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PSYCHIATRY ACADEMY

Methadone

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Disclosures

I have the following relevant financial relationship with a commercial interest to disclose:

Consultant:

MCSTAP Massachusetts Consultation Service for the Treatment of Addiction and Pain (funded by Massachusetts government)
Baycove Health and Human Services and Gavin Foundation

Advisory board, non-branded speaker:

Indivior

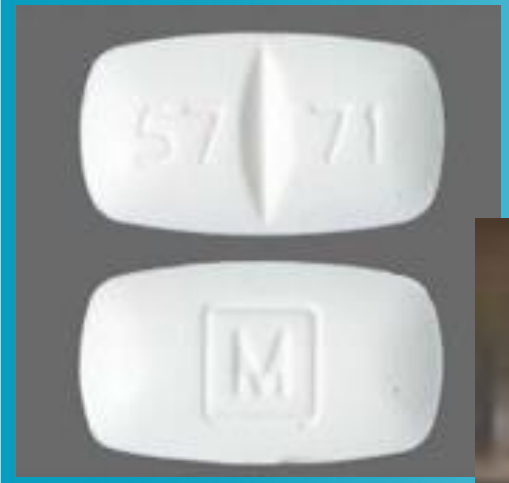
Medical Director:

Brightview Health OTP
Health Care Resources Centers OTP

Objectives

- Overview of pharmacology of methadone
- 42 CFR Final Rule Application
  - Initial Starting doses
  - Split doses
  - Take Home flexibilities
  - Removal of the “8 point criteria”
  - Person/patient- centered collaborative, individualized decision making

Methadone



Low Barrier Methadone More Important than Ever

Overdose deaths continue

Fentanyl/analogues have changed the landscape of the OD crisis

- thought due to lipophilic nature and protracted excretion phase
- precipitated withdrawal with buprenorphine
- poisoned drug supply/adulterants (xylazine)
- short effect/infectious complications of IDU

Increased demand and need for methadone

Methadone Pharmacology

- Binds to μ-opioid receptors
- Blocks effects of other opioid agents, such as heroin/fentanyl
- Oral methadone is 70 to 95% bioavailable
- Stored extensively in the liver and secondarily in other body tissues
- No ceiling effect

Pharmacokinetics of Methadone

- Pharmacokinetics vary greatly among patients
- Even after the administration of the same dose, different concentrations are obtained in different patients
- metabolized in the liver via CYP450 3A4
  - CYP3A4 varies among patients
  - CYP2D6, CYP2B6 and CYP1A2 are also involved
- Main metabolite is the N-demethylation by CYP3A4 to EDDP (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine), an inactive metabolite
- Genetic and environmental factors can act on those enzymes, leading to a high degree of individual variation in methadone's apparent potency

Methadone Side Effects

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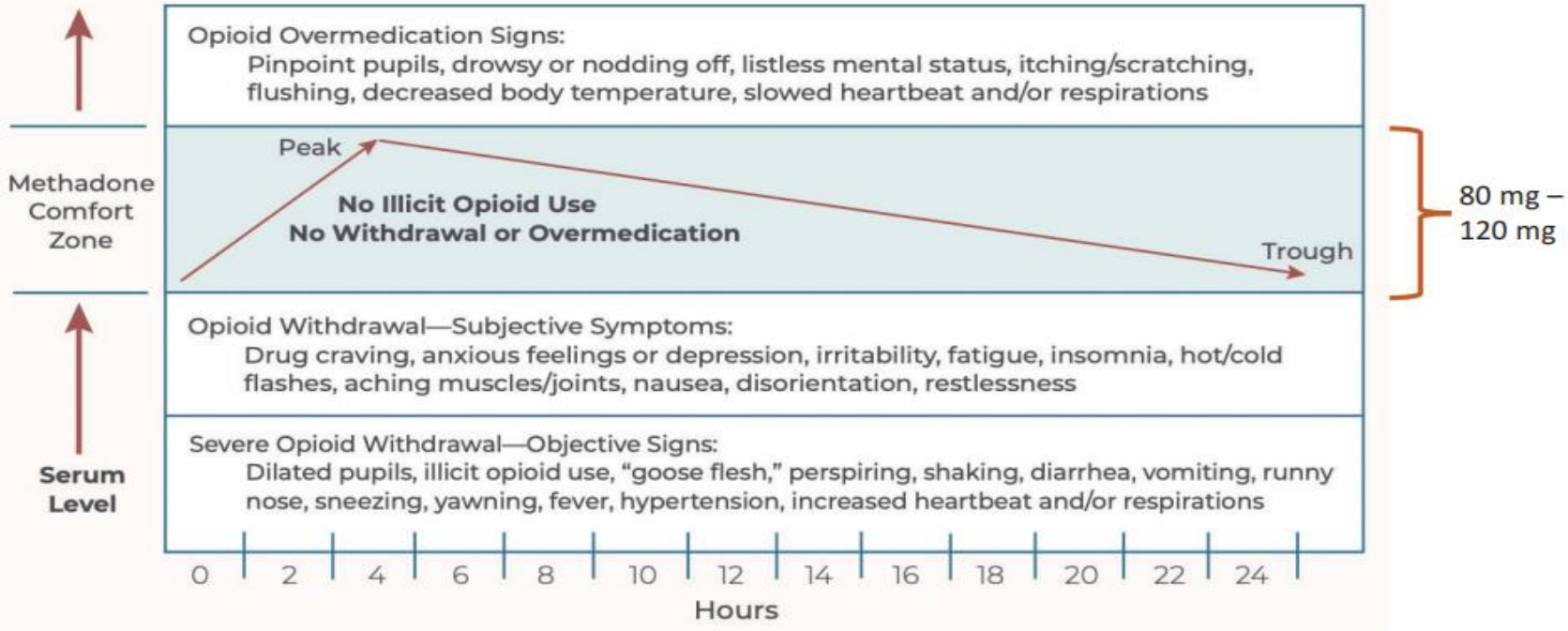
- Constipation
- Diaphoresis
- General Opiate/Opioid effects
  - Sedation
  - Increased overdose risk if mixed with sedative hypnotics or alcohol
  - Maintained physiologic dependence
  - Hypogonadism (not as severe as with heroin/fentanyl and may be dose dependent)
- QTc prolongation with torsades de pointe (>500) *rare

