Evolving Treads in Medication Assisted Treatment

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Disclosures

- Speaker of Alkermes Pharmaceutical
- I can't spell

Topics of today’s training

- Review the epidemiology of opiate use, opiate dependency, and over dose deaths.
- Review opiate receptor theory, opiate agonists and opiate antagonists.
- Discuss mortality rates following release from residential treatment.
- Discuss mortality rates following release from prison.
Topics of today’s training
- Methadone maintenance
- Buprenorphine maintenance
  - Suboxone
  - Zubsov
  - Bunavail buccal patch
  - Probuphine – Buprenorphine implant
- Oral Naltrexone – Revia
- Injectable Naltrexone – Vivitrol

Topics of today’s training
- The pregnant population
- Limitations of current studies on MAT

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*
Number of Prescriptions Written
Oxycodone and Hydrocodone

Prescriptions written in millions

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%.

Over Dose Deaths
Opioid use During Pregnancy

Cases per 1000 births

CDC data on heroin overdose deaths

Pa. Drug Deaths (All drugs)

- 2015 Pa. drug deaths = 3383 (9/day)
- About 80% 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 affect 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>Heroin and Xanax</th>
<th>Xanax</th>
<th>Heroin</th>
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<tbody>
<tr>
<td>Normal</td>
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<td></td>
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<tr>
<td>Sedated</td>
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<tr>
<td>Stupor</td>
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<td></td>
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<tr>
<td>Coma</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Death</td>
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</table>
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 overdose

- Previous overdose
- 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.

Residential treatment for opiate use disorder

- Detox is not treatment, it stabilizes the patient so they are able to get treatment.
- Those who go through detox only, 70% will relapse within the first 30 days.
- Given tolerance is reduced following detoxification, and relapse rates are so high, could we be putting them at greater risk of overdose by doing detox only?
Mortality rates based on length in treatment

- 137 individuals with opiate dependency were admitted to a 28 day residential treatment program.
- 43 left AMA during detox – 0 over dose deaths at 1 year
- 57 finished detox but left rehab AMA – 0 over dose deaths at 1 year
- 37 finished rehab – 3 over dose deaths at 4 months


Opiate over dose deaths before and after residential treatment

<table>
<thead>
<tr>
<th>Days 1-28 after discharge</th>
<th>Mortality in 1000 patient years</th>
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</thead>
<tbody>
<tr>
<td>Pre-treatment</td>
<td>4.3</td>
</tr>
<tr>
<td>Days 1-28 after discharge</td>
<td>18.8</td>
</tr>
</tbody>
</table>

English Addiction 2016

Is residential treatment a bad thing?

- Treatment does work and the longer a person has been abstinent and the longer they are in treatment, the less likely they are to relapse.
- Unfortunately those that do relapse are at a higher risk of an overdose.
- Question” Is there something we can do to lower the relapse risk or lower the over dose risk for those leaving residential treatment?
Initiating MAT in residential treatment
- Can we identify those who are at greater risk of relapse or overdose?
- In those at higher risk, should we be offering MAT?
  - Giving Vivitrol prior to discharge
  - Starting Suboxone maintenance
  - Referral to a methadone maintenance program
- Insurance considerations, providers, patient preference.

Weekly mortality rates upon release from prison

Mortality following release from prison
- All cause mortality was high in the first 2 weeks upon release, with opioid over doses being the leading cause of death.
- Prescription opioids was the leading cause of over dose.
- Other cause of death:
  Disease > homicide > suicide > motor vehicle accidents
The role of MAT in the prison population

- If a person is stable on methadone maintenance at the time of incarceration, should they be destabilized and taken off methadone?
- What about those on methadone maintenance and go to Out mate (Work release)?
- Should Vivitrol be offered prior to release.

Obstacles for MAT in the prison population

- Medicaid is turned off when incarcerated so either the jail or the company that contracts for inmate healthcare (Primecare) has to pay.
- Transportation to the methadone clinic or bringing doses in from the clinic.
- Counseling requirements for patients on methadone maintenance.
- Who pays for the Vivitrol?

MAT options
The correct use of medications

- In general, medications for opiate dependency should not be used as “stand alone” treatment.
- Medication use improves the outcome of drug and alcohol counseling.
- Drug and alcohol counseling improves the compliance with taking medications.

Treatment of opiate dependency with Naltrexone (ReVia)

- 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 a 6 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 in treatment Vivitrol vs Oral Naltrexone

Sullivan et al 2015

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.
- Supplement Vivitrol if the person struggles with cravings the last few days before their next Vivitrol injection.
- Direct observed administration is preferred.

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.

VIVITROL®: A Targeted Approach
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

<table>
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<tr>
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<th>Counseling + Placebo</th>
<th>Counseling + Vivitrol</th>
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<tbody>
<tr>
<td>Abstinence (%)</td>
<td>23%</td>
<td>36%</td>
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Opiate free weeks during 6 months of counseling with and without Vivitrol

Opiate free weeks rates over 6 months

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<tr>
<th></th>
<th>Counseling + Placebo</th>
<th>Counseling + Vivitrol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free weeks (%)</td>
<td>35%</td>
<td>90%</td>
</tr>
</tbody>
</table>

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

Does Vivitrol reduce mortality?
- As of now, there is only 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

Over doses following residential treatment

- Because relapse rates are high following release from residential treatment and tolerance is reduced, the first 28 days upon release from rehab is a high risk period of time.
- Overdose rates more than quadruple after discharge.
- This suggests we should be aggressively offering Vivitrol at the time of discharge from rehab.

