We've Been Doing it Wrong! Improving Methadone Restarts in the Fentanyl Era

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Disclosure Information

- Joshua Blum MD
  - No Disclosures
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- Hannan Braun MD
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Learning Objectives

- Understand the conventional wisdom around dosing recommendations for methadone restarts
- Apply principles of cross-tolerance and a population-based, harm reduction approach to inform updated restart protocols
- Review observational safety data and client and staff satisfaction from the Denver Health experience to make evidence-informed decisions around restart doses
- Utilize case discussions to weigh the harms of an aggressive restart protocol versus the harms of inadequate restart dosing

Agenda

- Cases
- Review of cross tolerance
- Review of clinic protocols & outcomes data
- Case studies– small group

Case: Darius

35-year-old male with OUD x 8 years. Enrolled in methadone clinic x 2 years, titrated to 120 mg/day.

Car impounded, lost transportation. Missed 7 days of dosing. Notes interval fentanyl use, smoking 3-5 fentanyl tablets per day, last use was previous evening 8 pm. COWS = 8.

Restarted at 60 mg/day, increase by 10 mg each pickup day back to prior dose. Patient upset, states, “you’re punishing me!”

Darius

Doses x 4 days, then misses another 12 days.

Reports ongoing transportation problems and “hustling” to get fentanyl to prevent withdrawal.

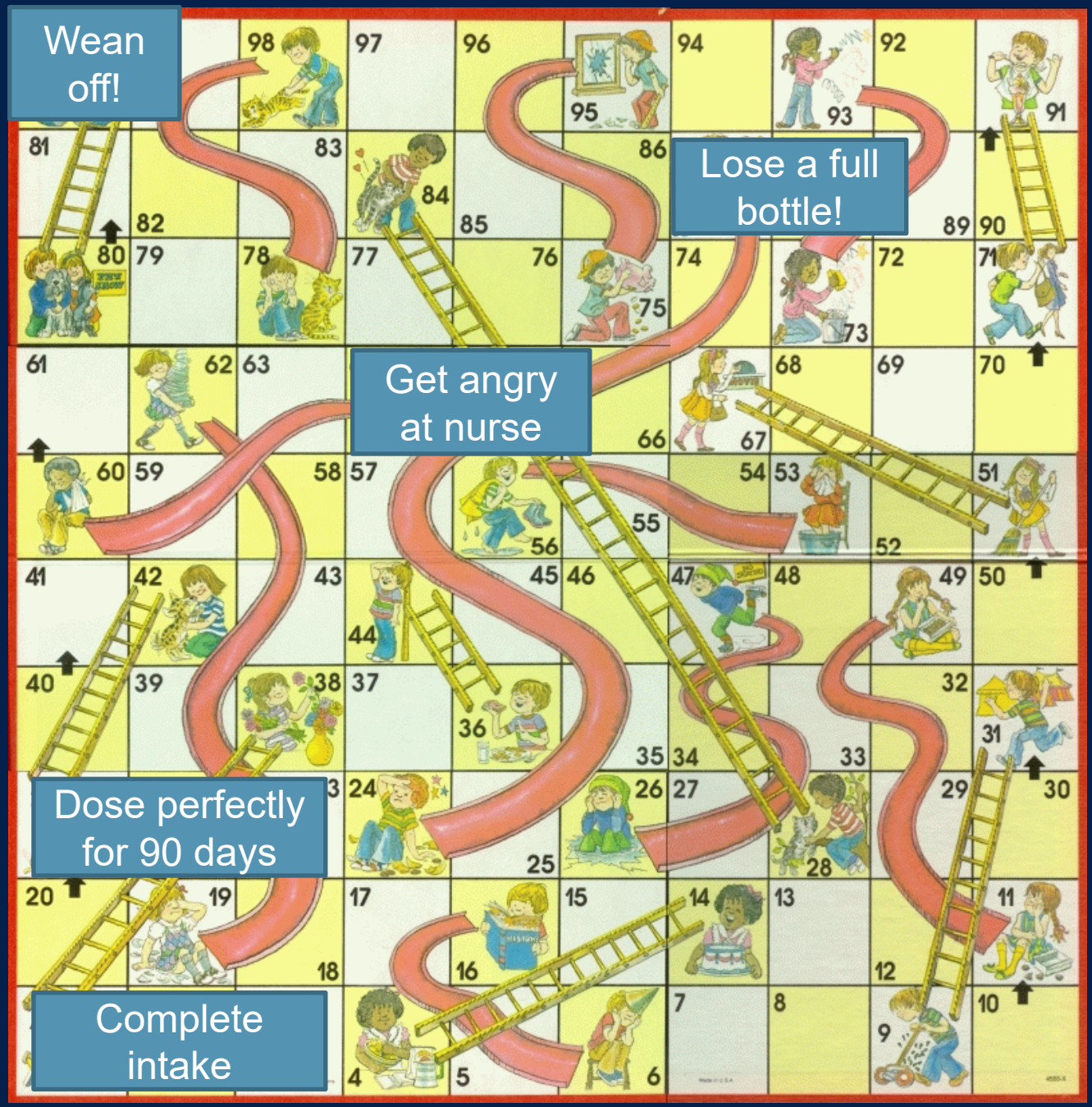
Restarted at 40 mg/d x 1 day, then increase by 10 mg/day to 80 mg with appointment for dose evaluation in 1 week.

