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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:

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Advisory board, non-branded speaker:

Indivior

Medical Director:

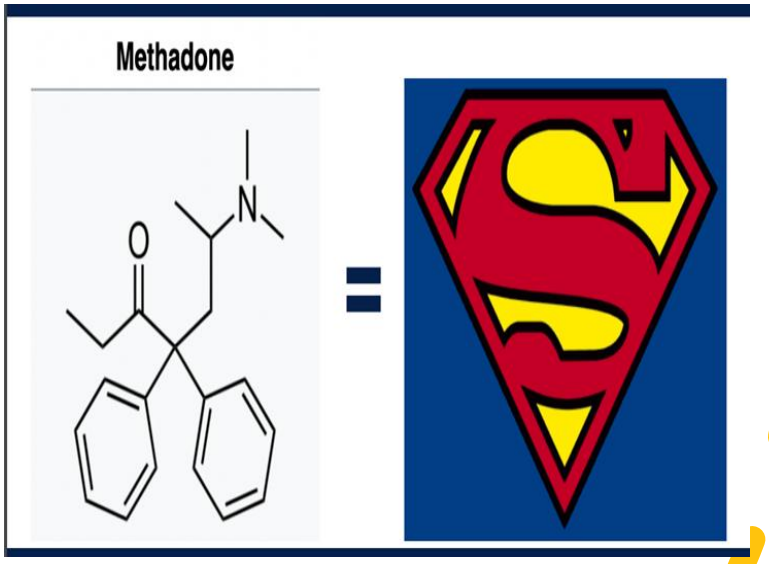
Health Care Resources Centers OTP

Objectives

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

Methadone

A first line treatment for opioid use disorder (OUD) [1–3]	•Reduces all cause mortality •Increases treatment engagement •Reduces HIV and HCV
Methadone for OUD is limited to Opioid Treatment Programs (OTP)[4]	•DEA and SAMHSA license and certify OTPs •Set strict standards for pt eligibility, dosing, and other requirements
Number and capacity of OTPs is insufficient [5–7]	•Delays in enrollment associated with morbidity and mortality
Significant racial and socioeconomic entry in OTP enrollment and retention [8–9]	
Adequate dosing is an important determinant of treatment retention	
Urgent need for low barrier methadone	•Fentanyl/analogues/contaminants have changed the landscape of the OD crisis



Graphic courtesy of Dr. Ruth Potee

1. Alavian, 2013. 2. Bruce 2010. 3. Mattick 2014. 4. Certification and Treatment Standards for OTPs. 5. Jones 2015. 6. Rosenbloom 2011. 7. Sigmon 2014. 8. Gryczynski 2011. 9. Lo 2018. 10.Bao 2009.

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

Methadone

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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

- 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
- 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

Case

- 50 yom with severe OUD, past methadone in OTP (3 yr ago)
- Currently using IV fentanyl 5 g daily
- High risk, recent OD, uses alone, hx endocarditis
- Works full time – new job
- Has missed several intakes at your OTP
- Very uncomfortable, in obvious withdrawal

❑Next Steps?

The OTP medical Intake

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Provider

- ❑What do you need to know?
- ❑What do you need to do?

Patient

- ❑What does your patient need to know?
- ❑What does your patient need to do?

Goals of Therapy

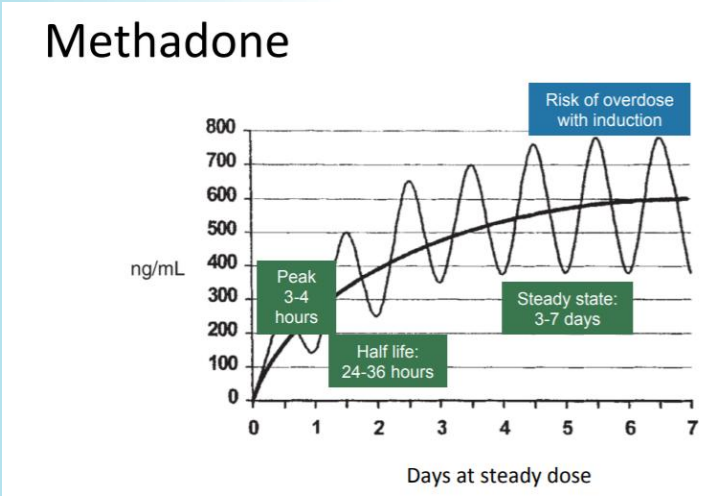
- Alleviate withdrawal
- Maximal function
  - Stabilization and normalization of the brain
  - Establishment of durable hedonic tone
  - Engagement in care and recovery
  - Prevention of disease transmission
  - Restoration of health
  - Prevention of death
- Achieve appropriate dosage
- NOT to see how fast a patient can taper off medication

What are the patient's goals?