Different treatment models

- Inpatient detox and rehab
- Physician's office
  - Injection site
- Outpatient drug and alcohol provider

Different treatment models

- Inpatient detox and rehab
- Outpatient drug and alcohol provider that offers Vivitrol
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.
- After care: There is limited physicians or outpatient programs that inject Vivitrol.

Initiating Vivitrol
- It is fairly easy to start Vivitrol in the inpatient setting, only having to wait 7 – 10 days upon completion of detox before giving the injection.
- Initiating Vivitrol in the outpatient setting in someone who is actively using opiates is challenging!
  - Refer to inpatient detox and rehab.
  - Attempt outpatient detox with Suboxone – 7 day taper, followed but 7 days of abstinence. Only 30% will maintain abstinence and get their first Vivitrol injection.

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.
**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**

- 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.

**Frequently asked questions**

- 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 overdose if Vivitrol is discontinued.
- Do you stop the Vivitrol?

Treatment vs harm reduction

- Now Chris is no longer getting any treatment, frequently uses cocaine, and challenges the Vivitrol blockade 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.
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.

The Unknown

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

Methadone maintenance clinics date back to the early 1970s. Methadone for the purpose of maintaining the opiate dependent individual can only be administered through a licensed methadone clinic; however methadone can be prescribed by any physician with a DEA number for other medical conditions (chronic pain).

Methadone pharmacology

- It is a full opiate agonist (stimulates opiate receptors); hence as the dose increases, the effect increases.
- Tolerance is slow to develop – Patient may remain on the same dose for many years.
- Methadone has a stronger receptor “affinity” than most other opiates – It binds more strongly to opiate receptors; hence may block the effects of other opiates.
**Methadone pharmacology**

- Doses < 80 mg/day may reduce cravings in many but doesn't have a “blocking effect” – Low dose maintenance.
- Doses > 80 mg/day has a “blocking effect” if illicit opiates are taken – High dose maintenance.
- Several studies have shown “high dose maintenance” is more effective as defined by less positive urines for heroin and better retention in treatment.

**Methadone dose and heroin use**

![Recent Heroin Use by Current Methadone Dose](image)

**Pyramid Healthcare**

![Methadone Dose Distribution](image)
Mortality rate on Methadone maintenance

Proven benefits of methadone maintenance

- Reduction in heroin use.
- During an average of 72 months (4 ½ years) of follow up:
  - Pretreatment 100%
  - During treatment 1%

Dole and Joseph 1978

Proven benefits of methadone maintenance

- Reduction in crime rate, reduced arrests.
- During an average time of 72 months (4 ½ years) of follow up arrest rates had fallen significantly:
  - Pretreatment 90 out of 100 opiate addicts were arrested yearly.
  - During treatment 5 out of 100 opiate addicts were arrested yearly.

Dole and Joseph 1978
Proven benefits of methadone maintenance

- Reduction in mortality. Swedish study of “street heroin addicts” followed for 5 to 8 years, 1990.
- Sweden’s national death rate = 10.2/1000 yearly.

115 untreated addicts (Control group) 63 times mortality rate (643/1000 yearly)
166 on Methadone 8 times mortality rate (82/1000 yearly)
Involuntary discharge 55 times mortality rate (561/1000 yearly)

- Reducing in new cases of HIV and Hepatitis C.
- Slowing of the progression of HIV to AIDS.
- Patients on methadone maintenance become more functional as measured by various quality of life indicators.
- Opiate dependent pregnant women:
  * Improved fetal outcomes (birth weight, less premature births, less miscarriages, less fetal deaths)
  * Improved parenting (improved baby growth)

Potential disadvantages of methadone maintenance

- Restricted life style.
- Cost – Only covered by MA
- Doesn’t prevent the simultaneous use of other illicit drugs.
- Prolonged detox if the individual wishes to come off of it. As many as 70% - 98% will relapse in the first year.
- How are they perceived in the recovering community?
- May preclude entrance into drug court programs or sober living.
Potential disadvantages of methadone maintenance

- It may take a month or more to stabilize a patient as their methadone dose is titrated up.
- Because methadone causes physiologic dependency, withdrawal will occur if it is abruptly discontinued. This is a problem during periods of incarceration.
- Ethical question: Should inmates have access to the same medical treatment as others? Factor in the high mortality rate upon release when MAT is denied.