Doses x 3 days, then falls out of care. Cell phone not accepting messages. Discharged from clinic after 30 days.

Fatal overdose 93 days from last dose.

Questions

- Does your OTP have a restart policy?
- Does your OTP routinely lower doses to a set dosage (i.e. 50% reduction after >4 days?)
- Does your SOTA have a policy on restarts?
- Have you had a patient like Darius?


Wean off!
Lose a full bottle!
Get angry at nurse
Dose perfectly for 90 days
Complete intake

Background

- References take a cautious approach to restarts
  - TIP 63:
    - "Patients who **miss more than 4 doses** must be reassessed. Their *next methadone dose should be decreased substantially* and built back up gradually. It may be necessary to restart the dose induction process from Day 1."
  - TIP 43:
    - "For patients who are out of treatment for a significant time *and might have lost tolerance*, *dosage reduction or reinduction is advisable*. Thereafter, increases of 5 to 10 mg per dose up to the previous level can be ordered."

Background

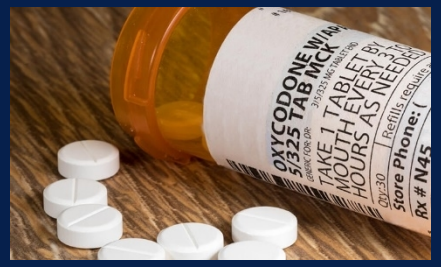
- WHO 2009 Guidelines:
  - *3 missed doses: reduce by 25%.* If well tolerated, return to previous dose levels
  - *4 missed doses: reduce by 50%*. If well tolerated, doses can be increased over several days to previous levels
  - *>4 missed doses: restart induction from baseline*

- META:PHI 2021:
  - *4 consecutive missed doses: dose reduce by 50% or to 30 mg*, whichever is higher
  - *≥5 consecutive missed doses: restart at maximum of 30mg and titrate* according to patient need. SROM at maximum starting dose of 200mg can be added on the day of restart, as long as patient not completely opioid-abstinent.
  - "Tolerance to methadone is partially lost after just a few days of abstinence."

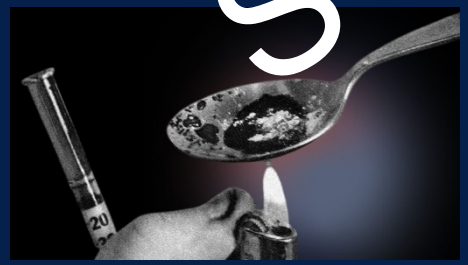
Comparable paradigm: initiation

- Advocates suggest that old initiation schedules inadequate to address high degree of tolerance seen in fentanyl era
- Initiation at methadone 30 mg has insufficient impact on withdrawal symptoms, illicit fentanyl use

