Methadone and Naltrexone ER

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Objectives

• Review Full Opioid Agonist Methadone
• Review Full Opioid Antagonist Naltrexone
• Case Examples
Methadone and Naltrexone have a similar pharmacology/similar mechanism of action, but Naltrexone can be administered in a primary care setting

A) True
B) False
Medication Therapy

• Opioid Agonists
  – Full: Methadone (Methadose or Dolophine)
  – Partial: Buprenorphine/Naloxone, Buprenorphine (Suboxone or Subutex)

• Opioid Antagonist
  – Naltrexone ER (Vivitrol)
Pharmacology of Treatments
### Characteristics of Medications for Opioid-Addiction Treatment.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Methadone</th>
<th>Buprenorphine</th>
<th>Naltrexone</th>
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</thead>
<tbody>
<tr>
<td><strong>Brand names</strong></td>
<td>Dolophine, Methadose</td>
<td>Subutex, Suboxone, Zubssolv</td>
<td>Depade, ReVia, Vivitrol</td>
</tr>
<tr>
<td><strong>Class</strong></td>
<td>Agonist (fully activates opioid receptors)</td>
<td>Partial agonist (activates opioid receptors but produces a diminished response even with full occupancy)</td>
<td>Antagonist (blocks the opioid receptors and interferes with the rewarding and analgesic effects of opioids)</td>
</tr>
<tr>
<td><strong>Use and effects</strong></td>
<td>Taken once per day orally to reduce opioid cravings and withdrawal symptoms</td>
<td>Taken orally or sublingually (usually once a day) to relieve opioid cravings and withdrawal symptoms</td>
<td>Taken orally or by injection to diminish the reinforcing effects of opioids (potentially extinguishing the association between conditioned stimuli and opioid use)</td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>High strength and efficacy as long as oral dosing (which slows brain uptake and reduces euphoria) is adhered to; excellent option for patients who have no response to other medications</td>
<td>Eligible to be prescribed by certified physicians, which eliminates the need to visit specialized treatment clinics and thus widens availability</td>
<td>Not addictive or sedating and does not result in physical dependence; a recently approved depot injection formulation, Vivitrol, eliminates need for daily dosing</td>
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<tr>
<td><strong>Disadvantages</strong></td>
<td>Mostly available through approved outpatient treatment programs, which patients must visit daily</td>
<td>Subutex has measurable abuse liability; Suboxone diminishes this risk by including naloxone, an antagonist that induces withdrawal if the drug is injected</td>
<td>Poor patient compliance (but Vivitrol should improve compliance); initiation requires attaining prolonged (e.g., 7-day) abstinence, during which withdrawal, relapse, and early dropout may occur</td>
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Goals of Therapy

• Maximal function
  – Stabilization and normalization of the brain
  – Establishment of durable hedonic tone
  – Engagement in care and recovery
  – Prevention of disease transmission
  – Restoration of health
  – Prevention of death

• Achieve appropriate dosage

• NOT to see how fast a patient can taper off medication
Knowledge Check

Although effective in decreasing illegal opioid use, patients treated with methadone in an OTP are often highly impaired from the methadone.

A) True
B) False
Methadone

- Long acting, full opioid agonist
- Binds to and occupies mu–opioid receptors
- Prevents euphoria from other mu agonists
- Alleviates withdrawal symptoms
- Administered in licensed OTP
Methadone

• Federal law: initial dose 10-30 mg, not to exceed 40 mg in day 1
• Suppresses cravings (60-120mg+)
• Can prolong QTc with risk of Torsades de Pointes
• Respiratory depression can be a side effect at any dose
• Increases overdose risk significantly if mixed with sedative hypnotics and ETOH
Start Low and Go Slow

Steady State Simulation - Methadone Maintenance
Steady State attained after 4-5 half-lives - 1 dose every half-life

In the graph above the wavy line represents the blood levels of methadone as well as the "effect" it has on the individual patient.
Methadone Myths

- Substitutes one addiction for another
- Prevents true recovery
- Should not be used long term and dose should stay low
- Babies born to mothers treated with Methadone are “addicted”
- Rots teeth
- Turns people into “zombies”
- Causes overdoses
- “Liquid Handcuffs”
- Everyone needs regular serum levels checked
Peak and Trough and Therapeutic Range
Methadone Side Effects

• General Opiate effects
  – Sedation
  – Maintained physiologic dependence
  – Hypogonadism (not as severe as with heroin/fentanyl and may be dose depende

• Constipation

• QTc prolongation (Martell et al)

• Sweating
Methadone Facts

• “Opioid Agonist Therapy:” Medication, or Treatment preferred
  – Reduces drug use
  – Reduces the risk of infectious disease transmission
  – Reduces criminal activity
  – Reduces the risk of overdose
  – Reduces death
  – Increases treatment retention
  – Improves social functioning
  – Cost-effective
  – Safe

Hospitalized Patients

• Initiating methadone in hospital:
  – 82% present for follow-up addiction care

Opioid Agonist Therapy Reduces Recurrence

Opioid Agonists Save Lives

Dose Needs to be Therapeutic

Relationship between methadone dose and heroin use
(adapted from Ball and Ross, 1991)

% OF CLIENTS USING HEROIN
(LAST 30 DAYS)

0 100

1-10 11-20 21-30 31-40 41-50 51-60 61-70 71-80 81-90 90+
METHADONE DOSE (MG)
To Taper or to Maintain, That is the Question...

