Is Your Methadone Clinic Helping or Hurting in the Era of Fentanyl?

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Disclosure Information

- Ruth A. Potee, MD, DFASAM, FAAFP
 - No Disclosures
- Laura G. Kehoe, MD, MPH, FASAM
 - Disclosure: Indivior, advisory board
- ◆ Zoe Weinstein, MD, MS
 - ♦ No Disclosures
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Learning Objectives

- Review the recent updates to 42 CFR Part 8 Final Rule
- Review the evidence for current methadone outpatient titration guidelines
- Discuss implications of emerging inpatient and outpatient more rapid induction strategies on outpatient methadone care
- Interpret the 5 Point Criteria to expand methadone take home bottles
- Discuss the urgency of individualizing care within evolving regulations



42 CFR Part 8 Final Rule First Update since 2001

- Promotes practitioner autonomy
- Removes discriminatory or outdated language
- Creates a patient-centered perspective
- Reduces barriers to receiving care



Getting the Dose Right

- Overdose crisis, stakes are high
- Methadone reduces morbidity and mortality by >50%
- Early treatment is a critical window for treatment retention
- Adequate dosing is an important determinant of treatment retention



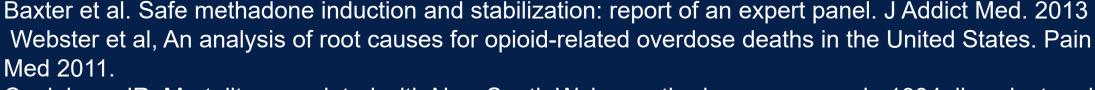
Longtime Standard of Care

- 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



Safety Concerns Drive Conservative Care

- ◆ In 1990s international report of OD deaths in 1st 2 weeks of treatment, with concerns this was due to long half life of methadone, individualized metabolism and/or dose stacking
- ◆ In 2010s trend of disproportionate share of overdoses with methadone identified- though NOT ever clear was OTP pts and likely instead pts on methadone for pain
- Need to balance w risk related to use on top of subtherapeutic methadone







TIP 63 Dosing Guidance

Day 1	 1st dose for opioid tolerant patients: 10-30mg 30mg is max single dose and 40mg is max total daily dose at OTPs per federal regulations, unless additional documentation With additional documentation may give additional doses
Dose titration (weeks 1-2)	 ASAM expert panel: Increase methadone dose by 5mg or less every 5 or more days. Other expert recommendations suggest faster such as 5-10mg no sooner than 3-4 days.
Dose titration (weeks 3-4)	 Increase by 5mg increments every 3-5 days based on opioid withdrawal or sedation.



AATOD Training Guidance

- The American Association for the Treatment of Opioid Dependence, Inc. (AATOD) represents more than 1,000 Opioid Treatment Programs (OTPs) in the United States
- Delivers education including provider training
- Early titration (first 1-3 days, and until COWS <5 at peak)
 - Attempt to observe at peak
 - Increase 5-10mg every 1-3 days until no acute withdrawal symptoms at peak (COWS <5)
- ◆ Later titration, once no acute WD at peak
 - ♦ Increase by 5-10mg every 3-5 days until comfortable at dose for a full 5d



New CFR from SAMHSA 2024!

(ii) For each new patient enrolled in an OTP, the initial dose of methadone shall be individually determined and shall include consideration of the type(s) of opioid(s) involved in the patient's opioid use disorder, other medications or substances being taken, medical history, and severity of opioid withdrawal. The total dose for the first day should not exceed 50 milligrams unless the OTP practitioner, licensed under the appropriate State law and registered under the appropriate State and Federal laws to administer or dispense MOUD, finds sufficient medical rationale, including but not limited to if the patient is transferring from another OTP on a higher dose that has been verified, and documents in the patient's record that a higher dose was clinically indicated.



