New Horizons/Approaches in Medications Development for SUDs

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• No Conflict of Interest

• Medications and compounds that may not approved by the FDA for the specific indication will be mentioned
Outline

• Introduction
• Medications under clinical evaluation
• 10 most wanted
• Promising approaches
• Conclusions
Molecular Neurobiology of Substance Use Disorders

- Enkephalin or Dynorphin Inhibitory Neuron
- Glutamate Excitatory Input
- Enkephalin or Dynorphin Inhibitory Neuron
- GABA Inhibitory Neuron
- Dopamine Neuron
- GABA-A Receptors
- Presynaptic Opioid Receptors (μ, δ)
- Ventral Tegmental Area (VTA)
- Nucleus Accumbens (NAc)
- Dopamine Receptors
- GABA Inhibitory Feedback
- REWARD
FDA Approved Medications for SUDs

- Opioid
  - Methadone
  - Buprenorphine
  - Naltrexone
  - Naloxone
  - Lofexidine
- Nicotine
  - NRT
  - Bupropion
  - Varenicline
- Cocaine, Methamphetamine, Cannabis: None
Cocaine

– Clinical Studies

- Lorcaserin (Belviq XR®)
- EMB-101 (Oxazepam + Metyropone)
- Buprenorphine + Opioid Antagonist
- Ketamine
- Oxytocin
- Bupropion/Naltrexone (Contrave®)
- Topiramate/Fentermine (Qsymia®)
- L-Tetrahydropalmatine (L-THP)
Methamphetamine – Clinical Studies

- Mirtazapine
- Monoclonal Antibody
- Vaccine
- Naltrexone
- Ibudilast
- Bupropion
- Buspirone
- Oxytocin
Opioid - Clinical Studies

- OLANI (6-month naltrexone implant)
- Tradipitant (NK-1 antag)
- Duloxetine (SNRI)
- Brivoligide (oligo EGR1 inh)
- Brixadi (Bup. 1 wk, 1 mo. Inj)
- Guanfacine (alpha2 agonist)
- PF614 (Abuse deterrent prodrug)
- Ketamine (NMDA antag)
- Suvorexant (OX1/2 antag)
- Gabapentin
- Dronabinol (THC)
- CBD
- Lorcaserin (5HT2c agonist)
- OPNT003 (Nasal nalmefene)
- Long-acting formulations nalmefene, buprenorphine, methadone
NIDA’s Role in the NIH HEAL Initiative

Revised February 2019

NIDA is playing a major role in the National Institutes of Health (NIH) HEAL initiative (Helping to End Addiction Long-term), launched in June 2018 to provide scientific solutions to the national opioid overdose crisis, including improved treatment strategies for pain as well as opioid use disorders (OUDs). This new initiative, funded by Congress, brings new hope for people, families, and communities affected by this devastating crisis.

NIDA will be coordinating four overarching research projects around the country:

- **Focused OUD Medications Development Research Project**
- **HEALing Communities Study**
- **The Clinical Trials Network OUD Research Expansion Project**
- **The Justice Community Opioid Innovation Network**
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**PAM** positive allosteric modulator, **NAM** negative allosteric modulator, **AMPA** α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, **GABA** γ-aminobutyric acid, **NOP** nociceptin opioid peptide receptor, **ORL** opioid receptor like, **mGluR** metabotropic glutamate receptor, **SHT** 5-hydroxytryptamine, **MOP** mu opioid protein

Other mechanisms of interest:
- SHT2C agonists or PAMs, with or without SHT2A antagonist/NAM activity [41, 42]
- Biased Mu Opioid agonists or PAMs [43, 44]
- NOP/MOP bifunctional agonists or PAMs [45, 46]
- Respiratory stimulants (including nicotinic agonists) [47, 48]
Orexin / Hypocretin

• **Orexin**, from *orexis*, meaning "appetite" in Greek

• **Hypocretin**, because it is produced in the hypothalamus and bears a weak resemblance to *secretin*, another peptide.

• The use of both terms is now a practical necessity
  • *Hypocretin* is used to refer to the genetic
  • *Orexin* is used to refer to the protein products
10,000–20,000 orexin-producing neurons in the human brain
- Located predominantly in the perifornical area and lateral hypothalamus
- Project widely throughout the central nervous system
- There are two types of orexin peptide and two types of orexin receptor
- Regulates arousal, wakefulness, reproduction, and appetite.

