Methadone Update

Changes in the field

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Objectives:

- Review pharmacology of methadone
- Understand changing treatment strategies with methadone in the age of fentanyl
- Understand updated guidelines and laws concerning methadone use

References:

1. *SAMHSA 42 CFR Part 8 Final Rule*
2. *Medications for the Treatment of Opioid Use Disorder. A Rule by the Health and Human Services Department on 02/02/2024. The Federal Register, A Daily Journal of the United States Government.*
3. *New Federal Regulations for Opioid Treatment Programs An Overview of Key Changes to 42 CFR Part 8. https://www.vitalstrategies.org/wp-content/uploads/FederalOTPRegulations_Explainer_FINAL.pdf*
4. *Impact of Fentanyl Use on Initiation and Discontinuation of Methadone and Buprenorphine/Naloxone Among People with Prescription-Type Opioid Use Disorder: Secondary Analysis of a Canadian Treatment Trial. M. Eugenia Socias. Addiction. 2022 Oct; 117(10): 2662–2672. 2022 Jun 17. doi: 10.1111/add.15954*
5. *To Address the Fentanyl Crisis, Greater Access to Methadone Is Needed. By Nora D. Volkow, MD; The ASAM Weekly for July 23rd, 2024*
6. *Bromley L, Kahan M. Methadone Treatment for people who use Fentanyl: Recommendations. Toronto, ON: META:PHI; 2021 www.metaphi.ca*
7. *Comparative Effectiveness of Different Treatment Pathways for Opioid Use Disorder. Sarah E Wakema, Marc R Larochelle. DOI: 10.1001/jamanetworkopen.2019.20622*
8. *Safety and Efficacy of Rapid Methadone Titration for Opioid Use Disorder in an Inpatient Setting: A Retrospective Cohort Study. Klaire, Sukhpreet MD; Fairbairn, Nadia MD; Journal of Addiction Medicine 17(6):p 711-713, 11/12 2023. | DOI: 10.1097/ADM.0000000000001207*
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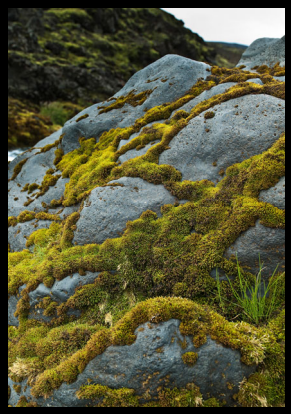
12. *Alabama will allow people to take methadone at home under new federal rules: Associated Press. Published September 20, 2024 at 3:25 PM CDT*
13. *Code of Federal Regulations Title 42*
14. *ALABAMA LEGISLATIVE SERVICES AGENCY / ADMINISTRATIVE CODE: Rule 580-9-44-.29 - Level I-O: Opioid Maintenance Therapy*

Foreword



Updated Language

CFR 42 part 8

- Medication Assisted Therapy, MAT
- Maintenance Treatment
- Detox
- Addicts

- Medications for Opioid Use Disorder, MOUD
- Comprehensive Treatment
- Withdrawal Management
- People who use unregulated drugs

A Word on Abbreviations

MTD

methadone

MAMP

methamphetamine

More Abbreviations

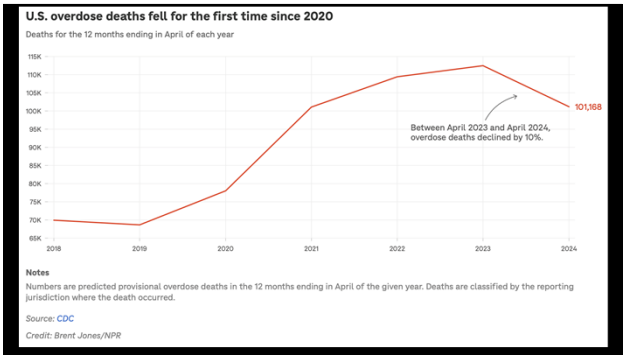
- OTP - outpatient treatment facility (methadone clinic)
- MOUD - medications for Opioid Use Disorder
- OAT - Opioid Agonist Therapy

Stats

a good trend

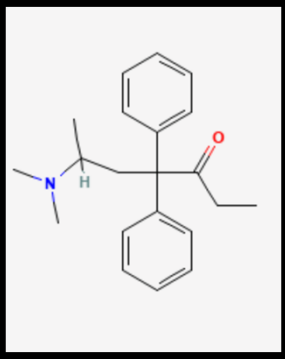
The CDC reported that 94,758 individuals died because of drug overdoses in the 12 month period ending May 2024

- 15% drop from the previous 12-month period.



