.8 exhibit reduced mechanical allodynia in models of inflammatory and neuropathic pain
- Recently, Vertex demonstrated that NaV1.8 inhibitors effectively reduce pain in patients with small fiber neuropathy, osteoarthritis and following surgery (bunionectomy, abdominoplasty)
- No drug candidate targeting NaV1.8 has yet reached approval
- SiteOne Therapeutics has identified a development candidate targeting NaV1.8 with potency (IC50 < 1 nM at hNaV1.8), selectivity over off-target NaV isoforms (>8000-fold), and pharmaceutical properties suitable for once daily oral dosing
- Development candidate will advance through single and multiple ascending dose studies in healthy volunteers and Phase 2 proof-of-concept studies in acute postsurgical and chronic neuropathic pain

UG3DA058552 PI:John Hunter, SiteOne Therapeutics

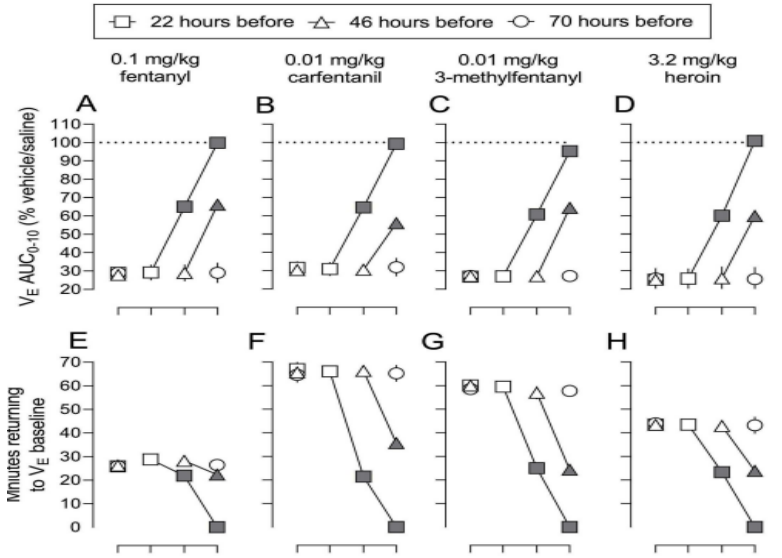
OUD/Overdose – Preclinical

Early Preclinical	Late Preclinical
NTR1 modulator	BTRX-246040
5HT2R agonist	PF5190457
HBS087/HBS093	AT-121
PN6041/PN6047	TRN-228
D-CYSee	NaV1.8 inhibitor
SBI-0801315/SBI-0799220	CS-1103
Opioid biased agonist	**Methocinnamox**
MOR Selective agonist	Mitragynine analogs
Oxy/Fentanyl nano-vaccine	R-methadone prodrug
Fentanyl/heroin vaccine	MOR modulator
GDNF gene therapy	GM-3009 (Oxa-iboga analog)
	CSX-1004 (Fentanyl mAb)
	Heroin vaccine
	M-KLH (Heroin Vaccine)
	Fentanyl vaccine
	mAb Fentanyl

Methocinnamox - Novel, long-acting, μ-opioid receptor antagonist for OUD



MCAM

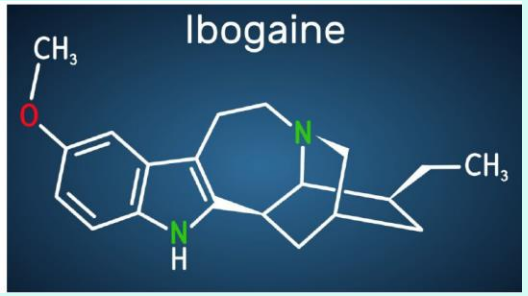


- Dose-dependently reversed hypoventilation induced by MOR agonists (3-methylfentanyl, carfentanil, fentanyl, or heroin)
- 1.0 mg/kg MCAM administered i.v. 22 hours prior, prevented hypoventilation induced by MOR agonists, whereas naloxone did not (JPET April 2024)
- MCAM reverses and prevents hypoventilation by MOR agonists in animals. The project is moving forward toward testing in clinical studies

