Methadone Dosing in the Fentanyl Era

New drug supply, new SAMHSA rules…
same dosing protocols?

David Lawrence, MD FASAM

Maine Substance Use Disorders Learning Community

September 17th, 2025

Disclosures

The presenter has no relevant financial relationships to disclose with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients.

Thoughts and opinions of the presenter are their own and do not represent those of their employer or affiliate institutions.

Note on language

Terms to avoid (1)	Instead, say…
Addict, user, abuser	Person with an opioid use disorder, patient, client, person who uses opioids
Abuse	Use
Opioid substition therapy Opioid replacement therapy Medication assisted treatment (MAT)	Opioid agonist therapy (OAT), medication for OUD (MOUD), Pharmacotherapy, Medications for addiction treatment (MAT)
Clean	For toxicology screen results: negative For non-toxicology purposes: Being in remission or recovery, abstinent,
Dirty	For toxicology screen results: positive For non-toxicology purposes: person who uses drugs
Relapse	Return to use, resuming use

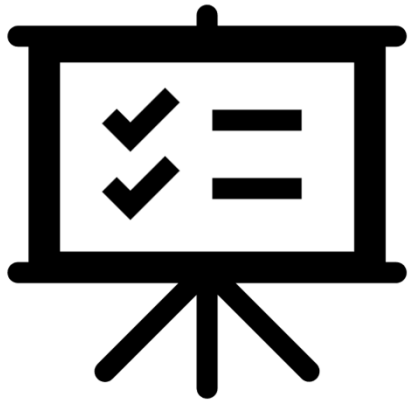
"Initiation" rather than "induction" (2)

- Feeling stigmatized can **reduce willingness to seek treatment**.(3,4)
- Stigmatizing views can **lead others to feel pity, fear, anger, and a desire for social distance from people with a SUD**.4
- Stigmatizing language can **negatively influence health care provider perceptions** of people with SUD, which can **negatively impact the care they provide**.5

1. NIDA Positive Language Guidelines Words Matter
2. ASAM 2020 OUD NPG
3. Addict Sci Clin Pract. 2018 May 7;13(1):15.
4. Curr Opin Psychiatry. 2017 Sep;30(5):378-388
5. Substance Use & Misuse, 54(8), 1376–1384

Learning Objectives

- Identify at least two (2) mortality risks during methadone initiation, maintenance, and discontinuation
- Specify two (2) methadone dosing strategies shown to increase treatment retention
- Verify at least two (2) of the common inclusion and exclusion criteria for “rapid” protocols
- Explain two (2) possible beneficial effects of “rapid” protocols on treatment outcomes
- *Time permitting:* Contrast two (2) distinct approaches to re-starting methadone after a missed dosing period



Today's Roadmap

Part 1: **Why** should new methadone dosing protocols be considered?

Part 2: **How** can new methadone dosing protocols be implemented?

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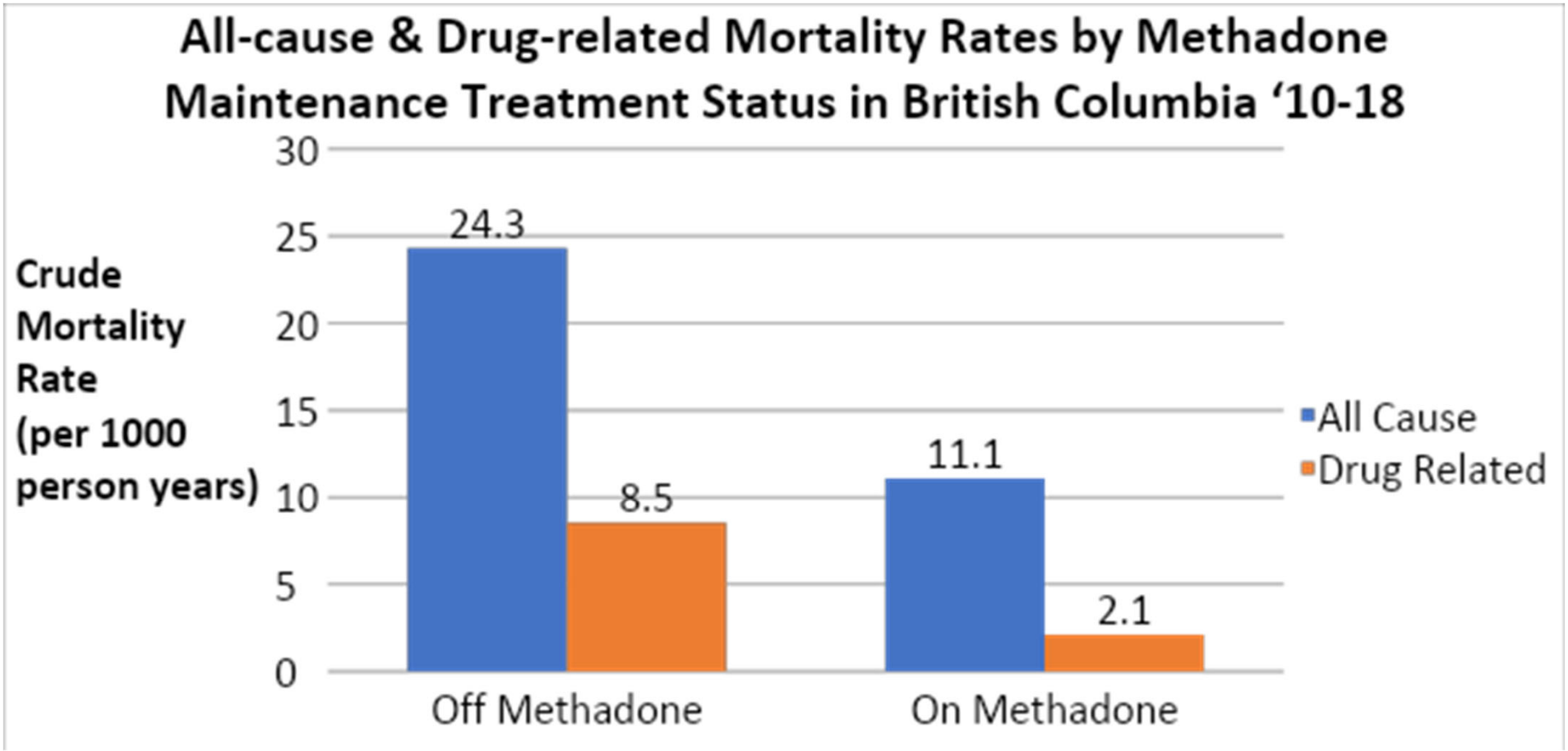
Part 2: **How** can new methadone dosing protocols be implemented?

Case

- John, a 58-year-old man, walks-in to your opioid treatment program (OTP) lobby asking for help
- History of severe opioid use disorder, hypertension, PTSD
- No current medications, no known allergies
- Historically has used heroin, and was successful with buprenorphine for the past 3 years
- But lost his partner 6 months ago & returned to opioid use
- “I cant get heroin anymore” - currently smoking 1.5 grams of fentanyl daily
- Has made 2 attempts at resuming buprenorphine “either it makes me sicker, or it just barely takes the edge off”
- Tried a friend’s methadone bottle & it helped immediately
- Enrolled in an OTP a few months ago, but felt “stuck at like 45 mg – it didn’t seem worth the trouble”
- Had 2 accidental overdoses in the past few weeks
- “I am scared. I need help.”

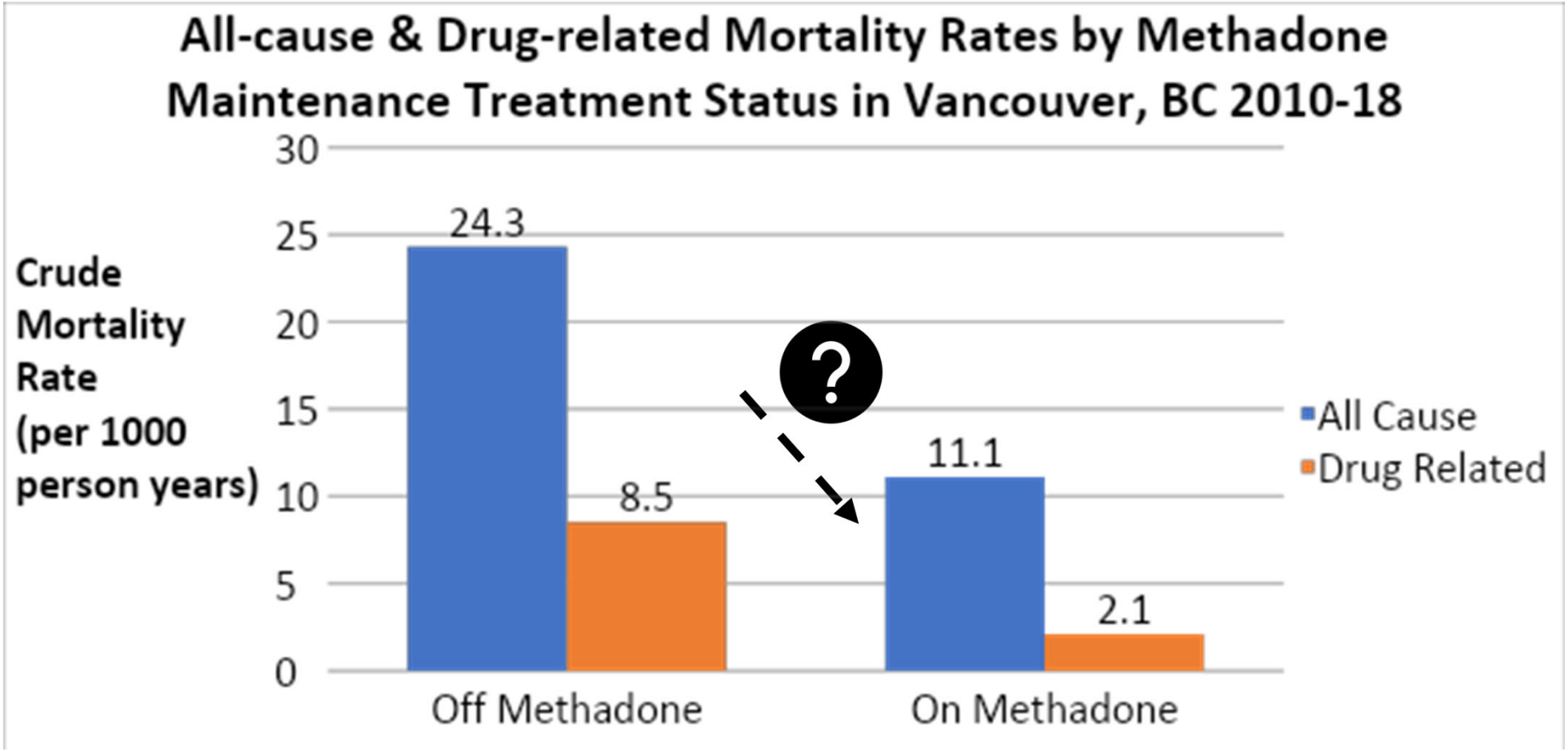
Inspired by: Harm Reduct J. 2024 Aug 24;21(1):156

