Pharmacology of Fentanyl and Its Implications for Treatment of Opioid Use Disorder

Sandra D Comer, PhD

Professor of Neurobiology
Department of Psychiatry
Columbia University
New York State Psychiatric Institute
Disclosures

• Within the past 3 years, I have received research funding and/or study medications from Alkermes, BioXcel, Corbus, GoMedical (NIDA grant), Intra-cellular Therapies (NIDA grant), Janssen, and Lyndra (NIDA grant)

• I have also consulted for Alkermes, Mallinckrodt, and Opiant
Goals

• Current public health impact of fentanyl

• Pharmacology of fentanyl

• Impact on treatment of opioid use disorder (OUD)
  ○ Preclinical data
  ○ Early clinical data

• Possible solutions
What is fentanyl?

- Potent synthetic opioid that is currently approved by the FDA
- First used medically in the 1960’s as a general anesthetic
- Now used as a transdermal patch, lollipop, dissolving tablet and nasal spray for management of chronic or breakthrough pain
But **Pharmaceutical Fentanyl is Not Driving the Current Epidemic**

(Volkow, NIDA Council, May 2017)

**Fentanyl Synthesis from NPP**

**Criminal Chemistry**
Traffickers manufacturing fentanyl often purchase the key ingredient from China, which doesn’t regulate its sale. Here’s how the chemical building blocks become a highly profitable street drug.

The key ingredient is NPP, 25 grams of which can be bought from China for about $87.

NPP can be combined with about $720 of other chemicals to produce fentanyl.

The resulting 25 grams of fentanyl cost about $810 to produce... and are equivalent to up to $800,000 of pills on the black market.

- Large profit margin
- Easy to synthesize
- Easy to transport

**THE WALL STREET JOURNAL.**
12-month period ending in November 2021
102,568 drug-related deaths
- Synthetic Opioids – 67,293
- Stimulants – 31,129
- Heroin – 9,132

Source: The Multiple Cause of Death data are produced by the Division of Vital Statistics, National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC), United States Department of Health and Human Services (US DHHS).
### Increased Overdose Death Rates During COVID-19 Pandemic

12-months Ending July 2020 Compared to 12-months Ending July 2019

<table>
<thead>
<tr>
<th></th>
<th>ALL DRUGS</th>
<th>HEROIN</th>
<th>NAT &amp; SEMI - SYNTHETIC</th>
<th>METHADONE</th>
<th>SYNTHETIC OPIOIDS</th>
<th>COCAINE</th>
<th>OTHER PSYCHO-STIMULANTS (mainly meth)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>July 2019</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>July 2019 *</td>
<td>14,793</td>
<td>12,203</td>
<td>2,875</td>
<td>33,704</td>
<td>15,031</td>
<td>14,941</td>
<td></td>
</tr>
<tr>
<td>March 2020*</td>
<td>75,687</td>
<td>14,145</td>
<td>12,349</td>
<td>2,837</td>
<td>40,756</td>
<td>17,465</td>
<td>18,033</td>
</tr>
<tr>
<td>July 2020*</td>
<td>86,001</td>
<td>14,427</td>
<td>13,259</td>
<td>3,315</td>
<td>50,122</td>
<td>19,542</td>
<td>20,406</td>
</tr>
<tr>
<td><strong>July 2019-July 2020</strong></td>
<td><strong>+24.2%</strong></td>
<td><strong>-2.5%</strong></td>
<td><strong>+8.7%</strong></td>
<td><strong>+15.3%</strong></td>
<td><strong>+48.7%</strong></td>
<td><strong>+30.0%</strong></td>
<td><strong>+36.6%</strong></td>
</tr>
</tbody>
</table>

Why are the fentanyl derivatives driving the rates of fatal overdoses?
Lethal Doses of Heroin and Fentanyl

Fentanyl

✓ ~100x more potent than morphine (50x more potent than heroin)
The anomalous pharmacology of fentanyl

Eamonn Kelly | Katy Sutcliffe | Damiana Cavallo | Nokomis Ramos-Gonzalez | Norah Alhosan | Graeme Henderson
POTENCY

The graph illustrates the relationship between drug concentration ([Drug] in nM/L) and response (% Response). The EC₅₀ is the concentration at which the response is 50%. High potency drugs have lower EC₅₀ values, indicating a stronger response at lower concentrations. Low potency drugs, on the other hand, require higher concentrations to achieve the same response. The graph shows an increase in potency as represented by the lower EC₅₀ values from A to D.
EFFICACY

