Buprenorphine, Naltrexone and Diacetylmorphine
The Usual Stuff

I have conflicts of interest to report concerning this presentation
1. Have a passing acquaintance with the structures of opiates and semi synthetic Opioids.
2. Understand the importance of mu receptor binding affinity
3. Become familiar with the basic clinical properties of buprenorphine and naltrexone
4. Appreciate the overall strengths and weaknesses of Medication Assisted Treatment of SUD
The Three Sisters of the Poppy

Morphine

Codeine

Thebaine
Morphine and Heroin

Morphine

\[
\text{morphine} \quad \begin{array}{c}
\text{HO} \\
\text{O} \\
\text{H} \\
\text{HO} \\
\text{N-CH}_3
\end{array}
\]

Diacetylmorphine

\[
\text{diacetylmorphine} \quad \begin{array}{c}
\text{H}_3\text{C} - \text{O} \\
\text{O} \\
\text{H} \\
\text{H}_3\text{C} - \text{O} \\
\text{N-CH}_3
\end{array}
\]
Hydromorphone and Naltrexone

Hydromorphone

Naltrexone

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Naltrexone and Naloxone

Naltrexone

Naloxone
Thebaine and Buprenorphine

Thebaine

Buprenorphine

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# Mu Receptor Binding Affinity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Pk(i)</th>
</tr>
</thead>
<tbody>
<tr>
<td>buprenorphine</td>
<td>0.21–1.5 nM</td>
</tr>
<tr>
<td>naltrexone</td>
<td>0.4–0.6 nM</td>
</tr>
<tr>
<td>naloxone</td>
<td>1–3 nM</td>
</tr>
<tr>
<td>morphine</td>
<td>5.7–36 nM</td>
</tr>
<tr>
<td>meperidine</td>
<td>193 nM</td>
</tr>
<tr>
<td>oxycodone</td>
<td>0.34 nM</td>
</tr>
<tr>
<td>fentanyl</td>
<td>0.7–1.1 nM</td>
</tr>
</tbody>
</table>
19 FDA approve opioids were tested using the same methodology. They separated out into three groups:

- Those with $K_i$ greater than 100 nM; codeine, meperidine, propoxyphene and pentazocine
- Those with $K_i$ equal to 1-100 nM; morphine, hydrocodone, oxycodone, methadone, fentanyl and nalorphine
- Those with $K_i$ greater than 100 nM; buprenorphine, oxymorphone, hydromorphone, sufentanil and levorphanol.
Buprenorphine/Naloxone

- Indicated for opioid dependence (or pain)
- Combination product containing a partial agonist and an antagonist
- Available in 4 strengths: buprenorphine 2mg/naloxone 0.5mg, 4mg/1mg, 8mg/2mg, 16mg/3mg, respectively
- Given sublingually as a single daily dose
- Schedule 3 abuse potential
- Poor bioavailability - buprenorphine 10% if swallowed, 30-50% sublingually (vs. IV route). Naloxone - 2-5% oral
- Variable absorption, peak plasma concentrations in 30min - 3 hrs..
Buprenorphine/Naloxone

- **Side effects:** headache, N/V, Withdrawal symptoms, elevated LFTs, tongue pain
- Metabolized via CYP2D6, CYP3A4 - no black box warning
  - Drug interactions! Anti-retrovirals, benzodiazepines.
- Requires induction period - titrated to objective signs of withdrawal
Naltrexone

- Indicated for opiate dependence and alcohol withdrawal - pure antagonist, Chemical structure is similar to hydromorphone.
- 380mg once every 4 weeks IM
- Peak plasma concentration in 2 hrs., followed by a second peak in 2-3 days. Starts declining after about 14 days
- Metabolized by the liver, non-cytochrome P450 mechanism.
- Black box warning: Hepatotoxicity
- Side effects: site reactions, hypersensitivity, eosinophilic PNA, accidental overdose, depression/suicide, anxiety, nausea
  - Can cause pupillary constriction
- Requires wash out period (~1 week)
- Does not cause a disulfiram type reaction
- Reversal - regional anesthesia
Naloxone XR/Buprenorphine

Comparison Study Summary

HOW WAS THIS STUDY CONDUCTED?

- A randomized controlled trial to test buprenorphine/naloxone against naloxone XR in 570 individuals (287 receiving BUP/NAL and 283 receiving XR-NTX) for 6 months who were attending one of eight inpatient detoxification programs in the U.S.