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

Outdated dosing approach: 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

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Optimizing dose: experience grows in various settings

Study (Authors, Year)	Setting / Design	Rapid Methadone Protocol	Key Findings	Reference
Utilizing the 72-Hour Rule to Expand Rapid, Higher Dose Iniatiation of Methadone in a Hospital Based Bridge Clinic (2025)	Retrospective chart review in a hospital-based Bridge Clinic	Methadone initiation under the *72-hour rule*: ~51.6 mg initial, ~60.9 mg 2nd dose, ~67.1 mg 3rd dose	96.9% of patients linked to an OTP with ongoing treatment; feasible higher-dose start	Applewhite et al, *PubMed*. 2025. (PubMed)
Induction to Methadone 80 mg in the First Week of Treatment of Patients Who Use Fentanyl (2024)	Outpatient OTP case series	Rapid induction: 40 mg D1, 60 mg D2, 80 mg D3; target ≥80 mg by day 7	Feasible rapid induction; no oversedation/overdose; high 30-day retention	Steiger S et al. *J Addict Med*. 2024;18(5):580-585. (Lippincott Journals)
Piloting a Hospita-Based Rapid Initiation Protocol (2024)	Inpatient retrospective cohort	Rapid initiation: up to ~96 mg by day 7 (53 mg → 69 mg → 75 mg … 96.6 mg)	Rapid titration implemented without serious adverse events	Liu P et al *J Addict Med*. 2024. (PubMed)
Relationship Between Induction Dose and Retention (2025)	Retrospective cohort across OTP network	Higher day-7 doses (≥70 mg)	Higher early dose associated with improved 30-day retention	Sherrick RC. *J Addict Med*. 2025. (Lippincott Journals)
Rapid Inpatient Inductionin the Fentanyl Era: Systematic Review (2026)	Systematic review of inpatient rapid methadone induction	Initial ~30-40 mg with daily escalations to 60-100 mg within 5-7 days	Rapid protocols generally safe; low severe events; improved early stabilization	*Berisha L, Patel et al Curr Addict Rep*. 2026;13:5. (Springer Link)

Case continued

- Your pt returns for follow up 1 week later
- Dose: 100 mg (past stabilization on 190 mg, 3 yr ago)
- No peak sedation
- No palpitations, near syncope, syncope
- Dose lasts about 6 hr – then experiences opioid wd, insomnia
- Using 2 gram nightly (decrease from 5 g on intake)
- Notes he cannot get to clinic every day

❑Next Steps?