Methadone Reduces Mortality by More than 50%



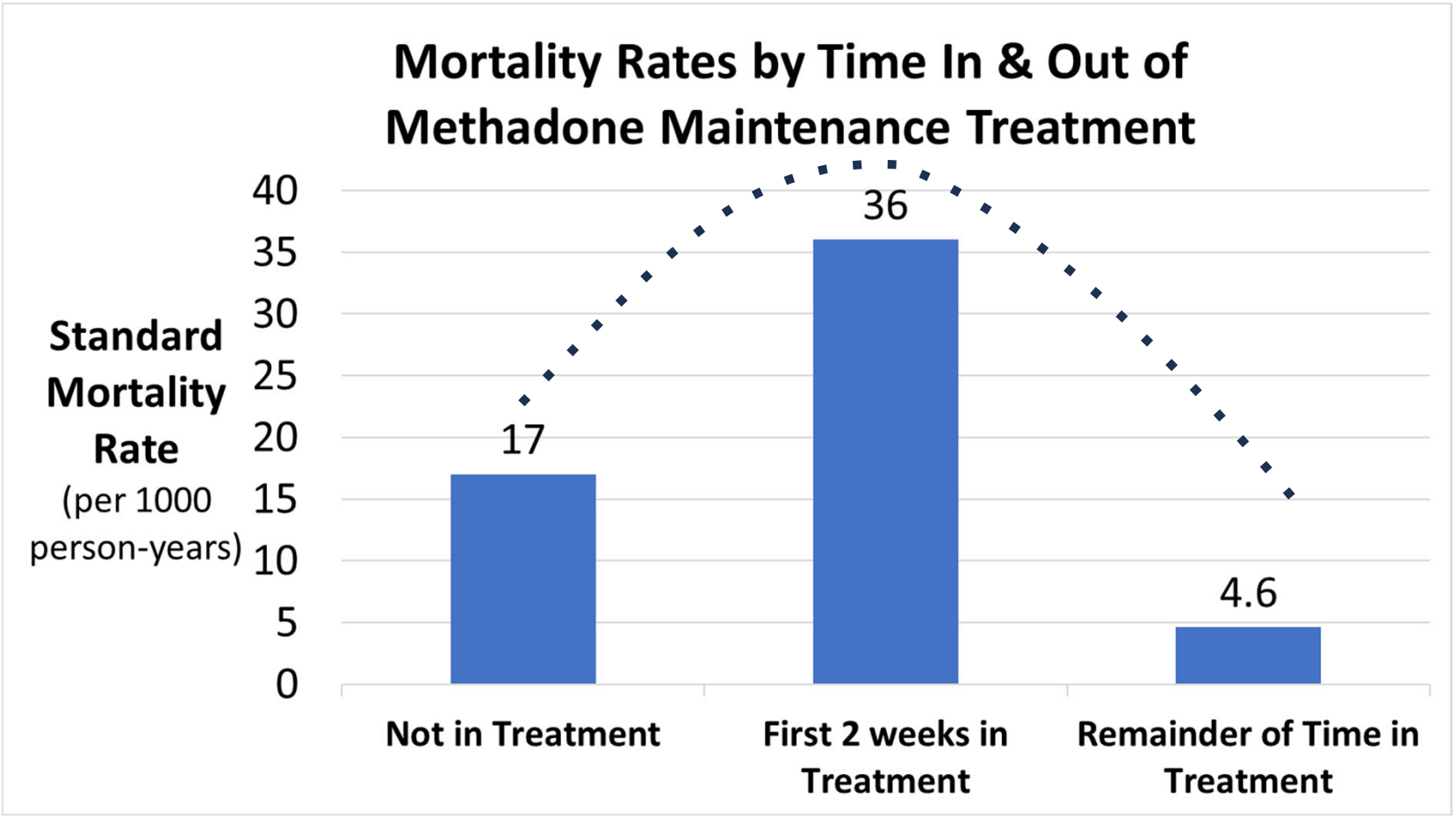
BMJ 2020;368:m772

But Is This Risk-Reduction Linear?



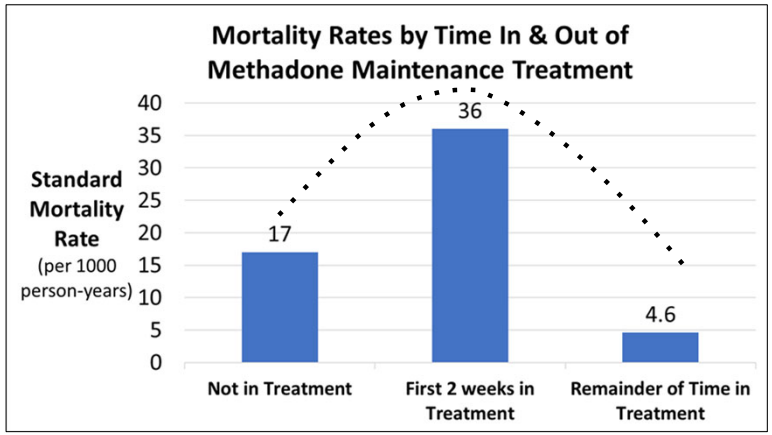
BMJ 2020;368:m772

Historically, there has been a curved risk trajectory



Degenhardt L, et al. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. Drug Alcohol Depend. 2009 Nov 1;105(1-2):9-15.

Why the Increased Risk During Initiation?



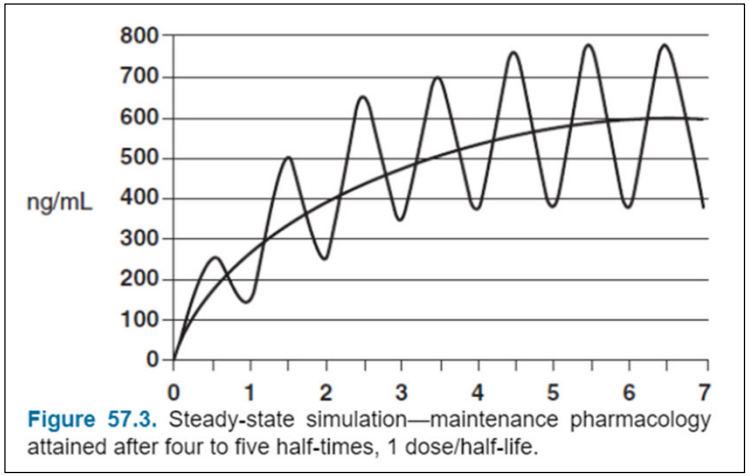


Figure 57.3. Steady-state simulation—maintenance pharmacology attained after four to five half-times, 1 dose/half-life.

From: ASAM Principles of Addiction Medicine sixth edition, 2019

Cause (1,2)	Scenario (3)	Example (3)
Mis-estimated opioid tolerance	Single Overdose	An opioid naïve individual enrolls in an OTP and receives 40 mg of methadone
Prolonged Half Life, Variable Metabolism	Accumulated Toxicity	Today's dose is not lethal, tomorrow's dose is not lethal, but the entire third day's dose combined with half of the second day's and one quarter of the first day's dose accumulate to a lethal level
Concurrent use	Combination of prescribed methadone with another CNS depressant	A patient is taking their methadone dose as prescribed, but supplementing it with non-prescribed opioid and benzodiazepine use

Adapted from: Addiction Med Publ 1997;13:346850.

1. Addiction Med Publ 1997;13:346850.
2. Drug Alcohol Rev 1998;17:9-17.
3. J Addict Med. 2013 Nov-Dec;7(6):377-86

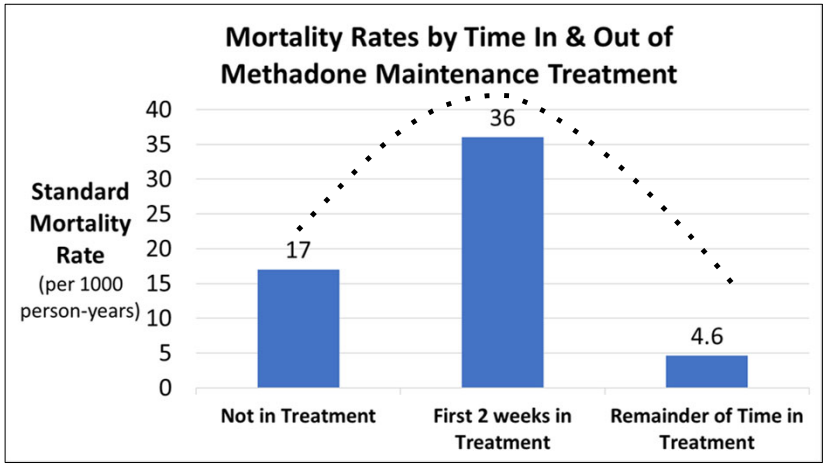
Guidance Has Thus Historically Urged Caution During Initiation