Orexin Antagonists

- Suvorexant (Belsomra®) (Merck & Co)
  - Approved FDA and Australia
  - 10 mg 30 min before going to bed
  - Schedule IV
- Lemborexant (Eisai)
- Nemorexant (Idorsia Pharma)
- SB-334,867 (Smart, 2001)
- SB-408,124
- SB-649,868 (Glaxo)
- TCS-OX2-29, OX2 selective (Hirose, 2003)
- RTIOX-276, OX1 selective (Levy, 2017)
- Paul Kenny
- Heptares
- Filorexant (Merck & Co, abandoned?)
- Almorexant (Actelion & GSK - abandoned)
Orexin 1 Antagonists – Why clinically?

- Sleep problems frequently precede SUD
- Sleep is directly impaired by SUD
  - Drug (opioids) modify the sleep-wake cycle (Orexin system)
- Drug withdrawal associated with sleep disruptions
- FDA public meeting on patient-focused drug development for chronic pain as a primary contributor to OUD treatment discontinuation
- Sleep problems have been independently associated with increased comorbidity
- Sleep aids are among the most widely-traded medications within OUD clinics
- Benzodiazepines are frequently abused in conjunction with opioids
  - Benzodiazepines co-administration with opioid agonists is associated with increased lethality
- Orexin system may underlie sleep disturbance in persons with OUD
- Orexin antagonist approved by FDA to improve sleep architecture and more...
OX1 Antagonists and Cocaine

- Reduce dopamine transporter sensitivity to cocaine in the VTA and NAc
- Disrupt the expression of Pavlovian associations formed by cocaine
- Reduce compulsive-like cocaine taking under long access self-administration conditions
- Suppress motivation to obtain cocaine under high effort conditions
- Reduce the strength of stress-, cue- and context-induced cocaine reinstatement.
Reduce stress-induced reinstatement of cocaine seeking in rats

Zhou et al., 2012
Orexin 1 Antagonists and Opioids

• Attenuated the acquisition of morphine-induced CPP
• Contribution to development of morphine reward-related behavior
• Development of drug seeking behaviors in the rats
• Increase number of hypocretin neurons
Intra-NAc administration of TCS OX2 29 (nM/0.5 μl DMSO) during 3-day conditioning period

Morphine (5 mg/kg; sc) during 3-day conditioning period
Postmortem brain tissue from heroin addicts shows an increased number of hypocretin-producing neurons.
Opiate addiction and narcolepsy: Opposite sides of the same coin?

The neurological mechanisms that maintain opiate addiction and prevent long-term withdrawal are not well understood. In a new study, Thannickal et al. found that human heroin addicts have, on average, 54% more hypocretin-producing neurons than do neurologically normal control individuals. They show that a similar increase in hypocretin-producing neurons could be induced in mice through long-term morphine administration. This long-lasting increase in hypocretin neurons may be responsible for maintaining addiction. Narcolepsy is caused by a loss of hypocretin-producing neurons. Morphine administration restored the population of hypocretin neurons in hypocretin cell-depleted mice back to normal numbers and decreased cataplexy in narcoleptic animals. Induction of specific long-term changes in neuropeptide production, outlasting the half-life of the administered drugs, may be useful in treating diseases characterized by loss of neurons producing these neuropeptides.
Clinical Studies

NCT02785406, PI: Scott Lane
• To evaluate the effectiveness of suvorexant in reducing anxiety, improving sleep, and reducing cocaine cravings or cocaine use. (n=20)
• Completed, results not available

NCT03789214, PI: Andrew Uuhn
• To evaluate if suvorexant (10 and 20 mg qd) will increase total sleep time in patients with opioid use disorder (OUD) undergoing supervised withdrawal (n=45).
• OUD patients seeking supervised withdrawal will be admitted into a clinical research unit and stabilized onto buprenorphine for three days before being randomly assigned to study condition.
• All participants will undergo a routine four-day buprenorphine taper, followed by a four-day post-taper phase.
• Participants will be randomized to receive either placebo, low dose, or high dose of suvorexant
• Hypothesis: suvorexant will improve total sleep time relative to placebo and improve outcome of opioid withdrawal
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Serotonin [5-hydroxytryptamine (5-HT)] Systems

• 14 distinct subtypes of 5-HT receptors
• The 5-HT2 family of receptors includes the 5-HT2A, 5-HT2B, and 5-HT2C receptors
• The 5-HT (2c) receptor has a widespread distribution in mammalian brain tissue, and is especially abundant in dopaminergic cell body regions of the substantia nigra and ventral tegmental area (VTA) as well as in terminal projection areas of the nucleus accumbens, striatum, and prefrontal cortex (Gurevich et al., 2002).

