Extended Release Naltrexone
Vivitrol

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Topics of today’s training

- Review the epidemiology of opiate use, opiate dependency, and overdose deaths.
- Review the neurobiology of addiction.
- Review opiate receptor theory, opiate agonists and antagonists.
- Oral Naltrexone – Revia
- Injectable Naltrexone – Vivitrol

The scope of opioid dependency

- Prescription pill addiction is rising more rapidly than any other addiction.
- ¾ of prescription pill abuse or addiction is to opioids.
- There has been a 300% rise in the prescribing of prescription pain medication from 1998 to 2008.

Center for Disease Control
The scope of opioid dependency

- During the same decade that the number of prescriptions written for opioids tripled (1998 – 2008):
  - The incidence (new cases) of opiate dependency tripled.
  - The number of opiate/opioid overdose deaths tripled.
  - The number of babies born with neonatal abstinence syndrome increased by 240%.
Opioid use During Pregnancy

Prescription Opioid and Heroin Use 2008

Most recent CDC data

- Although the overdose death rates for prescription opioid use tripled from 1998 to 2008, in a period of 2 years (2010–2012) the number of heroin overdose deaths doubled.

- 2010: 1779 US deaths.
General statistics

- Americans account for 4.6% of the world population, but consumes 80% of the world’s prescription opioids.
- Americans consume 99% of the world’s supply of hydrocodone (Vicodin).
- Purdue Pharma, the producer of OxyContin made 3.1 billion dollars in the sales of OxyContin in 2010 which accounts for 90% of that companies revenue.

General statistics

- The death rate for opiate/opioid dependent individuals is 2 to 4% per year. Considering these are frequently teenagers and young adults, this is exceedingly high.
- The life expectancy for the opiate/opioid dependent person is 27 years shorter than the general population.
- Female smokers life expectancy is shortened by 14.5 years, male smokers by 13.2 years.

US Drug Deaths (All drugs)

- 2014 U.S. drug deaths = 47,000
- Half were Rx pill over doses
- 61% (28,647) were due to opiates or opioids including heroin
- Someone dies every 20 minutes in this country due to an opiate/opioid over dose death.
  (That is 4.5 deaths during the time of my training)
Pa. Drug Deaths
(All drugs)

- 2014 Pa. drug deaths = 2500 (7/day)
- Over 50% were due to opiates/opioids
- Pa. ranks 9th of all states for overdose deaths

York county heroin overdose deaths

- According to the York County Coroner, 70% of overdose deaths occurred in individuals who were previously abstinent!
- Released from jail
- Released from detox
- Released from rehab

Definitions

- Opiate – Naturally occurring chemical from the poppy plant that binds to and stimulates opiate receptors causing analgesia (pain relief) – Morphine, Codeine, Thebaine.
- Synthetic opioids – Completely synthesized. Methadone, Fentanyl
Definitions

- Opiate agonist – Binds to opiate receptors and stimulates them. This causes analgesia, sedation, constipation, suppressed respirations, decreased BP. This includes all the opiates and opioids.
- Opiate antagonist – Binds to opiate receptors and doesn’t activate the receptor. It will block the receptor, and can reverse the effect of an opiate/opioid. Naloxone (Narcan), Naltrexone

Definitions

- Receptor affinity – How strongly a molecule will bind to a receptor.
- Drugs with a high receptor affinity are difficult to displace by drugs with a lower receptor affinity.

Synergistic effect

- An interaction of two or more drugs where the combined effect is greater than the sum of their separated effects.
- The risk of an overdose from an opiate is greatly increased when it is combined with a benzodiazepine or alcohol.
**Synergistic effect**

<table>
<thead>
<tr>
<th>Level of consciousness</th>
<th>6 bags of heroin</th>
<th>4mg of Xanax</th>
<th>Heroin + Xanax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td></td>
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<tr>
<td>Sedated</td>
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<td>Stupor</td>
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<td>Coma</td>
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<tr>
<td>Death</td>
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**What cause an opiate overdose?**

- With saturation of the opiate receptors with an opiate/opioid, respirations slow then stops. After several minutes, anoxic brain injury begins to occur and then cardiac arrest follows.
- The individual's tolerance is a factor in the risk of overdose.
- Tolerance decreases with periods of abstinence.

**Risk factors for over dose**

- Previous over doses
- Poly-substance use
- IVDU
- Chronic medical problems: COPD, liver disease, kidney disease
- Periods of abstinence and at high relapse risk:
  - Release from jail, detox or rehab
- Those with opiate dependency who are released from detox have a 70% relapse rate within the first month.