EXHIBIT 3B.4. Using Signs and Symptoms To Determine Optimal Methadone Level



Medications for Opioid Use Disorder: For Healthcare and Addiction Professionals, Policymakers, Patients, and Families: Updated 2021 [Internet]. Treatment Improvement Protocol (TIP) Series, No. 63. Rockville (MD): Substance Abuse and Mental Health Services Administration (US); 2018.

Goal is to have 24 hours of withdrawal control without any sedating effects at methadone's peak (2-4hrs after dose)

Reasons for Caution

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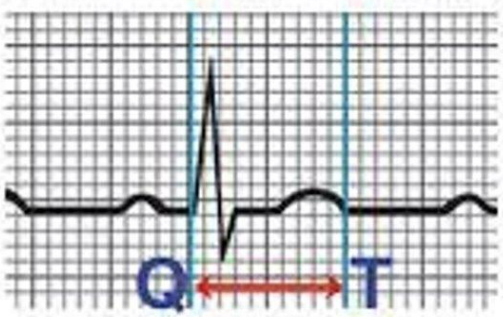
Arbitrary caps on methadone dosing are not recommended and not evidence based.

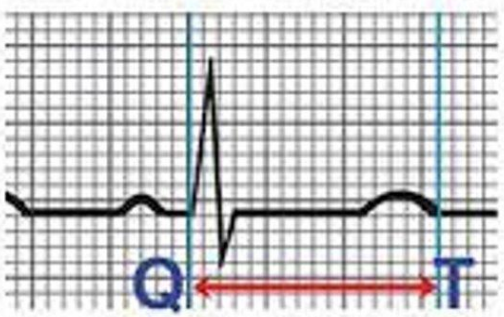
However, methadone:

- Can prolong QTc with risk of Torsades de Pointes at QTc >500msec
- Can increase overdose risk if mixed with sedative hypnotics (eg benzodiazepines) or alcohol
- Can cause sedation and respiratory depression at any dose