Take-Home Bottles: Key Changes to criteria

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

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

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

Early Use During Treatment Expected

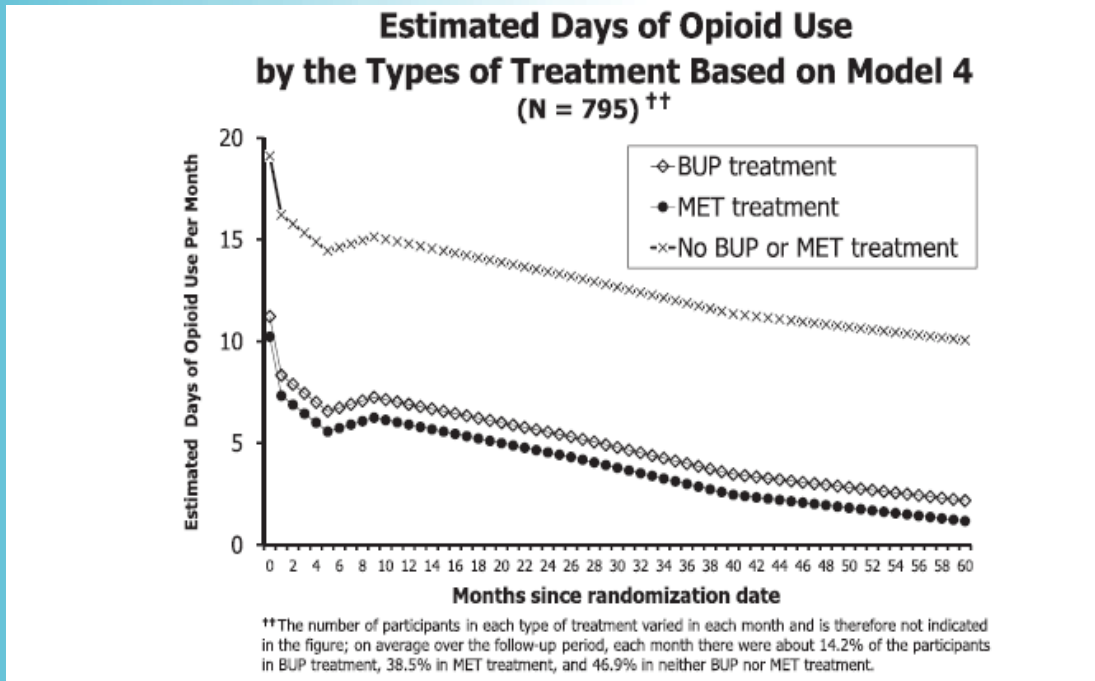


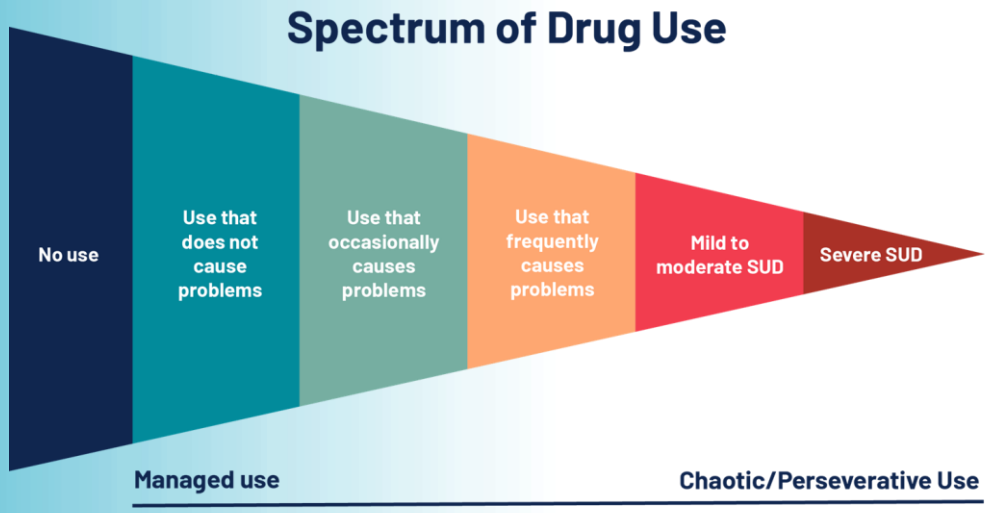
Figure 4 Estimated days of opioid use by the types of treatment based on model 4 (n = 795)††. BUP:buprenorphine; MET:methadone.

Hser et al. Addiction. 2016 Apr;111(4):695-705.

Case

- 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?



Graphic courtesy of Ruth Potee, MD

Case

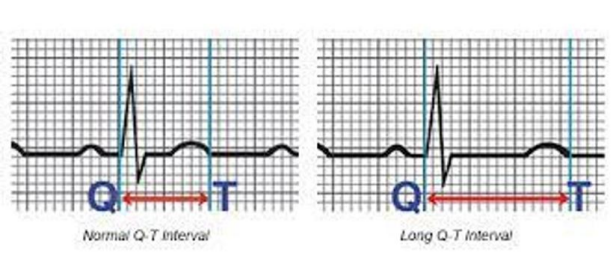
- Patient returns for follow up
- Dose: 190 mg
- Sweating all day long, embarrassing
- Dose lasts about 12 hr – then experiences opioid wd, insomnia
- Using 1/2 gram nightly (decrease from 5 g on intake)
- Frustrated and demoralized

❑Next Steps?

QTc and risk of Torsades de Pointe

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

- No consensus on when to obtain ECG
- Cardiac hx, family sudden death, sx of concern, other QTc prolonging drugs
- Dose MTD 120+ mg, depending on program
- Some clinics do ECG on site, others refer out
- Must balance risks