- Narcan distribution and Harm Reduction
- Lower barriers to adequate access & dosing for MOUD

Methadone Overview and Review



MTD overview

- It is included in the World Health Organizations list of essential medicines
- Developed in 1937 in Germany
- Approved in the US in 1947
- 1971 Controlled Substances Act restricts the use of MTD for OUD to highly regulated OTP settings

MTD overview

- Methadone produces considerably less euphoria, sedation, and respiratory depression than morphine at equianalgesic doses
- Methadone produces lower rates of self-administration and reinforcing behaviour in both human and animal subjects when compared to morphine

MTD overview

Chemistry

- MTD comes in racemic form
  - the racemic form is thought to retard the development of tolerance
- L -enantiomer active at mu opioid receptor
- D -enantiomer is an NMDA antagonist
  - purported antidepressant effects
  - purported improvement of neuropathic pain

MTD overview

pharmacodynamics

- Peak plasma levels in 2-7 hours
- Analgesic effect is 6-8hrs
- Half life 8-59 hours
- There is a 17 fold difference variability between patients in their rate of methadone metabolism
- The L-enantiomer has a mean half-life of ~36 hours

MTD overview

Dose adjustments

- No renal dosing adjustment for GFR > 10ml/min
- No hepatic adjustments per UpToDate
  - however, per expert opinion, Child-Pugh class 3 liver disease warrants dosing considerations

MTD overview

QTc

- QT interval prolongation is due to the D-methadone enantiomer
- The risk of arrhythmia appears greatest in doses > 200mg
- Keep in mind *mild* QTc prolongation can be seen in lower doses. But we do not begin to see **clinically significant** effects until we surpass 200mg.
- Drugs that interact with methadone affecting QTc
  - trazodone
  - levaquin
  - TCA's like imipramine, amitriptyline, doxepin, nortriptyline, etc

MTD overview

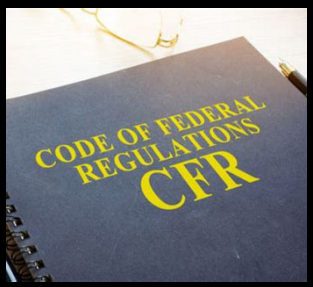
Urine Drug Screens

All the following have been reported to cause methadone false-positives on UDS:

- Chlorpromazine
- Clomipramine
- Doxylamine
- Diphenhydramine
- Quetiapine
- Thioridazine
- Verapamil

Expanded Access

Changes in the Federal Code



Rationale

Why make changes

- In 2020, illicitly manufactured fentanyl contributed to more than 80% of opioid-related overdose fatalities in both the United states and Canada[4]
- In response to COVID public safety measures, MTD access in OTPs was relaxed with lighter restrictions on take home medication and lowered barriers to access and initiation
- After relaxed restrictions the percentage of overdose deaths involving methadone relative to all drug overdose deaths declined from 4.5% to 3.2%[5]

Rationale

Why make changes

Comparing 40,000 individuals with OUD and comparing 6 distinct treatment models MTD, BUP, NTX, residential services, inpatient withdrawal management only or no treatment[6]

- MTD & BUP reduced mortality. 76% reduction at 3 months and 56% reduction at 12 months[6]
- MTD & BUP also reduced all cause acute care visits. 32% reduction at 3 months 26% reduction at 12 months[7]
- (btw, Naltrexone treatment was **not** associated with reduced overdose or serious opioid-related acute care use at 3 or 12 months[7])

Code Changes for Methadone Rules

Part 8 of Title 42 of the Code of Federal Regulations (CFR)
"The Final Rule"

Code Changes for Methadone Rules

The effective date of this final rule is April 2, 2024, and the compliance date is October 2, 2024.

