Safety and Efficacy of Rapid Methadone Titration Protocols in Opioid Use Disorder: A Systematic Review

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BACKGROUND

- Methadone is one of the first-line treatments for opioid use disorder (OUD), improves all-cause mortality and retention in treatment[1-3]
- Due to the risk of methadone toxicity from dose accumulation, current protocols require titration over weeks to months before achieving a therapeutic dose [4-7]
- During this initiation period, patients may experience persistent opioid withdrawal and craving, increasing their risk of continued drug use and fatal overdose [1,8]
- Despite the established efficacy of methadone, retention in treatment remains low, particularly during the initiation phase [1,7,9]
- Retention has also become increasingly challenging in the setting of an evolving toxic drug supply dominated by fentanyl and other synthetic opioids [10,11]
- MOUD discontinuation within the first 4 weeks is associated with a 6 times higher rate of mortality, underscoring the need to identify strategies to maintain clients on therapy during the induction period [1]
- Most methadone dosing studies were performed prior to the introduction of fentanyl into the unregulated drug supply [11,12]
- Higher maintenance doses of methadone as well as flexible dosing strategies are associated with increased retention [13]
- Strategies are needed to more rapidly achieve therapeutic dose in patients using synthetic opioids with high opioid tolerance
- Early data suggests rapid titration of methadone can be performed safely in select populations and/or settings, however data are scarce [14]

STUDY OBJECTIVES

- To evaluate the safety and efficacy of rapid methadone titration in patients with opioid use disorder
- To describe the populations and clinical contexts in which rapid methadone titration protocols have been applied, as well as their associated clinical outcomes

METHODS

MEDLINE, EMBASE, Cochrane CENTRAL, via Ovid and psycINFO via EBSCOhost were searched from inception to June 2025. Article screening (title/abstract and full text) were performed in duplicate by two reviewers. Data extraction was completed with a standardized form. PROSPERO registration CRD42025636597

Study Protocol → Search Strategy → Title and Abstract Screening → Full Text Screening → Data Extraction → Data Analysis

Study Inclusion/Exclusion Criteria:
- Adults with opioid use disorder (defined by DSM or ICD criteria)
- Rapid methadone titration (defined as faster than major North American Guidelines [BCCSU, Ontario MetaPHI, ASAM] starting dose > 40 mg on day 1 or titration by more than 5-15 mg every 3-5 days) [6,7,11]
- Reported on outcomes of interest
- Any study design (RCTs to case reports)
- *Excluded*: Not in English language

Outcomes:
Safety
- Mortality
- Non-fatal overdose
- Methadone toxicity: oversedation, need for holding or reducing a dose

Efficacy
- Retention on therapy
- Illicit drug use

Meta-analysis could not be performed due to the heterogeneity of interventions/outcomes

