Nouvelles pistes thérapeutiques dans le traitement des addictions

Iván D. Montoya, M.D., M.P.H.
Deputy Director, Division of Therapeutics and Medical Consequences
NIDA
Substances for Which Most Recent Treatment was Received - 2013

Source: NSDUH, 2014
Substances for Which Most Recent Treatment was Received - 2013

Source: NSDUH, 2014
Opioid Overdose Deaths

Prescription Opioid Overdose

Source: CDC Wonder

Heroin Overdose Deaths

Source: CDC Wonder
Opioid Overdose
(FDA Approved 4/14)

Evzio: the first and only naloxone auto-injector

Your patients on opioids can have an additional safeguard with them on their pain management journey in the event of an opioid overdose. EVZIO is not a substitute for emergency medical care.

Evzio is an opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. EVZIO is intended for immediate administration as emergency therapy in settings where opioids may be present. EVZIO is not a substitute for emergency medical care.

Indication:
EVZIO is contra-indicated in patients known to be hypersensitive to naloxone hydrochloride or to any of the ingredients in EVZIO.

The following warnings and precautions should be taken when administering EVZIO:

http://www.evzio.com/hcp/
Opioid Overdose

Lightlake Therapeutics Inc. (licensed agreement with Adapt Pharma)

http://www.lightlaketherapeutics.com/index.html

Lightlake Therapeutics Inc. Announces Adapt Pharma Limited Submits NDA To FDA For Narcan® (naloxone) Nasal Spray

NEW YORK, July 29, 2015 /PRNewswire/ -- Lightlake Therapeutics Inc. ("Lightlake") (OTCQB: LLTP), a specialty pharmaceutical company developing addiction treatments based on its expertise in opioid antagonists, announced today that Adapt Pharma Limited ("Adapt"), Lightlake’s partner for treating opioid overdose with intranasal naloxone, has submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) for Narcan® (naloxone) Nasal Spray, an investigational drug intended to treat opioid overdose.

Narcan® Nasal Spray has been granted Fast Track Designation by the FDA. Narcan® Nasal Spray was developed in collaboration with the National Institutes on Drug Abuse (NIDA).
Opioid Overdose

Indivior PLC Announces FDA Acceptance of Naloxone Nasal Spray New Drug Application With Priority Review

07.29.2015 | PDF Version

Product Candidate Has Potential to Be First Nasal Naloxone Product to Treat Opioid Overdose In United States

Slough, UK, 29 July 2015 – Indivior PLC (LON: INDV) today announced that the New Drug Application (NDA) for naloxone nasal spray was accepted and received Priority Review by the U.S. Food and Drug Administration (FDA) for the treatment of opioid overdose. This naloxone nasal spray comes as a pre-filled device that contains naloxone specially formulated for optimal absorption into the nasal mucosa. The device has been designed to require minimal training so individuals may be better equipped to help an opioid overdose victim.
Opioid Withdrawal

DSM-5 Criteria for Opioid Withdrawal

Description: Lists the clinical criteria for opioid withdrawal.

DSM-5 Criteria for Opioid Withdrawal (APA, 2013)

A. Either of the following:
   1. cessation of (or reduction in) opioid use that has been heavy and prolonged (several weeks or longer)
   2. administration of an opioid antagonist after a period of opioid use

B. Three (or more) of the following, developing within minutes to several days after Criterion A:
   1. dysphoric mood
   2. nausea or vomiting
   3. muscle aches
   4. lacrimation or rhinorrhea
   5. pupillary dilation, piloerection, or sweating
   6. diarrhea
   7. yawning
   8. fever
   9. insomnia

C. The signs or symptoms in Criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

D. The signs or symptoms are not due to another medical condition and are not better accounted for by another mental disorder, including intoxication or withdrawal from another substance.