UH3DA048387 PI: Charles France, UT

OUD/Overdose – Preclinical

Early Preclinical	Late Preclinical	Phase I Clinical Trials	Phase II Clinical Trials	New Formulation
NTR1 modulator	BTRX-246040	C…		
5HT2R agonist	PF5190457			
HBS087/HBS093	AT-121			
PN6041/PN6047	TRN-228			
D-CYSee	NaV1.8 inhibitor			
SBI-0801315/SBI-0799220	CS-1103			
Opioid biased agonist	Methocinnamox			
MOR Selective agonist	Mitragynine analogs			
Oxy/Fentanyl nano-vaccine	R-methadone prodrug			
Fentanyl/heroin vaccine	MOR modulator			
GDNF gene therapy	**GM-3009 (Oxa-iboga analog)**			
	CSX-1004 (Fentanyl mAb)			
	Heroin vaccine			
	M-KLH (Heroin Vaccine)			
	Fentanyl vaccine			
	mAb Fentanyl			



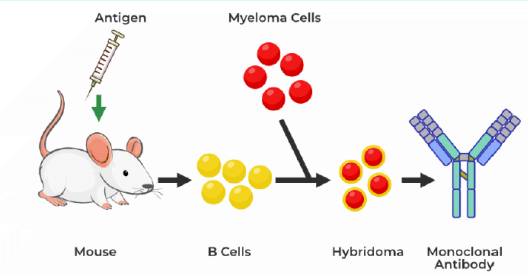
GM-3009 (Oxa-iboga analog)

- Gilgamesh Pharmaceuticals has developed, a new class of synthetic iboga alkaloids, named “oxa-iboga” analogs
- Unlike ibogaine, these compounds show no pro-arrhythmic potential, no neurotoxic effects, and enhanced efficacy in OUD-relevant preclinical behavioral assays.
- Oxa-noribogaine or GM-3009, will move into clinical studies following GMP-manufacturing and formulation, completion of IND-enabling toxicity studies, and determination of the expected therapeutic exposures and target engagement via translational biomarkers.
- GM-3009 will then advance to first-in-human trials, including safety and tolerability studies in healthy volunteers followed by a safety study with exploratory measures of efficacy in OUD patients undergoing opioid withdrawal..
- GM-3009 intends to be an innovative OUD therapy with rapid and long-term mitigation of acute and protracted withdrawal symptoms and cravings, which lead to non-medical opioid use

UG3DA060053 PI:Gerard Marek, Gilgamesh Pharmaceuticals

OUD/Overdose – Preclinical Trials

Early Preclinical	Late Preclinical	Phase I Clinical Trials	Phase II Clinical Trials	New Formulation
NTR1 modulator	BTRX-246040	Cannabidiol		
5HT2R agonist	PF5190457	Le		nt
HBS087/HBS093	AT-121			
PN6041/PN6047	TRN-228			
D-CYSee	NaV1.8 inhibitor			
SBI-0801315/SBI-0799220	CS-1103			
Opioid biased agonist	Methocinnamox			
MOR Selective agonist	Mitragynine analogs			
Oxy/Fentanyl nano-vaccine	R-methadone prodrug			
Fentanyl/heroin vaccine	MOR modulator			
GDNF gene therapy	GM-3009 (Oxa-iboga analog)			
	CSX-1004 (Fentanyl mAb)			
	Heroin vaccine			
	M-KLH (Heroin Vaccine)			
	Fentanyl vaccine			
	mAb Fentanyl			



CSX-1004 (Fentanyl mAb)

- high binding affinity and specificity to fentanyl and related analogs
- sequesters fentanyl and analogs in peripheral blood to mitigate opioid effects in the brain without interacting with μ-opioid receptors
- reverses and prevents fentanyl-induced respiratory depression in rodents and non-human primates (NHP) with efficacy that lasts over 3 weeks
- has advanced to clinical first-in-human trials in IV formulation
- will be evaluate for potency, efficacy, and duration of action on fentanyl self-administration and reinstatement in NHP
- PET/fMRI studies will document how CSX-1004 precludes fentanyl from entering the brain
- will be optimized for subcutaneous (SC) administration by reformulation and further non-clinical development including GMP manufacture and IND-enabling toxicology studies which will permit its eventual use in a wider clinical setting