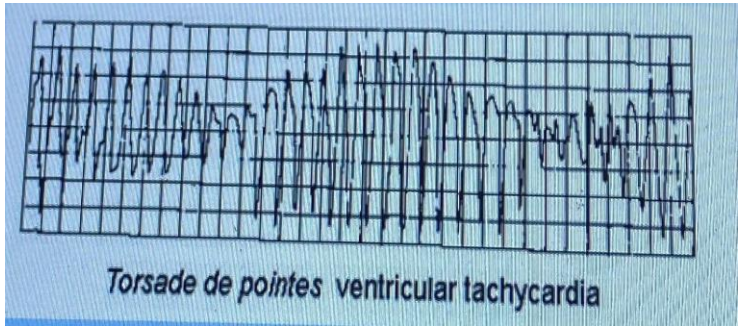
QTc and Risk of Torsades de Pointes



Normal Q-T Interval



Long Q-T Interval

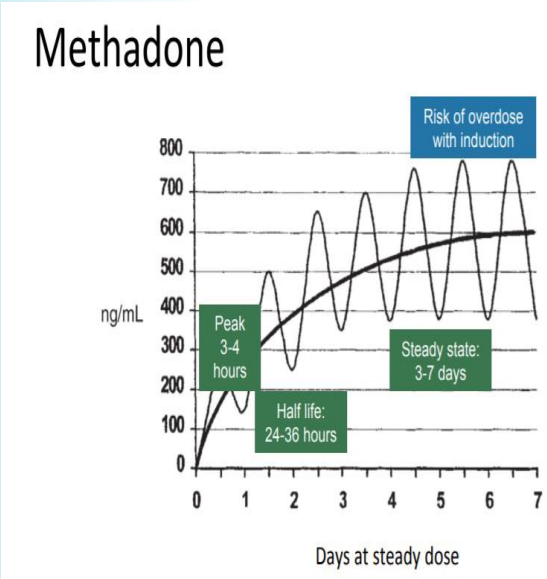

Torsade de pointes ventricular tachycardia

To ECG or Not to ECG?

- No consensus
- General guidelines
- Cardiac hx, family sudden death, sx of concern, other QTc prolonging drugs
- Dose MTD 120+ mg
- Some clinics do ECG on site, others refer out

Longtime Standard of Care

- Titration schedules often set by individual clinic company policies
  - "start low, go slow" standard care
- Patients may get automatic decreases for missing multiple days in a row
- All of this means pts may struggle to get to and stay on a therapeutic dose – which can be deadly



Baxter et al. Safe methadone induction and stabilization: report of an expert panel. J Addict Med. 2013

Inpatient and Non-OTP Experience Grows

- Growing # of addiction consult services, giving providers increased experience with methadone titration
- 72-hour rule -short term methadone in bridge clinics
- BMC Bridge clinic currently give day 1: 40mg; day 2: 50mg and day 3: 60mg; for pts w high use and no medical contraindications, piloting even faster

Table 3. Methadone Dose among Patients without Confirmed Recent Dosing, mg* .

	Day 1, n = 139	Day 2, n = 107	Day 3, n = 52
Mean Dose (SD)	28.4 (7.6)	37.2	42.9
Dose range	10–50	20–60	25–60
Dose median	30	40	40

Taylor et al. Bridge clinic implementation of "72-hour rule" methadone for opioid withdrawal management: Impact on opioid treatment program linkage and retention in care. Drug Alcohol Depend. 2022

Recent Publications on Rapid Inpatient Protocols

- 98 patients were included for a total of 168 visits
- 2 patients (1.2%) experienced a serious event
  - 1 naloxone for sedation
  - 1 ICU transfer for observation

TABLE 2 - Total Daily Doses of Methadone Received During First 7 Days of Titration (n = 135)

Day of Titration	1	2	3	4	5	6	7
Mean, mg	40.6	49.3	50.4	55.3	59.2	62.3	65.4
SD, mg	9.6	12.6	15.3	18.5	18.0	18.9	20.9

Klaire S, Safety and Efficacy of Rapid Methadone Titration for Opioid Use Disorder in an Inpatient Setting: A Retrospective Cohort Study. J Addict Med. 2023

Outpatient Rapid Titration Protocol From San Francisco General Hospital OTP

- Inclusion: OUD using fentanyl with history of high tolerance (usually self-reported use of 1 gram of fentanyl or more daily)
- Exclusion: CHF, advanced COPD, CKD

- Day 1: Methadone 30mg, first dose, plus additional 10mg
- Day 2: Methadone 60mg
- Day 3-5: Methadone 80mg
- Day 6-8: Methadone 100mg
- Day 9: methadone 120mg.
- Thereafter, generally wait 5 days before increasing dose

BayMark Pilot

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I. Inclusion criteria
   i. Patients endorsing fentanyl usage or high prevalence of fent in community
   ii. Patients with high opioid tolerance
II. Relative exclusion criteria
   1. Age >65
   2. Co-occurring substance use: alcohol, prescribed/non-prescribed benzodiazepines
   3. Co-occurring medical issues: known or suspected cardiac, renal, respiratory, hepatic issues
   4. Patients who have never been on methadone