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

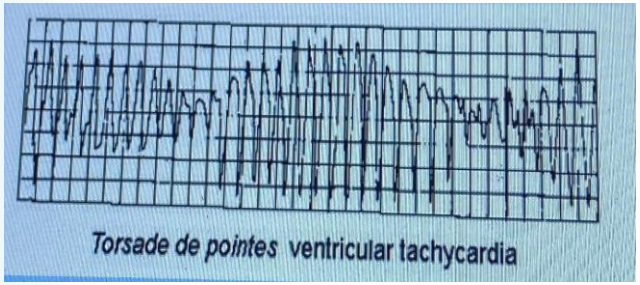
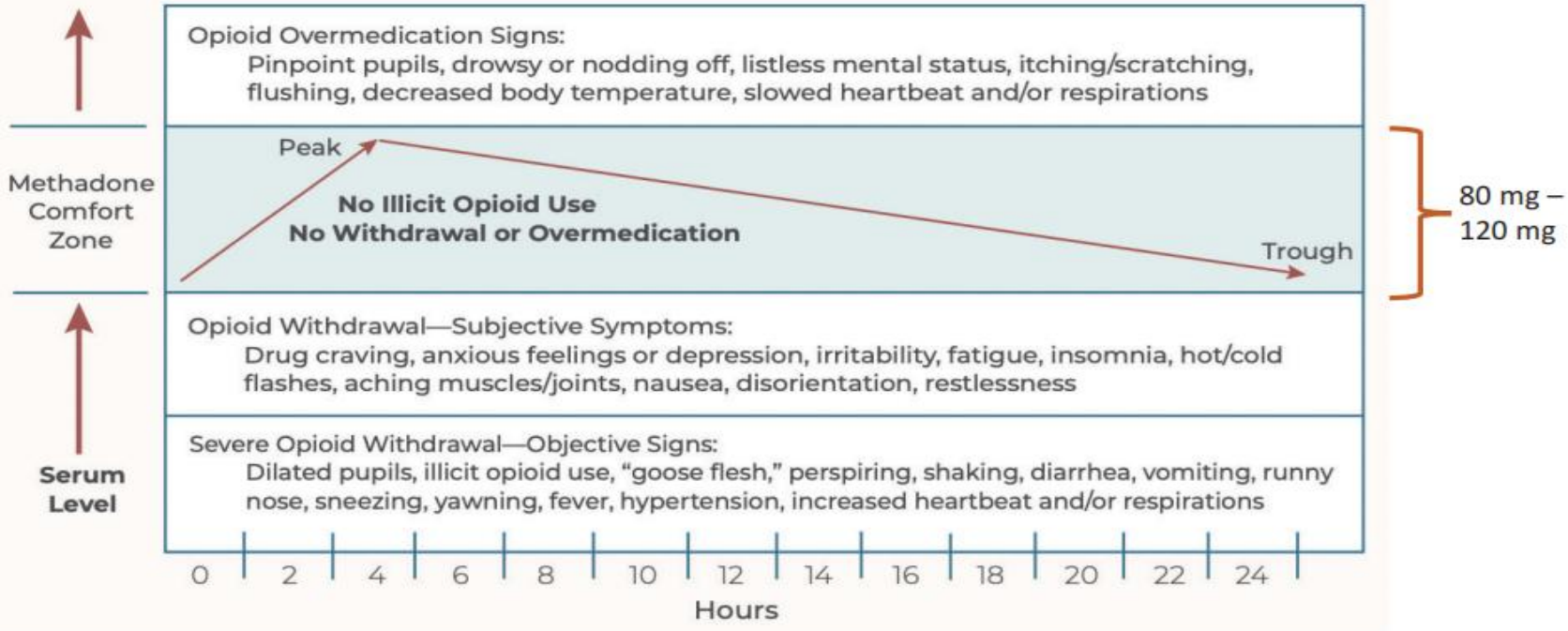


EXHIBIT 3B.4. Using Signs and Symptoms To Determine Optimal Methadone Level



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)

Split Doses-Rapid Metabolism

- Some 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

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Split Dosing - 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
- Split dosing is permissible in a range of clinical scenarios
- No specific additional documentation needed
- Split dosing is explicitly allowed for patients with take homes

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

SAMHSA. (2024, February 1). *The Federal Register*. https://www.federalregister.gov/documents/2024/02/02/2024-01693/medications-for-the-treatment-of-opioid-use-disorder