Available Evidence on Dose Titration Protocols

- Limited rigorous studies comparing dose titration protocols to inform actual risks of going faster than the guidelines
 - Many studies are now 50+ yrs old and may have limited applicability to current drug supply
 - Meta-analyses and show Higher doses of methadone and individualization of doses are each independently associated with better retention in MMT.
- Balance risks of subtherapeutic methadone and risks of death from methadone induction
- Structural racism in methadone clinic system contributes to lack of evidence on patient-centered outcomes



Methadone Treatment Works for Patients Using Fentanyl

- 12-month study of 154 pts comparing OTP outcomes of those who used fent vs not
- Similar retention rates (approx. 50% at 12 mos)
- ◆ 99% of patients who remained in treatment at 12 months achieved remission (avg. by 60ish days into tx, on 100mg)
- Pts w high tolerance started at 30 mg on the first day
 - ◆ Then titrated up 10 mg per day until 50
 - Increased again in 7d, with max 20mg increase per week thereafter



Methadone in Fentanyl Era Recommendations (2021)

Expert guidance from Canadian addiction medicine group on methadone as well as a patient advisory group

- Titrate up methadone as quickly and safely as possible starting at 30mg methadone, with increase of 10-15mg every 3-5 days.
- Faster titration (15mg) for those with low risk of methadone toxicity: not concurrently using high dose benzos or alcohol
- Slower titration for pts at risk of toxicity: higher age, sedating medications or alcohol, new to methadone
- Consider more rapid increase for patients on recently methadone (ie in the past week)
- Once at 75-80mg, increase 10mg every 5-7 days
- For pts on fentanyl, dose of 100mg or higher recommended per pt advisory panel
 - for providers in Canada consider co-prescribing slow release oral morphine (SROM)



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



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

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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

Outpatient Rapid Titration Protocol From San Francisco General Hospital OTOP

- 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



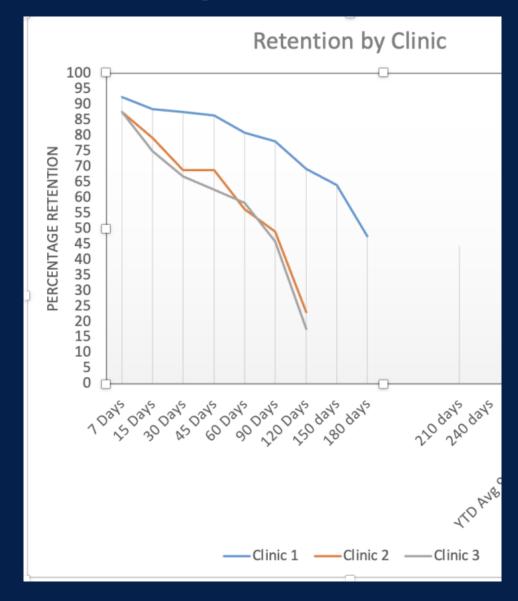
BayMark Pilot

- 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



BayMark Pilot Preliminary Results

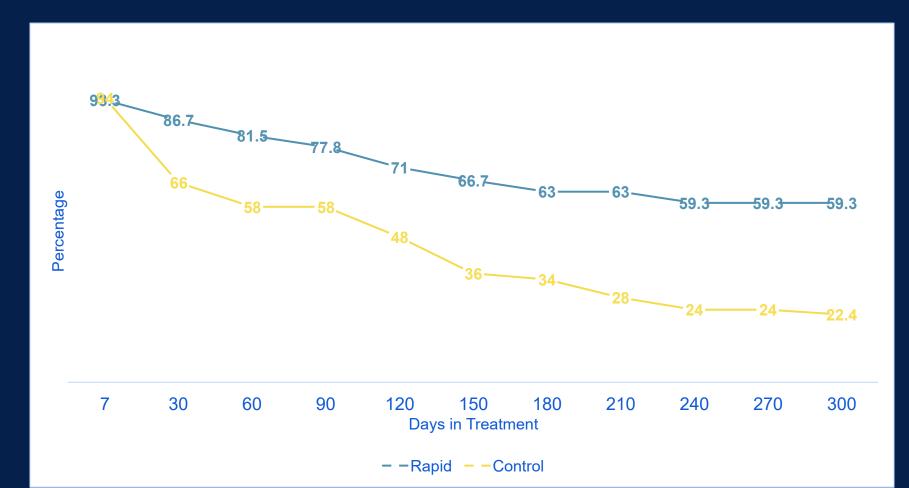
- ◆ 100 pts across 3 clinics in 3 states
- Avg days to 80mg = 6.2 days
- Avg peak dose= 120.6mg (but range based on state 101-165)
- The clinic with the highest peak dose had the best retention