Code Changes for Methadone Rules

Nicole Walden of the Alabama Department of Mental Health and Substance Services says:
"Alabama plans to align itself with the new flexible rules[12]"

42 CFR Part 8 Final Rule

	Old Rule	Final Rule
Comprehensive Treatment, General (Maintenance)	• **Patient must have 1-year history of OUD, with limited exceptions.**	• **Eliminates 1-year addiction requirement.** • Patient "meets diagnostic criteria for a moderate to severe OUD or OUD in remission, or is at high risk for recurrence or overdose."[v]
Comprehensive Treatment, Minors (Maintenance)	• Minor patients must have 2 documented unsuccessful attempts at short-term detoxification or drug-free treatment within a 12-month period. • Parental, guardian, or designated responsible adult consent necessary regardless of state law.	• Eliminates need for a minor patient to have 2 unsuccessful attempts at detoxification or drug-free treatment.[vi] • Parental, guardian, or designated responsible adult consent necessary unless not required by state law.[vi]
Withdrawal Management (Detoxification)	• Appropriateness determined by OTP medical personnel. • OTP may not admit a patient for more than two detoxification treatment episodes in one year.	• Focuses on "patients who *choose* to taper from MOUD" and requires such tapering to occur "at a *mutually agreed- upon* rate that minimizes taper-related risks."[vi] • No limit on number of admissions for withdrawal management per year.[vi]

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Withdrawal Management (Detoxification)	• Appropriateness determined by OTP medical personnel. • OTP may not admit a patient for more than two "detoxification" treatment episodes in one year.	• Focuses on "patients who *choose* to taper from MOUD" and requires such tapering to occur "at a *mutually agreed upon* rate that minimizes taper related risks."[vii] • No limit on number of admissions for withdrawal management per year.[viii]

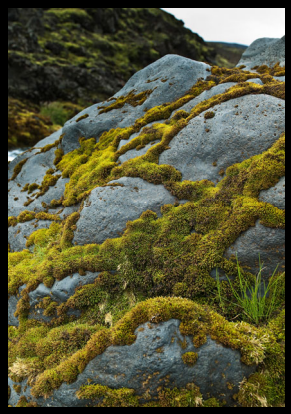
42 CFR Part 8 Final Rule

Time-in-Treatment for Methadone Take-Homes	Old Rule	Final Rule
1-14 Days	1 dose/week	Up to 7-day supply
15-30 Days	1 dose/week	Up to 14-day supply
31-90 Days	1 dose/week	Up to 28-day supply
91-180 Days	2 doses/week	Up to 28-day supply
181-270 Days	3 doses/week	Up to 28-day supply
271 Days to 1 Year	Up to a 6-day supply	Up to 28-day supply
1 Year to 2 Years	Up to a 2-week supply	Up to 28-day supply
2+ Years	Up to a 1-month supply	Up to 28-day supply

42 CFR Part 8 Final Rule

	Old Rule	Final Rule
Initial Dosages	• **Initial dose limited to 30mg.** • **Total dose for the first day limited to 40mg** unless the program physician documented that 40mg "did not suppress opioid abstinence symptoms."	• **Requires OTPs to consider "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." • Specifies that the total dose for the **first day should not exceed 50mg** unless the OTP practitioner finds and documents sufficient medical rationale for a higher dose.
Split Dosing	• Not addressed.	• Authorizes OTPs to provide split doses of MOUD, including methadone, "where such dosing regimens are indicated." • Includes split doses for take-home doses of methadone.
Guest Dosing	• Prohibited patient from obtaining "treatment in any other OTP except in exceptional circumstances."	• Patient may obtain treatment at another OTP "in circumstances involving an inability to access care at the patient's OTP of record," as determined by the medical director or program practitioner of the patient's OTP. • Circumstances include, but are not limited to, "travel for work or family events, temporary relocation, or an OTP's temporary closure."