Buprenorphine

- Suboxone Tablets
- Suboxone Film
- Zubsolv
- Subutex
- Bunavail Buccal Film

Buprenorphine – partial agonist

- Because of its "ceiling effect", there is less abuse potential and patients tend not to continue to escalate their dose.
- Self administration is safe.
- Mortality rates are cut in half compared to abstinence based treatment.
- Some opiate dependent individuals with very high tolerances may not be able to have their drug cravings controlled with the maximum dose of Suboxone (32 mg); therefore may need Methadone maintenance.
Potential advantages of Suboxone over Methadone

- Can be prescribed by a buprenorphine certified physician in 30 day supplies, avoiding the need to go to a clinic daily.
- Less of a lifestyle alteration.
- The physician visits and the cost of the medication may be covered by insurance.
- Discontinuation of the medication can be done more rapidly than with methadone.

Potential advantages of Suboxone over Methadone

- Less risk of overdose.
- There may be greater availability depending where in the state the individual lives.
- In pregnant women there is a lower risk of neonatal abstinence syndrome (withdrawal) when pregnant women are maintained on Buprenorphine (Subutex) compared to methadone:
  - 25% risk vs 50% risk

Potential problems with Suboxone maintenance

- High street value, high diversion risk.
- Less monitoring and accountability than with methadone maintenance.
- Physiologic dependency which is a problem during periods of incarceration.
- Frequent benzodiazepine abuse.
- May preclude entrance into drug court programs or sober living.
Opiate dependency and pregnancy

Working with the opiate dependent pregnant female

- Although Methadone maintenance has been considered “the gold standard” in the treatment of the opiate dependent pregnant female.
- Is Buprenorphine safe?
- In pregnant women the pure buprenorphine product should be used – Subutex.

The Mother Study

- Designed to compare the outcomes of pregnant opiate dependent females with Buprenorphine (Subutex) vs. Methadone maintenance.
- 175 participants in 7 study sights.
- Primary outcomes:
  - Buprenorphine vs. Methadone
    - Slightly less incidence of NAS (About 30% of babies will have NAS)
    - Much less morphine needed to treat the NAS (1.1 mg vs. 10.4 mg)
    - Shorter hospitalization (10 days vs. 17.5 days)
    - Less duration of treatment for NAS (4.1 days vs. 9.9 days)

Neonatal Abstinence Syndrome After Methadone or Buprenorphine Exposure, NEJM, 2010
Average morphine dose required to treat the baby

Average hospital days

Average days the baby needed treatment for NAS
The optimal treatment during pregnancy

- Based on the MOTHER study published in the NEJM and several previously done smaller studies, the evidence is growing that Buprenorphine (Subutex) may be a superior treatment option for the opiate pregnant female than Methadone.
- The one advantage that Methadone had over Buprenorphine in pregnant women was Methadone patients had a lower drop out rate than Buprenorphine. (There was better maternal retention with Methadone)

Three year outcomes

- Since the MOTHER study’s completion, the babies in the study were followed for 3 years post delivery.
- There was no increased risk of learning disabilities or delays in reaching developmental milestones in either the Methadone or Buprenorphine treated babies compared to “normal births”.

Probuphine

- This drug has recently obtained FDA approval for the treatment of opiate dependency.
- It is an implantable form of buprenorphine.
- It lasts for 6 months then needs removed or replaced.
- It is only recommended for those who have been stable on 8mg or less of Buprenorphine.
- It is a potential way to reduce diversion.
Potential obstacles for using Probuphine

- Does require minor office surgery to insert.
- Cost: $5000. May not be covered by insurances.
- May cost up to $500 to insert it.
- No accountability. Once inserted, the person can drop out of all treatment and monitoring for the next 6 months.

Probuphine
New injectable Buprenorphine

- There are 2 extended release injectable forms of Buprenorphine in phase 3 clinical trials.
- One is a 1 week injection that can be used in the early stages of treatment.
- One is a 4 week injection that can be used for maintenance.
- If it receives FDA approval, it will lower the risk of diversion if used to replace Suboxone film.

Comparison of different treatment options

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<th>Vivitrol</th>
<th>Buprenorphine</th>
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<tr>
<td>Reduces mortality</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<td>Reduces opiate use</td>
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<td>Reduces arrests</td>
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<td>Diversion risk</td>
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<td>Treats withdrawal</td>
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<td>Yes</td>
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<td>Use in pregnancy</td>
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Problems with our current studies on MAT

- Most of the medical studies on MAT are short term studies, typically 3 to 12 months; however addiction is a chronic relapsing disease.
- Participant numbers in many studies are small which can affect the validity of study results.
- Participants in the studies may be excluded if they have “real world” problems (Mental health diagnoses, poly substance use, medical conditions).
Problems with our current studies on MAT

- Studies with small number of participants followed for short periods of time can not give good mortality data. Since relapse rates are high a small number of people can be followed a short period of time to see changes in relapse rates; however most people that relapse will not die.
- Large studies following participants for long periods of time are needed to see changes in mortality rates.

Problems with our current studies on MAT

- Treatment recommendations and government policies in regards to MAT are being made based on limited short term data.
- There is certainly a push to move towards MAT, ASAM, SAMHSA, NIDA.
- What if we found out 5 or 10 year recovery rates or mortality rates were exactly the same following abstinence based treatment vs MAT?

The End