- No question, actually...
- Longer treatment, better outcomes
- Consistent with chronic disease model
- Think DM, CAD, COPD
- As with any medication – no set limit
- Continually reassessed and individualized
Treatment Must Maintained

Rapid Return to Injection Drug Use Following Premature Termination of Methadone Maintenance Treatment

- 28.9% in 1-3 Months
- 46.3% in 4-6 Months
- 57.6% in 7-9 Months
- 72.7% in 10-12 Months
- 82.1% in 10-12 Months

(N = 388 Male Patients)
WHO Guidelines

In 2005, methadone and buprenorphine were included in the WHO Model List of Essential Medicines
Safe Methadone Induction and Stabilization

A Report of an Expert Panel

(J Addict Med 2013;7: 377–386)
Naltrexone

- Full mu opioid antagonist
- Blocks euphoric effect of mu opioid agonists
- Monthly IM dosing improves adherence
- No dependence, no need to wean
- Not scheduled
Naltrexone

- Will precipitate withdrawal if agonists (full or partial) are occupying mu receptors
- Must be 7-10 days opioid free
- Increased risk of overdose if try to overcome blockade
- Increased risk of overdose end of month or missed dose because of loss of tolerance
- Substantially less stigma
Protracted Withdrawal: “Naltrexone Flu”

- Patients who start naltrexone right after medically supervised withdrawal commonly experience “flu-like” symptoms that are consistent with subacute opioid withdrawal
  - Somatic complaints: insomnia, GI distress, hyperalgesia, anergia
  - Anxiety, irritability, dysphoria, anhedonia
  - Symptom severity correlated with naltrexone dose
  - Severity may be lower if naltrexone initiation is postponed (but relapse risk)

- Partially alleviated with aggressive symptomatic treatment

- Most of these symptoms remit by 2-4 weeks
  - Unusual for these symptoms to occur after 2\textsuperscript{nd} and subsequent injections
Naltrexone Side Effects

- Generally well tolerated
- GI upset/vomiting
- Diarrhea
- Headache
- Injection site reactions
- Allergic pneumononitis
Naltrexone

• Caution opioid blockade and pain
• Contraindication if active opioid use or concurrent opioid maintenance
• Caution overdose potential
• Must review with patients, must inform of risk of overdose and set safety plan

Consider giving buprenorphine with comfort meas for OD prevention during transition
Knowledge Check

Naltrexone ER (Vivitrol) is as effective as oral naltrexone (Revia) for the treatment of opioid use disorder

A) True
B) False
Naltrexone

- Oral naltrexone ineffective re: adherence
- Retention rates worse with naltrexone
- Does not suppress cravings
- Decreases time to relapse
- No difference compared to placebo after treatment completion
- Extended-release naltrexone more effective than placebo

Naltrexone ER Injection

https://www.youtube.com/watch?v=lZBaDCIWSwg

https://pcssmat.org/overview-of-mat/naltrexone/
A study last year showed that naltrexone is as effective as buprenorphine.

A) True  
B) False
X-BOT: Somewhat Misleading Press

• Voluntary detox

• Patients randomized to daily buprenorphine vs monthly naltrexone ER

• Followed 24 weeks to assess relapse rate

• Analysis only reviewed people who actually started medication, and showed no difference
X-BOT Trial Summary

• Difficult to initiate naltrexone ER
  – Only 72% assigned received first dose
  – And among those assigned during detox, only 53% started the medication
  – Vs... 94% assigned to buprenorphine started Rx

• Relapses earlier and more likely with naltrexone ER vs. buprenorphine
  – Intention to treat analysis
    • 65% relapse NTX ER vs. 57% buprenorphine
  – Relapse immediate
    • Very early on as so difficult to initiate NTX (25% day 21 NTX vs 3% buprenorphine)

• More overdoses in those randomized to naltrexone ER vs. buprenorphine

X-BOT Wrap Up

• Important trial as no other head to head comparison

• Buprenorphine still first line treatment
  ➢ Easy to initiate
  ➢ Better engagement
  ➢ Fewer Overdoses

• Naltrexone ER another “tool in the shed” for those who can safely start and stay engaged
## Medically Supervised Withdrawal

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<th>Approach</th>
<th>Details</th>
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<td>Symptomatic-only treatment</td>
<td>A variety of adjunctive medications are used to decrease specific symptoms of withdrawal</td>
</tr>
<tr>
<td>Rapid medically supervised withdrawal using antagonist</td>
<td>Naltrexone is added few (3–4, days after the last dose of opioid starting with very low doses (3-6 mg) Emerging withdrawal symptoms are treated with adjunctive medications to minimize discomfort</td>
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The standard of care is that patients with opioid use disorder should first be treated with naltrexone ER before opioid agonist treatment to prevent ongoing opioid dependence

A) True
B) False
How to Choose?
ASAM Guidelines

- Providers must use clinical judgment considering multiple issues
  - *Patient preference*
  - Severity of opioid use disorder, recent OD
  - Patient history of treatment response
  - Co-existing medical and psychiatric conditions
  - Other medications and potential for interactions
  - Other substance use disorders
  - Job, travel, transportation, family needs
  - Pain
  - Patient beliefs about specific medications, in collaboration and discussion with family
  - *Pending incarceration*
Which Patients are Likely Better for Agonist Therapy?