Graph showing the relationship between drug concentration and response, with different curves representing varying efficacies. The graph indicates that EC\textsubscript{50} (affinity) is the same for all, but maximal response or efficacy increases with increasing efficacy.
**AFFINITY**

\[ K_d = \text{dissociation constant \((k_{off}/k_{on})\)} \]

**FIGURE 1.9** The Langmuir adsorption isotherm representing the binding of a molecule to a surface. Photo shows Irving Langmuir (1881–1957), a chemist interested in the adsorption of molecules to metal filaments for the production of light. Langmuir devised the simple equation still in use today for quantifying the binding of molecules to surfaces. The equilibrium is described by condensation and evaporation to yield the fraction of surface bound \((\theta_1)\) by a concentration \(\mu\).

\[ \theta_1 = \frac{\alpha \mu}{\alpha \mu + V_1} \]
AFFINITY vs EFFICACY

Occupation governed by affinity

Drug A (agonist) + R → AR

Activation governed by efficacy

AR* → RESPONSE

Drug B (antagonist) + R → BR

NO RESPONSE
TABLE 1C  Comparison of fentanyl and morphine in in vitro and in vivo assay systems: Radioligand binding (membrane homogenates)

<table>
<thead>
<tr>
<th>Species of μ receptor (tissue)</th>
<th>Fentanyl ($K_i$, nM)</th>
<th>Morphine ($K_i$, nM)</th>
<th>Relative affinity of fentanyl:morphine</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Na$^+$ (100–137 mM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>158</td>
<td>250</td>
<td>1.6-fold</td>
<td>McPherson et al. (2010)</td>
</tr>
<tr>
<td>Rat</td>
<td>157</td>
<td>132</td>
<td>0.8-fold</td>
<td>Emmerson et al. (1996)</td>
</tr>
<tr>
<td>Guinea pig (brain)</td>
<td>162</td>
<td>177</td>
<td>1.1-fold</td>
<td>Kosterlitz and Leslie (1978)</td>
</tr>
<tr>
<td>Human</td>
<td>2.8$^a$</td>
<td>6.4$^a$</td>
<td>2.2-fold</td>
<td>Schmid et al. (2017)</td>
</tr>
<tr>
<td>Zero Na$^+$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>1.6</td>
<td>4.0</td>
<td>2.6-fold</td>
<td>Hassanien et al. (2020)</td>
</tr>
<tr>
<td>Human</td>
<td>0.5</td>
<td>0.8</td>
<td>1.6-fold</td>
<td>Heusler et al. (2015)</td>
</tr>
<tr>
<td>Rat</td>
<td>0.135</td>
<td>0.252</td>
<td>1.9-fold</td>
<td>Eshelman et al. (2020)</td>
</tr>
<tr>
<td>Rat</td>
<td>0.35</td>
<td>0.58</td>
<td>1.7-fold</td>
<td>Torralva et al. (2020)</td>
</tr>
<tr>
<td>Rat</td>
<td>0.16</td>
<td>0.16</td>
<td>1.0-fold</td>
<td>Emmerson et al. (1996)</td>
</tr>
<tr>
<td>Guinea pig (brain)</td>
<td>4.2</td>
<td>2.7</td>
<td>0.6-fold</td>
<td>Kosterlitz and Leslie (1978)</td>
</tr>
</tbody>
</table>

$^a$In this study by Schmid et al., the authors state that the assay was performed in the presence of Na (100 mM), but the high affinity for both ligands (low nM values) would indicate the absence of Na. Either way it does not matter as the ratio is close to 1.
Kelly et al 2021: POTENCY & EFFICACY ([\[^{35}\text{S}\]]\text{GTP}\gamma\text{S} binding)
fentanyl 0.6-5.2x as potent as morphine
(or 13.9x using cell-based assays)
fentanyl and morphine have similar efficacy

