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Piloting a Hospital-Based Rapid Methadone Initiation Protocol for Fentanyl

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Objectives: Treating acute opioid withdrawal and offering medications for opioid use disorder (OUD) is critical. Hospitalization offers a unique opportunity to rapidly initiate methadone for OUD; however, little clinical guidance exists. This report describes our experience during the first 9 months following introduction of a hospital-based rapid methadone initiation protocol.

Methods: We conducted a retrospective chart review of hospitalized patients with OUD seen by our interprofessional addiction medicine consult service at an urban academic center between December 2022 and August 2023. We identified patients who initiated methadone using the rapid methadone initiation protocol, which includes dose recommendations (maximum 60 mg day 1, 70 mg day 2, 80 mg day 3, 100 mg days 4–7) and strict inclusion and exclusion criteria (end organ failure, arrhythmia, concurrent benzodiazepine or alcohol use, age >65).

Results: There were 171 patients that received methadone for OUD during the study period. Of those, 25 patients (15%) received rapid methadone initiation. The average total daily dose of methadone on days 1–7 was 53.0 mg, 69.2 mg, 75.4 mg, 79.5 mg, 87.1 mg, 92.2 mg, and 96.6 mg, respectively. There were no adverse events requiring holding a dose of scheduled methadone, naloxone administration, or transfer to higher level of care.

Conclusions: A rapid methadone initiation protocol for OUD can be implemented in the inpatient setting. Patients up-titrated their methadone doses quicker than with traditional induction methods, and there were no serious adverse events. Appropriate patient selection may be important to avoid harms.

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Illicitly manufactured fentanyl and other ultrapotent synthetic opioids (herein referred to as fentanyl) in the United States have made the unregulated opioid supply deadlier and complicate acute opioid withdrawal management.[1,2] Higher opioid tolerance among people using fentanyl causes traditional therapeutic doses of medications for opioid use disorder (MOUD) to be insufficient,[3] and traditional protocols typically require weeks of methadone titration in the opioid treatment (OTP) setting to achieve effective doses.[4]

Hospitalization is a reachable moment to initiate and coordinate addiction care.[5,6] Further, hospitalization provides a unique opportunity to closely monitor patients and potentially decrease the time to reach a therapeutic dose of methadone. Traditional inpatient methadone initiation protocols do not exceed 40 mg methadone on day 1, 50 mg methadone on day 2, and 60 mg methadone on days 3–6.[7-10] This shortens the time to reach an effective dose compared with the OTP setting, but may still be inadequate to control withdrawals and cravings, which can lead to higher rates of patient directed discharge.

Rapid methadone initiation could reduce the time to reach therapeutic doses, but concerns exist regarding harms including overdose and oversedation. Currently, there is little empiric evidence to guide addiction medicine providers.[8,9,11] Our interprofessional addiction medicine consult service,[12] the Improving Addiction Care Team (IMPACT),[5] developed a rapid methadone initiation protocol based on previously described rapid methadone protocols from St. Paul Hospital in British Columbia and case reports.[9,13] This report describes our experience during the first 9 months following protocol implementation.

METHODS

We performed a retrospective chart review of hospitalized patients with opioid use disorder (OUD) who were seen by IMPACT and underwent rapid methadone initiation between December 2022 and August 2023 at an urban academic center. All study procedures were approved by the Oregon Health & Science University institutional review board (eIRB #00010846).

Our interprofessional addiction medicine consult service offers all patients with OUD buprenorphine and methadone, with ultimate choice driven by multiple factors including outpatient treatment access, patient preference, and shared decision making. When starting methadone for MOUD, IMPACT team members routinely identify a suitable OTP for continued treatment and coordinate intake appointments for the day after

hospital discharge. We send necessary clinician documentation for continued methadone dosing and communicate with OTP clinicians as needed. Our hospital utilizes the 72-hour rule[14] to dispense methadone as a bridge to OTP intake appointments when necessary.

The rapid methadone initiation protocol recommends a maximum of 60 mg methadone on day 1, 70 mg methadone on day 2, 80 mg methadone on day 3, and 100 mg methadone on days 4–7 (Table 1). We included patients with OUD with routine fentanyl use and IMPACT consultation. We relied on patient report to determine routine fentanyl use, which we generally defined as whether patients used fentanyl as their primary opioid consumed. Exclusion criteria for the protocol included end organ failure, ventricular arrhythmias, prolonged QTc, concurrent use of benzodiazepines or alcohol, medications that affect methadone metabolism, and age greater than 65 years (Table 1). End organ failure refers to co-occurring end-stage renal disease, decompensated cirrhosis, decompensated heart failure, and advanced pulmonary disease, as determined by consulting clinician review of hospital record. We considered a history of ventricular arrhythmias as an exclusion and a QTc cutoff of greater than 500 milliseconds. We relied on our addiction specialists to determine the presence of medications that affect methadone metabolism. Patients on the rapid methadone initiation protocol could receive short-acting opioids as clinically indicated (eg, acute pain, untreated withdrawal).