U03DA05844 PI: Rajeev Desai, McLean Hospital

OUD/Overdose – Clinical Trials

Early Preclinical	Late Preclinical	Phase I Clinical Trial
NTR1 modulator	BTRX-246040	Cannabidiol
5HT2R agonist	PF5190457	Lemborexant
HBS087/HBS093	AT-121	**Lofexidine**
PN6041/PN6047	TRN-228	Dexmedetomidin
D-CYSee	NaV1.8 inhibitor	Dextromethorphan
SBI-0801315/SBI-0799220	CS-1103	CVL-354
Opioid biased agonist	Methocinnamox	INDV-2000
MOR Selective agonist	Mitragynine analogs	AZD4041
Oxy/Fentanyl nano-vaccine	R-methadone prodrug	KNX100
Fentanyl/heroin vaccine	MOR modulator	NYX-783
GDNF gene therapy	GM-3009 (Oxa-iboga analog)	EC5026
	CSX-1004 (Fentanyl mAb)	SBS-1000
	Heroin vaccine	Kindolor
	M-KLH (Heroin Vaccine)	MEB-1170
	Fentanyl vaccine	NRS-033
	mAb Fentanyl	ITI-333
		EPD-2520
		Oxycodone vaccine

Lofexidine for NOWS

- Alpha-2 agonist
- FDA approved oral tablet of 0.18 mg for opioid withdrawal in adults
- Development and PK evaluation of a pediatric-specific formulation
- Clinical trials
  - Identify optimal dosing regimen
  - Evaluate the risks and benefits

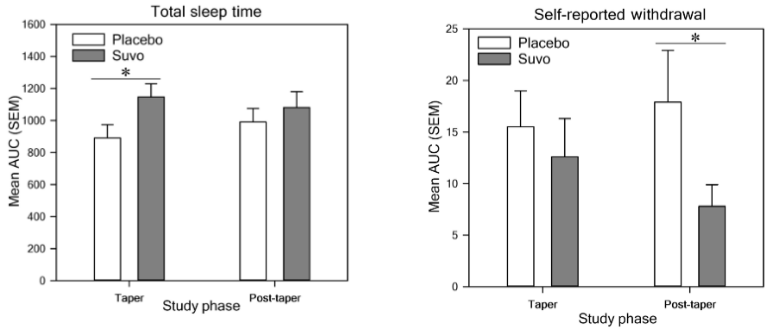
- Goal: improve withdrawal symptoms, limiting infant exposure to other off-label narcotic medications, and shortening the infant's overall stay in the hospital

UG3DA054799 PI: Kristen Gullo, U.S. World Meds

OUD/Overdose – Clinical Trials

Suvorexant

- Dual-orexin receptor antagonist
- Increased orexin/hypocretin signaling implicated in opioid withdrawal, sleep disturbances, and drug-seeking behaviors
- Aim: improve sleep and withdrawal outcomes when compared with placebo during a buprenorphine/naloxone taper
- Suvorexant 20 mg (n=14), 40 mg (n=12), placebo (n=12)
- In two-group comparisons, suvorexant increased total sleep time during the buprenorphine/naloxone taper and decreased SOWS during the post-taper period
- Suvorexant might be a promising treatment for sleep and opioid withdrawal in individuals undergoing a buprenorphine/naloxone taper



Huhn AS, Finan PH, Gamaldo CE, Hammond AS, Umbricht A, Bergeria CL, Strain EC, Dunn KE. Sci Transl Med. 2022 Jun 22;14(650)

