Medication-Assisted Therapy (MAT) to treat Opioid Use Disorder (OUD):

Key Takeaways (references for each below):

- High-dosage Methadone (with psychosocial therapies) is the overall best AND cheapest treatment option for treating opioid withdrawal with 84% retention vs. 59% with Buprenorphine and 21% with Naltrexone.
    - Use Suboxone [buprenorphine + naloxone] in patients in which MMT fails/has failed or is contraindicated (such as patients at high risk of or with QT prolongation, or hypersensitivity to methadone)
- Cannabinoids have potential to both directly relieve side effects of withdrawal in addition to spare opioid dosage during rehabilitation (although more research needs to be done, not cut and dry, most promising evidence comes from pain literature, not addiction/rehab)
- The addition of Contingency Management (CM) – providing incentives/rewards for illicit drug-free urine samples (cocaine, benzos, etc) – may also boost MAT efficacy
- "As many as 62% of adults in MAT present with co-existing chronic pain" - (Dunn, Brooner, & Clark, 2014)
- "Several studies have demonstrated that retention in treatment for opioid dependence was unaffected by the use of cannabis either prior to or during treatment" (Scavone et al., 2013)
- The addition of agonist maintenance (such as MMT) to relapse-prevention treatment doubles the chances an individual will achieve opioid-abstinence during treatment
- MAT has been adopted in less than 50% of private-sector treatment programs, despite being the most effective tool to treat OUD, and even in programs that do offer MATs, only 34.4% of patients receive them"

Opioid Receptor Agonists & Antagonists:

Methadone, full mu-opioid agonist, despite its issues (to be detailed below), is still the gold-standard of MAT and overall superior to Buprenorphine, Suboxone, or Naltrexone

"Methadone maintenance remains the gold standard [of MAT]"

- Mattick et al., 2014

- Multiple RCT meta-analyses consistently showed fixed doses of Methadone Management Therapy (MMT) had SUPERIOR retention in treatment of opiate abuse than comparable fixed doses of Buprenorphine Management Therapy (BMT)." -
    - Connock et al., 2007.
- Usually administered via an oral liquid
- Some of the highest rates of success of any therapy for OUD
- Lowest cost of all opioid agonist therapies, Generic AVAILABLE
- Most patients stabilize at 60-120 mg daily, rarely increase dosage based on tolerance beyond this
- Dose reduction schedules can take between 2-3 weeks to up to 6 months
    - *** The more rapid the reduction, generally the worse outcome
        - Senay et al., 1977
- Peaks within 2-4 hours of intake, 28 hour half-life

- Higher levels of dosing supervision REDUCES mortality rates
- Covered by Medicaid in ALL STATES, although few private insurance plans cover methadone via treatment programs (although in California this may be different?)
- 84% retention rate at 50mg daily
    - Ahmadi et al., 2003
- Long-proven track record and large trail of evidence.
- Should always be combined w/ psychosocial therapies, like all MATs, for optimal results
- Withdrawal symptoms start low and get worse throughout
- Low-dose methadone (20mg) daily was SIGNIFICANTLY WORSE than high-dose methadone (60-100mg)
    - 20% of low dose completed trial while 73% of high dose completed, plus methadone had the best results overall from the study
    - Johnson et al., 2000
- "Methadone maintenance demonstrates the highest patient retention rates in ALL STUDIES comparing methadone to buprenorphine"
    - Connery, H. S., 2015
- No significant difference in rates of serious AEs when comparing MMT & BMT
    - Connock et al., 2007
- Side effects:
    - Can be associated w/ risk for QTc prolongation, which can lead to 10-17% risk of cardiac arrhythmia (dose dependent)
    - Dose-dependent sedation, constipation, weight gain, depression, sweating, neuro-cognitive impairment, sexual dysfunction, dose-dependent respiratory depression (problems breathing)
    - Methadone tends to have a WORSE drug-drug and side effect profiles than either buprenorphine or naltrexone
    - Possible cardiovascular side effects
- Drug Interactions:
    - Alcohol/benzos: sedation & reduces respiratory drive
    - Antipsychotics, tricyclics antidepressants, calcium channel blockers (QTc prolongation, as mentioned above)
    - Anticholinergic psychotropics (constipation)

Buprenorphine, partial opioid agonist, when alone seems to be overall worse therapy than Methadone.