Old paradigm



YEARS



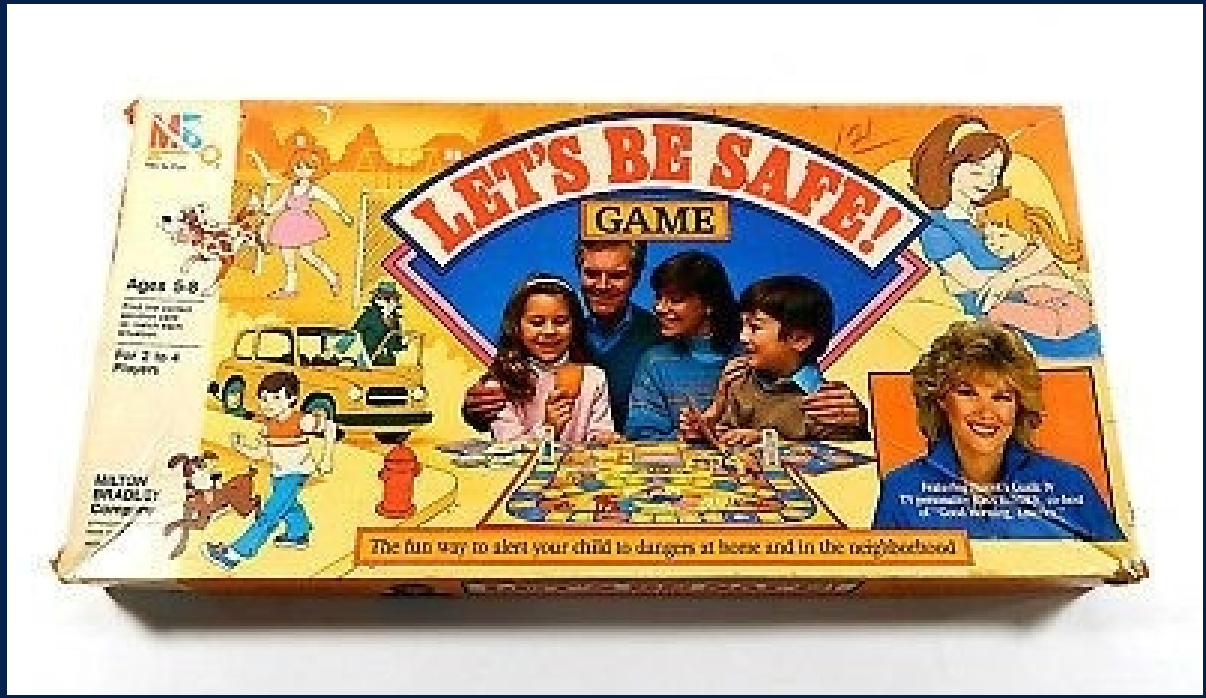
New paradigm

WEEKS

So many variables

- There isn’t one MOR
- Equianalgesic tables vary
  - Some don’t include adjustment for incomplete cross-tolerance
- Extensive plasma and liver binding
  - Severe liver disease: less methadone storage and earlier withdrawal symptoms? Or slower metabolism and greater accumulation?

Opioid Cross-Tolerance



Evidence for cross-tolerance

- Limited analgesic response to morphine in methadone-maintained patients (Athanasos et al., 2006)
  - Significantly higher doses needed for analgesia

- High affinity, high potency opioids like fentanyl used for analgesia in methadone-maintained patients (Davis et al., 2003)

Antinociceptive effects of high dose remifentanil in male methadone-maintained patients

Justin L. Hay [a,*], Jason M. White [a,b], Felix Bochner [a,c], Andrew A. Somogyi [a,c]

- Study of high-dose remifentanil in 8 methadone-maintained individuals
  - Variable remifentanil infusion rates: 0.5-3.5 mcg/kg/min
  - Increased pain tolerance at infusion rates of 2-3.5
  - Well-tolerated, mild sedation in 2 subjects, no hypoxemia
  - Typical post-op dose: 0.1 mcg/kg/min
- Authors' conclusions
  - Methadone-maintained individuals are also cross-tolerant to high-potency opioids (not just morphine)
  - "**Opioid doses up to 20-30 times** 'normal' may be more appropriate"

European Journal of Pain 12 (2008) 926–933

Methadone Tolerance Test

- Methadone doses >60 mg more effective than lower doses
- 75% of primary care methadone Rxs are for <40 mg
- Underdosage, rigidity of appointments frequent causes of dropout

Methadone Tolerance Test

- Extensive counseling and consents
- Confirm recent opioid use, including illicit methadone
- Asked user the methadone dose they expected would be sufficient to “hold” them
  - No doses >40 mg in methadone-naïve individuals
- Dosed/observed at a pharmacy, then sent back to clinic for further monitoring

Bakker A, Fazey C. BMJ 2006

Methadone Tolerance Test

- 84 men, 37 women, 16-51 years old (average = 26), 141 episodes
  - Dose range: 20-150 mg
    - Mean: 63 mg
    - Median: 70 mg
- 0 patients had signs/symptoms of methadone intoxication
- Average duration of care: 36 months; drop out rate: 8% (10
- No methadone-related deaths
  - 3 deaths total
  - 2 deaths from heroin following forced methadone discontinuation

Bakker A, Fazey C. BMJ 2006

Notes

- For whom is methadone dangerous?
  - Opioid naïve/intolerant
  - Older patients
  - Pulmonary disease
  - Chronic liver disease
  - Concomitant use of sedatives
- Higher margin of safety for:
  - Younger, healthier patients with opioid tolerance and no sedative use

Summary: cross-tolerance

- Individuals taking methadone demonstrate substantial tolerance to other opioids, including high-potency fentanyl analogues
- Individuals using illicit fentanyl are likely to have baseline tolerance to methadone

Other observations

- With missed doses, many patients frequently return to rapidly to previous fentanyl doses
  - Returning to fentanyl use may *increase tolerance*

- Resuming methadone at prior doses may be safe in this setting

Areas of concern

- Restart of methadone at same dose in absence of hepatic enzyme induction could increase risk
- Multiple studies suggest risk of death from overdose is increased in first 4 weeks of treatment

Denver Health OTP Restart Protocol

Hypotheses

- Interval use of opioids (particularly fentanyl) to treat or prevent withdrawal maintains sufficient tolerance to allow resumption of methadone at prior therapeutic levels.
- Resuming higher doses in individuals who have maintained opioid tolerance:
  - May be safe (especially relative to under-dosing methadone)
  - May assist with clinic retention
  - May be preferred by clients and staff

Exceptions:
Age >65
BZD, EtOH use
New oxygen req.
Prior incomplete restart in past 7 days
RN Clinical concern (psychosis, sedation, other)

Methadone Restarts

How many missed days?*

- 1-3 days → Continue same dose‡
- 4-7 days → Patient reports daily or near-daily opioid use?
  - Yes → Continue same dose‡
  - No → Reduce dose by 0-30%, increase by 10 mg/d until reaching prior dose (provider to review)
- >7 days → **Provider Evaluation**