- Longer history of use
- Patients with history of overdoses, particularly following detoxification
- Patients with serious mental illness, disorganized, homeless
- Patients who have been opioid-free but never felt “normal”
- Patients with chronic pain requiring chronic opioid treatment
Which Patients Are Good Candidates for Antagonist Therapy?

- Patients not interested in, or able to be on, agonist maintenance
- Shorter history of use
- High degree of motivation for abstinence
- Professions where treatment with agonist is controversial (healthcare professionals, pilots)
- Patients successful on agonist but who want to try abstinence
- Patients who are abstinent but at risk for relapse
Summary

• Menu of options

• Agonist maintenance is preferred treatment and length should be for as long as the patient benefits

• Methadone maintenance treatment consists of daily methadone
  – Requires opioid treatment program

• Antagonist treatment consists of once monthly injection
  – Anyone can prescribe naltrexone

• Induction onto extended-release naltrexone can be an effective strategy for relapse prevention for those unable or not interested in agonist
Kevin is a 52 year old software engineer with a remote hx of AUD, ADD, MDD, 5 year OUD with recent escalation to heroin. Does not want agonist therapy. Buprenorphine helps at 2 mg daily.

Considerations:
• Why doesn’t he want agonist?
• Transfer from agonist to antagonist possible
• Comorbidities, co-occurring SUD
Celeste

Celeste is a 35 year old woman with a 10 year history of IV heroin OUD, AUD, binge eating disorder, MDD, sexual trauma. Tried buprenorphine several times, max dose, intensified treatment, but cravings and heroin use persist, significant abscesses, protracted relapse, intermittent ETOH. Can’t seem to get back on Buprenorphine.

Considerations:

- Safety – Bup vs Methadone, Overdose risk
- AUD and OUD -> Naltrexone?
- Structure
- Eating Disorder
- Dual Diagnosis
Stephen

• 32 yom comes to you s/p fentanyl OD. Notes remote OUD (oral oxycodone, max 120 mg daily), inadvertant OD 2 weeks ago after 3 months abstinence post release from jail, and tox revealed fentanyl. He notes he wants to get into a sober house in another state today, no interest in any agonist. He requests IM naltrexone now.

• What do you do?
A) Start oral naltrexone 50 mg daily
B) Advise best outcomes are with agonists and you will only treat him if he accepts buprenorphine
C) Administer Naltrexone ER IM 380 mg q 4 weeks and document risks and benefits
Stephen continued

• Doing well on Naltrexone ER IM – here for fu – 3rd injection
• Tells you he wishes to stop Naltrexone as he really doesn’t like the injections/too painful and not really helping his cravings anyway. Will be returning back to independent living
• Has a mother who feels that medication is a “crutch”
• What do you do?

A) Tell him that is his choice, you are meeting where he is and schedule a fu in 4 weeks
B) Probe to find out why he has decided this
C) Educate him about risks/benefits, options of care, including option to start buprenorphine to prevent relapse and help with ongoing remission and symptoms
D) If he is willing, start buprenorphine today
E) B,C,D, E
Suzy

- 50 yof with severe OUD, numerous overdoses, many friends with open air drug use abounds where she lives.
- Difficult to make appts, struggling with starting buprenorphine and managing opioid use
- Frequent buprenorphine negative tox screens

A) You recommend stopping buprenorphine
B) You recommend stopping buprenorphine and refer to MMTP
C) You recommend trial of in office induction and close interval follow up
Knowledge Check

If a person continues to overdose after being reversed by intranasal naloxone, he is clearly not interested in stopping/hasn’t hit his rock bottom yet. He should be encouraged to return when he is ready.

a) True
b) False
Intranasal Naloxone

6/16/16

Had my first overdose after 20 years of IV drug use. I can describe my thoughts and feelings, after being saved by Narcan, in one word – alone... grateful! This medication/drug is saving lives. Thank God, God Bless. Keep the faith.

6/17/16

Today is my birthday and I have received the best present ever... another chance at life. So grateful for my family, so grateful for my health, so grateful for this program, and a grateful heart will never reverse.
“Access to medication – assisted treatment can mean [the] difference between life or death.”

Michael Botticelli, October 23, 2014
Director, White House Office of National Drug Control Policy
Thank you!

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Resources

- Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction  
- Medication-Assisted Treatment for Opioid Addiction: Facts for Family & Friends  
  [http://store.samhsa.gov/shin/content/SMA09-4443/SMA09-4443.pdf](http://store.samhsa.gov/shin/content/SMA09-4443/SMA09-4443.pdf)
- NIDA Info Facts: Treatment Approaches to Drug Addiction  
- Medication Assisted Therapy Toolkit  