UH3DA048734 PI: Andrew Huhn, Johns Hopkins

Early	Clinical Trials	Phase II Clinical Trials	New Formulation
NTP		Cannabidiol	Naltrexone 2-month injection
5		Guanfacine	BICX104 Naltrexone 3-month implant
		Pregabalin + Lofexidine	OLANI (Naltrexone 6-month implant)
		Suvorexant	DLP-160 (Naltrexone 6-month implant)
		Pramipexole	BIOPIN 6 (Naltrexone 6-month implant)
		Olanzapine	Novel Naltrexone transdermal patch (NNTP)
		Ketamine	LAAM
		Ketamine	LYN-014
		Semaglutide	LYN-013
		Buprenorphine + Naltrexone	Nalmefene implant
			Nanoparticle-based ADF
			PF614-MPAR (Nafamostat/Oxycodone ADF)
			NaxSwab (Pocket Naloxone Corp)
			Buprenorphine

OUD/Overdose – Clinical Trials

Early Pr	e I Clinical Trials	Phase II Clinical Trials	New Formulation
NTR1 mo		Cannabidiol	Naltrexone 2-month injection
5HT2R		Guanfacine	BICX104 Naltrexone 3-month implant
HBS08		Pregabalin + Lofexidine	OLANI (Naltrexone 6-month implant)
PN604		Suvorexant	DLP-160 (Naltrexone 6-month implant)
D-CYS	opion	Pramipexole	BIOPIN 6 (Naltrexone 6-month implant)
SBI-08		Olanzapine	Novel Naltrexone transdermal patch (NNTP)
Opioid		Ketamine	LAAM
MOR S		Ketamine	LYN-014
Oxy/Fe		**Semaglutide**	LYN-013
Fentan		Buprenorphine + Naltrexone	Nalmefene implant
GDNF			Nanoparticle-based ADF
			PF614-MPAR (Nafamostat/Oxycodone ADF)
			NaxSwab (Pocket Naloxone Corp)
			Buprenorphine

Semaglutide

- Glucagon-like peptide-1 (GLP-1) receptor agonists are widely used for the treatment of type 2 diabetes and obesity
- GLP-1 influences reward behaviors related to both food and drugs, reducing heroin self-administration, cue-induced heroin seeking, and drug- and stress-induced reinstatement of heroin seeking
- Unpublished but reported at the annual meeting of AAAS
- Liraglutide (n=10) or placebo (n=10)
- Treatment at a residential rehabilitation center taking buprenorphine
- Over 3 weeks, self-reported opiate craving was 40% lower in those taking liraglutide compared with placebo, and many of those treated reported no cravings at all
- Follow up with a larger trial using semaglutide

UG3DA050325 PI: Patricia Grigson, Penn State

OUD/Overdose – New Formulations

Early Preclinical	Late Preclinical	Phase I Clinical Trials	Phase II Clinical Trials	New Formulation
NTR1 modulator	BTRX-246040	Cannabidiol	Cannabidiol	Naltrexone 2-month injection
5HT2R agonist	PF5190457	Lemborexant	Guanfacine	**BICX104 Naltrexone 3-month implant**
HBS087/HBS093	AT-121	Lofexidine	Pregabalin + Lofexidine	OLANI (Naltrexone 6-month implant)
PN6041/PN6047	TRN-228	Dexmedetomidine	Suvorexant	DLP-160 (Naltrexone 6-month implant)
D-CYSee				BIOPIN 6 (Naltrexone 6-month implant)
SBI-0801315/SBI-				Novel Naltrexone transdermal patch (NNTP)
Opioid biased ag				LAAM
MOR Selective a				LYN-014
Oxy/Fentanyl nar				LYN-013
Fentanyl/heroin v			exone	Nalmefene implant
GDNF gene thera				Nanoparticle-based ADF
				PF614-MPAR (Nafamostat/Oxycodone ADF)
				NaxSwab (Pocket Naloxone Corp)
				Buprenorphine

BICX104 (3-month Naltrexone implant)