No FDA-approved medication
Lofexidine for Opioid Withdrawal

- Alpha-2-adrenergic receptor agonist
- Approved in the United Kingdom for the treatment of opioid withdrawal
- More significant effects on decreasing opioid withdrawal symptoms with less hypotension than clonidine.
Lofexidine for Opioid Withdrawal

Yu, 2008

![Graph showing the effect of Lofexidine and Placebo on MHOWS (mean +/- SEM) over study days.](image)
Lofexidine Hydrochloride
for treatment of opiate withdrawal symptoms

Upon approval by the Food and Drug Administration (FDA), Lofexidine would be the first non-narcotic and non-addictive medication approved in the United States for the mitigation or relief of symptoms associated with acute withdrawal from short-acting opioids such as heroin and commonly used prescription pain medications like Vicodin®, Lortab®, and Oxycontin®.

Lofexidine is approved in the United Kingdom as BritLofex® and has been used in successful detoxification of more than 200,000 opiate addicts. US WorldMeds acquired the U.S. license for Lofexidine from Britannia Pharmaceuticals in 2003. Lofexidine has also been studied in six prior clinical trials in the United States, including an earlier Phase III study of 264 opiate-dependent patients.

Currently, investigators are recruiting opiate-dependent individuals seeking detoxification at 13 sites throughout the United States. The Phase III trial is a randomized, double-blind, placebo controlled investigation evaluating the safety and efficacy of Lofexidine in the treatment of opioid-withdrawal symptoms.

In collaboration with the National Institute on Drug Abuse (NIDA) US WorldMeds will continue to address an unmet medical need in the opioid-dependent population. The number of heroin abusers in the United States is estimated between 600,000 and 1 million. In addition, the United States Substance Abuse and Mental Health Services Administration recently reported that an estimated 22.5 million Americans, aged 12 or older, had used an illicit drug in the last month.¹ According to the National Institutes of Health (NIH), this growing population of illicit drug users “accounts for $181 billion in health care, productivity loss, crime, incarceration and drug enforcement.”²
Buprenorphine Implant

- **Probuphine®** subcutaneous implant delivers low, steady-state levels of buprenorphine for 6 months

- Ethylene vinyl acetate combined with buprenorphine
  - 26 mm x 2.5 mm, 80 mg buprenorphine

- **Possible Advantages**
  - Reduced risk of diversion
  - Improved compliance
  - Reduced side-effects associated with fluctuating drug levels
Example to understand this cumulative graph:
About 50% of patients in the buprenorphine implant group and also in the sublingual buprenorphine group had 20% or fewer of their 72 urines negative for illicit opioids over 24 weeks (50% were more successful), and about 80% of those in the placebo group had 20% or fewer negative urines (20% were more successful).
TITAN PHARMACEUTICALS REPORTS POSITIVE RESULTS FROM PHASE 3 STUDY OF PROBUPHINE FOR OPIOID ADDICTION

New Drug Application Expected to Be Resubmitted in Second Half of 2015
Titan to Host Conference Call Today at 9 a.m. EDT

South San Francisco, CA – JUNE 8, 2015 – Titan Pharmaceuticals, Inc. (OTCQB: TTNP) today reported positive topline results from the Phase 3 double blind, double dummy clinical study of Probuphine®, the company's subdermal implant containing buprenorphine HCl for the long-term maintenance treatment of opioid addiction. This study met the pre-specified primary endpoint of non-inferiority, as well as all secondary efficacy endpoints. It was conducted by Titan’s commercialization and development partner Braeburn Pharmaceuticals and developed in consultation with the U.S. Food and Drug Administration (FDA) prior to initiating the study.

Braeburn team in completing this study rapidly, and we would like to thank the subjects, clinical investigators and their staff who participated in this trial. We would also like to extend a special thanks to NIDA (National Institute on Drug Abuse) for its early support of the overall development program. We look forward to resubmitting the NDA later this year and to potentially securing approval for the product in the first half of 2016."