BayMark Pilot Preliminary Results

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





Source: Internal communication BayMark

Split Doses-Rapid Metabolism

- 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



New SAMHSA 42 CFR, Part 8

(3) Special services for pregnant patients. OTPs must maintain current policies and procedures that reflect the special needs and priority for treatment admission of patients with OUD who are pregnant. Pregnancy should be confirmed. Evidence-based treatment protocols for the pregnant patient, such as split dosing regimens, may be instituted after assessment by an OTP practitioner and documentation that confirms the clinical appropriateness of such an evidencebased treatment protocol. Prenatal care and other sex-specific services, including reproductive health services, for pregnant and postpartum patients must be provided and documented either by



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

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



New SAMHSA CFR

- 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

Split dosing means dispensing of a single dose of MOUD as separate portions to be taken within a 24-hour period. Split dosing is indicated among, but not limited to, those patients who: possess a genetic variant which increases methadone metabolism; concurrently take other medications or drink alcohol that also induce hepatic enzymes leading to more rapid metabolism of methadone; who are pregnant; or for whom methadone or buprenorphine are being used to treat a concurrent pain indication in addition to the diagnosis of OUD. This leads to more stable, steady-state medication levels.

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

Getting the Dose Right- Case

- 66 yo M, OUD severe, prior stable on MTD 110mg and oxycodone 10mg TID for chronic pain due to MVA injury. His PCP abruptly DC'ed his oxycodone due to a false+ utox, leading to worsening pain and depression—> pt walked off clinic at 90mg 6 mos ago, w resumption of daily IN fent use.
- Pt now re-engaging, on 60mg for past 2 wks from a local bridge clinic and at first expresses interest in tapering MTD
- Provider "What dose do you think would be good for you?"
- Patient replied: "No one has every asked me that before!"
- After conversation w pt re goal of MTD care and pain, offered to trial split dosing of methadone: 40 AM and 20 PM



SAMHSA



Methadone Take-Home Flexibilities Extension Guidance

This exemption only applies to <u>OTPs whose states concur</u> with the exercise of this exemption and its conditions within their states. The duration of this exemption shall be for the period of one year from the end of the COVID-19 Public Health Emergency, or until such time that final rules revising 42 C.F.R. part 8 are published by the U.S. Department of Health and Human Services, whichever occurs sooner. To be clear, this exemption will replace and supersede the exemption provided in the guidance published in November 2021, and the exemption announced in <u>SAMHSA's OTP guidance (PDF | 216 KB)</u> issued on March 16, 2020. All other requirements of 42 C.F.R. § 8.12(i) that are not in direct conflict with the exercise of this exemption will remain in force. SAMHSA will publish a list of States that have concurred with this exemption on <u>Statutes, Regulations</u>, and <u>Guidelines</u>.

doses of the patient's medication for opioid use disorder.

The state may request up to 14 days of Take-Home medication for those patients who are less stable but who the OTP believes can safely handle this level of Take-Home medication.



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

- (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



Old vs New

 (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?

 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



Is this a Substance Use Disorder?

36 yo male, on 155 mg methadone, stable dose for three months. Has 6 THBs and is moving to 13 THB. Most recent drug screen comes back with cocaine and fentanyl.

