Medication Treatment for Opioid Use Disorder

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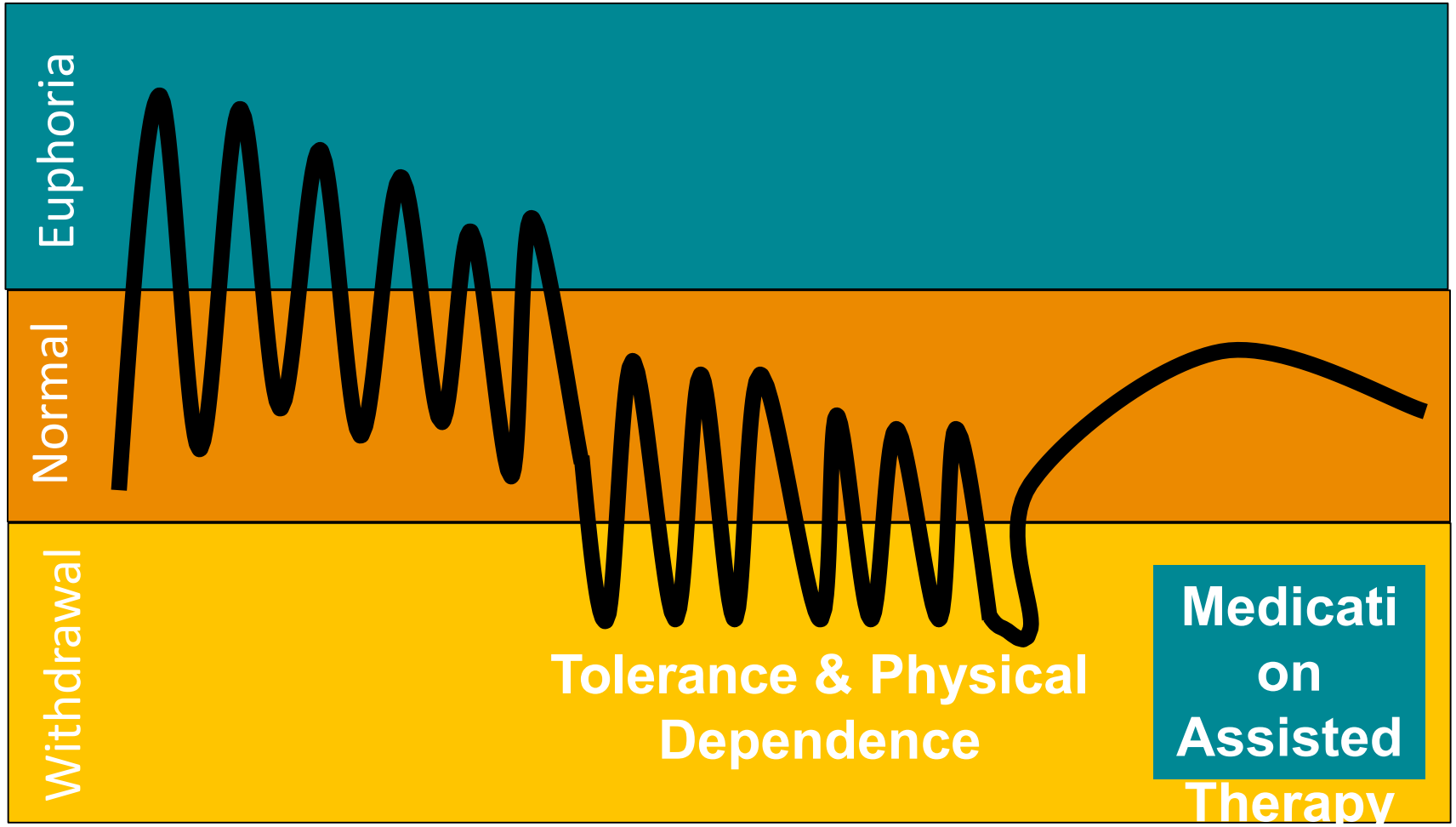


Acute Use

Chronic Use

Alford, Boston University, 2012

GOALS OF MOUD

- Keep patient alive and healthy
- Reduce/Eliminate Withdrawals
- Blunting the effects of illicit opioids
- Reducing or eliminating cravings
- Keep patients engaged in treatment

MAT vs MOUD

Historically, pharmacological treatment for opioid use disorder was referred to as “Medications for Addiction Treatment (MAT),” but more recently it has been determined that the more appropriate term is “Medications for Opioid Use Disorder (MOUD).”