*Med J. 2010;103(6):176-9*
Weekly mortality rates upon release from prison

Mortality per 100,000 people

Weeks after release

Opiate overdose deaths before, during and after residential treatment

Mortality in 1000 patient years

Pre-treatment During treatment Post-treatment and relapse

The Neurobiology of Addiction
The Neuron (brain cell)

Dendrite  Cell Body  Axon

Synapse

The Reward Pathway

VTA

Amygdala

The Frontal Lobes

NA

Alcohol

Drugs
The Reward Pathway

- Most addicting drugs bind to receptors on the neurons of the ventral tegmental area (VTA).
- The axons of the VTA connect with the nucleus accumbens (NA), the pleasure center.
- Drug or alcohol use results in a release of dopamine into the nucleus accumbens resulting in euphoria.
- The NA has neurons that extend to the frontal lobes and the amygdala.

The Reward Pathway

- Normal survival behaviors result in the release of dopamine in the NA:
  - Sex
  - Eating, drinking
  - Physical activity
- Addicting drugs over ride the pleasure center creating tremendous release of dopamine in the NA.
- Sex, food, drinking become less important to the brain compared to drug or alcohol use.
The Reward Pathway (Nucleus accumbens)

- The amount of dopamine released when a certain drug is used is in part genetically mediated.
- The alcoholic has a greater release of dopamine when they ingest alcohol compared to the non-alcoholic.
- The opiate addict has a greater release of dopamine compared to the non-opiate addict when they use an opiate.

The Reward Pathway

- The NA connects to the amygdala.
- The amygdala is the area of the brain where emotional memories are stored and plays a major role in fear and the “fight or flight response”.
- The pleasurable memories of drug use (euphoric recall) is in part stored in the amygdala.
- Electrical stimulation of the amygdala in lab animals results in a “fight or flight” response.
The Reward Pathway (Amygdala)

- Repeatedly traumatizing of lab animals has been shown to cause the amygdala to enlarge.
- Individuals with PTSD and panic disorders have abnormal activity in the amygdala.
- Chronic pain has an emotional component and results in abnormalities in the amygdala.

The Reward Pathway (Amygdala)

- In early recovery, the addict is in a dopamine depleted state.
- The amygdala is no longer being “calmed down” by dopamine from the NA.
- This results in an almost “fight or flight” response: Anger, agitation, irritability, loss of emotional control.
- Counseling that results in an aggressive, “in your face” approach is counter productive.

The Reward Pathway
The Reward Pathway (Frontal lobes)

- The nucleus accumbens also connects to the frontal lobes (prefrontal cortex).
- The frontal lobes are responsible for:
  - Judgment and reasoning
  - Insight
  - Understanding cause and effect relationships
  - “Executive functioning”
  - Impulse control

Why do addicts and alcoholics make bad decisions?

- As addiction progresses, frontal lobe function is suppressed by the reward pathway.
- The ability to make good choices, and see the consequences of behaviors is impaired.
- Addiction is not a choice, it is a neurobiologic condition resulting in the loss of an ability to make good choices.
Diminished frontal lobe activity

![Brain imaging comparison](image)

Treatment of opiate dependency with Naltrexone (ReVia)

![Pills](image)
Treatment of opiate dependency with Naltrexone

- Naltrexone (ReVia) is an orally administered opiate antagonist (Blocker) that can be taken daily as a treatment for opiate dependency.
- It is a 50 mg pill taken once daily.
- The person has to be opiate free when initiating Naltrexone to avoid precipitating opiate withdrawal.
- If a person takes an opiate/opioid while on Naltrexone, the effect is blocked.

Ineffectiveness of oral Naltrexone

- Several studies done in the 1980s showed oral Naltrexone to be ineffective in the treatment of heroin addiction.
- In 6 a month study:
  - Within 1 month, there was a 40% drop out rate.
  - By 6 months there was a 90% drop out rate.
- Oral Naltrexone does not work for the heroin addicted population!

Retention in treatment with oral Naltrexone

- Retention rate decreases significantly from 40% at 1 month to 90% at 6 months.
Oral Naltrexone for opiate dependency

- There were 2 subgroups that did show a positive effect from oral Naltrexone therapy.
  - Healthcare professionals
  - Parolees

Retention in treatment: Vivitrol vs Oral Naltrexone

In 6 months, Vivitrol doubled the retention rate compared to oral Naltrexone.