The goal of the protocol is to help patients more rapidly reach doses of methadone that are sufficient to address withdrawals and cravings. When implementing the rapid initiation protocol, IMPACT clinicians reviewed the methadone initiation schedule, side effects to monitor for, and indications to hold methadone doses, including sedation and respiratory depression, with patients and nursing staff. IMPACT clinicians rounded on patients a minimum of once per day Monday through Friday. We considered day 1 of the rapid methadone initiation to be the first day that IMPACT was consulted. If patients remained in the hospital after completing the 7-day rapid methadone protocol, the consulting clinician used clinical discretion and shared decision making with the patient to guide further increases in methadone dosing.

We identified patients who met inclusion criteria where clinicians were planning to use the protocol through clinician-triggered real-time messaging with the research team and through weekly meetings wherein the research team prompted clinicians to report patients who had undergone or were planning to undergo the protocol. To define the cohort who received the rapid methadone protocol and are included in this study, we manually reviewed hospital charts and excluded patients who did not receive any methadone doses, received methadone maintenance from an OTP within 7 days of admission, or were transitioned to another form of MOUD within 2 days of admission. Finally, given the importance of patient selection and our strict inclusion/exclusion criteria, we thought it was important to characterize the group receiving rapid methadone within the larger cohort of hospitalized adults with OUD seen by our consult service. To do this, we used an EHR data extraction tool to identify patients seen by IMPACT who received at least 1 dose of methadone during the study period.

For the patients we identified as having received the rapid initiation protocol, we abstracted demographics, substance use disorder diagnoses, and prior MOUD history from the EHR. We then reviewed the EHR to obtain daily methadone dose, data on total morphine milligram equivalents (MME) of short-acting full opioid agonists, and adverse events. We defined adverse events attributable to methadone toxicity as holding a scheduled methadone dose, administration of an opioid antagonist (eg, naloxone), or transfer to a higher level of care due to methadone dose-effect (eg, oversedation, respiratory depression). We also reviewed ambulatory records and patient linkage tools within the EHR to obtain posthospitalization follow-up data.

RESULTS

Within our study period, our addiction consult service saw 171 hospitalized patients who received at least 1 dose of methadone for OUD. Of those, 37 planned to undergo rapid methadone initiation, and 25 (15%) actually underwent the protocol (Fig. 1). Seven patients were excluded because they had received methadone maintenance in the 7 days prior to admission, therefore were not new methadone initiations. Three patients received methadone for 1 day before transitioning to

TABLE 1. Rapid Methadone Protocol

Day	Max TDD of Methadone	Recommended Dosing
1	60 mg	30 or 40 mg ×1 + 10 mg q3h PRN × 2 or 3 doses
2	70 mg	50 mg ×1 + 10 mg q3h PRN × 2 doses
3	80 mg	60 mg ×1 + 10 mg q3h PRN × 2 doses
4–7	100 mg	70 mg (or average of TDD from prior days) ×1 10 mg q3h PRN × 3 doses

Patient selection:
Inclusion criteria:
- Routine fentanyl use
- Addiction medicine consult

Exclusion criteria
- End organ failure such as end-stage renal disease, decompensated cirrhosis, decompensated heart failure
- Ventricular arrhythmias, QTc > 500 ms
- Concurrent use of benzodiazepines or alcohol
- Medications that affect methadone metabolism
- Age >65

TDD, total daily dose.