- MAT connotes short term treatment
- MOUD involves a combination of a medications that targets the brain, and psychosocial interventions (e.g., counseling, skills development) aimed at improving treatment outcomes

MOUD

- Medications should be considered for all patients with OUD.
- Patients with OUD should be informed of the risks and benefits of medications to treat OUD, treatment without medication, and no treatment.
- Patients should be advised on where and how to get treatment with OUD medication

Medications for Opioid Use Disorder

Detox” has no long-term effect on outcomes; it is medication maintenance that saves lives and reduces relapse.

Treating Withdrawals/Overdose is not the same as treating the Primary Disorder; which in this case is one or more Substance Use disorders!!

MAT vs Medication free alternatives (Abstinence, placebo, detoxification)

Cochrane review article on Methadone

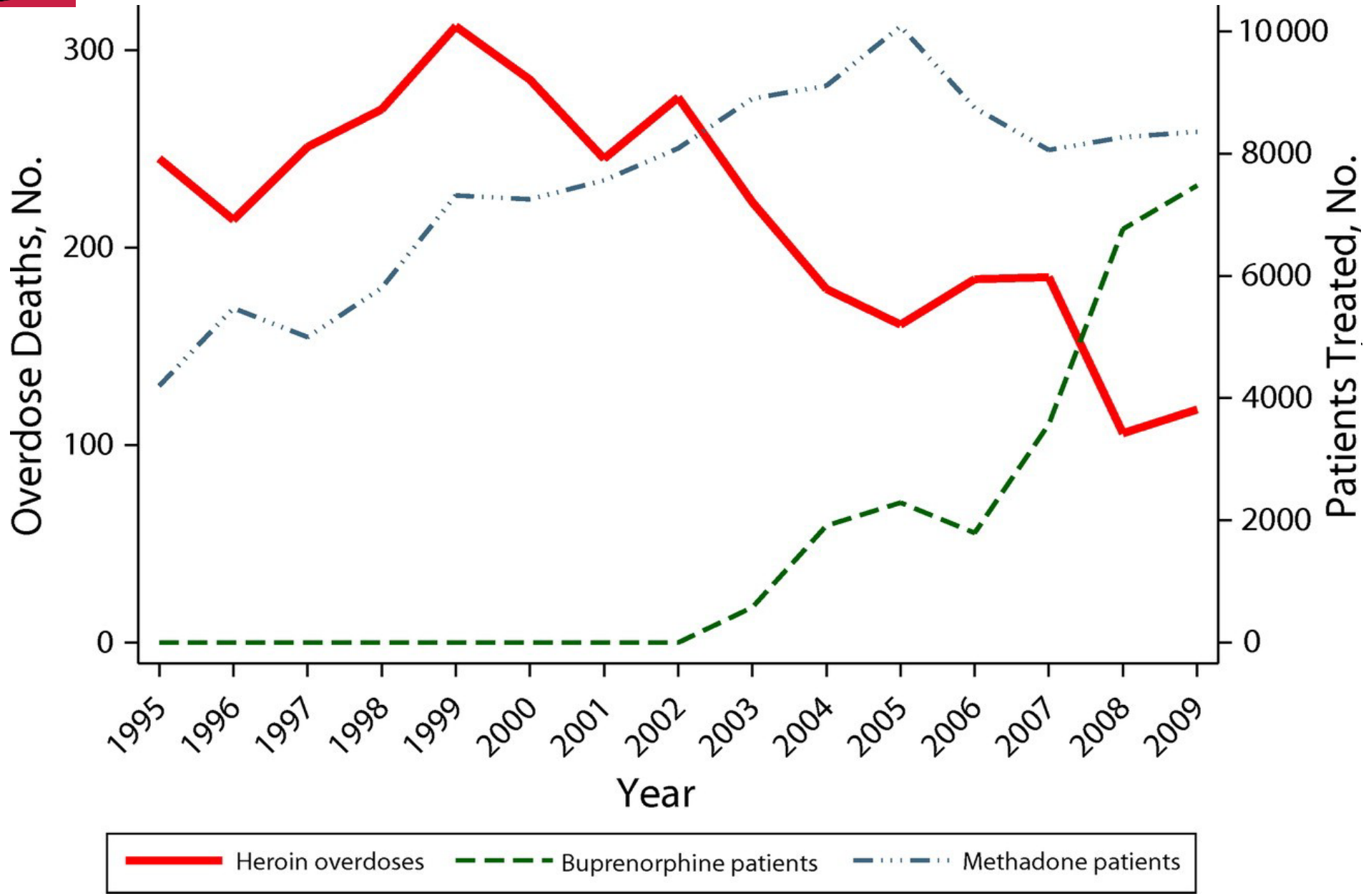
- Retention in treatment
  - 7 studies, 1287 participants
- Reduction in illicit opioid use
  - 6 studies, 1129 participants
- Reduction in self reported opioid use
  - 6 studies, 682 participants