REVIEW

Safe Methadone Induction and Stabilization

Report of an Expert Panel

J Addict Med. **2013** Nov-Dec;7(6):377-86



- *"In general, the safety principle of "**start low, go slow**" applies to the induction dose (…)*
- *The initial dose of methadone typically is in the range of 10–30 mg per day (…)*
- *The total daily dose of methadone on the first day of treatment should not exceed 40 mg (…)*
- *The first day's dose should be titrated upward every five or more days in increments of 5 mg or less"*

But There Is Uncertainty About This Approach

When dose is too low, many people 'top-off' with non-prescribed opioids, alcohol, or benzodiazepines to manage unrelieved withdrawal – **could "low and slow" paradoxically <u>increase</u> the risk of polydrug use and methadone toxicity**? (1)

A survey of 50 drug related deaths during the first week of methadone maintenance in Australia found (2):

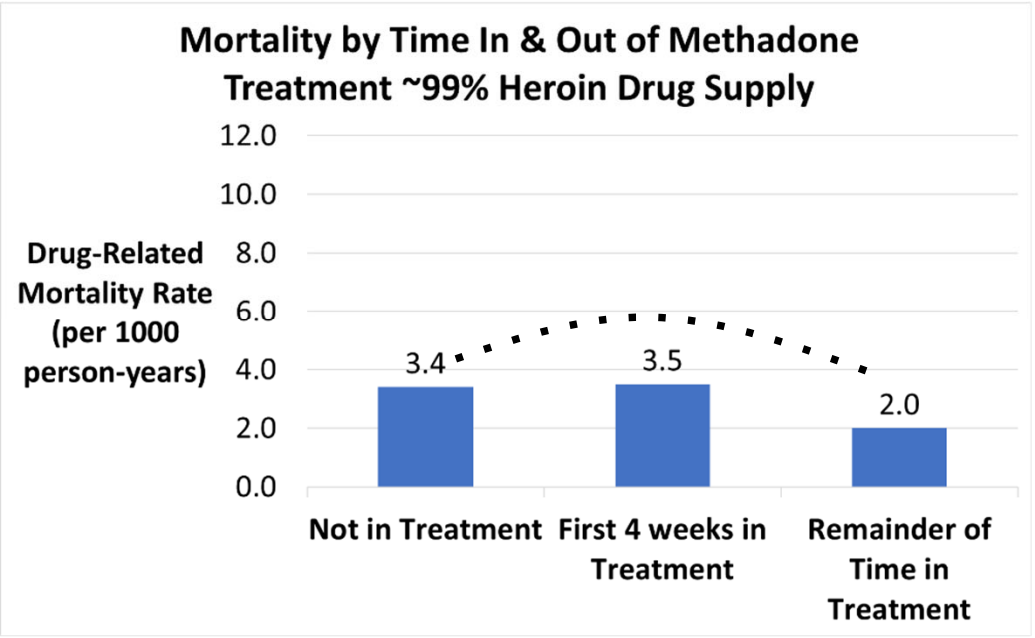
- evidence of multiple drug use in 46 cases (92%)
- only four of the 50 had had methadone prescribed at doses above those recommended by (contemporary) guidelines.

1. BMJ. 2006 Nov 18;333(7577):1056-9
2. Addiction. 2000 Jan;95(1):77-84

Is initiation risk still high in the Fentanyl Era?

Systematic review and meta-analysis of 19 cohort studies published between 1974-2016 following a total of 122,885 people receiving methadone for between 1.3 to 13.9 years

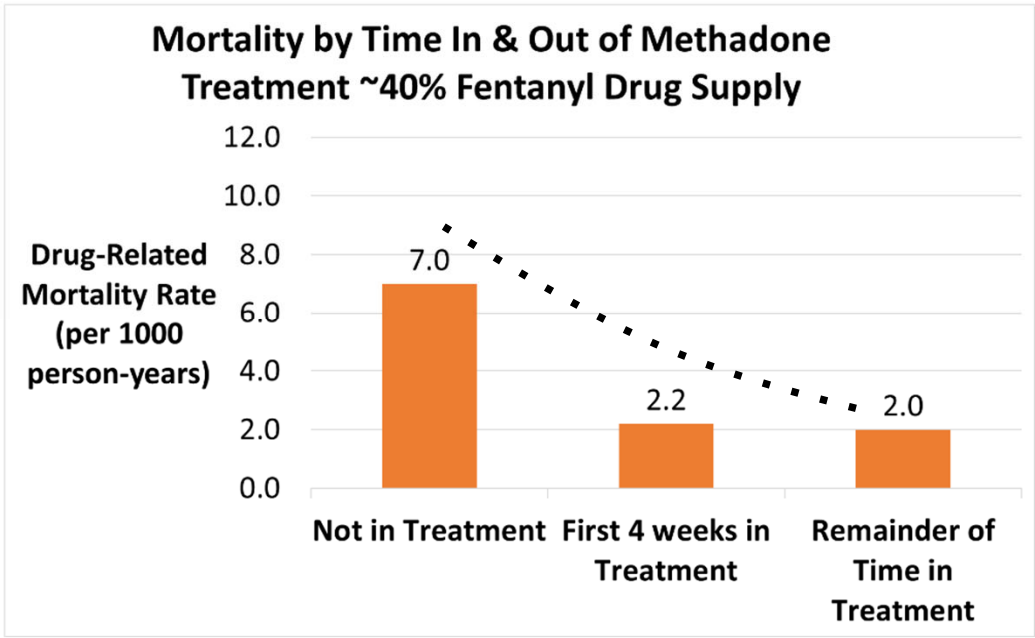
(~99% Pre-Fentanyl)



BMJ 2017;357:j1550

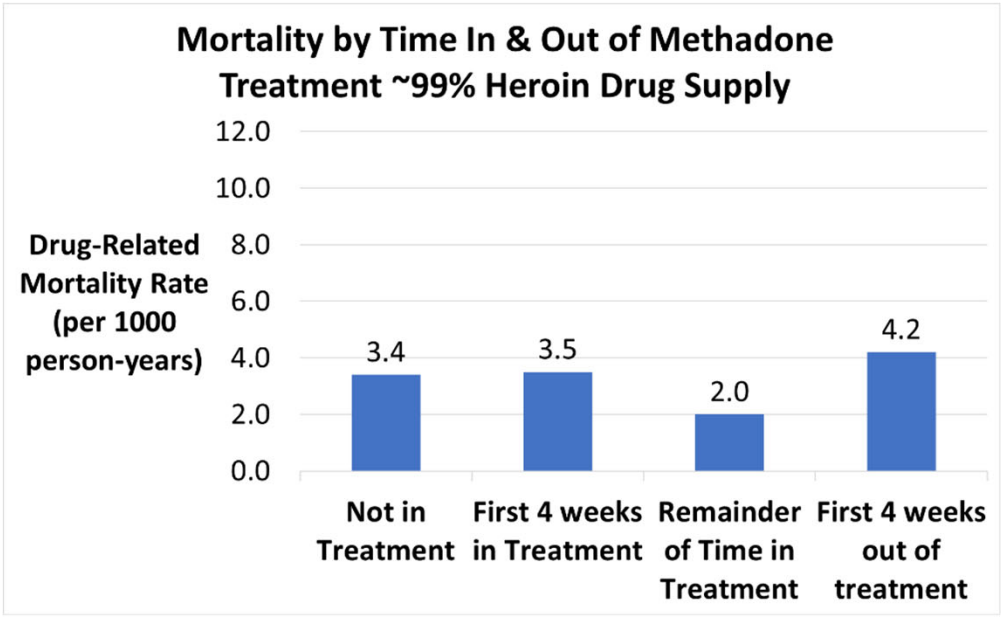
Retrospective cohort of 55,347 people with OUD in British Columbia, mortality observed for 1996-2018, BC fentanyl public health emergency declared in 2016

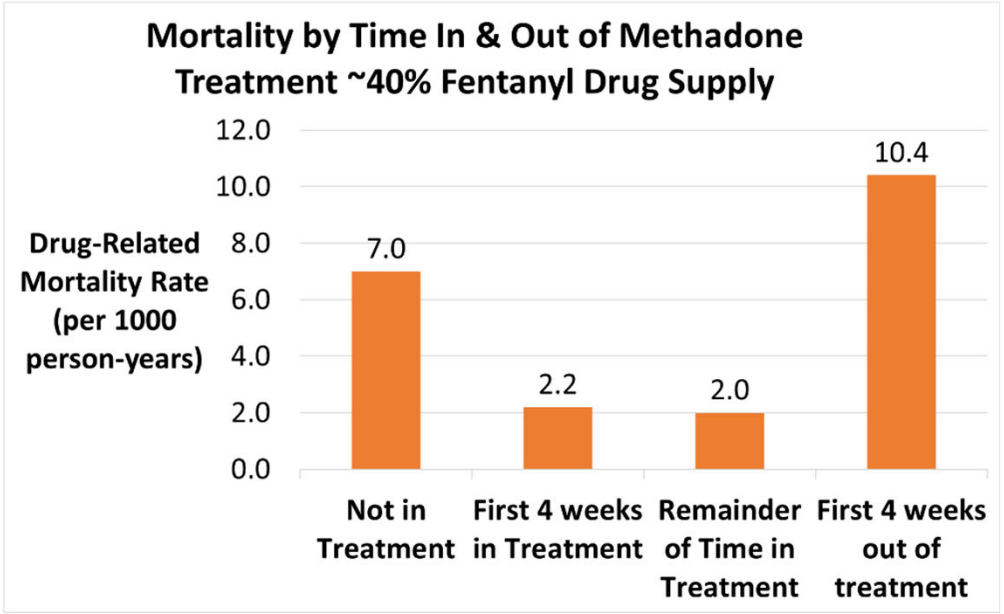
(~40% Post-Fentanyl)



BMJ. 2020; 368: m772 (see supplemental tables A7 and A8).

And what about the risk of treatment disengagement?