- High intensity
  - Day 1: 40mg: 30mg initial dose followed by additional 10mg
  - Day 2: 60mg
  - Day 3: 80mg
    - Hold dose for 3 days before any further increases
- Moderate intensity
  - Day 1: 40mg: 30mg initial dose followed by additional 10mg
  - Day 2: 50mg
  - Day 3: 60mg
  - Day 4: 70mg
  - Day 5: 80mg
    - Hold dose for 3 days before any further increases
- Further dose increases
  - by 10-15mg every 2-3 days

Source: Internal communication BayMark

BayMark Pilot Preliminary Results

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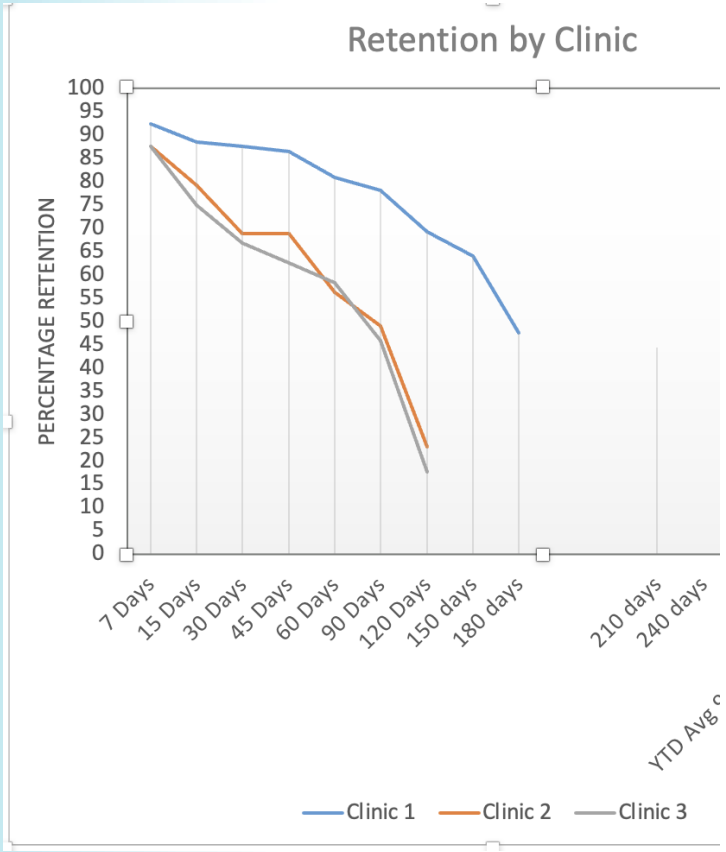
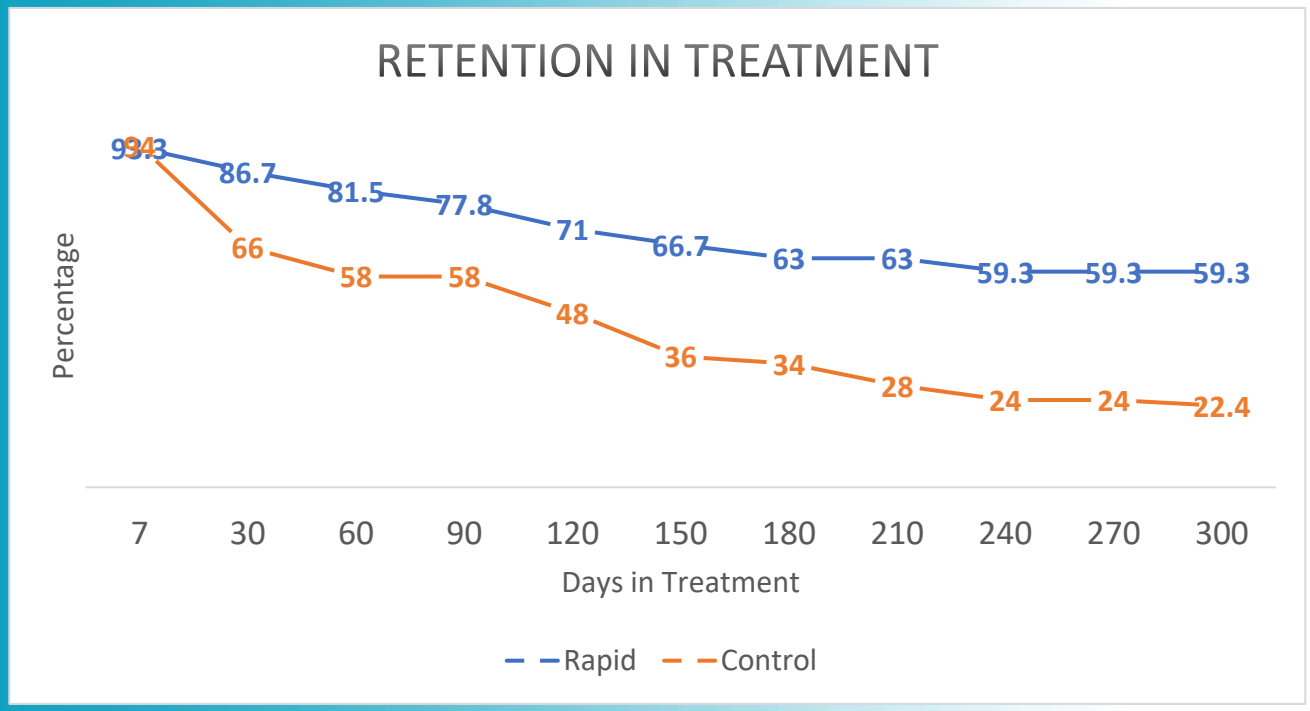
- 100 pts across 3 clinics in 3 states
- Avg days to 80mg = 6.2 days
- Avg peak dose= 120.6mg (but range based on state 101-165)
- The clinic with the highest peak dose had the best retention