Other studies show reduced risk of HIV and hepatitis C infection, Lower rates of cellulitis, Lower rates of HIV risk behavior, reduced criminal behavior

MAT vs Medication free alternatives (Abstinence, placebo, detoxification)

Buprenorphine

- Buprenorphine in its sublingual form retains patients in treatment and reduces illicit opioid use more effectively than placebo.
- It also reduces HIV risk behaviors
- Continued buprenorphine was superior to buprenorphine dose taper in reducing illicit opioid use



Schwartz, AJPH, 2012

MAT vs Medication free alternatives (Abstinence, placebo, detoxification)

Studies with vivitrol

- reduces illicit opioid use and retains patients in treatment more effectively than placebo and no medication
- In a two-group random assignment study of adults followed for 6 months
  - Longer time to return to substance use (10.5 weeks versus 5.0 weeks).
  - A lower rate of return to use (43 percent versus 64 percent).
  - A higher percentage of negative urine screens (74 percent versus 56 percent).

MAT vs Medication free alternatives (Abstinence, placebo, detoxification)

Cost Effectiveness and Cost Benefits

- Methadone and buprenorphine are more cost effective than OUD treatment without medication.
- Counseling plus buprenorphine leads to significantly lower healthcare costs
- Lower healthcare usage and costs than treatment without medication

Before commencing treatment

- Substance use history- Frequency of use, amount used, route of use, last use; other substances
- Treatment History- past induction, highest doses, reasons for past treatment failure
- Physical Examination- vitals, signs of withdrawals or intoxication, track marks, abscess
- PDMP check
- UDS and Scales
- Must meet criteria (Diagnostic and Statistical Manual, DSM-V) for opioid use Disorder (OUD)

Before commencing treatment

- Informed consent/agreement
- Overdose education
- Prescription for Naloxone rescue kit
- Patients should be advised on where and how to get treatment with OUD medication
- Handouts on how to take medication
- Discuss safe storage of medications with patients
- Wallet card for (LAI)
- Information about local recovery resources- AA/NA meetings
- Patient is able to follow treatment plan