• Tonic inhibitory influence over the activity of ascending DA neurons
• Regulation of feeding (hypothalamus), as well as motor control, motivation, and reward (Hannon and Hoyer, 2008).
5-HT2C Agonist - Lorcaserin

- Clinically available
- Selective agonist at the 5HT2c receptor
- Modulate mesolimbic dopamine, decreasing dopamine release
- FDA-approved for weight loss
  - Lorcaserin (Belviq®) 10 mg bid
  - Lorcaserin XR (Belviq XR®) 20 mg qd
- Schedule IV

- Arena Pharmaceuticals - Eisai Inc.
Lorcaserin Pre-clinical Studies - Stimulants

- Decrease cocaine self-administration and the reinstatement of responding for cocaine (Grottick et al., 2000; Burmeister et al., 2004; Burbassi and Cervo 2008; Cunningham et al., 2011; Manvich et al., 2012; RüediBettschen et al., 2015, Howell and Cunningham 2015).
- Attenuates self-administration of cocaine (Collins et al., 2016; Harvey-Lewis et al., 2016) and nicotine (Levin et al., 2011; Higgins et al., 2012, 2013)
- Tolerance does not develop to the effects of lorcaserin on cocaine self-administration (Collins et al., 2016)
- Attenuates the ability of stress or conditioned cues to stimulate cocaine-seeking behavior in rats with a prior history of cocaine self-administration (Fletcher et al., 2008)
- Efficacy against methamphetamine cue reinstatement and nicotine
Lorcaserin Cocaine Self-Administration in Monkeys
Effects of Lorcaserin on Responding for Cocaine or Food in Rhesus Monkeys
Selective serotonin 2C receptor agonist
Modulates the dopaminergic reward system.
Approved by the FDA for chronic weight management
Lorcaserin Pre-clinical Studies - Opioids

• Decreases the reinforcing effects of heroin, but not food, in rhesus monkeys (Kohut, 2018)
• Reduces rewarding effects of heroin by reducing its reinforcing strength (Kohut, 2018).
• In rhesus monkeys, lorcaserin can reduce heroin-primed reinstatement of remifentanil self-administration (Gerak, 2018).
Lorcaserin reduces heroin self-administration in rhesus monkeys
Lorcaserin blocks heroin-induced reinstatement of remifentanil self-administration and is slightly more potent than it is for blocking cocaine-induced reinstatement of cocaine self-administration in rhesus monkeys.
Reduces the self-administration of alcohol (Rezvani et al., 2014)
Lorcaserin for Nicotine

12-week, RCT
N=600 smokers
Body Mass Index of 18.5–35 kg/m², averaging at least 10 cigarettes/day
lorcaserin 10 mg once daily (QD)
10 mg twice daily (BID) or placebo;

Primary endpoint:
Exhaled carbon monoxide confirmed
Continuous Abstinence Rate for weeks 9–12 (month 3)
Lorcaserin for Nicotine

Graph showing the percentage of abstinence over treatment weeks for Placebo, Lorcaserin 10 mg q.d., and Lorcaserin 10 mg b.i.d. groups. The graph indicates a statistical significance difference between the Lorcaserin 10 mg b.i.d. group and the Placebo group, with p < 0.05 and p < 0.01 for different comparisons.

Shanahan, 2016
Lorcaserin for Cocaine
– Clinical Trials

**NCT03007394**
- Phase 2 multicenter RCT - NIDA
- N=272
- 10 mg bid * 13 weeks
- Recruitment complete
- Data analysis in progress
- Primary endpoint: proportion of subjects that successfully achieve abstinence from cocaine during the last three weeks of treatment in the "pre-qualified for primary efficacy endpoint" (PPEE) population [Time Frame: Treatment weeks 11 - 13]

**NCT03192995**
- Pilot RCT (n=45) UCSF
Lorcaserin for Opioids

• **NCT03169816** PI: Frances Levin, MD

• Lorcaserin in Combination With XR-Naltrexone for Relapse Prevention in Opioid Use Disorder

• Lorcaserin (N = 40), or placebo (N = 20)

• Outpatient detoxification and naltrexone induction followed by a relapse-prevention treatment with Extended release-naltrexone (XR-NTX)

• Recruiting subjects
Lorcaserin - Safety

- The mechanism of action of lorcaserin is identical to that of Schedule I hallucinogens (5HT2C and 2A agonism).
- It is likely that doses larger than 10 mg (BID) of lorcaserin will be required to produce clinically relevant outcomes (i.e., sustained abstinence) thereby increasing the likelihood for 5-HT2A receptor-mediated effects (e.g., hallucination) that could limit the therapeutic potential of lorcaserin to treat substance abuse.
- Some euphoria reported in clinical trials
- Abuse potential most similar to that of zolpidem (Schedule IV), and therefore, lorcaserin is Schedule IV of the Controlled Substances Act.
Summary