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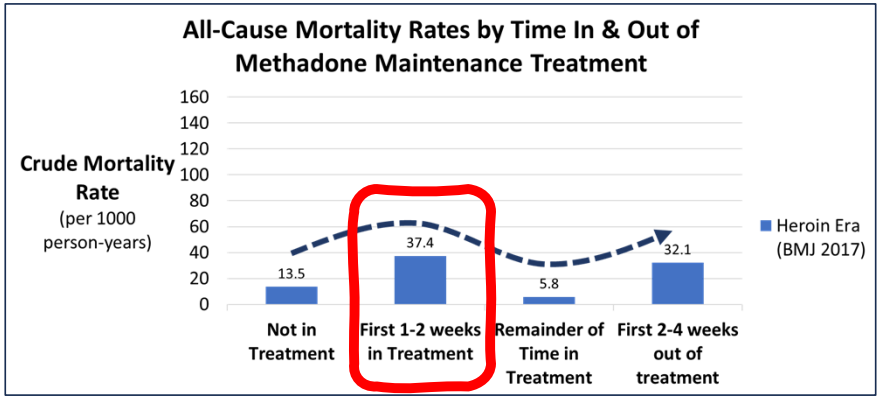
BMJ. 2020; 368: m772.

The risk balance for methadone dose titration is shifting

Heroin era



SLOW dose titration

↓

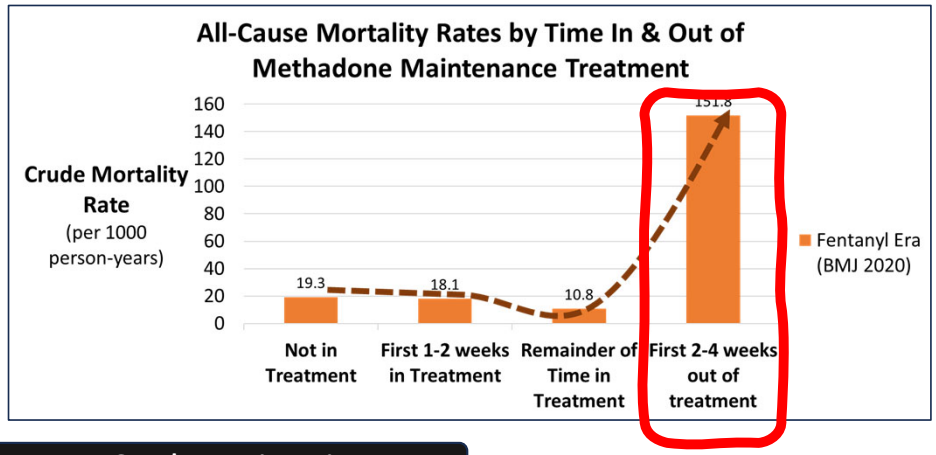
Reduces risk of methadone toxicity

↓

Reduce overdose risk from methadone toxicity

The risk balance for methadone dose titration is shifting

Fentanyl era



FAST dose titration

↓

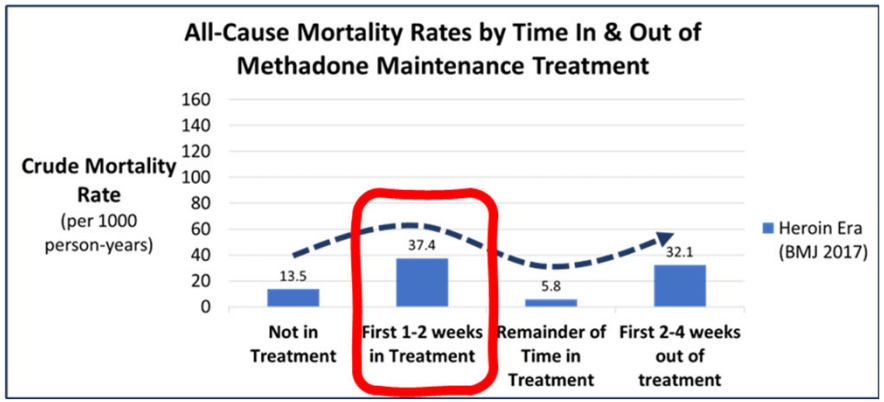
May reduce risk of disengagement

↓

May reduce overdose risk from fentanyl use

The risk balance for methadone dose titration is shifting

Heroin era

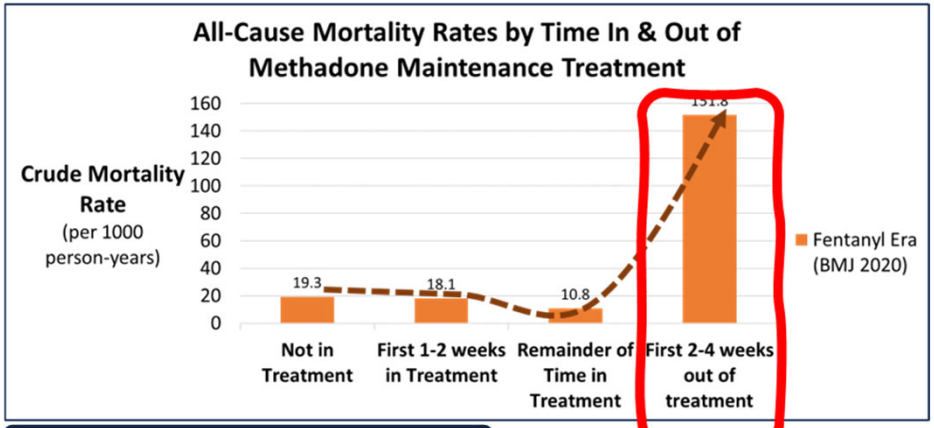


SLOW dose titration

Reduces risk of methadone toxicity

Reduce overdose risk from methadone toxicity

Fentanyl era



FAST dose titration

May reduce risk of disengagement

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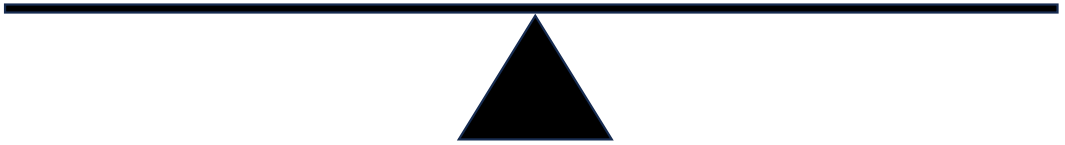
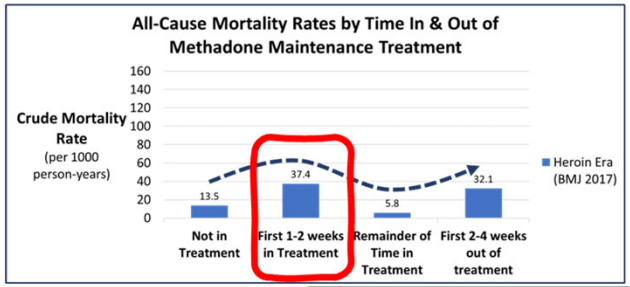


The risk balance for methadone dose titration is shifting

Heroin era



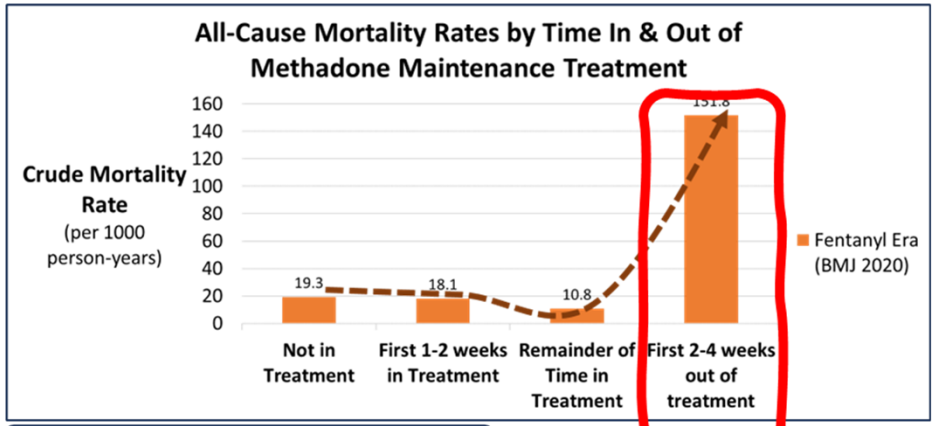
SLOW dose titration

Reduces risk of methadone toxicity

Reduce overdose risk from methadone toxicity

37 Deaths
Per 1000 person-years

Fentanyl era



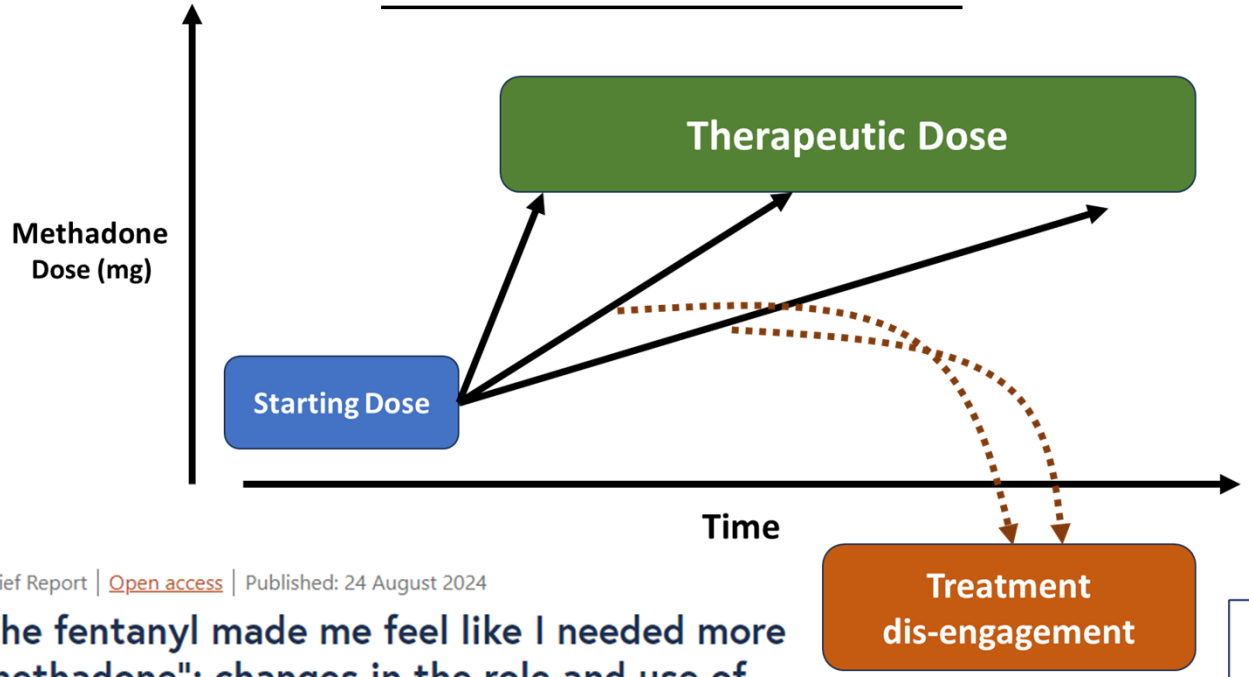
FAST dose titration

Reduces risk of disengagement

Reduces overdose risk from fentanyl use

152 Deaths
Per 1000 person-years

As Tolerance and Withdrawal have Increased, Has Dose Titration Rate Become More Relevant?