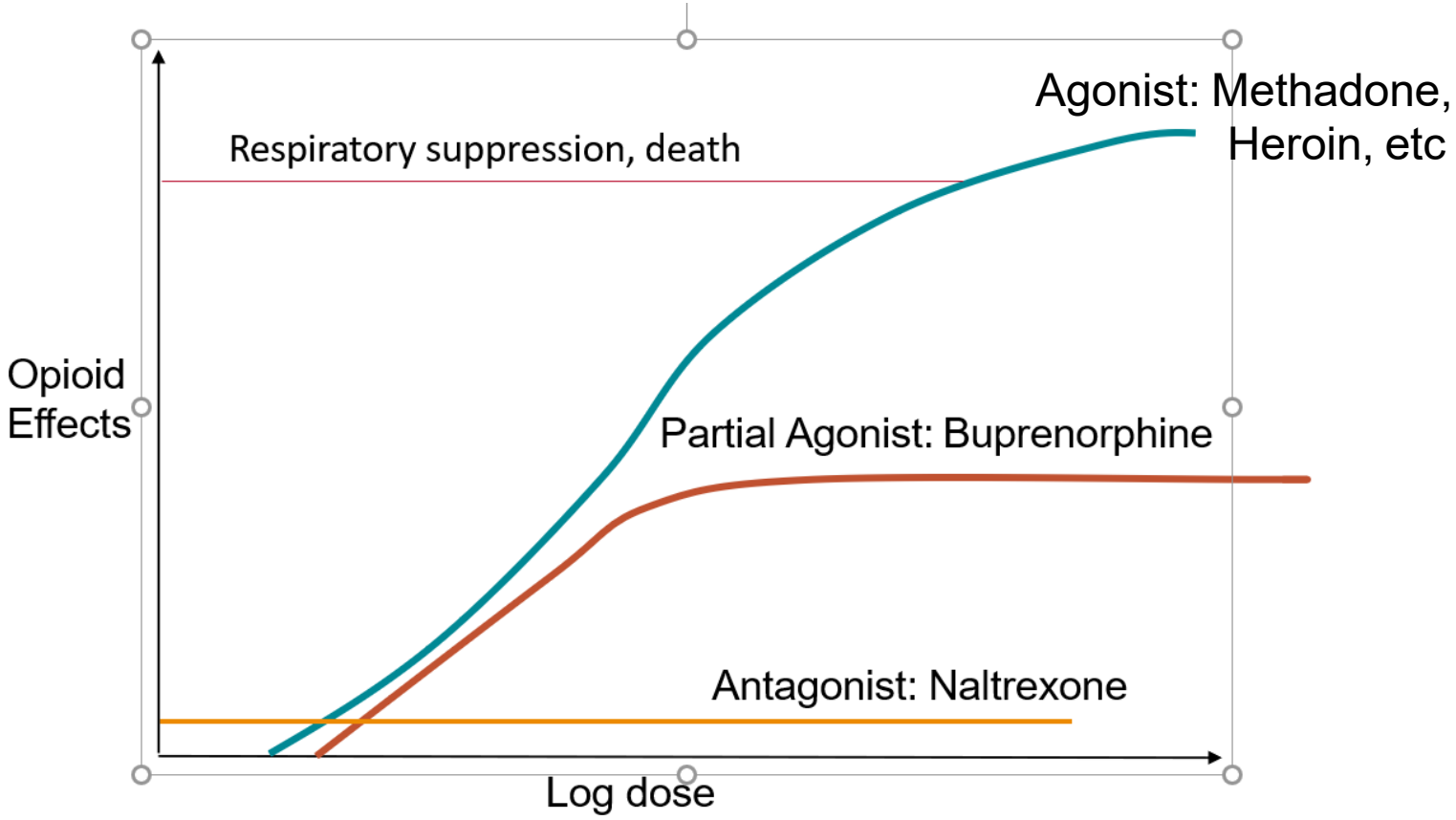
Treatment Agreements Elements

- *risk/benefit and discussion of other treatment options*
- *safe storage provision*
- *keep appointments*
- *single provider*
- *no early refills*
- *expectations for behavior in the clinic*
- *random urine drug testing*
- *pill counts*
- *intoxication*
- *risk of death from concurrent alcohol/benzo*
- *agree to addressing all recovery needs*

Medications for Opioid Use Disorder

- Buprenorphine (sublingual and implantable, LAI)
- Naltrexone (oral and extended release injectable)
- Methadone

Pharmacotherapy for Opioid Addiction



Methadone

- Most effective
  - ⬆ survival, treatment retention, employment
  - ⬇ illicit opioid use, hepatitis and HIV infections, criminal activity
- Cost-effective
  - Every dollar invested generates $4-5 in savings

Ball and Ross 1988

Methadone

- Approved by the FDA in 1947 for analgesic and antitussive uses
- Was shown to be effective in treating opiate addiction in the mid-1960s and was approved by FDA for this use in late 1972.
- Highly regulated, dispensed at Opioid Treatment Program (OTP)
  - Narcotic Addict Treatment Act 1974
  - Drug Addiction Treatment Act of 2000
  - Requirements under the Code of Federal Regulations 42 CFR
  - State laws may be more restrictive
- Patients who need a higher level of outpatient structure or supervision of medication adherence

Methadone

- Daily, observed dosing
  - Full opioid agonist
  - Onset within 30-60 minutes
  - Long-acting: Daily dosing effective for addiction