Hospital Based Methadone Initiation



Inpatient Methadone Initiation

for whom?

- Persons refusing BUP or who prefer MTD
- Persons who have difficulty with BUP induction
- Medically unstable patients who may not tolerate w/d
- People who are high risk for treatment drop out or who are an AMA risk with subsequent risk for fatal overdose
- Pregnancy: precipitated w/d from BUP increases risk for
  - Spontaneous abortion
  - Preterm labor

Inpatient Methadone Initiation

- Reduces AMA rate[6]
- Reduces 90 day all-cause readmission rates[6]

Induction and Dosing

Methadone is a first-line treatment for opioid use disorder (OUD). High rates of attrition are associated with the induction period and with lower overall doses, leading to poor retention.[3,4,5]

North American guidelines suggest initiation at 5 to 30 mg and titration of 5 to 10 mg every 3 to 7 days

With minimum therapeutic doses of 60 to 120 mg, weeks of titration are required to achieve effective doses.[6,7]

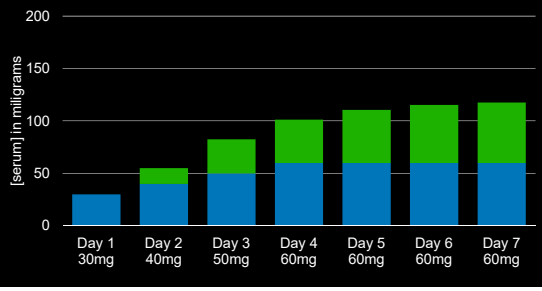
Fentanyl's higher potency compared with heroin suggests that the therapeutic range may be even higher and that dosing strategies require reevaluation.[8]

1. *Safety and Efficacy of Rapid Methadone Titration for Opioid Use Disorder in an Inpatient Setting: A Retrospective Cohort Study. Klaire, Sukhpreet MD; Fairbairn, Nadia MD; Journal of Addiction Medicine 17(6):p 711-713, 11/12 2023.*

Overview of MTD Titration Dynamics

5 half lives to reach steady state

MTD half live average ~36hours
(for simplicities sake, we will treat is as though it is 24hrs)



Induction and Dosing

- Methadone doses of 80-100 mg have greater benefits than doses below 50 in heroin-dependent patients
- For patients who use fentanyl, MTD doses of 100mg or higher are often needed.[6]
- Tennessee and Mississippi have “relaxed” the 125mg “limit” as titrations beyond 150-200mg are frequently required to quell cravings and achieve stability.

Inpatient Methadone Initiation

- Inpatient guidelines for methadone dose titration do not exist[8]
- Typical inpatient MTD initiation protocols mimic the outpatient model and do not reach therapeutic dose quickly enough
- Hospital setting allows for closer monitoring and an opportunity to reach effective dose before a patient directed discharge occurs
- Rapid MTD titration reduces time to therapeutic doses. But, there are concerns regarding harms such as overdose and sedation[9]
- Current publications indicate that rapid titration can safely be done in the setting of appropriate patient selection[8,9]

OTP Rapid Induction

Outpatient

Rapid induction was ordered for 93 patients and completed by 65 (70%).
No episodes of oversedation, nonfatal overdose, or death were observed.[11]

- 40mg day 1
- 60mg day 2
- 80mg day 3-7

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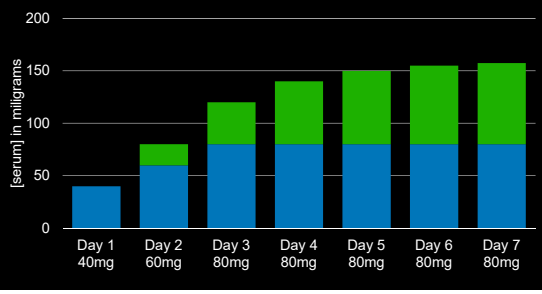

Inpatient Methadone Initiation

171 patients, 25% received rapid titration.
No incidents of AE's requiring holding a dose, narcan administration or transfer to higher level of care.[9]