Source: Internal communication BayMark

BayMark Pilot Preliminary Results

- Improved retention (and other outcomes!) vs quasi-matched usual care controls



Source: Internal communication BayMark

Split Doses-Rapid Metabolism

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- Minority of patients are rapid metabolizers of methadone
- Some states can temporarily cause rapid metabolism
  - Pregnancy
    - Split dosing is now **standard of care** for pregnant patients
  - Medications that increase methadone metabolism (older ARVs, Abx, chemo agents- typically CYP INDUCERS)
- Signs rapid metabolism are:
  - Sedation at peak
  - Withdrawal in afternoon/evening
- Patient with peak/trough ratio >2.1 c/w rapid metabolism

SAMHSA TIP63 2021 ; SAMHSA. Clinical Guidance for Treating Pregnant and Parenting Women With Opioid Use Disorder and Their Infants 2018
Addiction Treatment Forum. Methadone Dosing & Safety in the Treatment of Opioid Addiction. 2003

Split Dosing in Other Clinical Scenarios

- Split dosing may also help patients manage other chronic syndromes such as pain
- Split dosing may minimize side effects such as hyperhydrosis or nausea
- Risk-benefit balance and risk mitigation strategies should continue to be deployed

Braun & Potee. Individualizing methadone treatment with split dosing: An underutilized tool. JSAT. 2023

Paradigm Shift

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FROM	TO
All risk should be eliminated	Risks can be mitigated
No acceptable amount of risk	There is always some risk, and benefits can be weighed against risk
Provider and clinical staff determine risk and mitigation strategy	Risk weighed with patient and mitigation is shared responsibility

Harm Reduction Principles

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- SAMHSA's Harm Reduction Toolkit, Pillars of Harm Reduction:
  - "***Any positive change,*** as defined by the patient"
  - "There are many pathways to wellness; substance use recovery is only one of them. Abstinence is neither required nor discouraged."

Key Changes to criteria for Take- Home medications

- Abstinence is not required for take home medication
  - pt is assessed for risk from substance use
  - Distinction between ***substance use*** vs ***use disorder***
- Counseling is not required for take-home medication
  - Still recommended
  - Not a requisite to receive life saving medication

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Take Home Bottles: Essential Clinical Questions to Guide Decision-Making

1. **Will increasing the number of unsupervised doses support or harm the patient's recovery?**
2. **Is the patient likely to harm themselves with increased unsupervised doses?**
3. **Is the patient likely to harm others with take-home medication?**
4. **Why isn't the patient already on a reduced schedule?**

What's wrong with this picture?

- Winter in New England
- Elderly woman, COPD, O2 dependent, wheelchair bound
- In remission 6 yr, 80 mg/d, 1 weekend TH
- Elderly husband pushes her in wheelchair into OTP line for daily MTD
- He has pre-surgical Cspine dz and limited use of hands, in remission 8 yr, 100 mg /d, 13 TH

How can we improve their care and their risk?

What's wrong with this picture?

- 36 yom with severe OUD, past remission, s/p knee fracture and surgery 3 mo ago, in immobilizer, PT
- MTD 250 mg daily
- Ongoing pain, sl fatigue 3-4 hr after dose, hyerphidrosis, low energy
- 7pm PM sweating, anxiety, increased pain, insomnia, craving – uses ½ g fentanyl for sx relief and awakens in mild WD
- Works remotely as an administrator Mon-Fri
- Daily dosing, Sun closure Take home only

How can we improve his care and lower his risk?