• Pre-clinical and a few clinical studies suggest that Orexin 1 antagonists and 5TH2C agonist may have therapeutic efficacy for multiple substances of abuse.
• They may be efficacious to treat poly-substance abuse.
• Clinically available
• Both approaches carry the risk of side-effects
• More clinical research is needed
Regardless of whether lorcaserin proves to be effective at prolonging abstinence from drug use, it is important to remember that it has limited selectivity for 5-HT2C over 5-HT2A receptors, and that doses only slightly larger than those currently approved for use in humans (10 mg, BID) have been shown to produce adverse, “offtarget” effects that are likely mediated by 5-HT2A receptors (Shram et al., 2011). Taken together with data from preclinical studies in rodents and non-human primates in which relatively large doses of lorcaserin were required to decrease on-going drug selfadministration (or the reinstatement of extinguished responding), it is possible, if not likely, that doses larger than 10 mg (BID) lorcaserin will be required to produce clinically relevant outcomes (i.e., sustained abstinence) thereby increasing the likelihood for 5-HT2A receptor-mediated effects (e.g., hallucination) that could limit the therapeutic potential of lorcaserin to treat substance abuse.
Orexin Signaling Pathways
• Five postmortem brains from heroin addicts had, on average, 54% more immunohistochemically detected neurons producing hypocretin than did control brains from neurologically normal subjects.
• Similar increases in hypocretin-producing cells could be induced in wild-type mice by long-term (but not short-term) administration of morphine.
• The increased number of detected hypocretin neurons was not due to neurogenesis and outlasted morphine administration by several weeks.
• The number of neurons containing melanin-concentrating hormone, which are in the same hypothalamic region as hypocretin-producing cells, did not change in response to morphine administration.
• Morphine administration restored the population of detected hypocretin cells to normal numbers in transgenic mice in which these neurons had been partially depleted.
• Morphine administration also decreased cataplexy in mice made narcoleptic by the depletion of hypocretin neurons.
• Opiate agonists may have a role in the treatment of narcolepsy, a disorder caused by hypocretin neuron loss, and that increased numbers of hypocretin-producing cells may play a role in maintaining opiate addiction.
Reduce stress-induced reinstatement of drug seeking in rats

• Kappa Opioid Receptor Antagonists
• OX-1 Receptor Antagonists
• NOP Receptor Agonists
• PDE7 Inhibitors
Reduce cue-induced reinstatement of drug seeking

• OX-1 Receptor Antagonists
• 5-HT2C Receptor Agonists
• D3 Receptor Antagonists
• 5-HT2A Receptor Inverse Agonists
• mGluR2 Positive Allosteric Modulators
• PDE7 Inhibitors
Lorcaserin – Weight Loss

![Graph showing weight change over time with Lorcaserin treatment. The graph indicates a significant decrease in weight, with marked reductions of 2.5 kg, 3.7 kg, and 5.8 kg at different time points.](https://www.belqiq.com/-/media/Files/BelqiqConsolidation/PDF/Belqiq_Prescribing_information-pdf.PDF?la=en)
5HT2c Agonists

- Reduce food intake through the proopiomelanocortin system of neurons, and both neural circuits may be important in modifying eating behavior.
- In rodents, reduce the firing rate of mesocorticolimbic dopaminergic neurons, leading to reduced dopamine release in terminal regions of the nucleus accumbens and frontal cortex, and blockers have the opposite effect (Higgins et al.).
- In humans, **might** be effective in lessening the reward associated with substances of dependence, facilitating withdrawal, and achievement of abstinence.
Lorcaserin - Safety

- Valvular heart disease
- Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)–like reactions:
- Painful erections
- Changes in attention or memory
- Headache, dizziness, fatigue, nausea, dry mouth, constipation, cough, low blood sugar (hypoglycemia) in patients with diabetes, and back pain.
- Pregnancy and breastfeeding
- Hypersensitivity reactions

- Is a federally controlled substance (CIV) because it may be abused or lead to drug dependence.

- Drug interactions: triptans; tricyclics, lithium, selective serotonin reuptake inhibitors, selective serotonin-norepinephrine reuptake inhibitors, monoamine oxidase inhibitors, or antipsychotics; cabergoline; linezolid; tramadol; dextromethorphan, tryptophan or St. John’s Wort; or erectile dysfunction medicines.