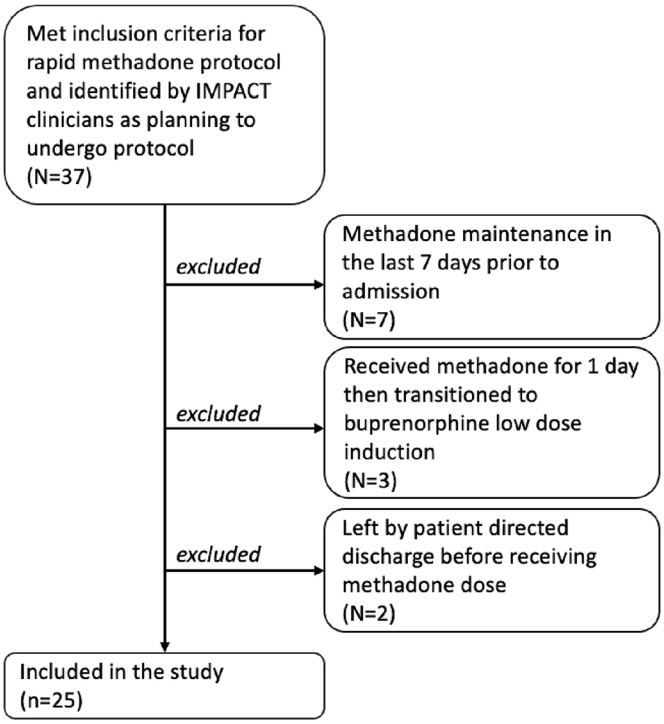

FIGURE 1. Patient flowchart.

buprenorphine low dose induction per patient preference, and 2 patients left by patient directed discharge before receiving any methadone doses. Of the 25 patients who received rapid methadone initiation, the average age was 37.5 years (SD, 11.2 years), and 9 (36%) were women. Most patients (96%) were admitted for infection, trauma, or obstetric reasons. All 25 reported daily fentanyl use leading up to admission, and 20 (80%) reported a history of remote methadone maintenance therapy (Table 2). All patients reported fentanyl use by inhalation, and 5 (25%) reported intravenous fentanyl use.

Eleven patients had been started on methadone in the hospital before IMPACT was consulted. Nine of those patients had received methadone for 1 day before IMPACT was consulted, and 2 patients had received methadone for 2 days before IMPACT was consulted. In these situations, the average total daily dose of methadone was 39 mg. The average total daily dose of methadone on days 1–7 after IMPACT consult and rapid protocol initiation was 53.0 mg, 69.2 mg, 75.4 mg, 79.5 mg, 87.1 mg, 92.2 mg, and 96.6 mg, respectively (Table 3). For patients who received 10 or more days of methadone in the hospital (n = 11), average discharge dose of methadone was 113.2 mg (SD, 29.6 mg).

Most patients (96%) also received short-acting full opioid agonists, though amounts and duration varied widely (mean 120.6 MME per day, range 0–1475 MME per day) (Table 3). Nineteen (76%) patients had an acute pain indication for short-acting full opioid agonists, in addition to acute opioid withdrawal.

No patient had any adverse events requiring holding a dose of scheduled methadone, naloxone administration, or transfer to a higher level of care. Four (12%) patients left the hospital by patient directed discharge. From chart review, all patients had future contact with the health system between 1 week and 8 months after discharge, and no encounters were related to adverse events from methadone (eg, somnolence, sedation, respiratory depression, opioid overdose, or constipation).

DISCUSSION

A rapid methadone initiation protocol for hospitalized patients is feasible and acceptable for selected patients receiving methadone for OUD. Patients up-titrated methadone doses quicker than traditional dosing schedules, and we observed no adverse events attributable to methadone. Consistent with recommendations, short acting full opioid agonists, in addition to methadone, were used to treat withdrawal and pain in nearly all patients in our cohort, but the amounts and duration varied.

As fentanyl dominates the unregulated opioid supply, there have been calls to update current methadone dosing schedules,[3,15] and there is a pressing need to share experiences, even with small patient cohort sizes. Our study adds to the small but growing body of literature to inform discussions surrounding the efficacy and safety of rapid methadone initiation protocols for the hospital setting.[8,9,11] Consistent with prior studies, our rates of adverse events attributable to methadone were low (0%–3.5%).[8,9,11] Our study is also the first to characterize the MMEs of other full opioid agonists received by patients undergoing rapid methadone initiation. The daily range of MMEs in our study was very wide, speaking to the unprecedented and

TABLE 2. Patient Demographics

Unique Individuals	25
Age (mean ± SD)	37.5 ± 11.2
Female, n (%)	9 (36%)
Race, n (%)	
White	23 (92%)
Black	1 (3.8%)
No information	1 (3.8%)
Ethnicity, n (%)	
Non-Hispanic	23 (92%)
Hispanic	1 (3.8%)
No information	1 (3.8%)
Admission diagnosis type, n (%)	
Obstetrics	3 (12%)
Infection	17 (68%)
Trauma	4 (16%)
Vascular	1 (4%)
Insurance type, n (%)	
Medicaid	22 (88%)
Medicare	2 (7.7%)
Houseless	16 (64%)
Substance use diagnosis, n (%)	
Opioid use disorder with active fentanyl use	25 (100.0%)
Methamphetamine use disorder	14 (56%)
Alcohol use disorder	0 (0%)
Benzodiazepine use disorder*	2 (8%)
Route of fentanyl use	
Inhalation	25 (100%)
Intravenous	5 (25%)
MOUD history, n (%)	
Prior methadone	20 (80%)
Prior buprenorphine	12 (48%)
LOS, d (mean ± SD)	13.7 ± 10.5

*No patients reported active benzodiazepine use at time of clinical encounter.
MOUD, medications for opioid use disorder.