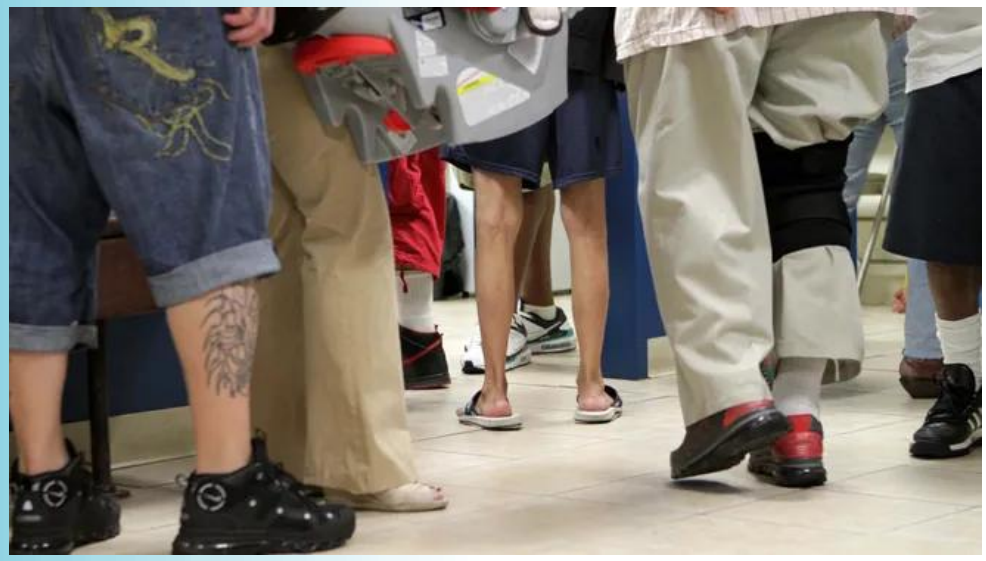
Case

- Dosing nurse calls you for reinstatement order
- Patient has missed dosing for 4 days in a row
- He also missed 2 days the previous week

- What do you need to know?

Clarifying questions

1. WHY is he missing dosing?
2. Length of time on this most recent dose
3. Current nursing assessment
4. Drug use in the interim
    1. i.e. have they continued to use opioids (tolerance)?
    2. Past higher dose?
5. Has he had a medical evaluation recently?
6. What does he feel he needs to be able to access his medication daily?



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

Responding to missed doses

Recent Study: Patient-Centered Restart Protocol

- Compared pre- vs post-implementation of a new restart protocol in a safety-net OTP.
- Restart doses individualized based on interim opioid use and clinical assessment.

Key Findings

- Smaller dose reductions (↓3.4%) vs traditional reductions (↓32.8%).
- No significant increase in opioid-related harms (ED visits, mortality).
- 90-day treatment retention remained stable.

Clinical Implications

- Safer, individualized dosing based on patient tolerance.
- Aligns with the trend toward personalized opioid treatment strategies.

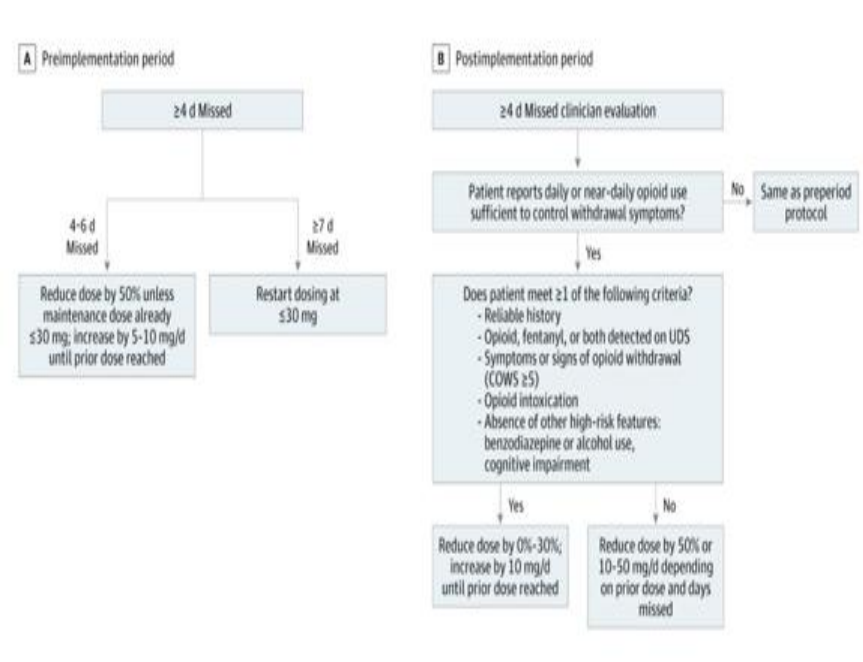

Figure Legend:

Methadone Restart Protocol at the Denver Health Opioid Treatment Program Before and After 2022 ChangesCOWS indicates Clinical Opiate Withdrawal Scale; UDS, urine drug stream.