<table>
<thead>
<tr>
<th>Species of (\mu) receptor</th>
<th>Fentanyl (\text{EC}_{50}) (nM)</th>
<th>Morphine (\text{EC}_{50}) (nM)</th>
<th>Relative potency of fentanyl: morphine</th>
<th>(E_{\max}) (relative efficacy) of fentanyl: morphine (c.f. DAMGO 100)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recombinant receptors</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Human</td>
<td>32</td>
<td>150</td>
<td>4.7-fold</td>
<td>89.98</td>
<td>Hassanien et al. (2020)</td>
</tr>
<tr>
<td>Human</td>
<td>43</td>
<td>64</td>
<td>1.5-fold</td>
<td>80.81</td>
<td>Schmid et al. (2017)</td>
</tr>
<tr>
<td>Human</td>
<td>2.6</td>
<td>3.6</td>
<td>1.4-fold</td>
<td>112:111</td>
<td>Heusler et al. (2015)</td>
</tr>
<tr>
<td>Human</td>
<td>27.8</td>
<td>125</td>
<td>4.5-fold</td>
<td>107:90</td>
<td>Obeng et al. (2021)</td>
</tr>
<tr>
<td>(\text{Ga}_{\text{1}})</td>
<td>119</td>
<td>213</td>
<td>1.8-fold</td>
<td>69:66</td>
<td>Saidak et al. (2006)</td>
</tr>
<tr>
<td>(\text{Ga}_{\text{0a}})</td>
<td>67</td>
<td>89</td>
<td>1.3-fold</td>
<td>72:88</td>
<td></td>
</tr>
<tr>
<td>Rat</td>
<td>21.4</td>
<td>26.1</td>
<td>1.2-fold</td>
<td>89:82</td>
<td>Eshleman et al. (2020)</td>
</tr>
<tr>
<td>Rat</td>
<td>18</td>
<td>38</td>
<td>2.1-fold</td>
<td>92:86</td>
<td>Torralva et al. (2020)</td>
</tr>
<tr>
<td>Rat</td>
<td>56.8</td>
<td>97.5</td>
<td>1.7-fold</td>
<td>110:94</td>
<td>McPherson et al. (2010)</td>
</tr>
<tr>
<td>Rat</td>
<td>58</td>
<td>73</td>
<td>1.3-fold</td>
<td>86:74</td>
<td>Clark et al. (2006)</td>
</tr>
<tr>
<td>Mouse</td>
<td>59.7</td>
<td>36.3</td>
<td>0.6-fold</td>
<td>–</td>
<td>Zaki et al. (2000)</td>
</tr>
<tr>
<td>Mouse</td>
<td>23</td>
<td>120</td>
<td>5.2-fold</td>
<td>110:106</td>
<td>Selley et al. (1997)</td>
</tr>
<tr>
<td>Native tissue (species)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SK-N-SH cells (human)</td>
<td>37.5</td>
<td>138</td>
<td>3.7-fold</td>
<td>66:73</td>
<td>Selley et al. (1997)</td>
</tr>
<tr>
<td>SH-SY-5Y cells (human)</td>
<td>15.2</td>
<td>26.7</td>
<td>1.8-fold</td>
<td>91:75</td>
<td>Traynor and Nahorski (1995)</td>
</tr>
<tr>
<td>Spinal cord (mouse)</td>
<td>135</td>
<td>407</td>
<td>3.0-fold</td>
<td>83:78</td>
<td>Madia et al. (2012)</td>
</tr>
<tr>
<td>Thalamus (rat)</td>
<td>117</td>
<td>434</td>
<td>3.7-fold</td>
<td>58:56</td>
<td>Selley et al. (1997)</td>
</tr>
</tbody>
</table>
Kelly et al 2021: Fentanyl may interact with the orthosteric binding pocket of MORs in multiple ways
Kelly et al 2021: Fentanyl may have multiple binding pathways

**FIGURE 3** The lipid binding pathway for fentanyl identified by coarse-grained molecular dynamics simulations. (a) A molecule of fentanyl approaches and then enters the lipid membrane, before entering the μ receptor through a pore between transmembrane domains 6 and 7 of the receptor and eventually entering the orthosteric binding pocket. (b) A molecule of morphine approaches and then enters the μ receptor from above the receptor (the aqueous route).
In morphine-dependent animals, cross-tolerance to morphine is greater than cross-tolerance to fentanyl.

Fentanyl does not produce tolerance as readily as morphine.
How does fentanyl differ from heroin (morphine)?