Implant vs. Oral Buprenorphine

Six-month treatment
Sublingual buprenorphine/naloxone (n=89)
Buprenorphine implant (n=84)
Opioid withdrawal and cravings, safety: no difference

* p < .05

Unpublished data. Braeburn press release 8/6/15
“Regular” users:
2006: 3.1 M
2013: 5.7 M

Source: NSDUH, 2014
Pharmacotherapies for CUDs

CB1 Agonist
- Dronabinol
- THC nasal

CB1 Antagonist
- Rimonabant
- AM251
- AM 5109
- FAAH Inhibitors
- AM 374
- URB597
- AM5206
- A7nAchr antag. - Methyllycaconitine

Marijuana → Receptor → NT signal

Additional medications:
- Buspirone
- Fluoxetine
- Lofexidine
- Naltrexone
- Divalproex
- Topiramate
- Quetiapine
- Buprenorphine
- Selegiline
- Clozapine
- Risperidone
- Bupropion
- Lithium
- Nefazodone
## Cannabis Pre-clinical Studies

<table>
<thead>
<tr>
<th>PI</th>
<th>Compound</th>
<th>Mechanism</th>
<th>LI</th>
<th>LO</th>
<th>Pre-Clin</th>
<th>IND</th>
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<tbody>
<tr>
<td>Jack Bergman</td>
<td>AM3506</td>
<td>FAAH inhibitor</td>
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<td>Alex Makriyannis</td>
<td>AM7499</td>
<td>CB1 agonist</td>
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<tr>
<td>Lance McMahon</td>
<td>CP 55,940</td>
<td>CB1 agonist</td>
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## Cannabis – Clinical Studies

<table>
<thead>
<tr>
<th>PI</th>
<th>Compound</th>
<th>Mechanism</th>
<th>Indication</th>
<th>P1</th>
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<tbody>
<tr>
<td>Kevin Hill</td>
<td>Nabilone (Cesamet®)</td>
<td>Synthetic cannabinoid</td>
<td>Craving</td>
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<tr>
<td>Barbara Mason</td>
<td>Aprepitant (Emend®125 mg/d)</td>
<td>NK1 antagonist</td>
<td>Withdrawal</td>
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<tr>
<td>Meg Haney</td>
<td>Varenicline +/- Nabilone</td>
<td>Nicotinic / CB Ag.</td>
<td>Withdrawal</td>
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<td>Bernard LeFoll</td>
<td>Nabiximols (Sativex®)</td>
<td>Cannabis extract</td>
<td>Craving</td>
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<td></td>
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<td>CBD:THC 1:1 ratio.</td>
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<td>Joshua Lile</td>
<td>Pregabalin &amp; Tiagabine</td>
<td>GABA Ag.</td>
<td>Dependence</td>
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<td>Meg Haney</td>
<td>Celecoxib (400 mg/d)</td>
<td>Cox 2 inhibitor</td>
<td>Dependence</td>
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<td>Kevin Gray</td>
<td>NAC</td>
<td>Glutamatergic</td>
<td>Dependence</td>
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<td>Barbara Mason</td>
<td>Gabapentin (1200 mg/d)</td>
<td>GABA agonist</td>
<td>Dependence</td>
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<tr>
<td>Ryan Vandrey</td>
<td>Zolpidem (Ambien®)</td>
<td>GABA-A g.</td>
<td>Insomnia withdrawal</td>
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<tr>
<td>John Mariani</td>
<td>Quetiapine (Seroquel®)</td>
<td>D, 5HT, NE, H1 Antag.</td>
<td>Dependence</td>
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<td>Alan Green</td>
<td>Clozapine</td>
<td>DA, NE antag.</td>
<td>Schizophrenia + CUD</td>
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<td>Deepak D’Souza</td>
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<td>FAAH Inhibitor</td>
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Cocaine Use Disorder
Past-Year Prevalence

+ Difference between this estimate and the 2014 estimate is statistically significant at the .05 level

NSDUH, 2015
Cocaine Addiction – Candidate Medications

- Vigabatrin
- Buspirone
- Modafinil
- Topiramate
- Cocaine vaccine
- Buprenorphine
- Nepicastat
- Butyrylcholinesterase
Cocaine Addiction – Candidate Medications