Christine PJ, Blum J, Tillman AR, *et al. Evaluation of a Novel Patient-Centered Methadone Restart Protocol*. *JAMA Netw Open*. 2025;8(8):e2529393. DOI:10.1001/jamanetworkopen.2025.29393

Baymark OTP Guidance on Missed Dosing: Maintenance Patients

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Missed Dose Guidance: Maintenance Patients		
Days Missed	**If ongoing opioid use and no concerning clinical features**	**If NO ongoing opioid use and/or concerning clinical features**
1–4 days	• Resume full maintenance dose	• Resume full maintenance dose
5–7 days	• Restart dose: 80% of maintenance dose • Next day: Resume full maintenance dose	• Restart dose: 50% of maintenance dose (dose should not be <40 mg if maintenance dose is >100 mg) • Next day: Resume full maintenance dose
8–10 days	• Restart dose: 60% of maintenance dose • Next day: Resume full maintenance dose	• Restart dose: 50% of maintenance dose (dose should not be <40 mg if maintenance dose is >100 mg) • Next day and beyond: Increase by 10mg daily until full maintenance dose is achieved
11–14 days	Restart rapid induction: • Restart dose: 40–50mg • Next day and beyond: Increase by 10–20 mg daily until full maintenance dose is achieved	Restart traditional induction: • Restart dose: ≤30mg • Next day and beyond: Increase by 5–10 mg every 3 days until full maintenance dose is achieved

***Note:** Patients may resume at or near full maintenance dose at the provider's discretion.

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Baymark OTP Guidance on Missed Dosing: Induction/New Initiation Patients

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a. **Induction Patients**

Missed Dose Guidance: Induction Patients		
Days Missed	**Rapid Induction**	**Traditional Induction**
1–6 days	• Resume last dose and continue titration as scheduled	• Resume last dose and continue titration as scheduled
7–14 days	Restart rapid induction: • Restart dose: 40-50 mg • Next day and beyond: Increase by 10-20 mg every day until target dose is achieved	Restart traditional induction: • Restart dose: ≤30 mg • Next day and beyond: Increase by 5–10mg every 3 days until target dose is achieved

Shared with permission from Baymark

Case

- You receive an order request to taper methadone down by 2 mg every 14 days from 200 mg to 100 mg with goal to taper off

- Tox: methadone and cannabis only

- ❑ What do you want/need to know?

Methadone Dose Change Conversation Checklist
(For use when a patient asks to lower or taper their dose)
Patient Name: _____ **Date:** _____
Current Dose: _____ mg **Staff:** _____

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☐ **1. Reason for Wanting a Dose Change**
Ask: *"What's making you want to lower your dose right now?"*
☐ Clinic schedule, transportation, or logistics are difficult
☐ Clinic environment feels stressful or triggering
☐ Still using substances / feels methadone isn't working well
☐ Experiencing side effects (describe): _____
☐ Worried about losing access to methadone (court, probation, jail)
☐ Belief that a lower dose is "better"
☐ Pressure from others (family, partner, court, peers)
☐ Other: _____
Notes:

☐ **2. Clarify the Type of Change**
Ask: *"Is this a one-time decrease or part of a longer taper?"*
☐ One-time decrease to see how it feels
☐ Short-term stabilization at a lower dose
☐ Gradual taper over time
☐ Unsure / still deciding

☐ **3. Long-Term Goal**
Ask: *"What's your end goal?"*
☐ Stay on a lower dose
☐ Fully taper off methadone
☐ Be medication-free
☐ Not sure yet
If tapering off:
☐ Aftercare plan discussed
☐ Other MOUD options reviewed (buprenorphine, injectables, naltrexone)
☐ Medical visit offered / scheduled

☐ **4. Taper Preferences**
Ask: *"How would you want this to go?"*
☐ Very slow
☐ Moderate pace
☐ Faster taper (explore why)
Patient's preferred pace and reasoning:

☐ **5. Risks & Expectations Reviewed**
Patient understands possible effects of lowering dose:

Person Centered Care

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- As with any other chronic, recurring condition:
  - Establish patient's goals
  - Recognize discrepancies in provider goals vs those of the patient
  - Expand definitions of therapeutic support
  - Individualize care
  - Weigh risks and benefits
  - Empower teams to partner with our patients to make OTPs places people want to come for care
  - Take time to empower, inform and support your patients

A Chance to Do it Better

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"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. "

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
- 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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