Goals of Therapy

Alleviate withdrawal

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

What are the patient's goals?

- Less chaotic use?
- Improved function?
- Abstinence?

Final Rules – April 2, 2024
5 POINT CRITERIA FOR THBs

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- (i) Absence of active substance use disorders, other physical or behavioral health conditions that increase the risk of patient harm as it relates to the potential for overdose, or the ability to function safely;
- (ii) Regularity of attendance for supervised medication administration;
- (iii) Absence of serious behavioral problems that endanger the patient, the public or others;
- (iv) Absence of known recent diversion activity;
- (v) Whether take-home medication can be safely transported and stored; and
- (vi) Any other criteria that the medical director or medical practitioner considers relevant to the patient's safety and the public's health

Is this a Substance Use Disorder?

36 yo man, on 155 mg methadone, stable dose for 12 years, sustained remission.

Works in construction, married, 2 teen boys

Has 27 Take Home Bottles.

Most recent drug screen returns with cocaine and fentanyl.

Is this a substance use disorder?

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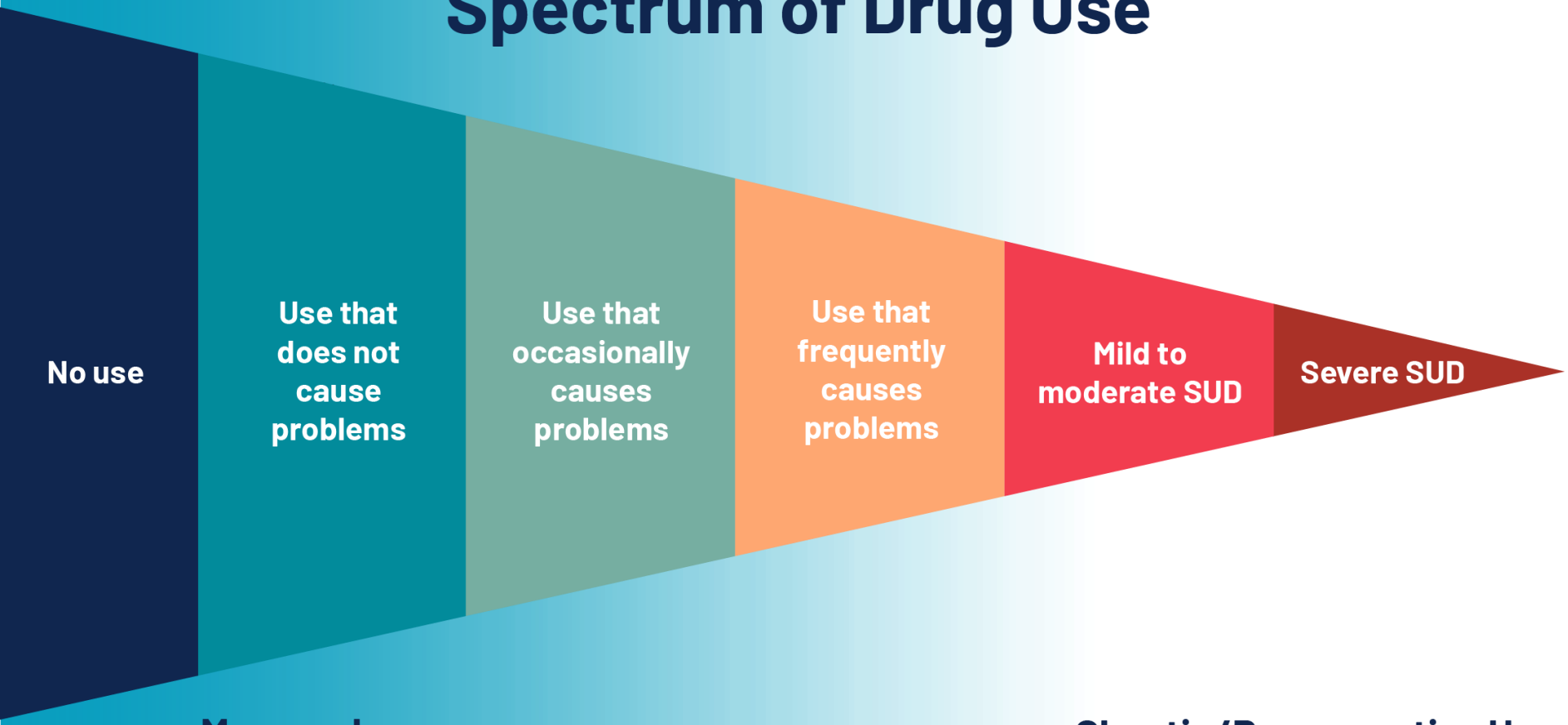
Spectrum of Drug Use



Old vs. New

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- (i) Absence of recent abuse of drugs (opioid or nonnarcotic), including alcohol;

- (i) Absence of active substance use *disorders*, other physical or behavioral health conditions that increase the risk of patient harm as it relates to the potential for overdose, or the ability to function safely;

What Should You Test For?