Subcutaneous implantable Naltrexone pellet by BioCorRx Pharmaceuticals

- Completely biodegrades eliminating the need to remove after implantation
- Nearly pure naltrexone pellet devoid of polymers
- Simple in-office procedure in approximately 15 minutes using local anesthetic
- Received FDA Clearance of Investigational New Drug (IND) application for BICX104 in 2021
- Phase 1 human trial completed March 22, 2023
- Interim data demonstrate that BICX104 is well-tolerated and achieves desired 84-day therapeutic naltrexone levels

UH3DA047925 PI: Katherine Beebe DeVarney, BioCorRx Pharmaceuticals

OUD/Overdose – New Formulations

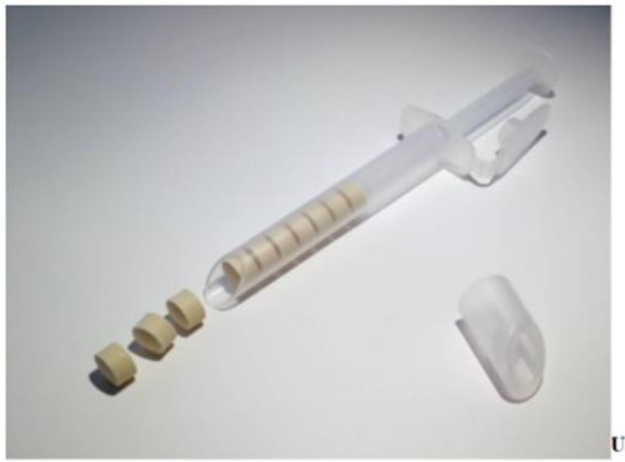
Early Preclinical				New Formulation
NTR1 modulator				Naltrexone 2-month injection
5HT2R agonist				BICX104 Naltrexone 3-month implant
HBS087/HBS093				**OLANI (Naltrexone 6-month implant)**
PN6041/PN6047				DLP-160 (Naltrexone 6-month implant)
D-CYSee				BIOPIN 6 (Naltrexone 6-month implant)
SBI-0801315/SBI				Novel Naltrexone transdermal patch (NNTP)
Opioid biased ag				LAAM
MOR Selective a				LYN-014
Oxy/Fentanyl nan				LYN-013
Fentanyl/heroin v			one	Nalmefene implant
GDNF gene thera				Nanoparticle-based ADF
				PF614-MPAR (Nafamostat/Oxycodone ADF)
				NaxSwab (Pocket Naloxone Corp)
				Buprenorphine

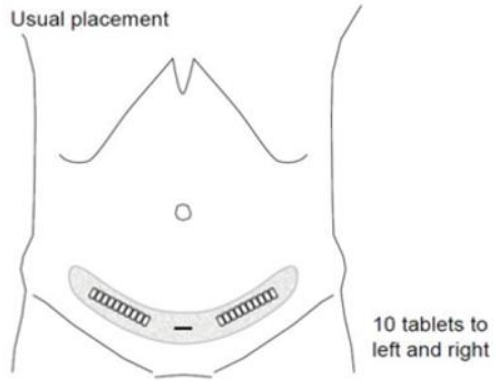
O'Neil Long Acting Naltrexone Implant (OLANI)

6-month Naltrexone implant

Biodegradable abdominal Naltrexone implant by Go Medical Industries

- **Expected to produce Naltrexone blood levels sufficient to block the effects of opioids for 6 months after implant**
- **Development path towards a New Drug Application (NDA) via the 505 b(2) pathway with Vivitrol as a comparator product**