- 60mg day 1
- 70mg day 2
- 80mg day 3
- 100mg days 4-7

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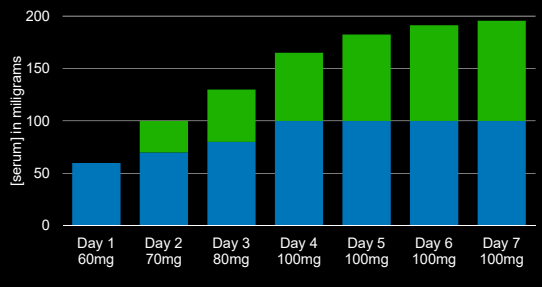

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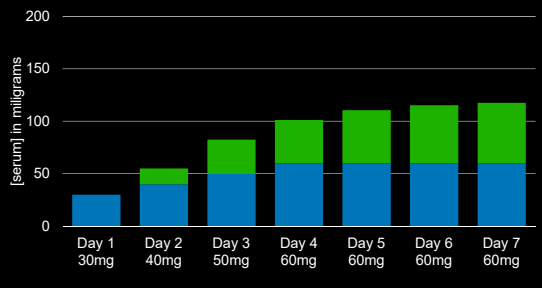

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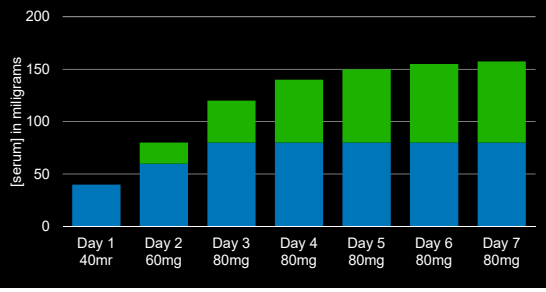

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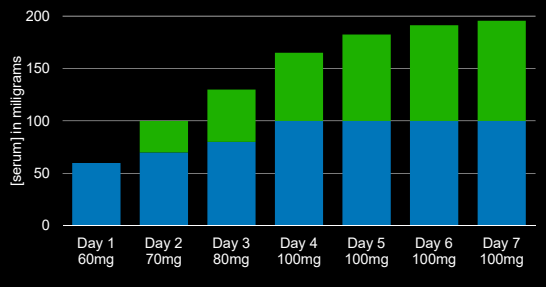

Now What?

The “72 hour rule”

42 CFR Part 8 Final Rule

"72 Hour Rule"	Old Rule	Final Rule
21 CFR 1306.07(b)	• Any physician is authorized to administer narcotic drugs to a person for the purpose of relieving acute withdrawal symptoms while arrangements are being made for referral for treatment. • Not more than **one day's** medication may be administered to the person or for the person's use at one time.	• Not more than a **three-day** supply of such medication may be dispensed while arrangements are being made for referral for treatment. • Such emergency treatment may not be renewed or extended

FYI,

80% of those who attempt taper relapse, this includes those considered rehabilitated before tapering.

In Summary

- Methadone is a long acting opioid which has been shown to mitigate overdose rates and all cause hospital admission/re-admission rates
- Used correctly it is remarkably safe
- With the pressure of the fentanyl crisis lawmakers have been forced to address outdated and unreasonable restrictions on it's use

In Summary

Expanded access to methadone is associated with

- lower methadone overdose rates
- lower overall opioid overdose and death rates
- greater treatment retention

In Summary

Hospitalization is “reachable moment” and provides an opportunity to engage patients in OUD treatment with MOUD

In Summary

42 CFR changes “the final rule”

- MTD initiation is based on DSM criteria, one year requirement is abolished
- Minors have lower barrier to treatment
- Take home medication access is expanded with accelerated schedule
- Dose limits are increased with greater ability to rapidly up-titrate doses
- “Guest” dosing is simplified
- Split dosing recognized and accepted
- 24 hour rule expanded to 72 hour rule

Thank You!

References:

1. *SAMHSA 42 CFR Part 8 Final Rule*
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