<table>
<thead>
<tr>
<th></th>
<th>Morphine</th>
<th>Fentanyl</th>
</tr>
</thead>
<tbody>
<tr>
<td>Little to no MOR internalization</td>
<td>MOR internalization</td>
<td></td>
</tr>
<tr>
<td>beta-arrestin 2 KO mice</td>
<td>beta-arrestin-2 KO mice</td>
<td>Tolerance not affected</td>
</tr>
<tr>
<td></td>
<td>No analgesic tolerance</td>
<td>Locomotor sensitization not changed</td>
</tr>
<tr>
<td></td>
<td>No locomotor sensitization</td>
<td>Tolerance JNK-independent</td>
</tr>
<tr>
<td></td>
<td>Tolerance JNK-dependent</td>
<td></td>
</tr>
<tr>
<td>Tolerance is GRK3-independent</td>
<td>Tolerance is GRK3-dependent</td>
<td></td>
</tr>
<tr>
<td>RGS9-2 KO increases analgesia</td>
<td>RGS9-2 KO decreases analgesia</td>
<td></td>
</tr>
<tr>
<td>No ERK1/2 activation (via b-arrestin-2)</td>
<td>ERK1/2 activation (via b-arrestin-2)</td>
<td></td>
</tr>
<tr>
<td>Potency = 1</td>
<td>Potency = 0.01 morphine equivalent</td>
<td></td>
</tr>
<tr>
<td>Less lipophilic</td>
<td>More lipophilic</td>
<td></td>
</tr>
<tr>
<td>Slow CNS entry</td>
<td>Rapid CNS entry</td>
<td></td>
</tr>
</tbody>
</table>

Comer and Cahill (2019)
FDA-approved medications for treating OUD

✓ Maintenance medications
  • Methadone (full mu agonist)
  • Buprenorphine (partial mu agonist)
  • Naltrexone (antagonist)

✓ Overdose reversal
  • Naloxone (antagonist)
  • Nalmefene (antagonist)
FDA-approved medications for treating OUD

✓ Maintenance medications
  • Methadone (full mu agonist)
  • Buprenorphine (partial mu agonist)
  • Naltrexone (antagonist)

✓ Overdose reversal
  • Naloxone (antagonist)
  • Nalmefene (antagonist)
Methods


Species: Mice

Assay: Warm water (55°C) tail withdrawal

Dependent measure: Latency to withdrawal

% Maximum possible effect = \frac{\text{Test latency} - \text{Control latency}}{15 \text{ sec} - \text{Control latency}} \times 100

Antagonists: Naltrexone or C-CAM

Test drugs: Morphine, fentanyl
The potency of naltrexone against morphine and fentanyl was the same, suggesting that they were producing their effects through the same receptors ($\mu$).

However, higher doses of an irreversible antagonist were needed to produce downward shifts in the dose-effect curve for fentanyl compared to morphine.

MCAM, a pseudoirreversible antagonist, produced a long-lasting reduction in fentanyl self-administration in rhesus monkeys.

THE ANTAGONIST IS IMPORTANT – COMPETITIVE VS NON-COMPETITIVE INTERACTIONS
Fentanyl and carfentanil produce effects that are similar to heroin in rats. But carfentanil produces longer lasting effects than fentanyl.
Although naltrexone antagonizes fentanyl and heroin to a similar extent, it is less effective against carfentanil.
THE AGONIST IS IMPORTANT TOO – FENTANYL VS CARFENTANIL
FDA-approved medications for treating OUD

✓ Maintenance medications
  • Methadone (full mu agonist)
  • Buprenorphine (partial mu agonist)
  • Naltrexone (antagonist)

✓ Overdose reversal
  • Naloxone (antagonist)
  • Nalmefene (antagonist)
Kelly et al 2021:
NALOXONE REVERSAL – 10X HIGHER DOSES NEEDED FOR FENTANYL
Higher naloxone dosing may be required for opioid overdose

Russell Bardsley, Pharm.D., BCPS, BCCCP, Emergency Department, Catholic Medical Center, Manchester, NH.

Higher doses of naloxone are needed in the synthetic opioid era

Ronald B. Moss* and Dennis J. Carlo

Characteristics of Fentanyl Overdose — Massachusetts, 2014–2016

Nicholas J. Somerville, MD1,2; Julie O’Donnell, PhD1,3; R. Matthew Giadden, PhD4; Jon E. Zibbell, PhD4; Traci C. Green, PhD5; Morgan Younkin, MD6; Sarah Ruiz, MSW2; Hermik Babakanlou-Chase, MPH2; Miranda Chan, MPH2; Barry P. Callis, MSW2; Janet Kuramoto-Crawford, PhD1; Henry M. Nields, MD, PhD7; Alexander Y. Walley, MD2,5

Carfentanil: a narrative review of its pharmacology and public health concerns

Carfentanil: étude narrative de sa pharmacologie et problématiques de santé publique

Jessica L. S. Leen, MD · David N. Juurlink, MD, PhD
Special Section on The Opioid Crisis

Noradrenergic Mechanisms in Fentanyl-Mediated Rapid Death Explain Failure of Naloxone in the Opioid Crisis

Randy Torralva and Aaron Janowsky

CODA Inc., Research Department, Portland, Oregon (R.T.); Research Service, VA Portland Health Care System, Portland, Oregon (R.T., A.J.); and Department of Psychiatry, Oregon Health & Science University, Portland, Oregon (R.T., A.J.)