- When combined at a 4:1 ratio with Naloxone (opioid antagonist) called Suboxone, it can be as effective as methadone but not significantly better in the majority of analyses.
    - Naloxone acts as an opioid antagonist to block the high if crushed or injected but not when administered normally
- Dosing: Most effects plateau at 12-16mg, but doses up to 32mg daily (90% occupancy of mu-opioid Rs at 16mg)
- Withdrawal symptoms start AWFUL but rapidly get better
- 59% retention at 5mg daily (may be a bit low dosage though)

    - Ahmadi et al., 2003
- 2nd cheapest option, Generic AVAILABLE
- Heroin addicts tend to do <u>WORSE on Buprenorphine than prescription opiate addicts</u>… but nobody knows why?
- No euphoria during treatment in opioid-tolerant individuals
- <u>Requires mild-moderate opioid withdrawal prior to dosing</u> BUT relief within 24-72 hours of induction
- Can be taken every other day as opposed to daily w/ methadone
- <u>Side Effects:</u>
    - Drowsiness, dizziness, constipation, sleep problems, anxiety, or headache
    - Severe: breathing problems, liver problems
    - Significantly lower fatigue rates than similar methadone (Maglione et al., 2018)
- <u>Drug Interactions</u>:
    - Rifampin (reduces buprenorphine concentrations)
    - Atazanavir (increased bupre concretions and impairment)
    - Other Depressants (alcohol, benzos, etc) can increase risk of breathing problems

<u>Naltrexone</u>: Shown to be INEFFECTIVE vs alternatives, although extended-release may be more promising

- Most expensive and <u>no generic</u>
- Only 21% retention rate at 1 year at 50mg daily
    - Ahmadi et al., 2003
- <u>Drug interactions</u>:
    - Opioids (blocks)
    - NSAIDs (reduced effectiveness)
- <u>Side effects</u>: insomnia, site-reactions to injection, hypertension, nasopharyngitis, possibly influenza

<u>Suboxone</u>: Combination of Buprenorphine & Naloxone at 4:1 ratio.

- Results in negligible absorption of naloxone sublingual but when crushed or injected will result in opioid receptor antagonism (and thus <u>no high or abuse</u>)
- *** Safety profile is SUPERIOR to pure Buprenorphine, specifically lower rates of overdose
    - Saxon et al., 2013
- Tends to be effective in populations where <u>methadone therapy has not worked</u>
    - Stotts et al., 2009)
    - West et al, 2000

Table 1

Comparison of FDA-Approved Medications to Treat Opioid Use Disorder with Physiological Opioid Dependence

Medication	MOR intrinsic activity MOR binding	Differential pharmacology affecting MOR activation at therapeutic dose	Mechanism of relapse prevention
Buprenorphine	Partial agonist High affinity K_i* = 0.2 nM	Slow MOR dissociation allows thrice-weekly sublingual dosing and possibility of high-dose weekly formulations[13–15] Highest known MOR affinity makes rescue from overdose by naloxone less effective;[16] rapid precipitation of withdrawal if full agonists present	Reduces opioid craving, withdrawal, and stress reactivity Competitively blocks or reduces the reinforcing effects of other opioids
Methadone	Full agonist High affinity K_i* = 3.4 nM	Long terminal half-life (up to 120 hours) with delayed steady-state efficacy poses increased MOR toxicity risk during induction phase[17] Multiple drug-drug interactions pose both opioid-toxicity and withdrawal risks during treatment[18]	Reduces opioid craving, withdrawal, and stress reactivity Reduces the reinforcing effects of other opioids
Naltrexone ER	Antagonist	Lack of MOR agonism associated with delayed	Competitively blocks reinforcing