Is this a substance use disorder?



Spectrum of Drug Use

Use that Use that Use that occasionally frequently does not Mild to **Severe SUD** No use moderate SUD causes cause causes problems problems problems



Managed use

Chaotic/Perseverative Use

Active SUD Assessment Tool

Protective Factor Question	Client Quotes / Response
Let's talk about how you're doing overall -	
how has your methadone treatment improved	
your life or reduce your substance use?	
In what ways does having THB help support	
your recovery?	
Can you tell me about something that's going	
well right now or that you're proud of with	
your recovery?	



When did you (recently) start using? How much were you using at that time, and how much are you	Criteria 1
using now?	
(if they report an increase) Is there a reason you have started to use more?	Criteria 10
(look for indication of tolerance)	
Have you recently tried to stop using? (Describe)/ "How did that go?"	Criteria 2
Have you noticed any withdrawal symptoms if you haven't used in a while?	Criteria 11
Are you having any physical or mental issues or concerns? When did these begin? Have you seen a	Criteria 9
doctor? Do you see ways in which your use impacts your mental health? Does it put your physical health	
at risk?	
How often are thoughts about using crossing your mind?	Criteria 4
How do you get your supply? (look for how much time they are spending) do you spend a lot of time	Criteria 3
working to get the money that you need to buy drugs?	
Where are you using and with who? Have you ever felt unsafe?	Criteria 8
What times of the day or week are you using? Has it ever effected your ability to work or get things	Criteria 5/3
accomplished at home?	
(hopefully you have some knowledge of this client's typical activities and you can ask them how they are	Criteria 7
going, how often they are engaging in them)	
(if no knowledge of typical activities, inquire) Tell me about your hobbies or things you like to do How	
often are you able to participate in these things? Has there ever been a time recently that you missed	
these activities because you had an opportunity to use instead? Have you recently missed an	
activity because you were busy purchasing?	
Has anyone asked you recently if you were using or suspected you were using?	Criteria 6
i. What do you think made them ask?	
Has anyone recently asked you to stop using?	
Do you feel like your relationships are affected by using?	



Criteria	Description	Client Quotes / Response	Criteria Met? Y/N
1	Substance is taken in larger amounts		
	over longer period than was intended		
2	Persistent desire, or unsuccessful efforts		
	to reduce or control use		
3	A great deal of time spent in activities		
	necessary to obtain, use, and recover		
4	Craving, strong urges to use		
5	Failure to fulfill obligations (work, school,		
	home) as result of substance use		
6	Continued use despite experiencing		
	social/interpersonal problems caused by		
	or increased by the effects of substance		
	use		
7	Important social, occupational, or		
	recreational activities are given up or		
	reduced because of substance use		
8	Recurrent substance use in situations in		
	which it is physically hazardous		
9	Substance use is continued despite		
	knowledge of having a persistent		
	physical or psych problem that is likely to		
	have been caused or increased by the		
	substance use		
10	Tolerance (a need for increased amounts		
	to achieve desired effect OR reduced		
	effect from using same amounts)		
11	Withdrawal		