"stuck at 45 mg – doesn't seem worth the trouble"

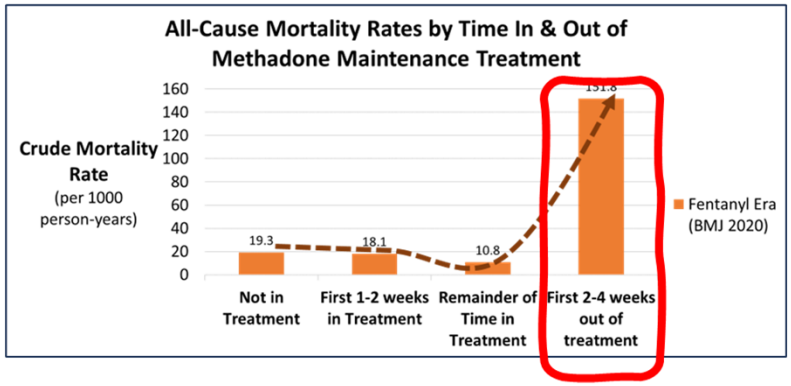
Brief Report | Open access | Published: 24 August 2024

The fentanyl made me feel like I needed more methadone": changes in the role and use of medication for opioid use disorder (MOUD) due to fentanyl

Maria Bolshakova, Kelsey A. Simpson, Siddhi S. Ganesh, Jesse L. Goldshear, Cheyenne J. Page & Ricky N. Bluthenthal

Harm Reduction Journal **21**, Article number: 156 (2024) | Cite this article

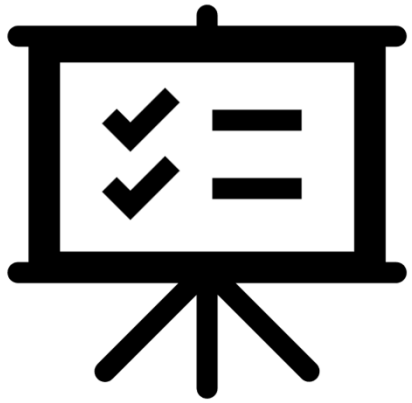
Fentanyl era



Part 1: Conclusions

Why consider new initiation protocols?

- Transitions both in and out of methadone maintenance treatment have risk
- Caution during initiation stage was an evidence-based practice in the first and second waves of the opioid crisis
- Fentanyl, however, has shifted the risk balance, significantly increasing the risks both of not being in treatment and disengaging from treatment, relative to that of initiating treatment
- New dosing strategies that safely promote successful completion of initiation and ongoing retention in treatment should be considered



Today's Roadmap

Part 1: Why should new methadone dosing protocols be considered?

Part 2: **How** can new methadone dosing protocols be implemented?

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SAMHSA Rules Have Evolved

Old SAMHSA rules	New SAMHSA rules*
42 CFR §8.12(h)(3)(ii): "The initial dose of methadone shall not exceed 30 milligrams and the total dose for the first day shall not exceed 40 milligrams, unless the program physician documents in the patient's record that 40 milligrams did not suppress opioid abstinence symptoms."	42 CFR §8.12 (h)(3)(ii): "the initial dose of methadone shall be individually determined […]. The total dose for the first day should not exceed 50 milligrams unless the OTP practitioner […] finds sufficient medical rationale […] and documents in the patient's record that a higher dose was clinically indicated."
	*effective April, 2024

Heroin era ----------→ Fentanyl era

Effects of dose on OUD outcomes

- Many studies have shown a dose of 80-120 mg is more effective than doses < 80 mg for retention and abstinence (1)
- Some studies have shown higher dose goals (e.g >= 100 mg) are more effective still for reducing non-prescribed opioid use (2, 3)
- Increasing methadone dose towards a set threshold (100 mg) or in response to opioid use, is more effective for reducing nonprescribed opioid use than keeping the dose constant (4)
- Yet nearly half (43%) of MMT patients in the United States receive a dose of < 80 mg daily (1)

1. J Subst Abuse Treat. 2019 Jan;96:18-22
2. Addiction, 100(10):1496–1509, 2005
3. Drug and alcohol dependence, 79(2):231–240, 2005
4. Drug Alcohol Depend. 2022 Oct 1;239:109609

Evolving Outpatient Methadone Initiation Guidelines & Protocols

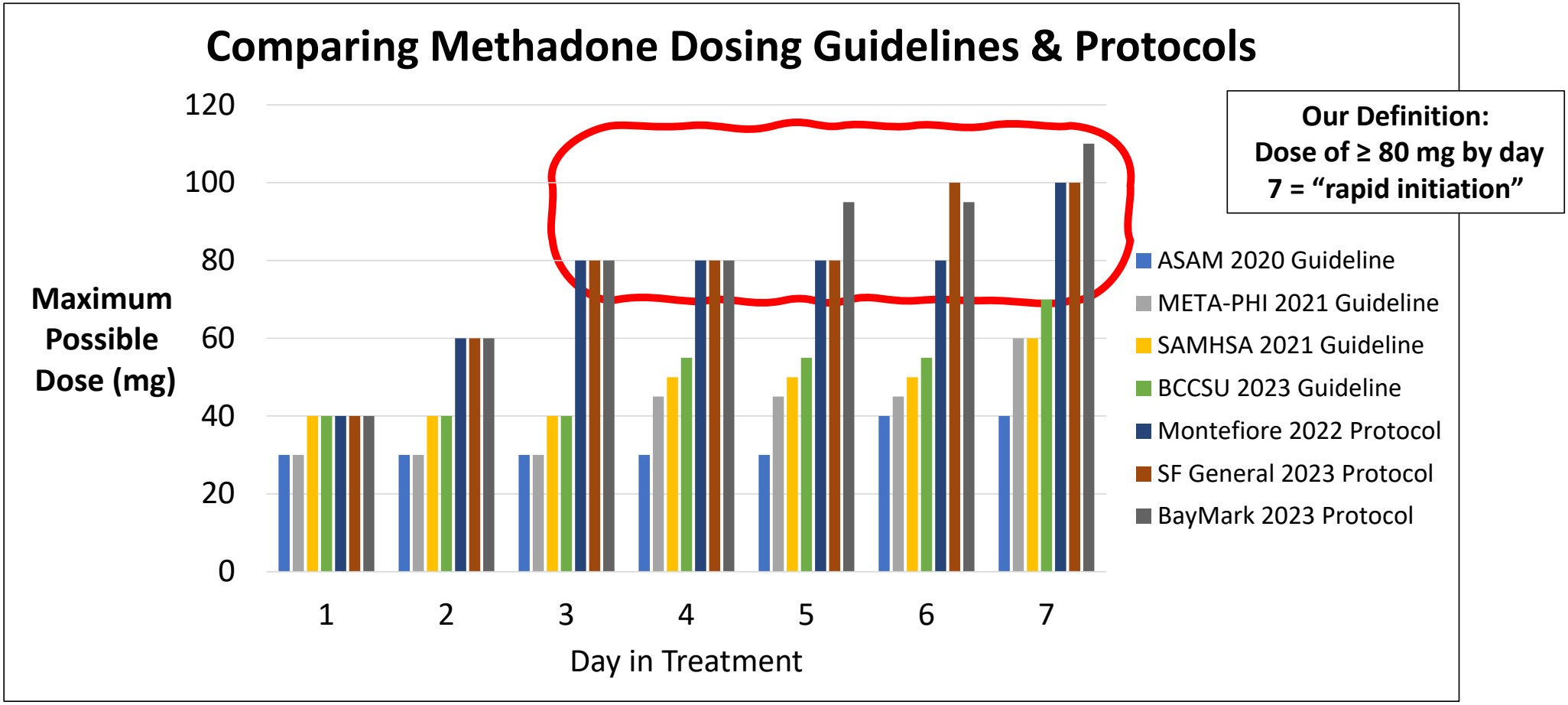
Source	Max starting dose	Increase by up to	Until	Then by, up to**	Potential max dose
					Day 7
ASAM '20 Guideline (1)	30 mg	10 mg q5 days	-	-	40 mg
SAMHSA '21 Guideline (2)	40 mg*	10 mg q3 days	Week 3-4	5 mg q3 days	60 mg
META-PHI '21 Guideline (3)	30 mg	15 mg q3 days	75-80 mg	10 mg q5 days	60 mg
BCCSU '23 Guideline (4)	40 mg	15 mg q3 days	85 mg	10 mg q3 days	70 mg
Montefiore '22 Protocol (5)	40 mg*	20 mg q1 day	80 mg (day 3)	20 mg q4 days until 140 mg	100 mg
SF General '23 Protocol (6)	40 mg*	20 mg q1 day	80 mg (day 3)	20 mg q3 days until 120 mg	100 mg
BayMark '23 Protocol (7)	40 mg*	20 mg q1days	80 mg (day 3)	15 mg q2 days	110 mg

*30 mg + 10 mg as per old SAMHSA rules, *new rules permit up to 50 mg as a single dose on day 1*

