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Safety and Efficacy of Rapid Methadone Titration for Opioid Use Disorder in an Inpatient Setting: A Retrospective Cohort Study

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Abstract

Objectives: Inpatient guidelines for methadone titration do not exist, while outpatient guidelines lack flexibility and do not consider individual opioid tolerance. The evaluation of rapid, adaptable titration protocols may allow more patient-centered and effective treatment for opioid use disorder in the fentanyl era.

Methods: Retrospective chart review of patients ≥ 18 with opioid use disorder who were initiated on methadone at a single academic urban hospital using a rapid divided dose protocol between November 2019 and November 2020. The primary outcome was adverse events associated with methadone, specifically opioid toxicity or sedation requiring increased medical observation or intervention. The secondary outcome was total daily dose of methadone received on day 7 of titration.

Results: Ninety-eight patients were included for a total of 168 visits. Sixty-five (66%) were male, with a median age of 38 years (IQR 31 to 42). Sedation occurred in 2 (1%) patients, who required either naloxone administration or transfer to an intensive care unit for monitoring. Of the 135 visits where patients received at least 7 days of methadone, the mean dose on day 1 was 41mg (SD 9.6) and on day 7 was 65mg (SD 20.9).

Conclusions: In this inpatient cohort, rapid methadone titration was well tolerated and resulted in patients reaching higher doses of methadone than would be possible with a standard schedule, with few adverse events. Given the known effective dose range, this approach may result in shorter time to clinical stabilization and suggests that alternative methadone titration schedules may be safe and effective in appropriately selected patients.

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Conflicts of Interest: All co-authors are consultant physicians within the Division of Addiction Medicine at the study site, St. Paul's Hospital in Vancouver, Canada.

List of Supplemental Digital Content

1. Severe Adverse Event Case Summary Table

Keywords

methadone; opioid agonist therapy; opioid use disorder

Introduction

Methadone is a first-line treatment for opioid use disorder (OUD), but initiation and titration requires close monitoring.[1,2] High rates of attrition are associated with this period and with lower overall doses, leading to poor retention.[3–5] North American guidelines suggest initiation at 5–30mg and titration of 5–10mg every 3–7 days with minimum therapeutic doses of 60–120mg, resulting in weeks of titration to achieve effective doses.[6,7] Fentanyl's higher potency compared to heroin suggests that the therapeutic range may be even higher, and that dosing strategies require re-evaluation.[8]

Hospitalization presents an opportunity to safely decrease the time to therapeutic dosing through alternative administration schedules and monitoring for toxicity. However, institutional approaches are inconsistent and guidelines for inpatient titration do not exist. This study describes the safety and efficacy of "rapid" methadone titration at a hospital in Vancouver, Canada. Our hypothesis was that titration would safely occur faster than possible with outpatient guidelines.

Methods

This retrospective cohort study was conducted at an urban, academic hospital with a dedicated addiction medicine consult service. Ethics approval was obtained through the University of British Columbia-Providence Health Care Research Ethics Board (H20–02915). Eligible admissions occurred between November 2019 and November 2020. Inclusion criteria were age ≥ 18, diagnosis of OUD, hospital stay ≥7 days, and initiation of rapid methadone titration (use of a standardized order set including a scheduled dose of 30–40mg and as-needed (PRN) doses of 10mg every 3 hours for opioid cravings/withdrawal). There is a limit of 3 PRN doses every 24-hours, up to a maximum daily dose of 70mg on day 1, decided on internally based on clinical experience. Scheduled doses of up to 30–40mg are based on provincial guidelines and are increased every 3–5 days based on the cumulative use of PRN doses[9]. PRN short-acting opioids are frequently also ordered for persistent withdrawal symptoms. Data on short-acting opioids or other sedatives were not collected for this study. Receipt of sedatives (ex. benzodiazepines) is not considered an absolute contraindication but may factor into decision-making around appropriateness.

Participant characteristics included demographic and hospital admission details: age, gender, housing status, admitting service, discharge diagnosis, length of stay, discharge type (planned vs. patient-initiated), and previous admission during the study period. Medical and substance use variables included HIV status, urine drug screen results, co-occurring substance use disorders, active injection opioid use, and prior opioid agonist therapy (OAT) exposure.

The primary outcome of interest were adverse events attributable to toxicity from methadone, including naloxone administration and/or transfer to ICU. Data was also collected on any doses of methadone that were held, reduced, or if methadone was discontinued. The medication administration record was reviewed for the 7 days following methadone initiation. If an adverse event was identified, the nursing and physician documentation was reviewed for additional information.

Total daily doses for the first 7 days of administration were also collected, with the dose on day 7 being a secondary outcome.

Results

In the study period, 207 admissions ≥7 days in length including a rapid methadone initiation were identified. 39 were excluded due to lack of PRN doses being ordered, plans to utilize methadone in conjunction with buprenorphine "low dose induction", or continuation of a patient's community prescription. The remaining 168 encounters represented 98 unique patients (Table 1).