Oral Naltrexone for opiate dependency

- Possible value as a short term bridge while waiting to be initiated on Vivitrol.
- Direct observed administration is preferred.
- Aberrant behaviors:
  - Cheeking the medication
  - Microwaving the pills neutralizes them
What’s new for opiate addiction?
Vivitrol (injectable Naltrexone)

- Vivitrol got FDA approval for the use in opiate dependency in 2010.

Opiates in the brain

- Our brain’s natural opiate is called endorphins, and they bind to opiate receptors.
- Other opiates/opioids like heroin or Oxycodone (called opiate agonists) bind to the same receptors but much more intensely stimulate them.
- Vivitrol blocks those receptors so opiates can’t bind there and doesn’t activate the receptor.

How well does it work

- Vivitrol improves complete abstinence rates.
- Vivitrol reduces the number of relapses in those patients that do relapse, preventing them from falling back to opiate dependency.
- Vivitrol reduces cravings for opiates.
- Vivitrol improves retention rates for patients in out-patient drug and alcohol treatment (Patients are less likely to drop out of counseling).
Vivitrol is intended to be used with counseling

- Vivitrol works at the level of the reward pathway.
- Counseling works at the frontal lobe, our thinking and reasoning area of the brain.

Six month study of Vivitrol for opiate dependency

- A double blind placebo trial where 126 participants received monthly Vivitrol injections and biweekly counseling and 124 received a placebo injection and biweekly counseling.
- Prior to study entrance, detox and residential treatment was done if necessary.
- The average length of time in residential treatment prior to study entrance was 18 days.

Lancet 2011; 377:1506-1513

Complete abstinence from opiates during 6 months of counseling with or without Vivitrol

Complete abstinence rates over 6 months

- Counseling + Placebo: 23%
- Counseling + Vivitrol: 36%
Opiate free weeks during 6 months of counseling with and without Vivitrol

Vivitrol reduces cravings over a 6 month period
(Those who did not get Vivitrol had a slight increase in cravings by the end of 6 months)

Retention in treatment during 6 months of counseling with and without Vivitrol

Average number of days retained in treatment
Does Vivitrol reduce mortality?

- As of now, there is limited data to show if Vivitrol reduces mortality from opiates. (More to follow)
- We may assume with a reduction in relapses and improved abstinence rates with Vivitrol, that mortality rates improve.
- Studies that show reduction in drug use can be done with a small number of participants, but mortality studies require a large population and following them for a long period of time.

Maybe Vivitrol does reduce mortality

- As part of a re-entry program, about 300 inmates were assigned to get Vivitrol injections for 6 months after release from prison or “treatment as usual”.
- In the 6 months on Vivitrol, relapse rates were lower than the “treatment as usual group”.
- At 72 weeks (18 months):
  - Vivitrol group: 0 deaths
  - Control group: 7 deaths

Lee et al. NEJM, March 31, 2016

Different treatment models

Inpatient detox and rehab

Physician's office
Injection site

Outpatient drug and alcohol provider
Potential obstacles

- Ordering Vivitrol, doing the prior authorization and receiving the product can take 7 to 14 days.
- Detox may take 5 to 7 days and Vivitrol can not be administered until 7 to 10 days after detox. Shortening lengths of stay may result in the patient being discharged before receiving the Vivitrol.
- There is limited physicians that inject Vivitrol.

Different treatment models

- Inpatient detox and rehab
- Outpatient drug and alcohol provider that offers Vivitrol

- Physician's office
- Outpatient drug and alcohol provider
Frequently asked questions

Can someone overdose on Vivitrol?

- If someone has had a Vivitrol injection recently and are fully “blocked”, there is a risk of overdose if the person continues to take large amounts of opiates to try to over ride the Vivitrol.
- If someone is getting close to 30 days from their last injection, they are not fully “blocked”. Since they have been abstinent for at least a month, their tolerance will be low. Using opiates at this time can lead to an overdose.
- Missing an injection and then using opiates can also lead to an overdose since there is no protection from the Vivitrol.

What if someone needs emergency surgery, a medical procedure or dental procedure?

- Vivitrol can be over ridden by high potency and high dose opioid but it has to be done in a controlled environment with close monitoring.
- General anesthesia for surgery is not blocked by Vivitrol.
- Epidural and spinal injections are not blocked by Vivitrol.
- Local agents like Novocain for dental work is not blocked by Vivitrol.
- Non-opiate pain relievers like Tylenol and Ibuprofen are not blocked by Vivitrol.