*** Note this table summarizes the maximum possible dose increases, not necessarily the actual dose increases that were typically ordered as determined by the OTP practitioner*

1. ASAM National Practice Guideline for Opioid Use Disorder, 2020 Focused Update
2. SAMHSA TIP 63: Medications for Opioid Use Disorder, 2021
3. Bromley L, Kahan M, Regenstreif L, Srivastava A, Wyman J. Methadone treatment for people who use fentanyl: Recommendations. Toronto, ON: META:PHI; 2021
4. British Columbia Centre on Substance Use, BC Ministry of Health, and BC Ministry of Mental Health and Addictions. A Guideline for the Clinical Management of Opioid Use Disorder. Published November 2023.
5. Buresh M, et al. Adapting methadone inductions to the fentanyl era. J Subst Abuse Treat. 2022 Jun 27;141:108832.
6. Steiger S, et al. Induction to Methadone 80 mg in the First Week of Treatment of Patients Who Use Fentanyl: A Case Series From an Outpatient Opioid Treatment Program. J Addict Med. 2024 Aug 16
7. Personal communication from Nick Van Dyke, Baymark Health Services, August 2024

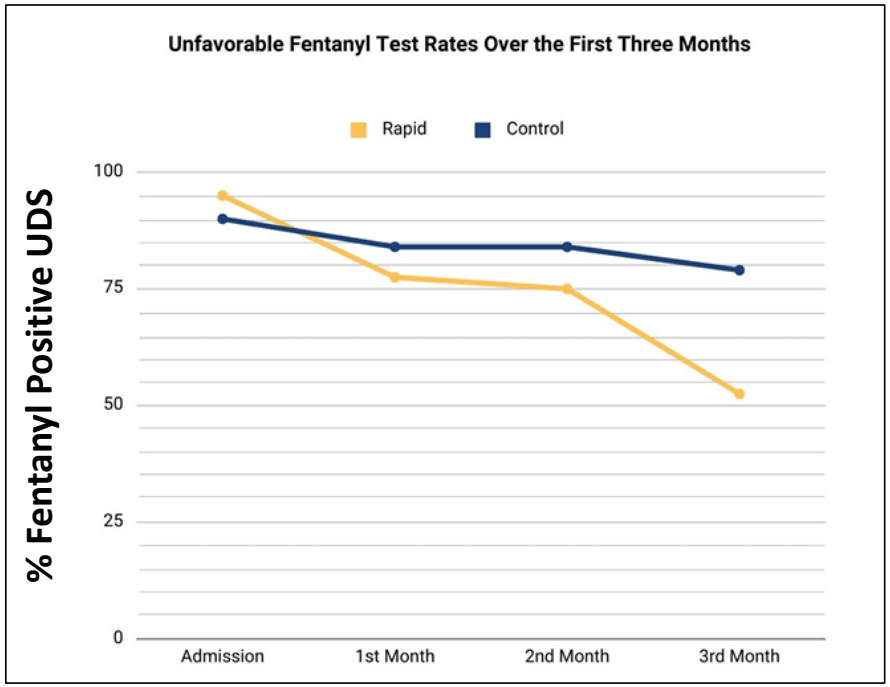
Defining Methadone “Rapid Initiation”



Rapid Initiation Outcomes: Baymark

Baymark:

- Large network of OTPs across US and Canada operating under various local names (BAART, CATC, MedMark, HRCC)
- 2023 OTP Outcomes Report
- Observed fentanyl in 62% of UDS for patients in first 3 months of treatment, and those patients spent 50% fewer days in treatment
- Launched rapid initiation protocol at pilot clinics, hoping to improve outcomes for patients using fentanyl
- Rapid initiation protocol outcomes
  - 90-day retention 77% rapid v. 70% control
  - Fentanyl + UDS rates at 90 days: 50% rapid v 80% control
  - No safety outcomes reported



Publicly Available White Paper, Nick Van Dyke, OTP 2023-Treatment-Outcomes-Report.pdf (baymark.com)

Rapid Initiation Outcomes: Baymark

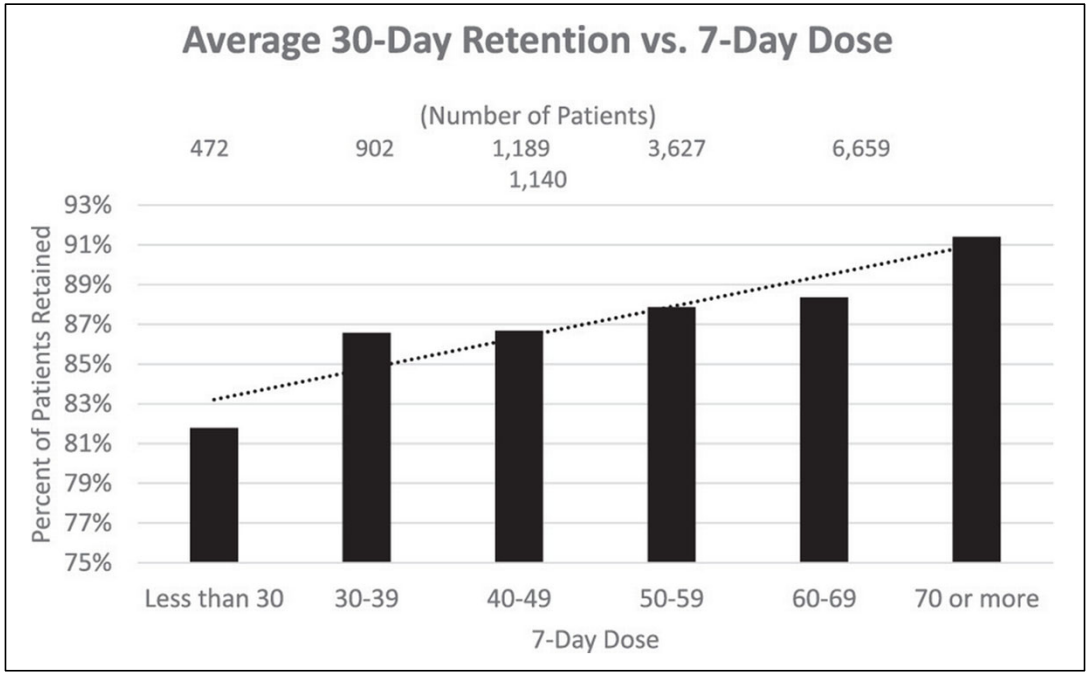
Relationship Between Methadone Induction Dosing and Retention in Treatment in Opioid Treatment Programs

Sherrick, Robert C. MD, DFASAM

Author Information

Journal of Addiction Medicine 19(4):p 446-448, July/August 2025. | **DOI:** 10.1097/ADM.0000000000001473

- Retrospective cohort of 14,489 new admissions to a network of 64 OTPs between 2020-2023
- Day-7 methadone dose found to be strongly associated with 30-day retention ($p<0.0001$)
- Patients receiving 70 mg or more on day 7 had a 91.24% retention rate, vs 79.5% for those receiving 30 mg or less



Sherrick RC. Relationship Between Methadone Induction Dosing and Retention in Treatment in Opioid Treatment Programs. J Addict Med. 2025 Jul-Aug 01;19(4):446-448. PMID: 40062577.

Rapid Initiation Outcomes: SF General

- Large OTP (~700 active patients) in urban San Francisco on SF General Campus
- Retrospective case series Jan-Dec 2022
- Of 202 new patients starting methadone, 129 met eligibility criteria for rapid initiation protocol
- 96 patients elected rapid initiation, 68 (71%) completed the protocol (reaching 80 mg within first week)
- Mean dose on day 7 was 89 mg (SD 9.6 mg) for completers v 49 mg (SD 14 mg) for non-completers
- Main reasons for not completing were missed dosing days
- **No episodes of oversedation, nonfatal overdose, or death recorded in any patients**
- At 30 days, of those who completed rapid initiation, 82 (85%) were retained, versus 22/28 (79%) retention for those who did not complete rapid initiation (OR 2.1, 95% CI 0.6 – 6.6)
- Positive impact on recruitment: 2024 intakes on pace to double the 2021-2022 average

Steiger S, et al. (2024) Induction to Methadone 80 mg in the First Week of Treatment of Patients Who Use Fentanyl: A Case Series From an Outpatient Opioid Treatment Program. *J Addict Med*

Details on SF General Rapid initiation protocol

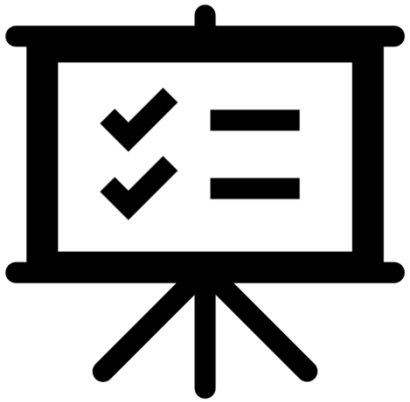
- **Patient selection is KEY – protocol only available to:**
  - New patients reporting daily fentanyl use
  - Age < 65, no known heart failure, end-stage renal disease, cirrhosis, advanced pulmonary disease
  - Notably, concomitant substance use, including alcohol and BZD use were not exclusion criterion
- Specific verbal consent provided: “There may be an increased risk for overdose and death with this rapid titration approach. If you notice sleepiness at all, talk to the nurse. We will be holding your dose after your 3rd day of 80 mg to check in and see if further adjustments are needed.”

Steiger S, et al. Induction to Methadone 80 mg in the First Week of Treatment of Patients Who Use Fentanyl: A Case Series From an Outpatient Opioid Treatment Program. J Addict Med. 2024 Aug 16.

Part 2 Conclusions:

How can new methadone dosing protocols be implemented?

- Doses of at least 60-120 mg are needed to promote retention and reduce non-prescribed use –higher doses are likely needed for those with regular fentanyl use
- Rapid initiation protocols may improve recruitment, retention and opioid use outcomes versus more gradual dosing strategies, with favorable safety outcomes in existing study data
- Patient selection is key; evaluating opioid tolerance and medical risk factors is necessary for appropriately selecting candidates for rapid initiation
- While a promising emerging practice, more data are needed on this approach!