Usual OLANI placement

UH3DA047720 PI: Adam Bisaga, Columbia/NYSPI

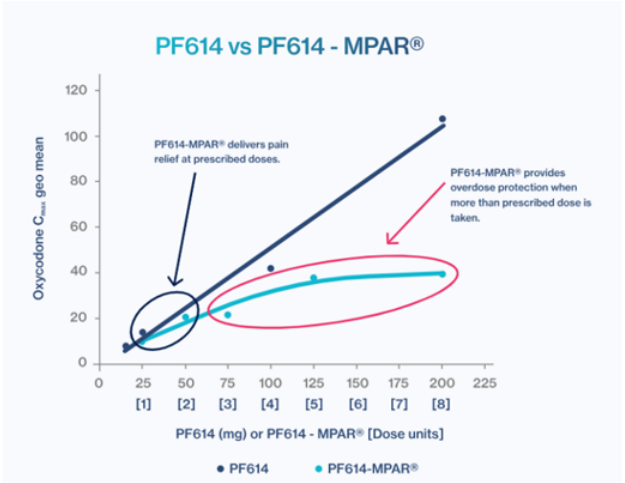
OUD/Overdose – New Formulations

Early Preclinical	Late Preclinical	Phase I Clinical Trials	Phase II Clinical Trials	New Formulation
NTR1 modulator	BTRX-246040	Cannabidiol	Cannabidiol	Naltrexone 2-month injection
5HT2R agonist	PF5190457	Lemborexant	Guanfacine	BICX104 Naltrexone 3-month implant
HBS087/HBS093			fexidine	OLANI (Naltrexone 6-month implant)
PN6041/PN6047				DLP-160 (Naltrexone 6-month implant)
D-CYSee				BIOPIN 6 (Naltrexone 6-month implant)
SBI-0801315/SBI-0799220				Novel Naltrexone transdermal patch (NNTP)
Opioid biased agonist				LAAM
MOR Selective agonist				LYN-014
Oxy/Fentanyl nano-vaccine			ltrexone	LYN-013
Fentanyl/heroin vaccine				Nalmefene implant
GDNF gene therapy				Nanoparticle-based ADF
				PF614-MPAR (Nafamostat/Oxycodone ADF)
				NaxSwab (Pocket Naloxone Corp)
				Buprenorphine

PF614-MPAR (Nafamostat/Oxycodone ADF)

Treatment of Pain (ADF)
Ensysce Biosciences
PF614-MPAR – FDA Breakthrough Therapy Designation

Overdose Protection: PF614-MPAR® has been evaluated in a Phase 1 clinical study for safety and its pharmacokinetic properties and has been shown to effectively reduce oxycodone release from PF614 if greater than 2 dose units (anticipated to be a maximum prescribed dose) are taken simultaneously.



UH3DA047682 PI: Lynn Kirkpatrick, Ensysce Biosciences

National Institute on Drug Abuse

Stimulant Use Disorder and Overdose

Early Preclinical	Late Preclinical	Clinical Trials			
		Phase I	Phase Ib	Phase II	Phase III
SBI-0801315/SBI-0799220 CocH5-Fc(M6) Cocaine hydrolase SBX-518	OMS 182399 PPL-138 IXT-m200 Long –Acting NHB 1109	Zolmitriptan TMP-301 Cocaine hydrolase gene therapy dAdGNE h2E2 CS-1103	Cariprazine Mirtazapine Clavulanic acid Ketamine Exenatide BICX104/Bupropion	Pioglitazone Rotigotine Bupropion/Naltrexone TNX-1300 IXT-m200 (OD)	

Stimulant Use Disorder and Overdose

Early Preclinical	Late Preclinical	Clinical Trials			
		Phase I	Phase Ib	Phase II	Phase III
SBI-0801315/SBI-0799220 CocH5-Fc(M6) Cocaine hydrolase SBX-518	OMS 182399 PPL-138 IXT-m200 Long –Acting NHB 1109	Zolmitriptan TMP-301 Cocaine hydrolase gene therapy dAdGNE h2E2 **CS-1103**			

CS-1103

- Small molecule sequestrant for the treatment of acute METH intoxication
- Selectively binds METH and accelerates its removal from the body
- Provides long-lasting reversal of acute METH intoxication in pre-clinical studies in animal models
- Well-tolerated based on First-in Human Phase I trial completed in June 2024

U01DA053054, Xinhua Li, Clear Scientific

Stimulant Use Disorder and Overdose

Early Preclinical	Late Preclinical	Clinical Trials			
		Phase I	Phase Ib	Phase II	Phase III
SBI-0801315/SBI-0799220 CocH5 Coca SB	OMS 182399	Zolmitriptan	Cariprazine Mirtazapine Clavulanic acid Ketamine **Exenatide** BICX104/Bupropion	Pioglitazone Rotigotine Bupropion/Naltrexone TNX-1300 IXT-m200 (OD)	