Received April 2, 2019; accepted September 3, 2019
FDA-approved medications for treating OUD

✓ Maintenance medications
  • Methadone (full mu agonist)
  • Buprenorphine (partial mu agonist)
  • Naltrexone (antagonist)

✓ Overdose reversal
  • Naloxone (antagonist)
  • Nalmefene (antagonist)
Methods


Species: Rats

Assay: Warm water (55°C) tail withdrawal

Dependent measure: Latency to withdrawal

% Maximum possible effect = \frac{\text{Test latency} - \text{Control latency}}{15 \text{ sec} - \text{Control latency}} \times 100

Maintenance drug: Buprenorphine

Test drugs: Etonitazene, etorphine, morphine, buprenorphine, GPA 1657
Buprenorphine was not as effective in antagonizing the analgesic effects of higher efficacy agonists.
What about self-administration? Does the same phenomenon hold true for that effect?
Methods

Winger & Woods Drug & Alcohol Dependence (2001)

Species: Rhesus monkeys
Assay: IV drug self-administration
Dependent measure: Rate of responding (responses/sec)

Maintenance drug: Morphine
Test drugs: Alfentanil, heroin, morphine, nalbuphine, buprenorphine, and cocaine
Responses per second

Mg/Kg/Inj Alfenanil

Mg/Kg/Inj Cocaine

Pre-Morphine

During Morphine
<table>
<thead>
<tr>
<th>Assay</th>
<th>Species</th>
<th>Authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug Discrimination</td>
<td>Rats</td>
<td>Young, Kapitsopoulos, &amp; Makhay, 1991</td>
</tr>
<tr>
<td>Analgesia</td>
<td>Rats</td>
<td>Paronis &amp; Holtzman, 1992</td>
</tr>
<tr>
<td>Drug Discrimination</td>
<td>Rats</td>
<td>Paronis &amp; Holtzman, 1994</td>
</tr>
<tr>
<td>Analgesia</td>
<td>Mice</td>
<td>Duttaroy &amp; Yoburn, 1995</td>
</tr>
<tr>
<td>Analgesia</td>
<td>Monkeys</td>
<td>Walker, Zernig, &amp; Woods, 1995</td>
</tr>
<tr>
<td>Analgesia</td>
<td>Rats</td>
<td>Walker, Zernig, &amp; Young, 1998</td>
</tr>
<tr>
<td>Analgesia</td>
<td>Monkeys</td>
<td>Pitts, Allen, Walker, &amp; Dykstra, 1998</td>
</tr>
<tr>
<td>Response rates for food</td>
<td>Rats</td>
<td>Smith &amp; Picker, 1998</td>
</tr>
<tr>
<td>Analgesia</td>
<td>Rats</td>
<td>Walker &amp; Young, 2001</td>
</tr>
<tr>
<td>Analgesia</td>
<td>Rats</td>
<td>Barrett, Cook, Terner, Craft, &amp; Picker, 2001</td>
</tr>
<tr>
<td>Self-administration</td>
<td>Monkeys</td>
<td>Winger &amp; Woods, 2001</td>
</tr>
<tr>
<td>Drug Discrimination</td>
<td>Rats</td>
<td>Walker &amp; Young, 2002</td>
</tr>
<tr>
<td>Drug Discrimination</td>
<td>Pigeons</td>
<td>Barrett, Smith, &amp; Picker, 2003</td>
</tr>
<tr>
<td>Analgesia &amp; Resp for food</td>
<td>Monkeys</td>
<td>Negus, Brandt, Gatch, &amp; Mello, 2003</td>
</tr>
</tbody>
</table>
How translatable are these findings to humans?
Buprenorphine/Naloxone Maintenance and Intranasal Heroin Self-administration

Bup/Nx produced a dose-related reduction in heroin self-administration, but the effects of heroin were still robust.
“At this moment, my liking for drug is …”

A weeklong formulation of injectable buprenorphine reduced hydromorphone-induced drug liking in humans.

What about fentanyl?