Buprenorphine Restarts

How many missed days?*

- ≥5 days → **Provider Evaluation**
- ≤5 days → Continue same dose‡

*For patients with take-outs, confirm with the patient the date they last took medication
‡Continue same take-out schedule for patients on stable dosing

Exceptions:
Age >65
BZD, EtOH use
New oxygen req.
Prior incomplete restart in past 7 days
RN Clinical concern (psychosis, sedation, other)

Methadone Restarts

How many missed days?*

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Buprenorphine Restarts

How many missed days?*

- ≥5 days → **Provider Evaluation**
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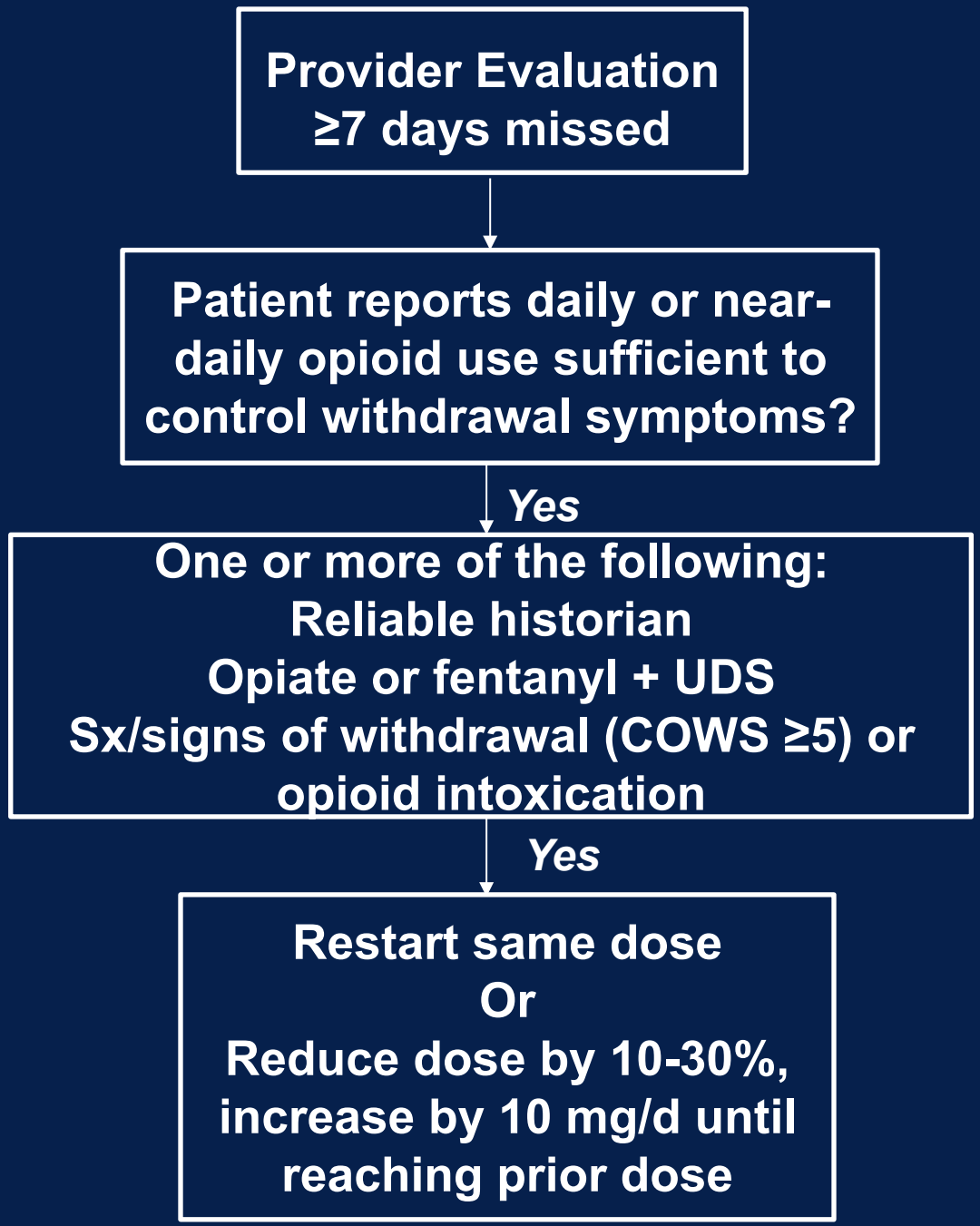
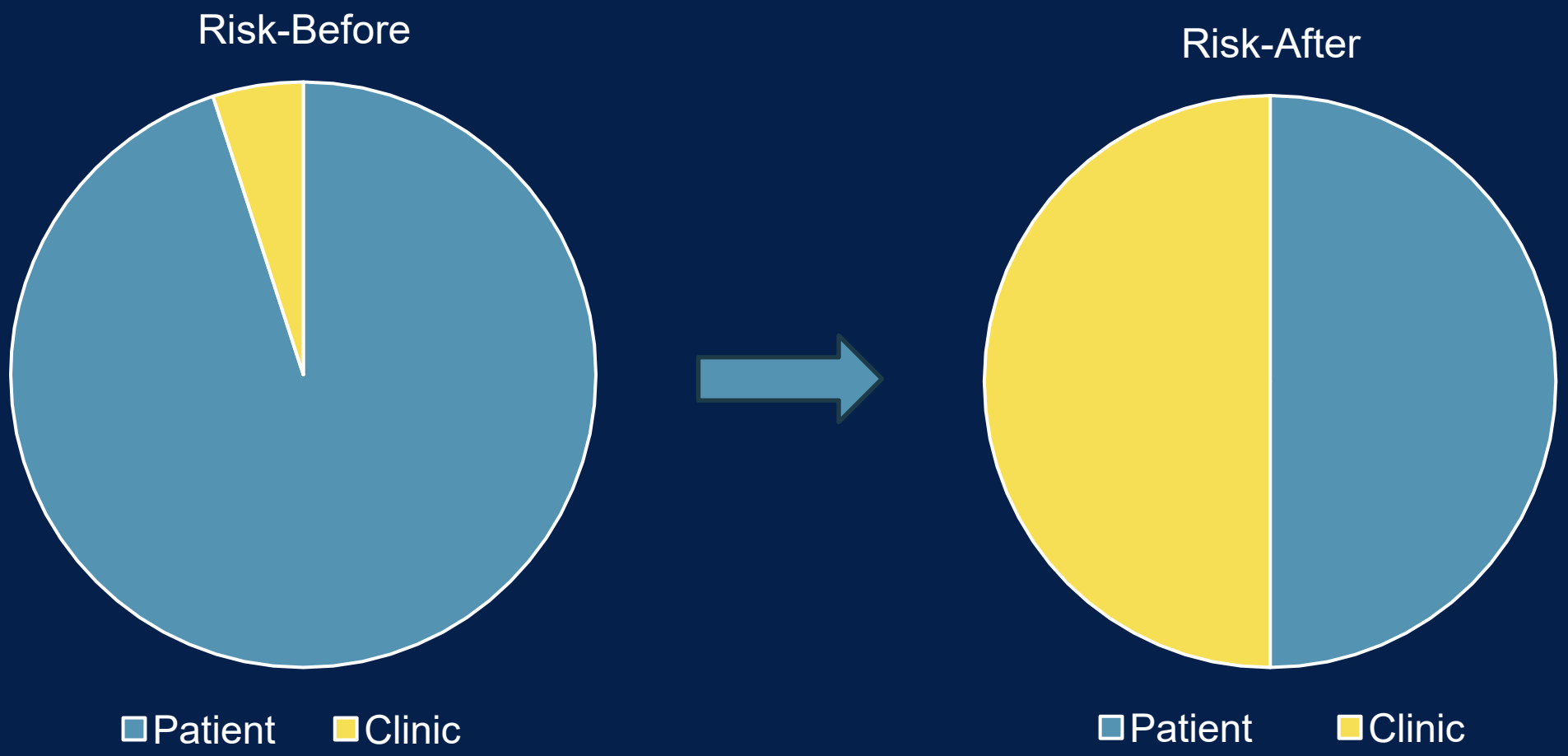
*For patients with take-outs, confirm with the patient the date they last took medication
‡Continue same take-out schedule for patients on stable dosing