Exenatide

- Assessing the efficacy of Exenatide extended release on cocaine self-administration, subjective effects and tolerance
- SC, once/weekly in non-treatment seekers, N=44

R21DA057411, Christopher Verrico, Baylor

Stimulant Use Disorder and Overdose

Early Preclinical	Late Preclinical	Clinical Trials			
		Phase I	Phase Ib	Phase II	Phase III
SBI-0801315/SBI-0799220 CocH5-Fc(M6) Cocaine hydrolase SBX-518	OMS 182399	Zolmitriptan	Cariprazine d pion	Pioglitazone Rotigotine **Bupropion/Naltrexone** TNX-1300 IXT-m200 (OD)	

Bupropion/Naltrexone

- Goal =replicate the results of the ADAPT-2 study
- Participants with moderate-severe Meth UD who want to reduce or stop METH use
- Bupropion ER (450mg q. d.) plus extended-release naltrexone (monthly injectable) for 12 weeks
- Age 18-65 years old, N= 360 and 10 sites

NIDA DTMC/VA IAA, PI: Ivan Montoya

National Institute on Drug Abuse

Cannabis Use Disorder Pipeline

Early Preclinical	Late Preclinical	Phase 1 Clinical trials	Phase II Clinical Trials	Phase III Clinical Trials
▪ CB1 antagonist for Acute Intoxication		▪ Guanfacine	▪ Varenicline ▪ PF-04457845 ▪ Cannabidiol/ Full spectrum hemp	▪ AEF0117

National Institute on Drug Abuse

Tobacco Use Disorder Pipeline

Early Preclinical	Late Preclinical	Clinical Trials			
		Phase I	Phase Ib	Phase II	Phase III
	•ATI-1013 (anti-nicotine monoclonal antibody)	•AT-1082 (α3β4 partial agonist)	•SBI-0069330 (mGlu2 PAM)	•Suvorexant •Isradipine •Ketamine •Varenicline + Guanfacine •Exenatide + NRT •Psilocybin •Varenicline (in adolescent e-cigarette users)	

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Therapeutic Devices Pipeline

Preclinical	Feasibility/Target Engagement/Early Efficacy	Efficacy	Pivotal
• Closed-loop system for Opioid Induced Respiratory Depression • Phrenic Nerve Stimulator for Opioid Overdose	• Transcranial Magnetic Stimulation for Cocaine Use Disorder • Transcranial Magnetic Stimulation for Nicotine Use Disorder • Transcranial Magnetic Stimulation for Nicotine Use Disorder • Deep Brain Stimulation for Methamphetamine Use Disorder • Low-Intensity Focused Ultrasound for Cocaine Use Disorder • Heart Rate Variability Biofeedback for Nicotine Use Disorder • Transcranial Direct Current Stimulation for Cannabis Use Disorder • Low-Intensity Focused Ultrasound for Opioid Use Disorder • Heart Rate Variability Biofeedback for Substance Use Disorder • Transcranial Magnetic Stimulation for Nicotine Use Disorder • Transcranial Magnetic Stimulation for Cocaine Use Disorder	• Sparrow Ascent System in PTSD and Opioid Use Disorder • Low-Intensity Focused Ultrasound for Opioid Use Disorder • Portable tDCS Device for Cocaine Use Disorder • Transcranial Magnetic Stimulation for Nicotine Use Disorder • NSS-2 Bridge Device following surgery (opioid sparing) • Transcranial Direct Current Stimulation for Opioid Relapse • Vagus Nerve Stimulation for Opioid Use Disorder • Vagus Nerve Stimulation for Lower Back Pain	• Bridge Device for Opioid Use Disorders • Transcranial Magnetic Stimulation for Nicotine Use Disorder

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Digital Therapeutics Pipeline