TABLE 3. Average TDD of Methadone and MME of Other Full Opioid Agonists Received

Day of IMPACT Consult	Day −1	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Average TDD methadone (mg) ± standard deviation	39.1 ± 14.5	53.0 ± 12.9	69.2 ± 11.2	75.4 ± 14.5	79.5 ± 15.6	87.1 ± 13.6	87.1 ± 13.6	96.6 ± 16.6
Number of patients who received methadone	11	25	25	23	21	17	16	16
Number (%) of patients who received other full opioid agonists	11 (100%)	21 (84%)	20 (80%)	18 (78%)	17 (80%)	13 (76%)	10 (63%)	11 (68%)
Median MME of other full opioid agonists (interquartile range)	43 (24–105)	92 (45–160)	128 (81–169)	158 (73–233)	120 (48–240)	120 (75–210)	169 (109–198)	120 (51–161)

IMPACT, Improving Addiction Care Team, the inpatient addiction medicine consult service; TDD, total daily dose; and MME, morphine milligram equivalents.

unpredictable opioid tolerance in people who use fentanyl. In our practice area, illicitly manufactured fentanyl in the form of counterfeit pills and powder has surpassed heroin as the most prevalent unregulated opioid.[16] The purity of illicitly manufactured fentanyl varies widely with a report from 2022 reporting powder samples contained an average purity of 13.6% and majority of tablets containing at least 2 mg of fentanyl.[17]

Our study has several important implications. First, as clinicians and researchers develop and evaluate new methadone dosing schedules, it will be important to emphasize appropriate patient selection to mitigate risk. Our study suggests that, in a carefully selected cohort of patients with daily fentanyl use without medical comorbidities including cirrhosis, end-stage renal disease, advanced pulmonary disease, advanced heart failure, or ventricular arrhythmias, higher methadone doses are feasible. Future work should examine methadone dosing in patients with the aforementioned comorbidities or age over 65 years and should follow patients over time given methadone's long half-life and the risks of potential for harms of rapid dose escalation that may occur after discharge. Second, our study describes rapid methadone initiation in the setting of concomitant short-acting opioid use in the hospital. By more effectively treating patients' withdrawal, cravings, and pain, we may improve the likelihood of patients staying in the hospital to complete their recommended treatment course.[18] Finally, it is important to contextualize our cohort in the broader scope of hospitalized patients with OUD and reiterate the caution we used in selecting patients. Although it is well known that retention in methadone maintenance treatment for OUD in the long term is associated with substantial reductions in the risk of all cause and overdose mortality,[19] studies have found that the first 4 weeks of methadone initiation are periods of elevated risk for nonfatal overdose.[20-22] Predictors of opioid-related death during methadone therapy include concurrent benzodiazepine or alcohol use, co-prescription of psychotropic medications, as well as pulmonary, hepatic, and cardiac disease.[23,24] Future work should specifically explore methadone dosing in patients who have higher risk profiles and explore necessary training for methadone initiation by nonaddiction specialists (eg, hospitalists) in general inpatient settings.

Limitations include that this is a small, unblinded, retrospective study. The study's generalizability may be limited due to its setting at a large academic medical center with a robust interprofessional addiction consult service. This retrospective study was not designed to evaluate for safety and effectiveness. We did not compare a rapid methadone initiation strategy with a traditional initiation strategy, and our study did not gather information on those with self-directed discharge and whether they were due to the methadone titration.

Future direction includes larger sample size to assess safety and efficacy, evaluating the patient experience and engagement rates at OTPs posthospital discharge. Future work should also consider the role for rapid methadone protocols based on characteristics of local drug supply and patient preferences.

CONCLUSIONS

A rapid methadone initiation protocol for hospitalized patients with OUD and fentanyl use is feasible and allows patients to reach a therapeutic dose of methadone quicker than with traditional methods. Appropriate patient selection may be crucial to avoid adverse events with a more rapid initiation schedule.

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