Provider Evaluation
≥7 days missed
Patient reports daily or near-daily opioid use sufficient to control withdrawal symptoms?
Yes
One or more of the following:
Reliable historian
Opiate or fentanyl + UDS
Sx/signs of withdrawal (COWS ≥5) or opioid intoxication
Yes
Restart same dose
Or
Reduce dose by 10-30%, increase by 10 mg/d until reaching prior dose

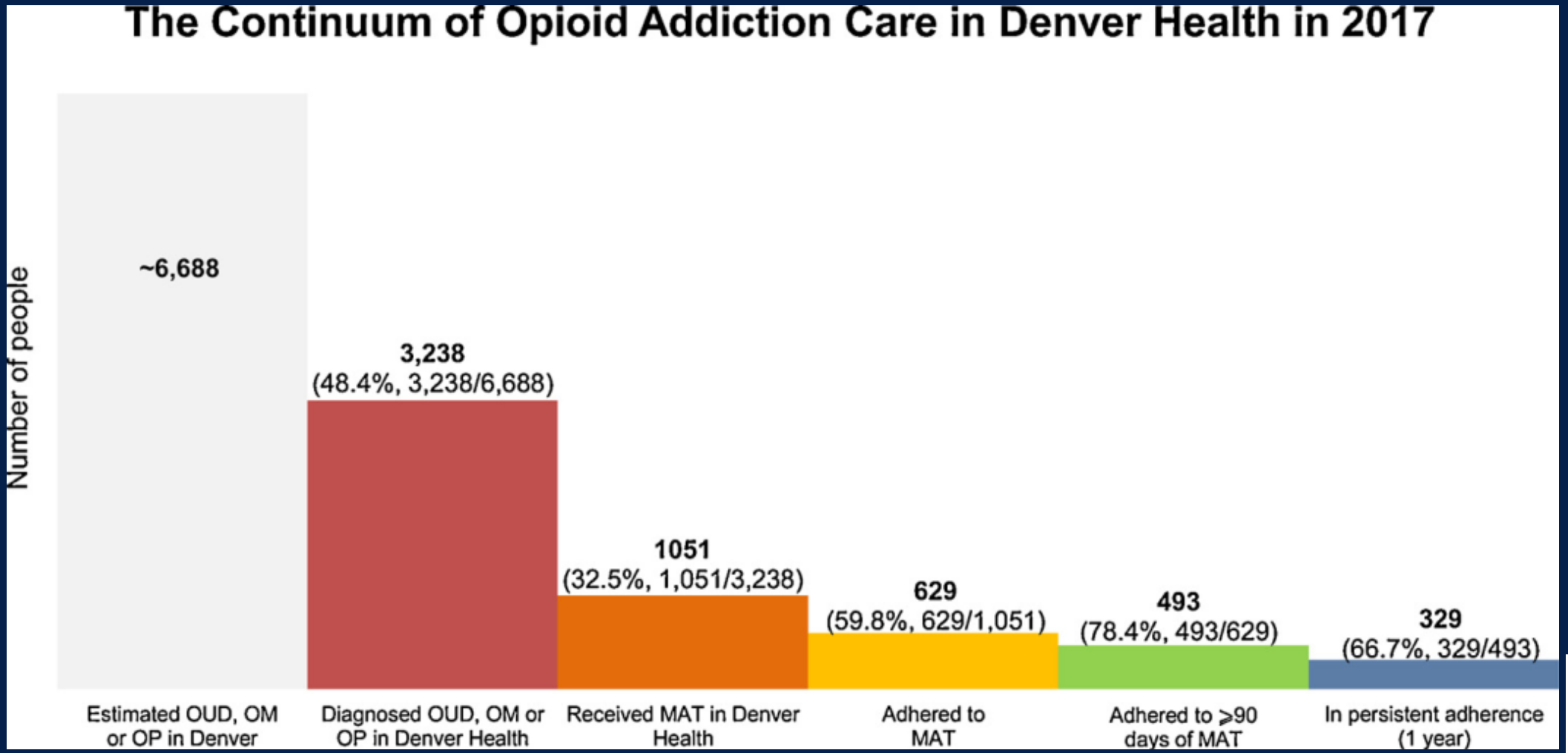
Assessing opioid tolerance

Objective	Subjective
Withdrawal (COWS)	Patient report
Intoxication	
Urine testing	

Shifting Risk



Who are your patients?



Results

Methods: Data Extraction

- Pulled client dose history from methadone dosing system and matched to EHR data
- Inclusion: Any client with a methadone dose in the period of interest
  - Pre-protocol change: Jan 1, 2020 – Dec 31, 2020
  - Post-protocol change: Oct 1, 2022 – Sept 30, 2023
- Restart defined as 3-29 days of missed methadone dose; 30 days is automatic discharge from OTP
- Clients can have multiple restarts within a period; clients can be in more than one period