Table 3

Opioid Use Disorder Formulary in the United States

Available formulary	Dosage forms (mg)	Induction dosing (mg)	Recommended dosing range for stabilization/maintenance (mg)
Methadone (HCl oral concentrate, per ml)			
Generic	5, 10	5–10 every 4 hours up to 40 in the first 24 hours	Gradual titration with close monitoring over 2 weeks to 60–120 daily; rapid metabolizers may require higher dosing
Methadose	10		
Methadose sugar-free	10		
Methadone HCL Intensol	10		
Buprenorphine + naloxone			
Sublingual tablet			
Generic	2/0.5, 8/2	2/0.5–4/1; repeat up to 16/4 in the first 24 hours	4/1–24/6 daily
Zubsolv	1.4/0.36, 5.7/1.4	1.4/0.36–2.8/0.72; repeat up to 11.4/2.8 in the first 24 hours	2.8/0.72–17.1/4.2 daily
Sublingual film			
Suboxone Film	2/0.5, 4/1, 8/2, 12/3	2/0.5–4/1; repeat up to 16/4 in the first 24 hours	4/1–24/6 daily
Buccal film			
Bunavail	2.1/0.3, 4.2/0.7, 6.3/1	2.1/0.3; repeat up to 8.4/1.4 in the first 24 hours	2.1/0.3–12.6/2.1 daily
Buprenorphine			
Sublingual tablet (generic only)	2, 8	2–4; up to 16 in the first 24 hours	4–24 daily
Naltrexone ER			
Vivitrol	380	380 IM following agonist clearance; oral naltrexone 50 mg daily may precede or supplement initial induction	380 IM every 4 weeks; oral naltrexone may be added to supplement in weeks 3–4 as needed

ER, extended release.

TABLE 2. Pharmacological Profile of Methadone, Buprenorphine, and Naltrexone

	Methadone	Buprenorphine	Naltrexone
Main effect	Mu full agonist, NMDA antagonist	Mu partial agonist	Mu antagonist
Bioavailability	70%-80%	50%	< 50% (approximately 100% ER)
Half-life	28 hours	37 hours	9 hours (4.95 days ER)
Clinically apparent drug interactions	Rifampin, phenytoin, several ART	Select ART	Opioids, NSAIDS (?)
Active metabolites	None	Nor-buprenorphine	6-beta-naltrexol

ART = antiretroviral therapy; NSAID = non-steroidal anti-inflammatory; ER = extended-release formulation; NMDA = N-methyl-D-aspartic acid.

Characteristics of Medications for Opioid-Addiction Treatment.

Characteristic	Methadone	Buprenorphine	Naltrexone
Brand names	Dolophine, Methadose	Subutex, Suboxone, Zubsolv	Depade, ReVia, Vivitrol
Class	Agonist (fully activates opioid receptors)	Partial agonist (activates opioid receptors but produces a diminished response even with full occupancy)	Antagonist (blocks the opioid receptors and interferes with the rewarding and analgesic effects of opioids)
Use and effects	Taken once per day orally to reduce opioid cravings and withdrawal symptoms	Taken orally or sublingually (usually once a day) to relieve opioid cravings and withdrawal symptoms	Taken orally or by injection to diminish the reinforcing effects of opioids (potentially extinguishing the association between conditioned stimuli and opioid use)
Advantages	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	Eligible to be prescribed by certified physicians, which eliminates the need to visit specialized treatment clinics and thus widens availability	Not addictive or sedating and does not result in physical dependence; a recently approved depot injection formulation, Vivitrol, eliminates need for daily dosing
Disadvantages	Mostly available through approved outpatient treatment programs, which patients must visit daily	Subutex has measurable abuse liability; Suboxone diminishes this risk by including naloxone, an antagonist that induces withdrawal if the drug is injected	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

Table 2

Opioid-Abstinence Rates with Medication Compared to Nonmedication[a]

Medication[b]	Percentage opioid free on medication	Percentage opioid free on placebo/detoxification	Study
Naltrexone ER	36	23	Krupitsky et al. (2011)[23]
Buprenorphine/naloxone	20–50	6	Fudala et al. (2003)[24] Weiss et al. (2011)[25,c]
Buprenorphine/naloxone	60	20	Woody et al. (2008)[26,d]
Methadone	60	30	Mattick et al. (2009)[27]

ER, extended release.

[a] The randomized, controlled clinical trials summarized here paired medication maintenance with evidence-based psychosocial treatments and opioid use self-report data that were confirmed with urine toxicology. Clinical settings for treatment delivery may affect the rates of opioid use in the nonmedication control groups. The trials predominantly used adult opioid use disorder populations, with the majority being heroin dependent or having mixed dependence on heroin and prescription opioids.

[b] All medications are FDA approved.

[c] Population was prescription opioid–dependent patients.

[d] Population was youth aged 14–21 years.

Non-Opioid Medications/Treatments:

<u>Levomethadyl Acetate (LAAM)</u>: A longer-acting cousin on Methadone (still a full mu-opioid agonist) that has the benefit of being dosed only 3x a week as opposed to daily.