- Vigabatrin
- Buspirone
- Modafinil
- Topiramate
- Cocaine vaccine
- Buprenorphine
- Nepicastat
- Butyrylcholinesterase
## Cocaine – Small Molecules
### Pre-Clinical Studies

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<tr>
<td>Fiona Marshall</td>
<td>SB-33867</td>
<td>Ox1 Antag</td>
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<tr>
<td>Kathy Cunningham</td>
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<td>5-HT2C Ag-like</td>
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<tr>
<td>Stephen Husbands</td>
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<td>KOR Antag/NOP Ag/Delta Antag</td>
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<td>Robert Luedtke</td>
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<td>D3 Antag</td>
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<td>Thomas Bannister/Nurulain Zaberi</td>
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<td>NOP Ag</td>
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<td>Magid Abou-Gharbia</td>
<td>MC-100093</td>
<td>GLT1 enhancer</td>
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<td>Jane Aldrich, Susan Lunte</td>
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<td>KOR Antag</td>
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<td>Robert Malcolm</td>
<td>NAC-ER</td>
<td>Glutamatergic</td>
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<td>Richard Foltin</td>
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<td>Orexin Antag</td>
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<td>Alvin Terry</td>
<td>Guanfacine</td>
<td>Alpha 2 A Ag</td>
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<td>Marie Thomsen</td>
<td>VU0152099</td>
<td>Muscarinic M4-selective PAM</td>
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# Cocaine – Small Molecules Clinical Studies

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<tr>
<td>Charles France &amp; Ken Grasing</td>
<td>Lorcaserin</td>
<td>5-HT2C Ag</td>
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<td>Elias Dakwar</td>
<td>Ketamine</td>
<td>Glu modulator</td>
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<td>Tom Newton</td>
<td>Modafinil/Doxasozin</td>
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<td>Rabi Wilfred</td>
<td>Oxytocin</td>
<td>Neuropeptide modulator</td>
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<td>Craig Rush</td>
<td>Bupropion/Naltrexone (Contrave®)</td>
<td>DA Antag/Opioid Antag</td>
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<td>Craig Rush</td>
<td>Topiramate/Fentermine (Qsymia®)</td>
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<td>Joy Schmitz</td>
<td>Levodopa/Carbidopa, Ropirinole</td>
<td>“Cognitive enhancement”</td>
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<td>William Stoops</td>
<td>Phendimetrazine</td>
<td>NE Ag (anorectic)</td>
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<td>Jia Bei Wang</td>
<td>L-Tetrahydropalmatine (L-THP)</td>
<td>DA Antagonist</td>
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<td>Michael Detke</td>
<td>EMB-101</td>
<td>oxazepam + metyropone</td>
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<td>Jennifer Plebani</td>
<td>Varenicline</td>
<td>Nicotinic partial agonist</td>
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<td>Tom Newton</td>
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<td>Levin/Kampman</td>
<td>Topiramate/ER-MAS</td>
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# Cocaine - Biologics

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<tbody>
<tr>
<td>Timothy Cardozo</td>
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<td>Norcocaine conjugated cholera toxin B (CTB) with inserted epitope targeted by protective HIV antibodies</td>
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<td>Kim Janda</td>
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<td>Catalytic vaccine</td>
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<td>Jai Rudra</td>
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<td>Synthetic nanofiber vaccine</td>
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<td>Chang-Guo Zhan</td>
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<td>Cocaine esterase</td>
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<td>Ron Crystal</td>
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<td>Second-generation Gene Transfer Vector-based Vaccine</td>
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<td>Andrew Norman</td>
<td>h2E2</td>
<td>Human monoclonal antibody</td>
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In Summary...

*Nouvelles pistes thérapeutiques*

- Intranasal naloxone for opioid overdose
- Buprenorphine implant for opioid dependence
- Lofexidine for opioid withdrawal
- Cannabis: pending P2 results of gabapentin, NAC, FAAH inhibitor, Zolpidem, Quetiapine, Sativex
- Cocaine: no short-term candidates