This patient population was characterized by OUD with evidence of high opioid tolerance, with 79 (80.6%) reporting use of injection opioids daily, 91 (92.9%) previously prescribed methadone, 43 (43.9%) previously prescribed buprenorphine/naloxone, and 25 (25.5%) previously prescribed slow-release oral morphine. In 112 of 168 possible encounters a urine drug screen was collected, with 106 (94.6%) positive for fentanyl. Stimulant use disorder was a common comorbidity in 68 (69.4%) patients.

Within the 168 encounters, 2 (1.2%) patients experienced a serious event, with one requiring naloxone for sedation and the other requiring ICU transfer for observation. Both were potentially related to inappropriate patient selection (see case summary table, Supplemental Digital Content 1). Episodes of mild sedation (requiring held, reduced, or cancelled methadone doses but no further medical management) occurred in 12 (8.9%) encounters. Of the 12 encounters with a mild adverse event, 9 were continued on methadone afterwards and 3 were switched to an alternate form of OAT.

Of the 135 encounters in which at least 7 days of methadone were administered, the mean dose on day 1 was 40.6mg (SD 9.6) and on day 7 was 65.4mg (SD 20.9). When restricted to the 79 encounters that were the initial visit for each patient during the study period, the mean dose on day 1 was 41.3mg (SD 9.8) and on day 7 was 64.5mg (SD 20.5). The total daily doses on days 1–7 of methadone administration are presented in Table 2. For patients with a length of stay of ≥ 14 days (n=55), the average discharge dose of methadone was 95.0mg (SD 39.1).

Discussion

In this retrospective study of a rapid methadone titration protocol, adverse events attributable to opioid toxicity were few with the majority not requiring intervention. The 2 severe adverse events were associated with either a loss of opioid tolerance due to recent hospitalization or a co-occurring severe medical illness and may have been mitigated

through optimization of patient selection. Importantly, neither the severe nor mild adverse events could be attributed specifically to methadone as patients often received other sedating medications, were admitted for severe illness, and/or were reporting ongoing substance use.

Established guidance for methadone focuses on safety in an outpatient setting Due to the long half-life of methadone and the potential for accumulation, it is recommended that doses only be titrated every 3–7 days.[6] Current recommendations are based primarily on studies involving patients utilizing lower potency opioids such as heroin.[1] Patients exposed to fentanyl are more likely to be dissatisfied with OAT and may require higher doses, suggesting that traditional protocols be updated to account for individual histories and needs.[10,11] These findings demonstrate that rapid titration of methadone is well tolerated and provides the opportunity to reach higher doses within a shorter period. The dose range safely administered reflects the ability to individualize titration.

Multiple titration protocols have been suggested that increase the frequency or quantity of doses.[12–14] To date, formal evaluation of these strategies remains limited, with this study building on a case report that presents the rationale for such a dosing approach.[15]

Generalizability may be limited by the high prevalence of fentanyl in our location and a high degree of previous methadone experience within the cohort. As well, retention in care after discharge was not assessed and adverse events that occurred beyond the first 7 days or after discharge were not captured. The absence of a comparison group prevents an assessment of whether adverse events were different from a standard titration protocol. As well, prescribers used clinical judgement to assess tolerance and suitability for PRN doses. Nonetheless, this represents an important description of how current titration protocols may be optimized to meet patient needs.

Future work should examine downstream effects of rapid titration (including retention in care) and the utility in settings where fentanyl is less common or specialized services are unavailable. While further evaluation is warranted, we suggest that the rationale and need for individualized approaches to methadone titration is clear and represents an opportunity to address the ongoing overdose crisis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of abbreviations

OUD	Opioid use disorder

OAT	Opioid agonist therapy
PRN	As-needed (*Pro re nata)*

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Table 1:

Characteristics of Unique Patients Undergoing Rapid Methadone Titration in the Hospital Setting

	Unique Patients (n=98)
	n (%)
Sociodemographic	
Age – mean (SD)	37.9 (10.0)
Gender	
Man	65 (66.3)
Woman	33 (33.7)
Unstable Housing	47 (48.0)
Admission Details *	
Admitting Service	
Infectious Disease	31 (31.6)
Internal Medicine	42 (42.9)
Psychiatry	19 (19.4)
Other	6 (6.1)
Length of stay, days – mean (SD)	19.2 (15.4)
Patient initiated discharge	31 (31.6)
Substance Use History	
Active stimulant use disorder	68 (69.4)
Active alcohol use disorder	8 (8.2)
Active sedative-hypnotic use disorder	5 (5.1)
Active injection opioid use	79 (80.6)
Medical History	
HIV Infected	14 (14.3)
OAT History	
Previous buprenorphine	43 (43.9)
Previous methadone	91 (92.9)
Previous slow-release oral morphine	25 (25.5)
Previous injectable OAT	3 (3.1)

* Reported for first titration during study period for patients with multiple eligible encounters

Table 2:

Total Daily Doses of Methadone Received During First 7 Days of Titration (n=135)

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