Methods: Restart Patterns

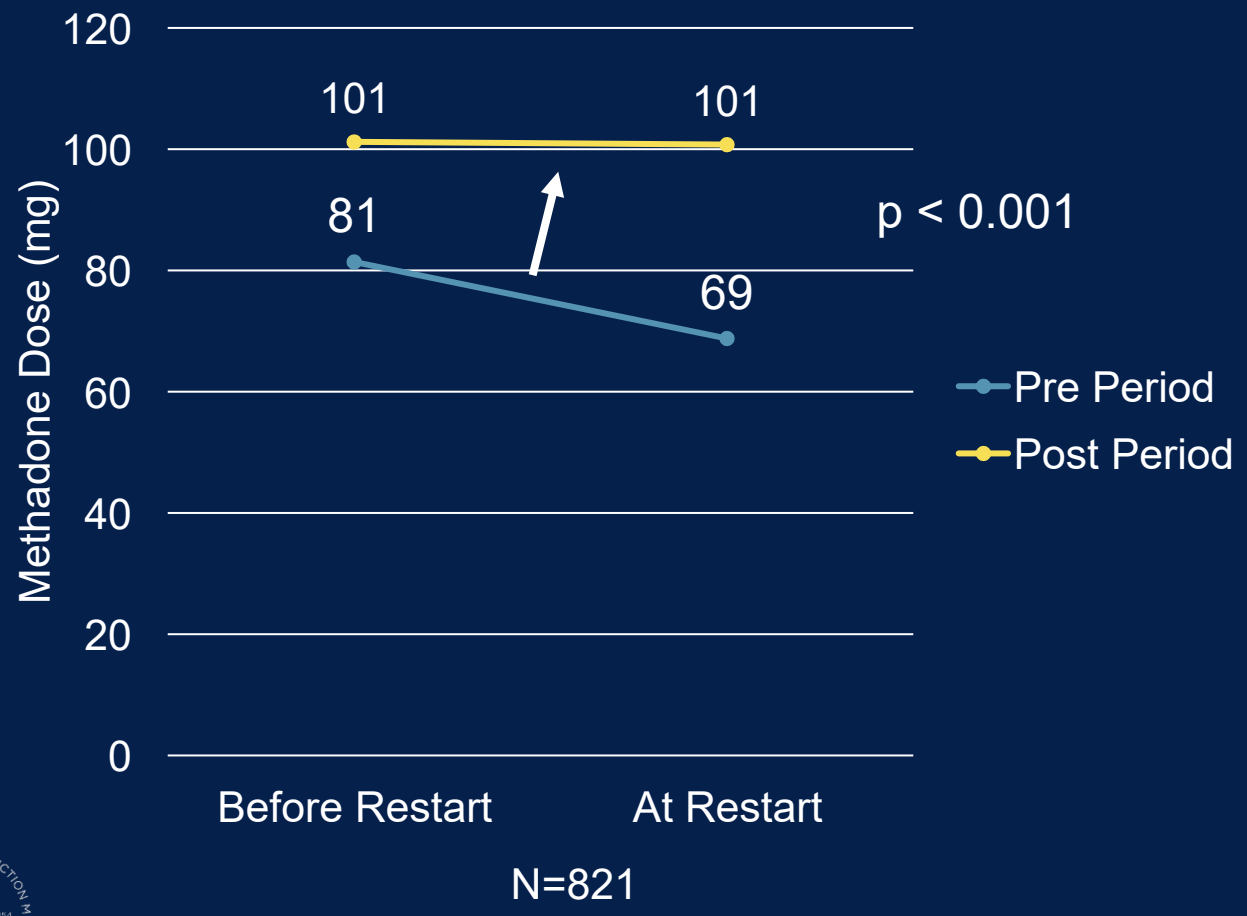
- Compare proportion of clients with a restart by period
  - Generalized estimating equation to test difference in proportions
- Among those with a restart:
  - Compare number of restarts per client in each period
  - Repeated measures ANOVA to model dose changes after restart by period

Results: Restart Patterns

	Pre Period		Post Period	
Total Unique Clients with Methadone Doses	1016	100%	1029	100%
Clients with a Restart				
Yes	288	28%	257	25%
No	728	72%	772	75%
Number of Restarts, among those with at least 1 restart				
One (1)	143	50%	130	51%
Two (2)	62	22%	44	17%
Three to Four (3-4)	44	15%	37	14%
Five or More (5+)	39	14%	46	18%