Methadone

- Formulations
  - Liquid concentrate
  - Powder (dissolved in water)
  - Dispersible tablets (dissolved in water)
  - Tablets (not routinely used in OTP)
- Half-life is between 8-59 hours, average 24-36 hours
- Steady state in 5 days
- has no ceiling effect

Methadone- eligibility

- Must have a one-year history of opioid use disorder unless released from jail, pregnant or prior client (2 yrs)
- Minimum age of 18 (unless there is a hx of 2 prior unsuccessful detoxifications in the last 12 months and parental consent,16-18)
- OTPs shall provide adequate medical, counseling, vocational, educational, and other assessment and treatment services.
- Monthly urine drug screening, case management

Methadone- dosing

- Start at 20-40mg
- Increase by 5mg every 3-5 days
- Dosing schedule
  - 0-90 days: attend 6 days a week (1 take home)
  - 90-180 days: attend 5 days a week (2 take homes)
  - 180-270 days: attend 4 days a week (3 take homes)
  - 27-365 days: attend once a week (6 take homes)
  - 1 -2 years : 2 weeks of take homes
  - > 2 years: 1 month supply

Methadone

- >80 mg for craving and "blockade"
- Avoid sedation/euphoria
- To evaluate stability, ask about take-home doses
- Main metabolite- EDDP
- Overdose potential, especially when combined with other drugs such as muscle relaxants, benzodiazepine
- **Multiple** medication interactions/metabolism- CYP 3A4, 2D6
- QTC Prolongation- EKG before start, approximately 2% increase, if >500 consider dose decrease

Methadone

- Advise staying in treatment until social, medical, psychiatric, legal, and family issues are stable.
  - "Detox" therapy has no long-term effect on outcomes
  - Longer duration, higher dose treatment most effective
  - For some patients, methadone therapy should be lifelong, as risk of relapse is high after cessation

Buprenorphine

- 2000 Federal Drug Addiction Treatment Act ("DATA-2000"):
  - Made office-based addiction treatment by physicians legal
  - Must complete 8-hour training and obtain federal waiver
- 2002: Suboxone (buprenorphine/naloxone) FDA approved
  - Outcomes much superior to psychosocial treatment alone
  - Longer treatment duration is more effective

Buprenorphine

- Compared to methadone:
  - Similar abstinence from illicit opioids and decreased craving
  - Lower retention in treatment
  - Can be prescribed in general practice, lowering barriers to treatment

Buprenorphine

- Partial opioid agonist, so safer than methadone
- High mu receptor affinity, so blocks or displaces other opioids
- “Ceiling effect” for respiratory or cardiovascular effects
- Some formulations may have naloxone to prevent injection diversion

Buprenorphine

- Formulations
  - Sublingual- Formulated with naloxone - abuse deterrent
  - Buccal film formulation: Bunavail
  - Implant- Probuphine- stable patients on ≤8 mg buprenorphine
  - Extended release subcutaneous injectable (Sublocade)
- Can precipitate withdrawal if full agonist are still in the body
- Requires induction after patient enters mild-moderate withdrawal