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- When conducting random drug testing, OTPs must use drug tests that have received the Food and Drug Administration's (FDA) marketing authorization for commonly used and misused substances that may impact patient safety, recovery, or otherwise complicate substance use disorder treatment, at a frequency that is in accordance with generally accepted clinical practice and as indicated by a patient's response to and stability in treatment, but no fewer than eight random drug tests per year patient

Response to Missed Doses

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- 33 yo working single mother of tween stabilizes on 120 mg methadone, often misses appts for counseling and 2 days per week of dosing.
- Intermittent fentanyl on toxicology
- Goal is abstinence

- What are your next steps?

Missed Doses

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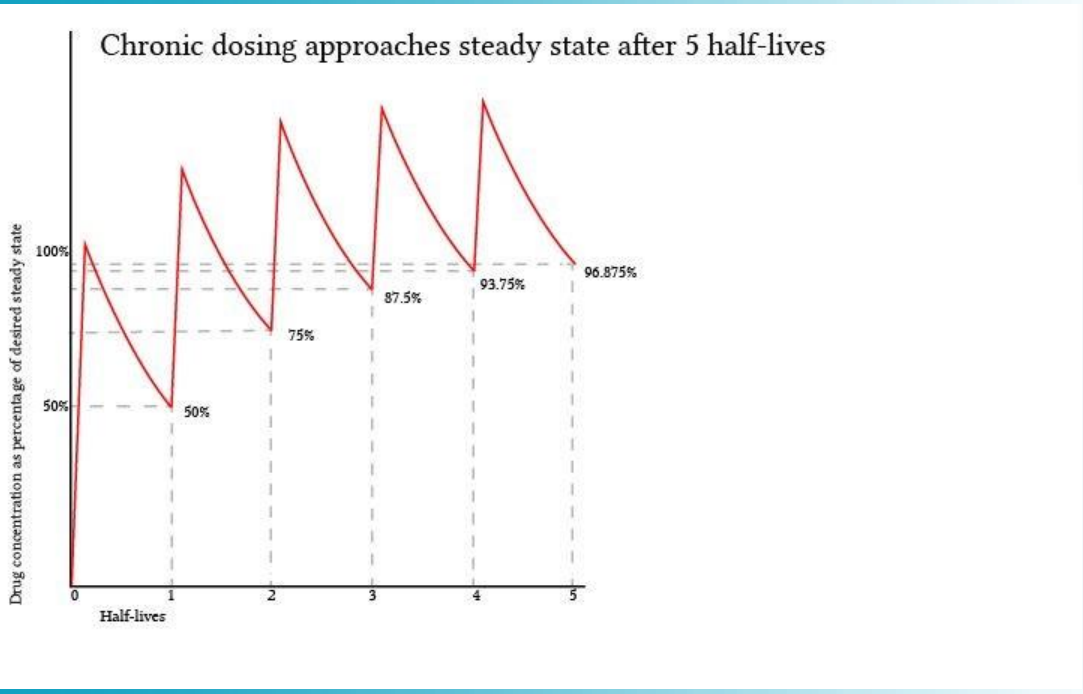
- Standard dose reduction protocols reflect concern about rapid loss of tolerance
- Plasma methadone levels drop day to day, but do not correlate with time-proportional loss of opioid tolerance
- Many pts continue to use dangerous opioid agonists (fentanyl) if miss methadone
- Risk of subtherapeutic methadone and illicit fentanyl > risk of maintaining methadone dose
- Clinical pharmacology studies
  - Pt with OUD maintained on methadone can safely tolerate acute changes in methadone (or other potent opioids) that exceed maintenance methadone

Greenwald M *et al. Mu*-Opioid Receptor Availability, Pharmacokinetic, Symptom and Blockade Effects During 52-Hour Omission of the Methadone Maintenance Dose. Unpublished data, shared with permission

Methadone and steady state



"a mean value of around 22 hours (range 5-130 hours) for elimination half-life"

Eap CB, et al. Interindividual variability of the clinical pharmacokinetics of methadone: implications for the treatment of opioid dependence. Clin Pharmacokinet. 2002

https://derangedphysiology.com/main/cicm-primary-exam/required-reading/pharmacokinetics/Chapter%20401/maintenance-dose-and-loading-dose