The primary outcome was “relapse”, measured after the first 3 weeks to prevent against detoxification-related opioid medication from being counted as opioid use, and defined as one of the following:

- 4 consecutive weeks of opioid use determined by urine drug test (a missed drug test was counted as “positive” indicating use)
- 4 consecutive weeks of opioid use determined by self-report
- 7 consecutive days of self-reported opioid use

Secondary outcomes were failure to initiate the medication, percent days using an opioid during the 6-month study period, and adverse events including overdoses.
All participants had opioid use disorder according to the diagnostic and statistical manual of mental disorders, 5th edition (DSM-5) and had used opioids in the past 30 days.

While the sites differed in terms of how they helped individuals medically withdraw from opioids (“detox”), all were short-term (3-7 days) and part of a community program that provided at least weekly therapy sessions (group or individual) on an outpatient basis during the study. The study was conducted as part of the National Institute on Drug Abuse’s Clinical Trials Network, which tests evidence-based treatments for substance use disorder in community settings. Of note, study site and severity in terms of opioid use were taken into account when randomizing patients to receive Bup/Nal vs. XR-NTX.

All patients received medical management at each study visit including psychoeducation about opioid use disorder, an adherence plan, advice to abstain from all substance use, monitoring of side effects, and encouraging attendance at therapy and mutual-help groups. The medical management schedule was the same for both Bup/Nal vs. XR-NTX—weekly for the first month, then every two weeks for the next 3 months, then every month for the final 2 months. Bup/Nal doses ranged from 8 to 24 mg depending on clinical need. XR-NTX was administered every 28 days, and of course, individuals needed to be abstinent from all opioids for at least 3 days, have a toxicology screen negative for opioids, and pass a “naloxone challenge” to be sure they would not withdraw from the XR-NTX.
Characteristics of Study Sample

- 34 years old, on average, 70% male, 75% White and 10% Black and 13-20% Latino.

- Most (80%) were heroin users, more than 60% were injection drug users, and 35-40% had prior treatment. Other substance use in the past 30 days was common: 47-57% with stimulant use, 25-32% with sedative use, 42-48% with cannabis use, and 25-27% with “heavy” drinking, which was not defined by authors but, according to the Substance Abuse and Mental Health Services Administration (SAMHSA), means 5 or more drinks for men or 4 or more for women on the same occasion at least 5 days in the past month.

- Nearly 70% reported a lifetime history of another psychiatric disorder, and they had “mild” depressive symptoms, on average, measured by the Hamilton Depression Scale. Individuals were not able to participate in the study if they had “serious medical, psychiatric, or substance use disorder” as determined by the study physician.
In the Bup/Nal group, 57% relapsed during the study, significantly less than the 65% who relapsed in the XR-NTX group (i.e., unlikely due to chance - a reliably large difference). Out of 24 weekly tox screens, Bup/Nal individuals had 10 negative opioid tox screens, and XR-NTX individuals had four negative opioid tox screens, on average. Out of 144 days, by self-report Bup/Nal individuals had 81 opioid abstinent days and XR-NTX 39 abstinent days. The Bup/Nal group also had a significantly longer time until they relapsed, on average (14 weeks vs. 8 weeks). More specifically, in any given week, if one person was abstinent in the Bup/Nal group and a similar person was abstinent in the XR-NTX group, the person in the Bup/Nal group had a 36% higher odds of avoiding relapse that week.

The good and the bad news: If you can’t start it, it isn’t equal...
WHAT DID THIS STUDY FIND?

- One noteworthy nuance from this study is that the advantage of Bup/Nal occurred early - in the first 6 weeks. For those who make it past 6 weeks, XR-NTX begins to show an advantage. Another distinction is that the advantage for Bup/Nal appears to come from the tougher time that individuals experienced who were assigned to XR-NTX when getting started on the medication - 94% of individuals assigned to Bup/Nal were successfully started (also called “induction”) while only 72% of those assigned to XR-NTX were successfully started on the medication. When only the individuals successfully started on medication were analyzed, the outcomes were similar. Also, XR-NTX individuals were more likely to be successfully started on the medication if entered the study more than 3 days after the last opioid use compared to less than 3 days after their last opioid use (84% started vs 53%, respectively). So having at least a few days abstinent made a difference for XR-NTX patients.
Is This as Good as it Gets?\textsuperscript{4,5}

- For inductions, there are indications that numbers can get better.

- For long term outcomes, many factors other then medications play a more important role. In some special populations, better outcomes are achieved with no long-term medications at all.

- But, “What medication provides the best long-term retention in a program?”
The Answer

Methadone at greater than 100mg per day

61.1% retention over 152 weeks with only 16% UDS positive urines
1. PDSP Ki Data Base, University of North Carolina, Chapple Hill

2. Volpe et. al. Uniform assessment and ranking of opioid Mu receptor binding constants for selected opioid drugs. Regulatory Toxicology and Pharmacology 59: (3) April 2011 385-390