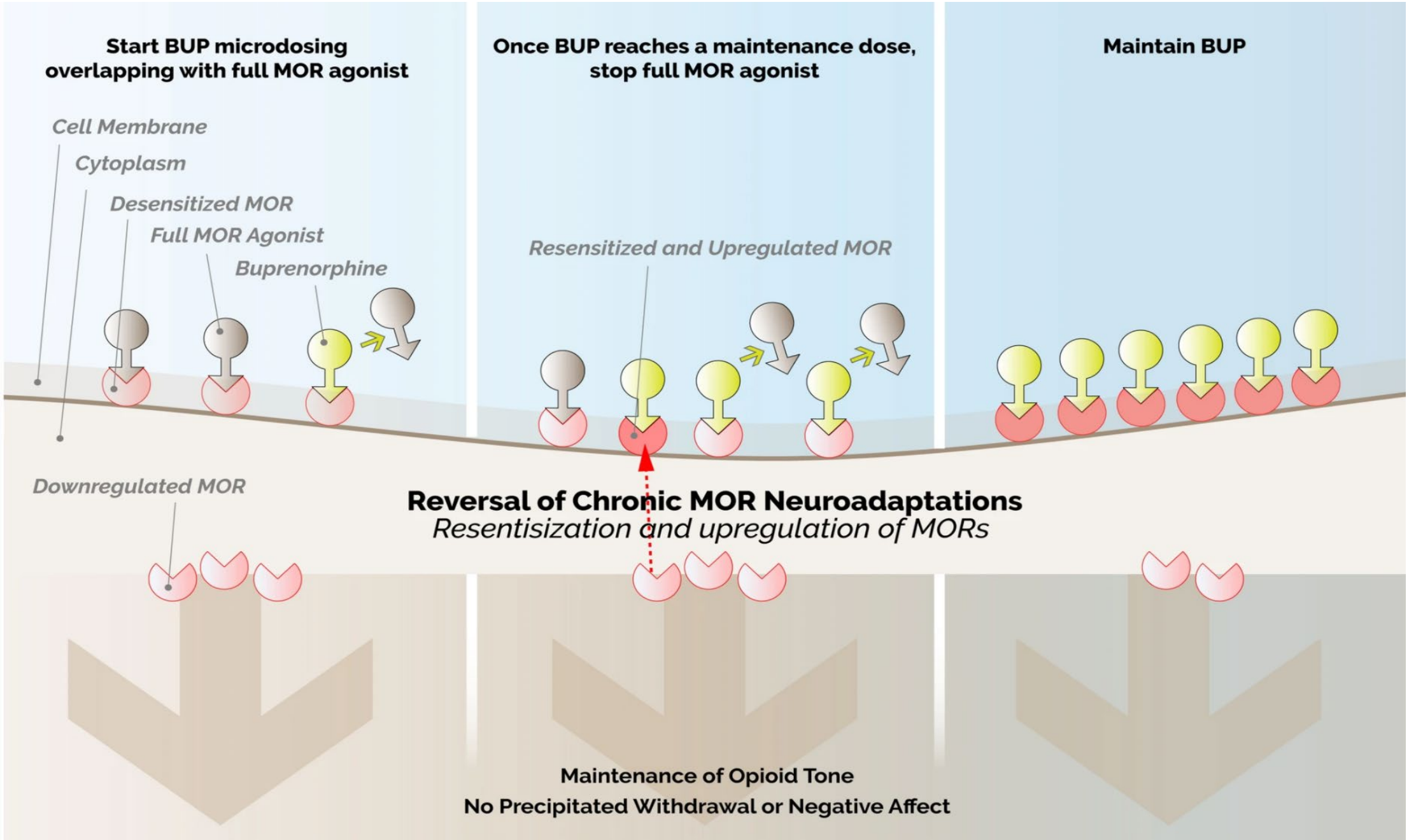
Buprenorphine

- Patients should be in mild to moderate withdrawal (COWS)
- Symptomatic treatment of withdrawals- diarrhea, nausea, anxiety, insomnia
- Period of abstinence depends on type of opioid and treatment setting
- Discuss precipitated withdrawals with patient- this can be best avoided by education and trust
- Initial dose of 2-8mg, repeat with 4-8mg after 2-4 hours

- Sublingual tablet
  - Buprenorphine
    - 50% bioavailable
  - Naloxone
    - Not well absorbed

- If tablet is crushed and injected:

  - Buprenorphine
    - Active
  - Naloxone: active
    - Displaces buprenorphine: withdrawal reaction
    - Patients do not favor injecting the combination Tablet


Start BUP microdosing overlapping with full MOR agonist
Once BUP reaches a maintenance dose, stop full MOR agonist
Maintain BUP
Cell Membrane
Cytoplasm
Desensitized MOR
Full MOR Agonist
Buprenorphine
Resensitized and Upregulated MOR
Downregulated MOR
Reversal of Chronic MOR Neuroadaptations
Resentisization and upregulation of MORs
Maintenance of Opioid Tone
No Precipitated Withdrawal or Negative Affect

Buprenorphine in Primary Care

- Advantages of buprenorphine in primary care:
  - Setting built for chronic disease management
  - Reduces the stigma of addiction treatment
  - Facilitates management of mental health and medical co-morbidities and preventive care
  - Important tool when problems arise during chronic opioid therapy
  - Public health benefit: increases local access to lifesaving care
- Highly gratifying form of treatment!

X- Waiver

The Drug Addiction Treatment Act of 2000 (DATA 2000) permits physicians who meet certain qualifications to treat opioid dependency with narcotic medications approved by the FDA – including buprenorphine – in treatment settings other than OTPs.