What are possible side affects from Vivitrol injections?

- Most people do not complain much about the actual shot, but injection sight soreness is not uncommon for the next few days.
- Some patients report mild nausea, fatigue, or feeling strange. If this occurs it usually only lasts from 4 hours to a day. It usually only occurs with the first injection but not following injections.
- If someone is actively using opiates, Vivitrol will induce opiate withdrawal. They must be 7 to 10 days opiate free to start it.
Frequently asked questions

- Can someone take Vivitrol if they have Hepatitis C?
  - Patients in liver failure or severe liver disease should not take Vivitrol.
  - If someone has Hepatitis C and their liver enzymes are only mildly elevated (Less than 3 to 5 times normal), most physicians will give Vivitrol.

Frequently asked questions

- Can someone take Vivitrol if they are pregnant or plan to get pregnant?
  - No. There is no safety data on its use in pregnancy.

- Can someone take Vivitrol if they are breast feeding?
  - No. There is currently no safety data on its use while breast feeding.

Frequently asked questions

- Can someone be on Vivitrol if they are on Suboxone or Methadone maintenance?
  - No. Vivitrol will block the affect of Suboxone and Methadone. If someone is already on Suboxone or Methadone maintenance, Vivitrol will precipitate opiate withdrawal.
Frequently asked questions

When can someone start Vivitrol?

- A person has to be 7 to 10 days off of opiates to get the first injection due to the risk of inducing opiate withdrawal. This also means they have to be that same length of time out of detox if Buprenorphine was used to detox them off of opiates.
- Patients previously on Suboxone or Methadone maintenance should be 14 days off those before starting Vivitrol.

Can someone take Vivitrol if they are on psychiatric medications?

- Yes. Vivitrol does not interfere with antidepressants, antianxiety medications, mood stabilizers or antipsychotics medications.
- Because in rare cases Vivitrol can cause or worsen depression, if this occurs it needs to be reported to the physician immediately.

Vivitrol as part of comprehensive treatment vs harm reduction

Case 1

- Chris is a 25 y/o male with opiate dependency. He has been in and out of detox and rehab multiple times. He completed a 90 day residential program and started Vivitrol while in out-patient treatment.
- He had several cocaine relapses.
- Do you stop Vivitrol?
He continues to have cocaine relapses and drops out of his out-patient treatment.

Do you stop Vivitrol?

He begins to challenge the Vivitrol and has used heroin several times a few days before each injection is due. He is now at a much higher risk of an opiate over dose if Vivitrol is discontinued.

Do you stop the Vivitrol?

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Treatment vs harm reduction

Now Chris is no longer getting any treatment, frequently uses cocaine, and challenges the Vivitrol blockaide with heroin at the end of each month.

He is not in recovery but he is being kept alive.

This can be viewed as a harm reduction model.

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Case 2

Shonna is a 23 y/o female with opiate dependency and is on probation. She completes 30 days of detox/rehab and receives her first Vivitrol injection in rehab.

She starts IOP and has received 2 additional Vivitrol injections.

She present for her 4th injection and has a positive pregnancy test.
Since Vivitrol is not approved for pregnancy and there isn’t good safety data, Vivitrol therapy was discontinued.

Two months later she calls and has been injecting heroin daily for the past 2 weeks and her PO is threatening to incarcerate her.

What options do you have?
- Refer to detox, Possible restart Vivitrol afterwards.
- Refer for Methadone maintenance.
- Start on Subutex maintenance therapy.

Initiating Vivitrol as an out-patient

- Ideally Vivitrol can be started in residential treatment and continued as an out-patient.
- Patients coming out of a 5 day detox have to remain abstinent for 7 to 10 more days before starting Vivitrol. Most will relapse before getting their injection.
- What do you do for the person who wants Vivitrol but is actively using opiates?

The Unknown

- There are new synthetic opioids on the street:
  - Fentanyl – 100 times more potent than morphine
  - Carfentanil - 10,000 times more potent than morphine
  - W-18 – 10,000 time more potent than morphine
- Does Vivitrol offer protection from these?
Summery

- Heroin and opioid overdose deaths are steadily rising.
- Oral Naltrexone (Revia) has been shown to be of minimal value in the treatment of opiate dependency.

Summery

- Vivitrol appears to be an affective treatment for opiate dependency, improving abstinence rates, reducing relapses, reduces cravings and improves retention in drug and alcohol treatment.
- Moral and ethical dilemmas can occur in regards to when to discontinue treatment in patients that are not compliant with treatment.

The End