Safety of Rapid Methadone Titration for Opioid Use Disorder in Hospitalized Patients: A Pilot Study

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Background

- **Fentanyl use in opioid use disorder (OUD) is associated with high opioid tolerance and diminished effectiveness of methadone for withdrawal management [Buresh, 2021].**
- **Current methadone dosing guidelines recommend initiation at 10-30 mg/day with incremental dose increases of 5-10 mg every 3-5 days [SAMHSA, 2021].**
- **We find this titration schedule is often inadequate in managing opioid withdrawal, and patients are discharged on a subtherapeutic dose of methadone.**
- **Here, we investigate the safety and preliminary outcomes of a rapid methadone titration protocol in hospitalized patients with OUD.**

Methods

- **We implemented a pharmacist-guided protocol titrating methadone from 40 mg to 60 mg in 10 mg/day increments.**
- **Patients were hospitalized at an urban, academic tertiary-care hospital in Philadelphia, PA between September and October 2022.**
- **Data was abstracted from the electronic health record into a secure platform (REDCap).**
- **The primary outcome was safety, evaluated by the requirement for naloxone administration, presence of oversedation (RASS ≤ -3 or POSS ≥ 3), or development of QTc prolongation.**
- **Secondary outcomes included time to methadone initiation, methadone dose on discharge, frequency of patient directed discharge (PDD), and length of stay (LOS).**

Demographics

Table 1. Patient demographics and clinical characteristics

Characteristics	*N = 11*
Age (years)	41.2 (9.0)
Sex	
Male	8
Female	3
Race	
Black	2
White	7
Other	1
Unknown	1
Urine Drug Screen	
Not collected	3
6-MAM	0
Fentanyl	8
Methadone	1
Buprenorphine/metabolites	0
Benzodiazepines	2
Benzoylecgonine	6
Amphetamines	1

Table 1. Patient demographics and urine toxicology results. Patients (N=11) were between 29 and 56 years of age (mean=41.2 ± 9.0), consisted of 8 males (72.7%) and 3 females (27.3%), and primarily identified as white (63.6%). Urine toxicology screening demonstrated the presence of fentanyl for all patients tested (N=8). The most common concurrent substance of use was cocaine (75%), illustrated by the presence of benzoylecgonine on UDS. No patients tested positive for 6-MAM, an active metabolite of heroin.

Methadone Dosing

Table 2. Methadone dosing and concomitant opioid agonist therapy

Completed titration	9
Time to initiation (days)	3 (range 0-26)
Received concomitant opioid agonist(s)	10
Day 1 (MME)	90 (150)
Day 2 (MME)	165 (202)
Day 3 (MME)	105 (120)
Received other sedative medication(s)	11
Avg. dose at discharge (mg)	72.8 ± 7.9

Table 2. Methadone titration and the presence of concurrent full opioid agonist(s). The median time to initiation of methadone was three days with an interquartile range (IQR) of 2 days. Nine patients (81.8%) completed the titration protocol with an average methadone dose (mean ± standard deviation) of 72.8 ± 7.9 mg at discharge. One patient stopped methadone because OTP follow up was not feasible. One patient left against medical advice before completing the protocol. Ten patients (90.9%) received concomitant full opioid agonist during hospitalization, reported as median morphine milligram equivalents (MME) per day (*interquartile range* shown in parentheses).

Safety Outcomes

Table 3. Average QTc intervals and relevant clinical factors

Baseline QTc (ms)	440.6 ± 24.0
Average QTc interval during titration	
Day 1	439.1 ± 33.4
Day 2	448.4 ± 25.1
Day 3	434.2 ± 15.2
Day 4	426.9 ± 17.7
Received concomitant QTc prolonging medications	36.4%
Required naloxone (*N=11*)	None
RASS ≤ -3 (*N=10*)	None
POSS ≥ 3 (*N=10*)	None

Table 3. Primary safety outcome measures. Two patients exhibited baseline QTc interval prolongation (504 ms and 457 ms) but were deemed safe to start methadone based on clinical history and evaluation. Four patients (36.4%) received concomitant QTc interval prolonging medications. No patients demonstrated clinically significant increases in QTc or adverse cardiovascular events during hospitalization. Naloxone administration and oversedation (RASS ≤ -3 or POSS ≥ 3) were not observed for any patients.