- Dosing regimen: "Monday–Wednesday–Friday schedule, starting at a daily 20-mg dose with every-other-day increments to a maximum alternate day dosing of 130/130/180 or 100/100/140 . As with methadone, stabilization doses vary widely across patients, in the range of 40 – 140 mg"
    - Vocci et al., 2005
- Still not an effective replacement for modern agonist therapies

Cannabis as an adjuvant?

- “In summary, pre-clinical studies provide robust evidence of the opioid-sparing effect of cannabinoids… prospective high-quality-controlled clinical trials are required to determine the opioid-sparing effect of cannabinoids” - 2017 Systematic Review & Meta-Analysis
    - Nielsen et al., 2017
- "In-treatment Cannabis use not associate with change in opiate use during ANY treatment phase” - Scavone 2013
    - “Cannabis use during methadone induction was not associated with any significant differences in time required = for dose titration or medication compliance. Furthermore, cannabis use did not significantly affect premature discharge status”
    - “Cannabis users preferentially fell into the low-severity withdrawal category while those that abstained from cannabis were more often in the moderate-level withdrawal category… when further characterizing in-treatment cannabis users as abstinent, occasional, or frequency use, 3x2 chi-square analysis demonstrated an INVERSE association between frequency of cannabis use and opiate withdrawal severity [X2(2)=6.71, p=0.035]. "
    - ALTHOUGH, it’s possible those using cannabis for some reason happened to be the less severe cases, HOWEVER, cannabis users did not significantly differ from cannabis-abstinent individuals based on other measures of severity of opiate dependence (include. cumulative years of opioid use and # of previous treatment episodes)
    - "Numerous studies of cannabinoid-opioid interactions in animal models of opiate addiction have provided strong evidence for an ameliorative effect of cannabinoids on opiate withdrawal symptoms
        - Frederickson et al., 1976
        - Yamaguchi et al., 2001
        - Cichewicz et al., 2003
        - Vela et al., 1995
    - Scavone et al., 2013
- Cannabis abuse is NOT a risk factor for treatment outcome in methadone maintenance treatment
    - Weizman et al., 2004
- “There were no significant correlations between cannabis use and the likelihood of testing positive for opioid, benzodiazepine or cocaine use in a group of buprenorphine-treated persons (Budney et al., 1998), or in methadone-maintained individuals“
    - (Saxon, 1993, Epstein and Preston, 2003, Scavone et al., 2013), FROM Scavone et al., 2013
- “Several studies have demonstrated that retention in treatment for opioid dependence was unaffected by the use of cannabis either prior to or during treatment”
    - (Saxon, 1993, Budney et al., 1998, Epstein and Preston, 2003, Weizman et al., 2004). FROM Scavone et al., 2013

- Negative evidence: No effect found of cannabis on opioid-withdrawal symptoms during methadone management therapy when account for self-efficacy
    - Epstein et al., 2015
- Negative evidence: among individuals receiving chronic opioid therapy for pain, the presence of cannabis use was a positive predictor of future opioid misuse (Reisfield et al., 2009).
- Cannabis use & dependence were associated with greater DECREASES in heroin and cocaine use during rehabilitation & treatment (Epstein & Preston, 2003)
- Cannabis use b/w 20-95% of those in rehabilitation for opiate addiction
    - Saxon et al., 1990, Nirenberg, 1996, Budney et al., 1998, Church et al., 2001, Epstein and Preston, 2003, Nixon, 2003, Aharonovich et al., 2005
- ~23-47% of patients at intake meet cannabis-use abuse criteria and have used for >3 months (Weizman et al., 2004, Wasserman et al., 1998, Epstein & Preston, 2003)
- Intermittent cannabis shown to diminish opioid withdrawal symptoms for individuals undergoing Naltrexone treatment
    - Raby et al., 2009
- No increase in risk taking behavior, infectious diseases, or psychological distress in methadone-maintained cohort who used cannabis vs. cannabis-negative methadone group (Weizman et al., 2004)
- Cognitive function & employment not significantly different b/w cannabis using and non-cannabis methadone maintained groups (Saxon, 1993)
- “Numerous studies have demonstrated that endocannabinoid or delta-9-tetrahydrocannabinol (Δ9-THC) exposure during morphine withdrawal in both mice and rats reduces the severity of morphine withdrawal symptoms”
    - Frederickson et al., 1976,
    - Vela et al., 1995
    - Lichtman et al., 2001
    - Valverde et al., 2001
    - FROM Scavone et al., 2013
- Cannabinoids + opioids superior to opioids alone for pain:
    - Reduction in symptoms, increased QOL, reduced pain, reduced opioid usage
        - Degenhardt,et al., 2015
    - 44% reduction in opioid usage after 6 months of adjunctive cannabis therapy for chronic pain
        - Haroutounian et al., 2008