Missed Doses of Methadone Guideline in the Fentanyl Era

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Any Dose

- Missed 1-4 days: same dose
- Missed 8 days or more: restart at 40 mg

  titrate up to maintenance more quickly

Low Dose (<60 mg)

- Missed 5-7 days: no dose change

High Dose (60 mg or greater)

- Missed 5 days: drop by 20%

  titrate up to maintenance quickly

- Missed 6 or 7 days: drop 50%, but not lower than 40 mg

  titrate up to maintenance quickly

Missed Dose Guideline, courtesy Ruth Potee, MD, BHN

Methadone treatment for people who use fentanyl: Recommendations[1]

AL

DEMY

Summary of recommendations

1. Indications for methadone treatment

(a) Methadone and buprenorphine are both first-line OAT options. Methadone may be preferable to buprenorphine for patients who are at high risk of treatment drop-out and subsequent fentanyl overdose. Methadone should also be considered as a first option for patients who have done well on methadone in the past; patients who do not want or have not benefited from buprenorphine; and patients for whom buprenorphine induction has not been successful.

2. Methadone dosing and titration

(a) The clinician should attempt to reach an optimal dose of methadone safely and quickly.
(b) Starting methadone at 30mg (i.e., the higher end of initial dosing guidelines) is recommended.
(c) The starting dose of methadone can be increased by 10–15mg every three to five days. Within this range, faster titration (i.e., 15mg rather than 10mg) is recommended for those who are not at high risk for methadone toxicity (e.g., not concurrently using high doses of benzodiazepines or alcohol), while slower titration is recommended for patients at higher risk of toxicity (e.g., older age, sedating medications or alcohol, patients new to methadone). Patients who have recently been on methadone dosing at higher doses (i.e., in the previous week) can be considered for more rapid dose increases based on their tolerance. Once a dose of 75–80mg is reached, the dose can then be increased by 10mg every five to seven days.
(d) Slow-release oral morphine (SROM) may be co-prescribed with methadone and can be maintained or tapered depending on clinical response. SROM should be dispensed as "observed dosing along with methadone".
(e) Patients who miss methadone doses should be assisted to resume previous doses quickly and safely. After four consecutive missed doses, the dose of methadone should be reduced by 50% or to 30mg, whichever is higher. For patients who miss five or more consecutive doses methadone should be restarted at a maximum of 30mg and titrated according to patient need. SROM at a maximum starting dose of 200mg can be added on the day of a restart, as long as the patient has not become completely opioid-abstinent.
(f) For patients who use fentanyl regularly, methadone doses of 100mg or higher are often needed.
(g) Methadone dose increases should not be delayed due to the absence of an ECG.
(h) Concurrent benzodiazepine use should be addressed and methadone dosing adjusted accordingly.

Person Centered Care

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- As with any other chronic, recurring condition:
  - Establish patient's goals
  - Understand patient's short-term objections
  - Hear what the patient needs to accomplish those objections
  - Recognize discrepancies in provider goals vs those of the patient
  - Expand definitions of therapeutic support
  - Individualize
  - Weigh risks and benefits

A Chance to Do it Better

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My own experience also supports the need for greater use of, and access to, take-homes for people on MMT. Since I was lucky enough to begin treatment at a clinic that used a harm reduction approach, I was able to access take-homes despite my occasional use of substances, eventually earning the maximum amount of 28 days. It was only because of the freedom that take-homes provided that I was able to transition from a life on the street to something more stable.

Had I been forced to attend the clinic every day, for years on end, I not only would have never been able to attend school and earn my PhD, I would have almost certainly left treatment and returned to daily heroin use. Yet before COVID-19, programs offering 28-day take-homes were so rare, that few patients were even aware they existed. In fact, there are patients who fly from out of state, every 28 days, to attend the same New York City clinic that I do, because they are unable to find that service any closer to where they live.

Frank D. A chance to do it better: Methadone maintenance treatment in the age of Covid-19. *J Subst Abuse Treat*. 2021;123:108246. doi:10.1016/j.jsat.2020.108246

Resources

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- Methadone Treatment Recommendations for People Who Use Fentanyl
- SAMHSA Methadone Flexibilities Extension Guidance
- ASAM 2021 Public Policy Statement on Methadone Regulations
- https://regulatorystudies.columbian.gwu.edu/federal-regulation-of-methadone
- TIP 63: Medications for Opioid Use Disorder (samhsa.gov)

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Thank you!

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https://www.massgeneral.org/substance-use-disorders-initiative

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