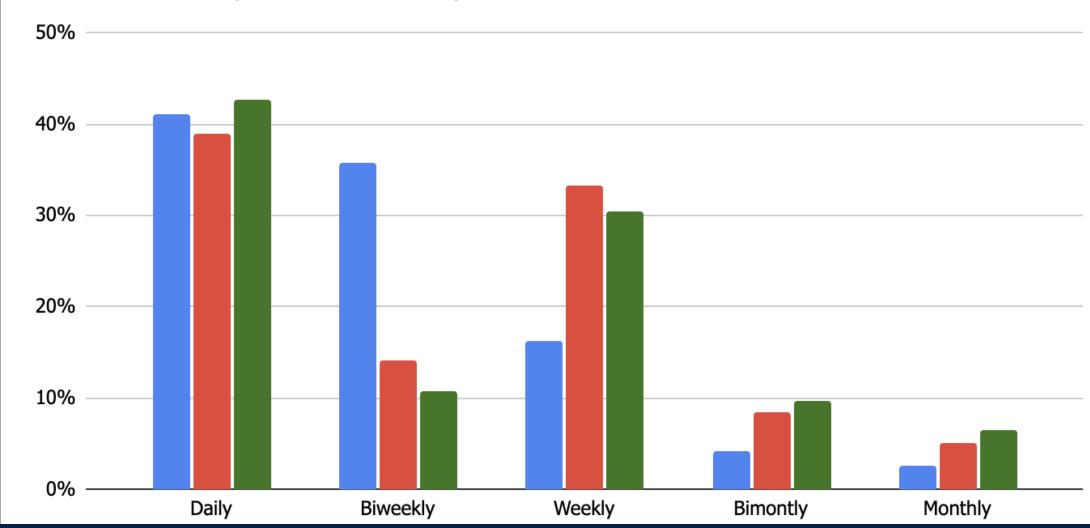


Potent	ial Risk Factors:
(any YE	S response will warrant a comment)
Y/N	Active Substance Use Disorder (see above assessment)
Y/N	Concern for inconsistent dosing attendance
Y/N	Serious behavioral problems that endanger the patient, the public, or others
Y/N	Known recent diversion activity
Y/N	Concern for client ability to safely transport and store Take Home Medication
Y/N	Other:
Determ (select	nination : one)
	THB privileges will be reduced at this time due to clinical concern for risk factors.
	THB privileges will remain intact at this time due to therapeutic benefits of THB outweigh the risks.
	THB privileges will be sent up to Multidisciplinary Team Meeting (MDT) for review at this time. Please see MDT or determination.
PLAN:	



Springfield OTP Dosing Schedules

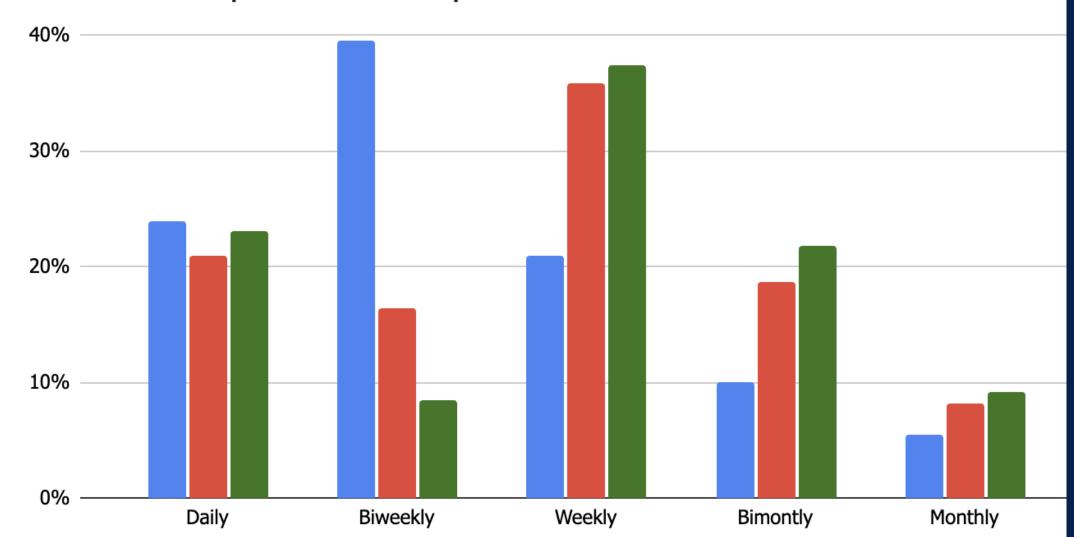
■ April 2023 ■ September 2023 ■ December 2023