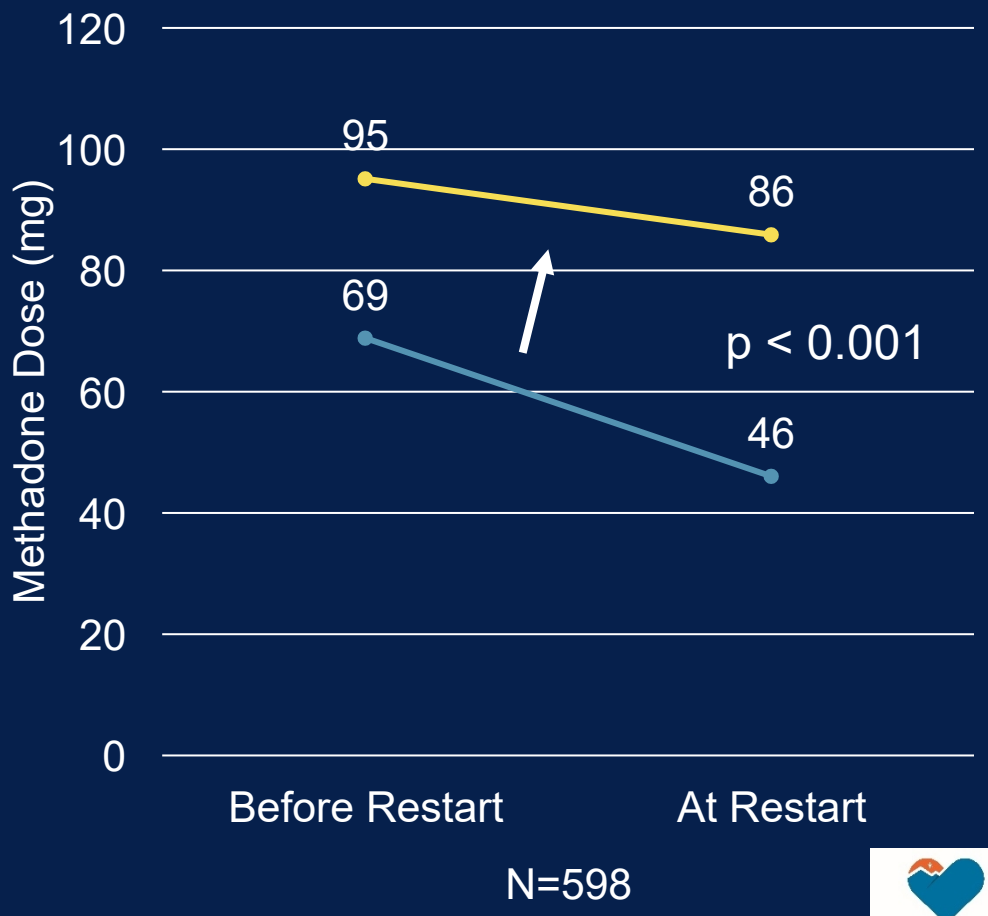
Results: Restart Dose Patterns

<7 days missed doses



N=821

7+ days missed doses



N=598

Methods: Outcomes

- Among those with a restart
- Outcomes:
  - ED visit within 7 days after restart (y/n)
    - With opioid overdose or opioid withdrawal ED diagnosis code (y/n)
    - (At our system ED)
  - Death within 90 days after restart (y/n)
    - Due to opioid overdose (y/n)
    - (From matched death certificate data from the state)
  - Retention in care 90 days after restart (y/n)
    - (No 30+ day breaks in dosing by 90 days after restart)
- Models:
  - Generalized estimating equations to model binary outcomes after a restart

Results: Outcomes after Restart

	Pre Period		Post Period		GEE OR (post to pre)	95% CI
Total Unique Clients with Methadone Doses	N=	707	N=	712		
ED Visits within 7 days of restart					0.61	(0.33, 1.10)
Yes	66	9%	56	8%		
No	641	91%	656	92%		
Retained 90 days after restart					0.71	(0.50, 1.01)
Yes	439	62%	421	59%		
No	268	38%	291	41%		

Results: Outcomes after Restart

Period	ED visit for withdrawal within 7 days of restart	ED visit for overdose within 7 days of restart	Death within 90 days of restart
Pre-implementation	2	1	3 (1 from overdose)
Post-implementation	0	1	2 (0 from overdose)

ED visit with overdose or withdrawal diagnosis and death were very rare

Methods: Satisfaction Surveys

- Clients: Convenience sample of clients with a methadone restart between July and December 2023
  - 10 item survey on symptoms after restart, comparison of restart dose to previous dose, satisfaction with dose at restart
- Clinicians: Current prescribing clinicians
  - 11 item survey on satisfaction with restart process
- Administered between Jan and Feb 2024

Results: Satisfaction Surveys

Clients

- N = 14 clients with any restarts between July and December 2023
- Among those with the same dose at restart, 7/8 were satisfied with their restart dose.
- Among those with a lower dose at restart, 2/6 were satisfied with their restart dose.

Clinicians

- 6/6 ordering clinicians took the survey
- 6/6 ordering clinicians were satisfied with the current restart process
- 6/6 ordering clinicians strongly agreed that starting a tolerant client back on a methadone dose at or near the prior dose is safe

Summary

- Conventional methadone restart recommendations are extremely conservative
- Illicit fentanyl demands a reappraisal of the risks vs. benefits of a more aggressive restart strategy.
- Opioid cross-tolerance and long methadone half-life provide a degree of safety from methadone overdose.
- Higher restart doses based on maintenance of tolerance may be safe and preferable to both patients and OTP clinicians.
- Further data are needed to determine safety and efficacy.

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Case Discussions

Case 1: Kim

28 yo female, methadone dose 165 mg/day with ongoing methamphetamine (0.5g 3x/week) and fentanyl use (5-10 tablets/day by smoking). Now has missed 18 days. In interim, fentanyl use increased to 10-20 tablets/day. Last use early this am. COWS = 12

At what dose would you restart?

Case 2: Arielle

Tx Days	Dose
1	30 mg
2	50 mg
3	50 mg
4	Miss
5	50 mg
6	60 mg
7	60 mg
8-14	Miss

35 yo female with fentanyl use, initiated treatment 2 weeks prior. Dosing history as noted in table. Presents for restart following 7 missed days.

Initial fentanyl use 10-15 tablets/day by inhalation, reduced to 3-5 tablets/day when on methadone 60 mg/day. No sedation.

Unable to return because of move from apartment. Returned to use of 10+ fentanyl tablets/day

Case 2

Tx Days	Dose
1	30 mg
2	50 mg
3	50 mg
4	Miss
5	50 mg
6	60 mg
7	60 mg
8-14	Miss

Last fentanyl use early this am before arrival in clinic

COWS = 2

What restart dose would you choose?

How would you titrate?

Case 2, alternate

Tx Days	Dose
1	30 mg
2	50 mg
3	50 mg
4	Miss
5	50 mg
6	60 mg
7	60 mg
8-14	Miss

Last fentanyl use yesterday around 8 pm (>12 hours ago)

COWS = 15

What restart dose would you choose?

How would you titrate?

Case 3: Travis

28-year-old male with longstanding fentanyl and methamphetamine use, history of congestive heart failure from non-ischemic cardiomyopathy.

Discharged from the hospital 2 weeks ago on methadone 80 mg/day (previous dose: 110 mg/day). No methadone x 14 days. Has been using fentanyl to stave off the worst of withdrawals but using much less than previous, typically 1-2 tablets every *other* day.

COWS = 16

What restart dose would you choose?