• No laboratory-based studies have measured the ability of buprenorphine (or methadone or naltrexone) to antagonize the effects of fentanyl in humans.

• One retrospective cohort study showed that treatment retention and opioid abstinence at 6 months after initiation of buprenorphine did not differ in patients who tested positive for fentanyl versus heroin at initiation of buprenorphine treatment (Wakeman et al., 2019) – but small sample sizes.

• Another retrospective cohort study showed that treatment retention at 12 months after initiation of methadone did not differ in patients who tested positive versus negative for fentanyl at initiation of treatment (Stone et al., 2020) – but fentanyl use during treatment was common; no fatal overdoses.
Initiation of Buprenorphine Treatment

Withdrawal can be severe in fentanyl users who are transitioning to buprenorphine

Method for Successfully Inducting Individuals Who Use Illicit Fentanyl Onto Buprenorphine/Naloxone

Denis Antoine, MD, Andrew S. Huhn, PhD, MBA, Eric C. Strain, MD, Gavin Turner, BS, Jasmyne Jardot, BA, Alexis S. Hammond, MD, PhD, Kelly E. Dunn, PhD, MBA
Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, Maryland

Commentary

A Plea From People Who Use Drugs to Clinicians: New Ways to Initiate Buprenorphine are Urgently Needed in the Fentanyl Era

Kimberly L. Sue, MD, PhD, Shawn Cohen, MD, Jess Tilley, and Avi Yocheved

J Addict Med • Volume 00, Number 00, Month/Month 2022
Initiation of Naltrexone Treatment

Fentanyl+ patients half as likely to initiate treatment overall

Fentanyl+ patients 11x less likely to initiate treatment with naltrexone

No evidence that fentanyl related to bup initiation

Cook et al. DAD (2021)
What can we conclude so far?

✓ Fentanyl is potent, has a rapid onset of action, and is short acting

✓ Naltrexone is effective in preventing the fentanyl-induced responses but is less effective against carfentanil (preclinical data)

✓ Naloxone appears to be less effective against fentanyl overdose (preclinical data and clinical case reports)
How well do methadone, buprenorphine, and naltrexone work for treating OUD in patients using fentanyl? Retrospective studies suggest that buprenorphine and methadone are effective.

But what about the analogs?

How do we most effectively transition patients from fentanyl to these treatment medications?

How do we most effectively manage fentanyl-related overdoses?
So what do we do?

Continue to develop medications
Vaccines for illicit drug use generate antibodies that bind drug in plasma and block entry to the brain.

A series of injections are given over several months in order to achieve maximal antibody production.
Candidate vaccines for heroin and prescription opioids

OXY-KLH targets oxycodone, hydrocodone, and oxymorphone.

M-KLH targets heroin, 6-AM, and morphine.

F-CRM targets fentanyl and its analogs.
Fentanyl Vaccine: Preclinical Data

**A**
- Serum levels increase

**B**
- Brain levels decrease

- Respiratory depression is reversed
- Naloxone reversal is unaffected
Challenge. Identify immunological mechanisms and biomarkers of vaccine efficacy to accelerate translation.

First-generation nicotine and cocaine vaccines showed clinical proof of efficacy in ~30% of immunized subjects that achieved highest antibody levels.
Biomarker. Vaccine efficacy is predicted by early antibodies and pre-immunization B cell frequency in mice

A. OXY-KLH efficacy in blocking oxycodone to brain

B. Antibody titers vs. efficacy
IgG subclasses vs. efficacy

C. OXY-specific B cell frequency vs. efficacy

Phase I trial includes exploratory biomarkers to select or stratify patients

Laudenbach et al., J. Immunology 2015
Laudenbach et al., Vaccine 2015
Comparison of opioid users and naïve individuals' opioid-specific B cells and TNF$\alpha$ expression

- Significant difference in the frequency of opioid-specific B cells
- No difference in the expression of TNF$\alpha$
- Correlation between TNF$\alpha$ expression and opioid-specific B cells only for opioid users

Is TNF$\alpha$ a viable biomarker to predict vaccine clinical efficacy?
THANK YOU!

Jermaine Jones, PhD
Rachel Luba, PhD
Jeanne Manubay, MD
Shanthi Mogali, MD
Felipe Castillo, MD
Claudia Tindall, NP
Janet Murray, RN
Nicholas Allwood, BS
Rebecca Abbott, BS
Freymon Perez, BS

UG3DA047711 (Comer)
T32DA007294 (Levin)