Lofexidine: Alpha 2-Adrenergic Receptor Agonist

- Just approved by FDA on March 27 2018, first non-opioid treatment option for opioid withdrawal
    - https://www.mdedge.com/internalmedicinenews/article/161899/addiction-medicine/fda-advisors-recommend-lofexidine-opioid
- *** Similar to Clonidine, but with a better side effect profile
- Recommended dosage : 2.4mg daily from FDA, 3.2mg from US WorldMeds, lower dose seems better. usually only 14 days of treatment
- "The signs and symptoms of withdrawal occurred and resolved earlier with alpha-2-adrenergic agonists, and the duration of treatment was significantly longer with reducing doses of methadone”

- BUT also no potential for abuse
- SIDE EFFECTS: potential for bradycardia (abnormally slow heart action) or very low blood pressure

Contingency Management (CM): Financial/voucher incentives for opiate, cocaine, benzos, etc-free urine samples

- Shown to be effective to enhance effects of both MMT & BMT
- Patients tend to see the most benefits during EARLY treatment (also when patients are subject to leaving, so may be very important
- Emerging evidence of its effectiveness when combined with medication assisted therapy
    - Petitjean et al., 2014
    - Rawsonet al., 2006
    - Ledgerwood et al., 2014

Sorting Algorithm: Flow-chart of questions during intake to automate each patients' treatment

- Ex from Connery et al 2015

Text Box 2
Evidence-Based Medication-Assisted Treatment Selection Algorithm for Treating Opioid Use Disorder in Adults[a]

A. Threshold questions
(1) Is the patient actively seeking abstinence from all illicit opioid use?
YES: consider antagonist or agonist medication-assisted treatment (MAT)
NO: consider agonist MAT to reduce risk of accidental opioid overdose death by maintaining opioid tolerance
(2) Does the patient have significant co-occurring chronic pain?
YES: consider agonist MAT to reduce pain-related opioid relapse
NO: consider antagonist or agonist MAT
B. Exclusions to extended-release antagonist maintenance
- pregnant or planning pregnancy
- foreseeable need for opioid analgesia during treatment
- recent opioid overdose or high risk for opioid overdose behavior

C. MAT treatment setting
(1) office-based outpatient care
- patients committed to abstaining from all substance use
- no recent history of accidental or intentional substance overdose
- no recent history of opioid diversion

(2) structured care setting (e.g., opioid treatment program, integrated mental health care clinic)
- recently stabilized sedative/hypnotic or alcohol use disorders
- recent history of accidental or intentional substance overdose
- patient is receiving agonist MAT and has recent history of opioid diversion

[a] This algorithm is flexible in that it includes local care options and is designed to reduce opioid overdose deaths and opioid diversion. Failure of one MAT trial would prompt reconsideration of other available MAT options or the relocation of treatment from an office-based practice setting to a structured clinical setting with closer patient monitoring.

OTHER KEY FACTS:

*** 2005 Cochrane review said that available evidence INSUFFICIENT for purely psychosocial treatment

- Mayet et al., 2005

*** "As many as 62% of adults in MAT present with co-existing chronic pain" - (Dunn Brooner & Clark, 2014)

- Dunn, et al., 2014

*** "MAT has been adopted in less than half of private-sector treatment programs, and even in programs that do offer MATs, only 34.4% of patients receive them"

- Knudsen et al., 2011

*** The addition of agonist maintenance (such as MMT) to relapse-prevention treatment DOUBLES the chances an individual will achieve opioid-abstinence during treatment

- Fudala et al., 2003.
- Weiss et al., 2011.
- Woody et al., 2008
- Mattick et al., 2009

*** "In 2007, prescription-opioid abuse cost insurers an estimated $72.5 BILLION"

- CDC, 2013

*** 61% of overdose deaths in the US involve opioids

- Rudd et al., 2016

*** Patients undergoing MAT demonstrated poorer working memory, cognitive speed, and were in more traffic accidents that non-users. But, there were no differences on these factors b/w methadone & buprenorphine therapies

- Maglione et al., 2018

*** Substance abuse disorders in chronic pain patients range from **3.25-18.9%**

- Rosenblum et al., 2008

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