Orange OTP Dosing Schedules

■ April 2023 ■ September 2023 ■ December 2023



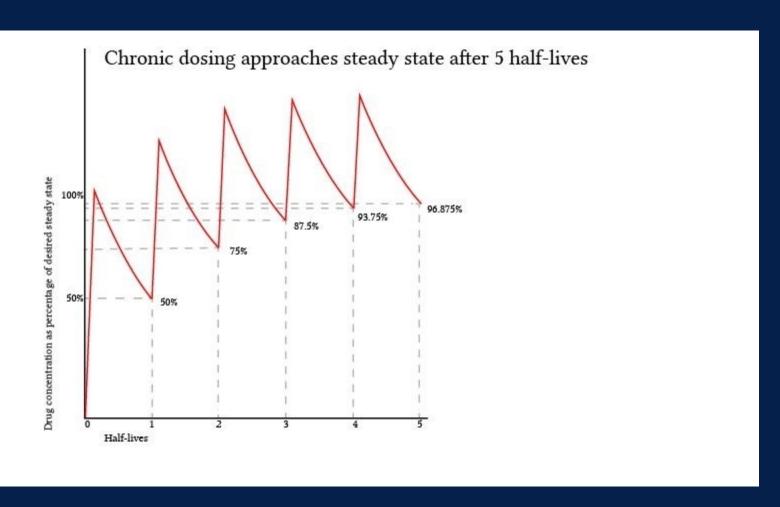


Missed Doses

- 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



Methadone and steady state

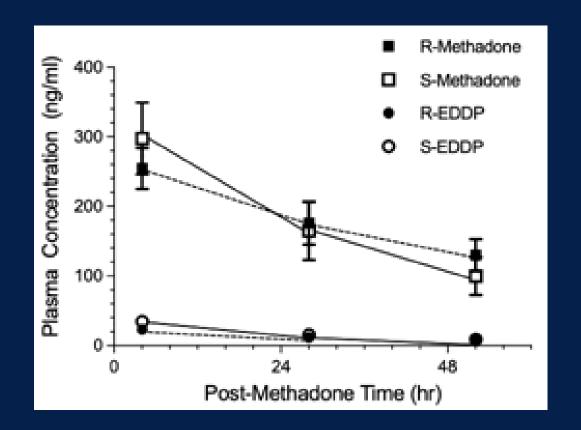


"a mean value of around 22 hours (range 5-130 hours) for elimination halflife"

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



Acute changes in methadone dose well tolerated



Opioid Tolerance Maintained

- 5 inpatient participants with OUD
- initially maintained on 100 mg/day methadone
- double-blind conditions substituted two placebo doses over two days
- Measured plasma methadone levels and EDDP isomers (and other symptom variables) at 4, 28 and 52 hr after the last 100 mg dose

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

- ¹ Substance Abuse Research Division, Department of Psychiatry and Behavioral Neurosciences Wayne State University, Detroit, Michigan
- ² Center of Human Toxicology, Department of Pharmacology and Toxicology, University of Utah, Salt Lake City, Utah
- ³ Department of Radiology, University of Michigan, Ann Arbor, Michigan
- ⁴ Molecular and Behavioral Neuroscience Institute and Departments of Psychiatry and Radiology, University of Michigan, Ann Arbor, Michigan



Missed Doses of Methadone Guideline in the Fentanyl Era

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



Response to Missed Doses

◆ 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 tox

What do you want to ask her?



Final Takeaways

- Updated regulations from SAMHSA now codify a wide range of important flexibilities OTPs can use to optimize care for patients by:
 - Promotes practitioner autonomy
 - Removes discriminatory or outdated language
 - Creates a patient-centered perspective
 - Reduces barriers to receiving care
- Using these flexibilities is essential to prevent death, especially in the fentanyl era



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Behavioral Health Network - Springfield, MA OTP Documents for Public Access



BHN SUD Assessment



BHN OTP
Take Home Bottle Policy