Early Feasibility	Feasibility	Pivotal
Vaper to Vaper (V2V): A Multimodal Mobile Peer Driven Intervention to Support Adolescents in Quitting Vaping	A game-based intervention for Opioid Use Disorder	Randomized Controlled Trial of a Novel Smoking Cessation Application Tailored to Individuals with Serious Mental Illness
Re-Connect: Personalized, Non-Monetary Smartphone-based Rewards for Smoking Cessation	Reducing Non-Medical Opioid Use: An automatically adaptive mHealth Intervention	Enhancing Hypnotic Medication Discontinuation in Primary Care through Supervised Medication Tapering and Digital Cognitive Behavioral Insomnia Therapy
Development of an mHealth Behavioral Sleep Medicine Intervention for use during Medication Assisted Treatment for Opioid Use Disorder	Development and Testing of a Depression-Specific Behavioral Activation Mobile App Paired with Nicotine Replacement Therapy Sampling for Smoking Cessation Treatment Via Primary Care	
	ACT on Vaping: Digital Therapeutic for Young Adult Vaping Cessation	
	Continuing Care App for Justice-Involved Individuals with Substance Use Disorders	
	A Randomized Controlled Trial of A Digital, Self-Guided, Avatar Assisted- Cognitive Behavioral Therapy Platform to Treat Addiction: Digital RITch®CBT vs. Standard CBT	

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Behavioral Therapies Pipeline

Stage I	Stage II	Stage III
Virtual Reality-Augmented Future Orientation in Stimulant Use Disorder Recovery	Brief Individual and Parent Interventions for Marijuana Misuse in Truant Adolescents	Treating Chronic Pain in Buprenorphine Patients in Primary Care Settings
An mHealth mood management tool to improve population-level tobacco cessation	Early Withdrawal Exposure and Negative Affect Withdrawal (NAW) Regulation Training for Smoking Cessation	Use of blinded tapering for hypnotic discontinuation
Mindfulness-Based Addiction Treatment Delivered Through Mobile Technology for Low-Income Smokers		Smoking Cessation Self-Help for Dual Users of Tobacco Cigarettes and E-Cigarettes
Testing the feasibility and acceptability of social media and digital therapeutics to decrease vaping behaviors		Randomized trial of telephonic pain self-management to promote opioid tapering
An mHealth mood management tool to improve population-level tobacco cessation		Repeated-dose behavioral intervention to reduce opioid overdose: a two-site randomized-controlled efficacy trial
Computerized Distress Tolerance Intervention for Cannabis Use Disorder		Targeting Hedonic Dysregulation to Address Chronic Pain and Opioid Misuse in Primary Care.
Pilot Study to Evaluate a Behavioral Activation Prenatal and Postpartum Intervention for Depressed Pregnant Smokers		Integrated Treatment for Veterans with Co-Occurring Chronic Pain and Opioid Use Disorder

2023-2024: Provisional* Drug Overdose Deaths 12-months ending in select months

	ALL DRUGS	HEROIN	NAT. & SEMI SYNTHETIC	METHADONE	SYNTHETIC OPIOIDS (illicit fentanyl)	COCAINE	OTHER PSYCHO-STIMULANTS (meth.)
11/2023*	111,708	4,339	10,745	3,509	77,576	31,130	37,602
5/2024*	100,642	3,561	9,589	3,449	67,381	28,401	34,889
11/2024*	82,059	2,806	8,080	3,213	50,283	22,688	29,767
Percent Difference 11/23-11/24	**-26.54%**	**-35.33%**	**-24.80%**	**-8.44%**	**-35.18%**	**-27.12%**	**-20.84**

***NCHS Provisional drug-involved overdose death counts are PREDICTED VALUES, 12 months ending in select months. The numbers for 2023 differ in slides 1 and 2 because provisional data for 12 months ending in select months includes all deaths that occurred in the US including foreign residents.**

Source: Provisional Drug Overdose Death Counts produced by the National Vital Statistics System, NCHS, CDC, UHHS.

Opportunities for Funding and Research Collaborations

https://nida.nih.gov/about-nida/organization/divisions/division-therapeutics-medical-consequences-dtmc

https://simpler.grants.gov/search

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