- Must receive waiver (known as "DATA Waiver") to prescribe. "Qualifying physician" must be
- Licensed under state law
- Registered with DEA to dispense controlled substances
- Qualified by training/certification
  - Addictions/addictions psychiatry certification OR
  - Approved 8-hour training course
- Capable of referring patients to counseling and other services
- DATE: Support for Patients and Communities Act (October 2018)
- Regulations have not been updated, but many of the provisions are effective immediately

Consolidated Appropriations Act 2023

- DATA- Waiver registration is no longer required Bup for OUD
- All prescriptions only require a standard DEA number
- No patient limits or caps
- Changes do not impact existing state laws
- Consideration for new training requirements for DEA licenses- New and renewals

Naltrexone

- Developed in 70s
- Approved for heroin addiction as oral version in 1984
- XR-NTX (Vivitrol) approved for alcohol use disorder 2006
- Injectable formulation approved for opioid use disorder 2010

Naltrexone

- Opioid antagonist that blocks other opioids (competitive Mu blocker)
- Does not lead to physical dependence, or to withdrawal when stopped
- Causes acute withdrawal in opioid-dependent patients
- Can be used in office-based settings without added training
- Effective in alcohol use disorder treatment
- Two formulations available:
  - Oral ReVia 50 mg PO daily (half-life 4 hours)
  - Injectable Vivitrol 380 mg IM monthly (half-life 5-10 days)

Naltrexone for Opioid Use Disorder

- Requires opioid abstinence prior to initiation, a major barrier since most treatment-seeking patients are actively using opioids
- Russian studies show benefit in population where opioid substitution therapy is not available
- Recent study (Lancet 2018) found that relapse events were higher with extended release naltrexone when compared to buprenorphine – most or all of the difference in relapse was due to induction failure with extended release naltrexone
  - In patients successfully initiated on naltrexone, relapse rates were
  - similar compared to buprenorphine

Naltrexone

- Equally effective if you can get the patient on it
- Requires a prolonged period of abstinence before it can be started without risk of precipitated withdrawals
- May not be as effective in reducing cravings as agonists
- Does not cause euphoria or mental status changes
- Zero abuse potential
- Will not help in pain management
- Injectable ensures compliance

	METHADONE	BUPRENORPHINE	NALTREXONE
EFFICACY	Most proven	Close if not equal to methadone	Less but mostly due to dropouts during induction
SIDE EFFECTS	Prolonged QT Constipation Low testosterone	Less cardiac Constipation Low testosterone Nausea, edema, HA, local	Nausea LFTs
RISK OF OVERDOSE	+++ if dose is too high or patient mixes with sedatives	Very low, possible when mixed with sedatives	None
PAIN CONTROL	Yes	Yes	No

	METHADONE	BUPRENORPHINE	NALTREXONE
MEDICATION INTERACTIONS	Yes (anticonvulsants, HIV meds, antidepressants…)	Yes (less severe)	Opioids
REGULATION	VERY High	Moderate	Minimal
CONVENIENCE	Very structured	Much less	Least restrictive
COSTS	Covered	Covered	Covered
WORK / MILITARY STATUS	Prohibited in certain job situations (CDL)	Less restrictive but often prohibited in CLD	None
DIVERSION RISK	Very low for 1st three months but higher after take homes are granted	Intially > methadone but less dangerous when diverted	None
EASIEST TO WEAN FROM	Difficult	Less difficult but still difficult	Minimal

WHICH MAT/MOUD

- Prior experience of patient (or friends) with MAT often drives the decision
- Many patients will not tolerate the required withdrawal period for naltrexone
- Prior use of diverted buprenorphine does not preclude OUD treatment with buprenorphine
- Opioid agonist therapy should not be denied to patients solely because they take benzodiazepines or other drugs
- Prior failure should not preclude another attempt

Summary:
Medications for Opioid Use Disorder

- Prescription opioid and heroin epidemics are major public health problems
- Medications are an essential component of evidence-based treatment
- Methadone and buprenorphine are the most effective pharmacotherapies for opioid use disorder
- Naltrexone can also be used, but patients must go through an opioid-free period (7-10 days) prior to induction
- Primary care teams can play an important role in treatment of opioid use disorders and prevention of overdose

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