Case Refresher

- John, a 58-year-old man, walks-in to your opioid treatment program (OTP) lobby asking for help
- History of severe opioid use disorder, hypertension, PTSD
- No current medications, no known allergies
- Historically has used heroin, and was successful with buprenorphine for the past 3 years
- But lost his partner 6 months ago & returned to opioid use
- “I cant get heroin anymore” - currently smoking 1.5 grams of fentanyl daily
- Has made 2 attempts at resuming buprenorphine “either it makes me sicker, or it just barely takes the edge off”
- Tried a friend’s methadone bottle & it helped immediately
- Enrolled in an OTP a few months ago, but felt “stuck at like 45 mg – it didn’t seem worth the trouble”
- Had 2 accidental overdoses in the past few weeks
- “I am scared. I need help.”

Inspired by: Harm Reduct J. 2024 Aug 24;21(1):156

Case Questions

Summary:

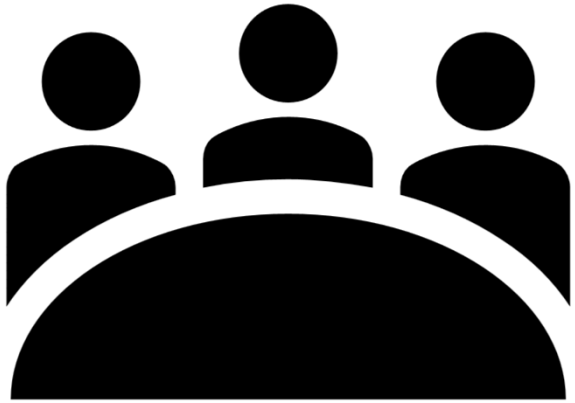
- John, a 58-year-old man with severe OUD, using 1.5 grams of fentanyl daily, with two recent accidental overdoses, walks-in to your opioid treatment program (OTP) lobby asking for help
- History of hypertension, PTSD – no known h/o cardiac, pulmonary, renal, or hepatic disease, no medications
- Two recent failed bup initiations, and one attempt at methadone maintenance
- Urine drug test: positive for fentanyl

Questions:

- Is he a candidate for buprenorphine, for methadone?
- If both, which should you recommend he try?
- If methadone, is he a candidate for a rapid methadone initiation?
- If so, how might you counsel him about what is known of the risks and benefits of standard versus rapid methadone initiations?

Inspired by: Harm Reduct J. 2024 Aug 24;21(1):156

Case Discussion



Case Conclusion

- John, a 58-year-old man with severe OUD, using 1.5 grams of fentanyl daily, with 2 recent accidental overdoses, walks-in to your opioid treatment program (OTP) lobby asking for help
- History of hypertension, PTSD – no known h/o heart, pulmonary, renal, or liver disease
- No medications
- Urine drug test: positive for fentanyl
- You offer choice of a re-trial of buprenorphine or methadone – he selects methadone
- You offer choice of standard or rapid methadone initiation – he selects the rapid initiation
- His dose is 80 mg by day six, and further increased by 20 mg at clinician visits on day 9 and day 13, now at 120 mg
- He is working with his counselor on grief and PTSD issues
- “I haven’t used in a week... I just feel normal now.”

Inspired by: Harm Reduct J. 2024 Aug 24;21(1):156

Acknowledgments

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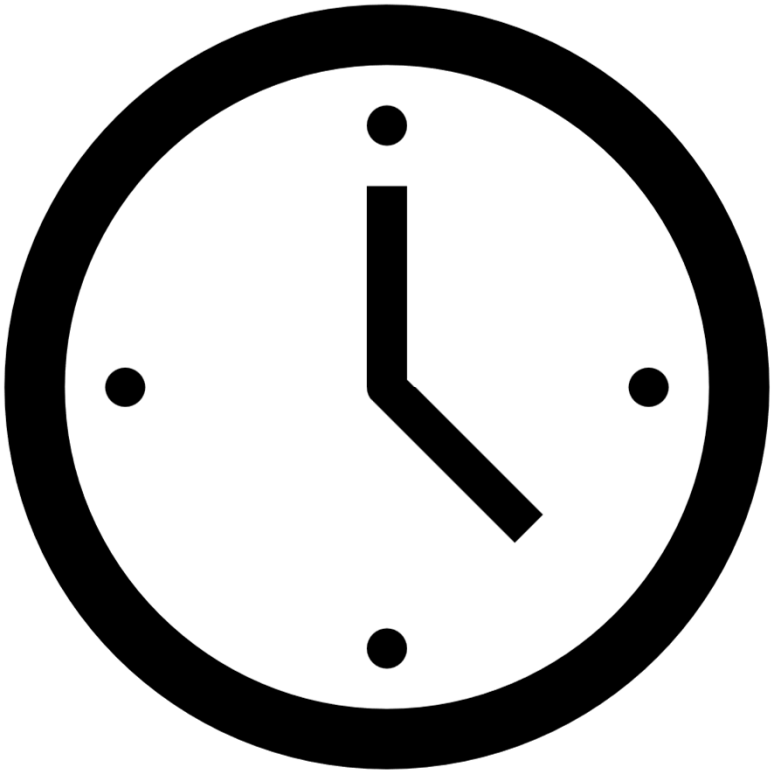
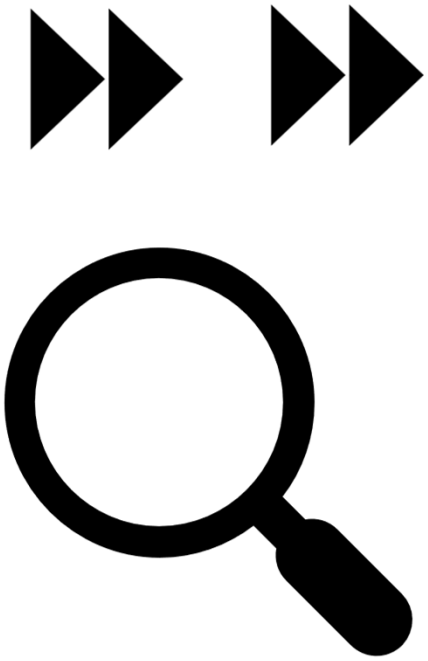
Thank You!

David.Lawrence3@va.gov



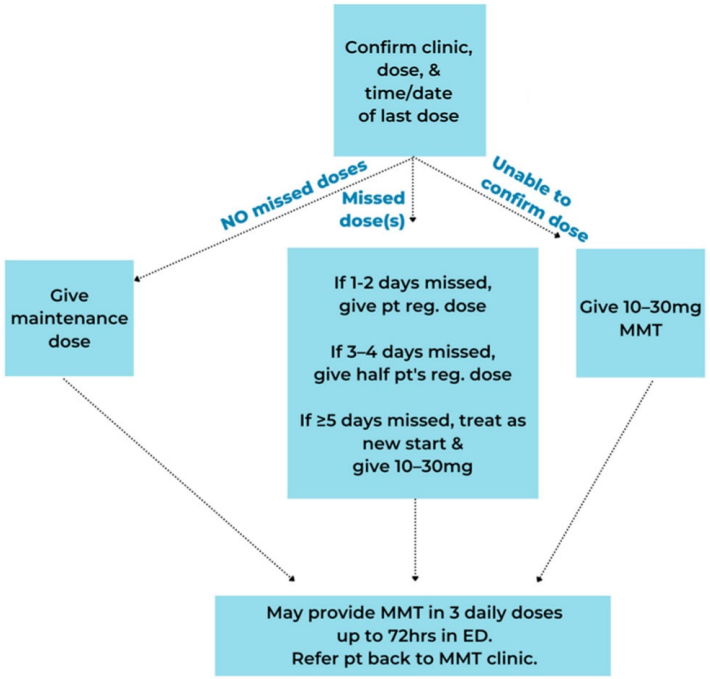


Case

- John, a 58-year-old man with severe OUD, PTSD, HTN, now stable on methadone at 140 mg daily x 2 months, with complete cessation of fentanyl use!
- Misses dosing for four consecutive days (Fri-Sun)
- Returns on day five (Mon): “Sorry for being absent, I unexpectedly had to travel to Houston for a funeral. I used a few doses from a friend while I was out.”

- What dose should you order for him?

Resuming After Missed Dose: Protocolized Approaches



Huo, Samantha, et al. "METHADONE INITIATION IN THE EMERGENCY DEPARTMENT FOR OPIOID USE DISORDER: A CASE SERIES." *The Journal of Emergency Medicine*, no. 3, Elsevier BV, Mar. 2023, pp. 391–96. *Crossref*, doi:10.1016/j.jemermed.2023.01.012.

Table 1: Adjustments for missed methadone doses

Days missed	Dose	Increases
Three (patient presents on day four)	Continue previous dose; no adjustment required	10–15mg every three days as per usual titration protocols
Four (patient presents on day five)	The higher of 50% of previous dose or 30mg	10mg daily for three days (not exceeding the most recent dose), then reassess and proceed as usual
Five or more (patient presents on day six or later)	Restart: 30mg +/- SROM maximum 200mg	10–15mg every three to five days

Bromley L, et al. Methadone treatment for people who use fentanyl: Recommendations. Toronto, ON: META:PHI; 2021. www.metaphi.ca.