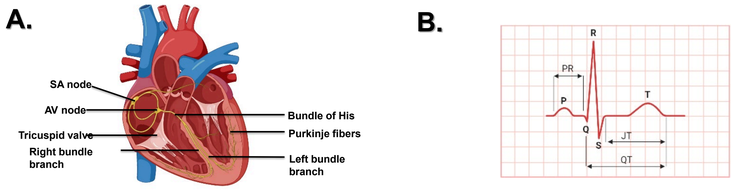

Figure 1. Cardiac conduction system and risk of arrhythmia. Methadone is an effective treatment for OUD but carries a risk of QTc prolongation and torsades de pointes (TdP). Concomitant use of other QT_c prolonging medications contribute to the risk of developing TdP. **Panel A-** Illustration of the cardiac conduction system (*yellow*). Ventricular depolarization starts at the atrioventricular node (AV) and travels through the Bundle of His to the left and right bundle branches. Disruptions along this path risk QT interval prolongation. **Panel B-** Electrocardiogram demonstrating a narrow QRS complex and normal QT interval.

Admission/Discharge Outcomes

Table 4. Length of stay and discharge disposition

Length of stay (days)	9 (25)
Opioid treatment program referral	81.8%
Disposition	
Home	63.6%
Substance use rehabilitation	27.3%
Skilled nursing facility	9.1%
Patient directed discharge	18.2%

Table 4. Hospital length of stay and discharge disposition. The median length of stay was 9 days with an interquartile range (IQR) of 25 days (range 5-65) across all patients. Nine patients (81.8%) were referred to an outpatient opioid treatment program (OTP) at discharge. The remaining two patients did not complete the protocol. The majority of patients were discharged home (63.6%) with three patients (27.3%) choosing to pursue inpatient substance use treatment. One patient was discharged directly to a skilled nursing facility (9.1%). Two patient-directed discharges were observed, both of which did not complete the titration protocol.

Discussion

- **Rapid methadone titration has been previously, successfully implemented in an otherwise healthy clinic population [Stone, 2020].**
- **Results of this pilot study support the conclusion that rapid methadone titration may be safe in certain medically hospitalized patients.**
- **No patients required naloxone administration, experienced oversedation, or demonstrated clinically significant QTc prolongation.**
- **Notably, a PDD of 18.2% with a median length of stay of 9 days was observed, as compared to a recent study by our group (N=23) demonstrating a baseline PDD rate of 69% and mean LOS of 3 days in patients with OUD [Thakrar, 2023].**

Conclusion

- **This pilot study provides preliminary support for safe, rapid methadone titration in hospitalized patients with OUD.**

References

1. **Buresh M., *et al.* (2022) Adapting methadone inductions to the fentanyl era. *J Subst Abuse Treat.* 141:108832**
2. **Stone A.C., et al. (2020) One year of methadone maintenance treatment in a fentanyl endemic area: Safety, repeated exposure, retention, and remission. *J Subst Abuse Treat.* 115:108031**
3. **Substance Abuse and Mental Health Services Administration (SAMHSA). (2021). Medications for Opioid Use Disorder Treatment Improvement Protocol (TIP) Series 63**
4. **Thakrar A.P., *et al.* (2023) Safety and preliminary outcomes of short-acting opioid agonist treatment (sOAT) for hospitalized patients with opioid use disorder. *Addict Sci Clin Pract.* 24;18(1):13**

Abbreviations: AV- atrioventricular node; 6-MAM- 6-Monoacetylmorphine; LOS- length of stay; OTP- opioid treatment program; OUD- opioid use disorder; MME- morphine milligram equivalents; PDD- patient-directed discharge; POSS- Pasero Opioid-induced Sedation Scale; RASS- Richmond Agitation Scale; TdP- torsades de pointes; UDS – urine drug screen