Absent Days	Dose Titration	Clinician visit
2	Resume Full Dose	As Needed
3		
4	80% baseline dose, then resume full dose	
5	70% baseline dose (d1), then 90% baseline dose (d2), then resume full dose (d3)	
6	60% baseline dose (d1), then 70% baseline dose (d2), then 80% baseline dose (d3), then resume full dose	
7	Individualized	Recommended

San Francisco Health Network Behavioral Health Services, Medication Use Improvement Committee. Methadone for Treatment of Opioid Use Disorder in an Opioid Treatment Program (OTP): Recommendations for Management in the Fentanyl Era. 2024 Oct 3 [cited 2024 Nov 15];

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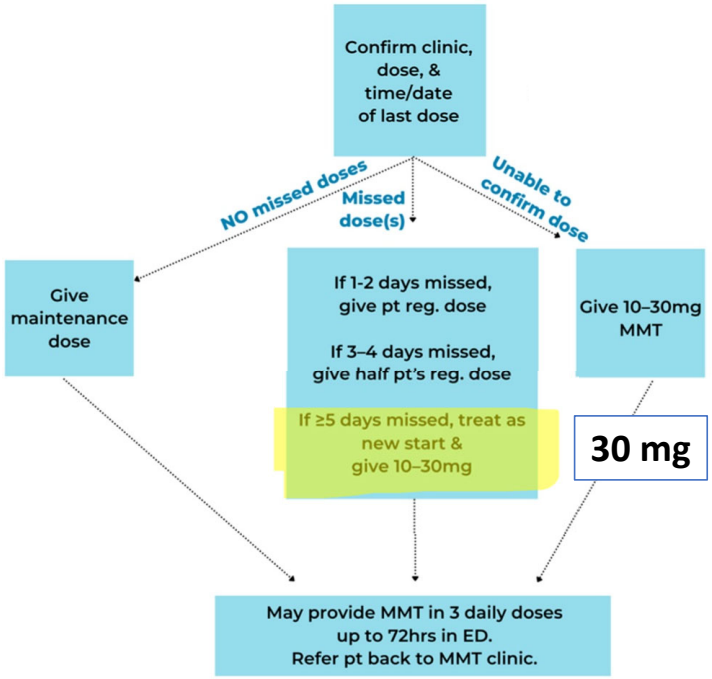

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140 * 0.5 = 70 mg

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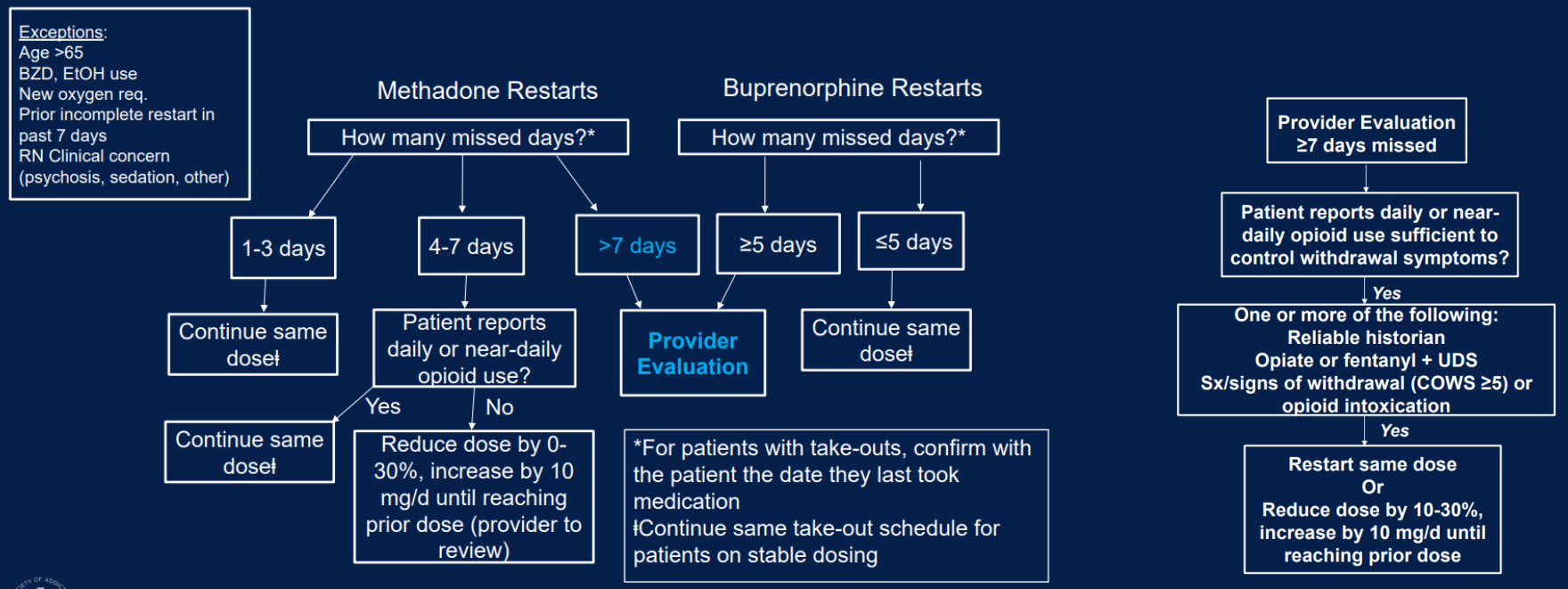
6	60% baseline dose (d1), then 70% baseline dose (d2), then 80% baseline dose (d3), then resume full dose	
7	Individualized	Recommended

140 * 0.7 = 98 mg

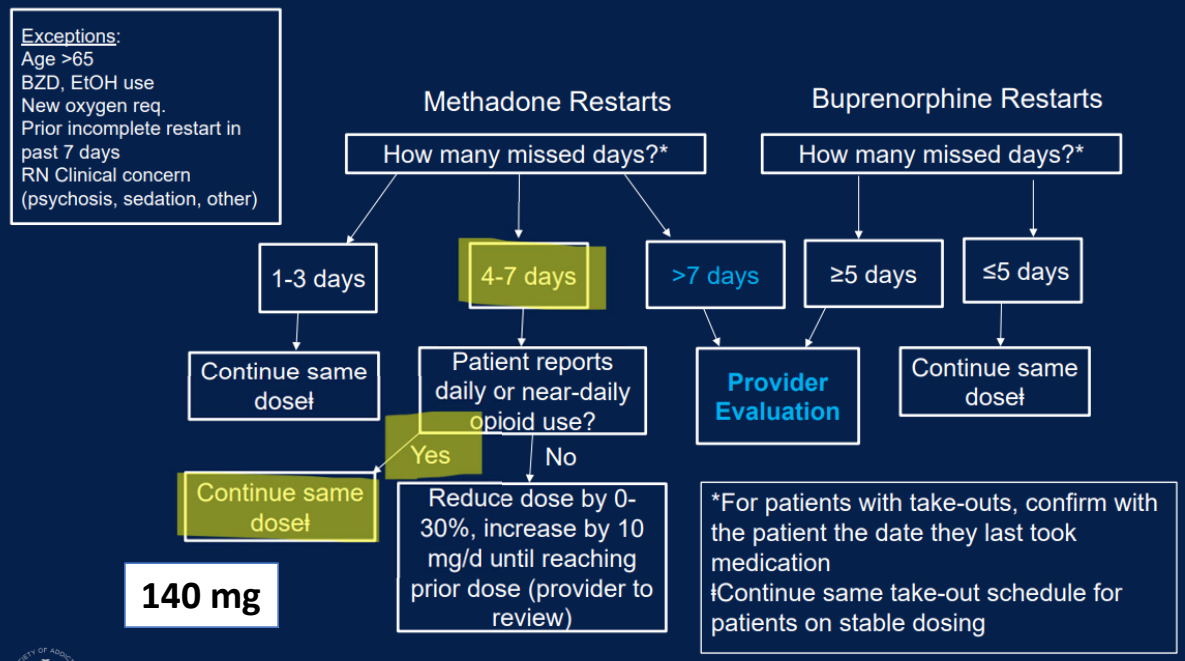
San Francisco Health Network Behavioral Health Services, Medication Use Improvement Committee. Methadone for Treatment of Opioid Use Disorder in an Opioid Treatment Program (OTP): Recommendations for Management in the Fentanyl Era. 2024 Oct 3 [cited 2024 Nov 15];

Resuming After Missed Doses: Individualizing to History

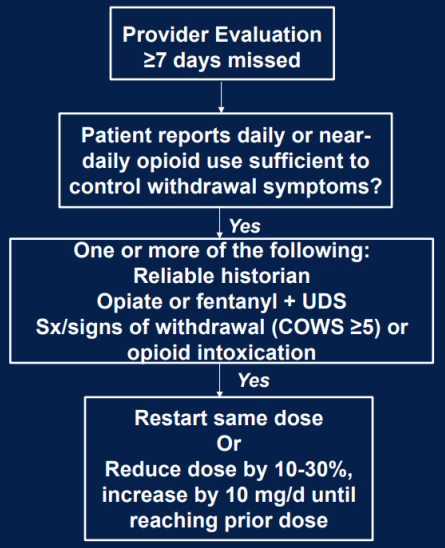


Blum J, Tillman A, Hinrichs M, Braun H, Hurley H. We've Been Doing it Wrong! Improving Methadone Restarts in the Fentanyl Era [Internet]. American Society of Addiction Medicine Annual Meeting; 2024; Dallas, TX. Available from: https://c36a7b585371cb8e876b-385db121fa2b55910fed97d2d3aaf4f8.ssl.cf1.rackcdn.com/2622619-1187220-003.pdf

Resuming After Missed Doses: Individualizing to History



140 mg



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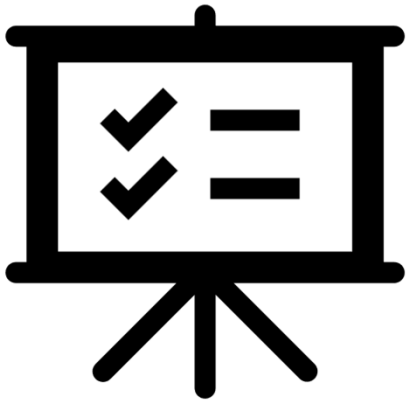
Bonus Section Conclusions

- When resuming methadone after missed doses providers must balance the risk of toxicity due to loss of tolerance against that of treatment disengagement from sub-therapeutic dosing – fentanyl has shifted this risk profile
- Opioid cross tolerance and methadone half-life offer a degree of safety from methadone toxicity
- Higher restart doses based on maintenance of tolerance; either as a less abrupt dose reduction protocol, or via an algorithm individualized to the patients reported interval use, may be safe and preferable to both patients and clinicians
- Further studies are needed to characterize optimal methadone resumption protocols and outcomes!



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