RESULTS

Figure 1. PRISMA Flow Diagram

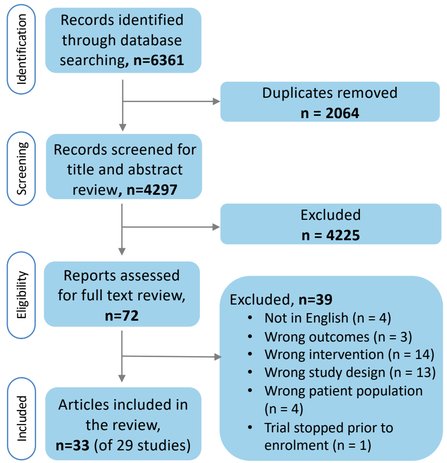


Table 1. Characteristics of Included Studies

Author, year	n	Study Setting	Reported Outcomes: Mortality	Overdose	Methadone Toxicity	Illicit Drug Use	Retention
Randomized Controlled Trials							
Fischer 1999	60	Outpatient				x	x
Greenwald 2006	34	Outpatient	x	x			
Holbrook 2013	175	Inpatient	x				x
Jones 2005	18	Inpatient	x				
Prospective Observational Studies							
Pinto 2010	361	Outpatient	x		x	x	x
Retrospective Observational Studies							
Casey 2023	112	Inpatient	x	x	x		
Iyer 2024	174	Inpatient		x			
Klaire 2023	98	Inpatient	x	x	x		
Liu 2024	25	Inpatient	x	x	x		
Manmish 2025	95	Inpatient	x	x	x		
Racha 2023	25	Inpatient	x	x	x		
Sherrick 2025	14,489	Outpatient					x
Case Studies/Case Reports							
Azar 2025	1	Outpatient	x	x	x		
Bakker 2006	121	Outpatient	x	x	x		x
Delaye 2022	1	Inpatient	x	x	x		
Drummer 1992	10	Outpatient	x				
Freymuth 1971	6	Inpatient	x				
Hemmons 2019	1	Inpatient	x	x	x		
Ickowicz 2022	1	Inpatient	x	x	x		x
Lamberson 2025	1	ED	x	x	x		
Landefeld 2022	2	Inpatient	x	x	x		
Martin 2025	17	Inpatient	x	x	x		
Padda 2023	3	Inpatient	x	x	x		
Pilgrim 2013	206	Not specified	x				
Rodger 2023	12	Inpatient	x	x			x
Steiger 2024	93	Outpatient	x	x	x		
Todaro 2023	11	Inpatient	x	x	x		
Turner 2021	1	Inpatient	x	x	x		
Wolff 1991	1	Inpatient	x	x	x		

Figure 2. Average methadone doses achieved on day 1, 3, and/or 7 days.

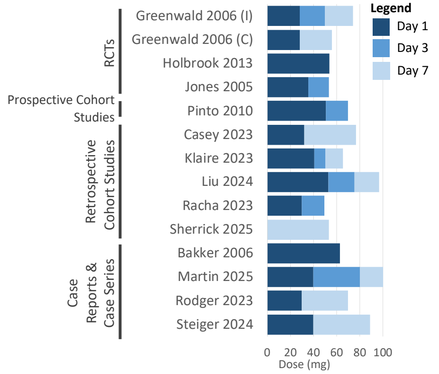


Figure 3. Most Common Titration Schedules

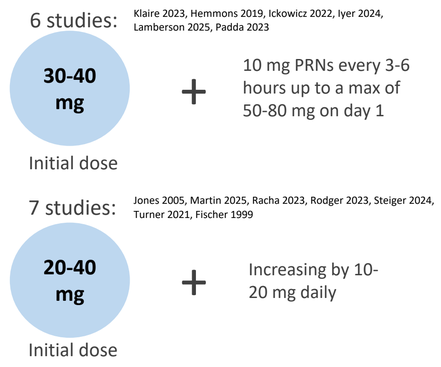
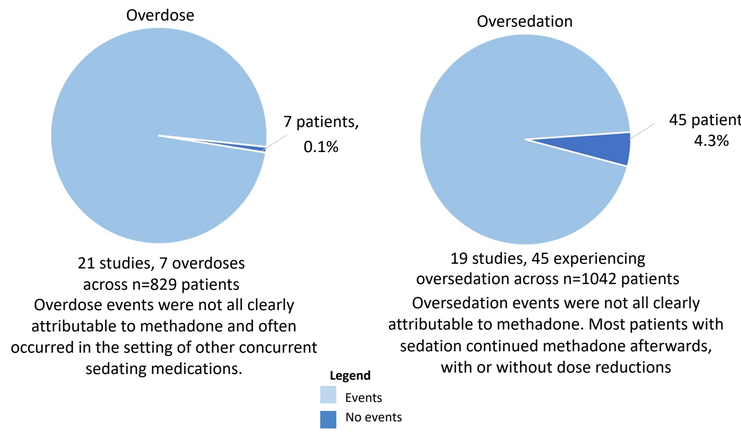


Figure 4. Number of overdose and oversedation adverse events



21 studies, 7 overdoses across n=829 patients
Overdose events were not all clearly attributable to methadone and often occurred in the setting of other concurrent sedating medications.

19 studies, 45 experiencing oversedation across n=1042 patients
Oversedation events were not all clearly attributable to methadone. Most patients with sedation continued methadone afterwards, with or without dose reductions

Retention Outcomes

Sherrick *et al.*, 2025 noted a significant dose-response relationship, with higher day-7 doses predicting increased 30-day retention (p<0.0001)

Mortality Outcomes

Among 26 studies (n=1431) reporting on mortality, there were:
- **2 deaths** from a prospective cohort study, involving concurrent heroin use or other sedation medications
- **61 deaths** were from 2 case series that preselected specifically autopsy studies from coroner's cases. Not all deaths were attributable to methadone and studies were performed in patients with unclear tolerance, with heroin or prescription opioid use
- No deaths reported in the remaining 23 studies
- No deaths in studies **in the fentanyl era** (after 2013, n=705 patients from 18 studies)
- No deaths **in inpatient studies** (n=604 patients from 18 studies)

DISCUSSION

- Methadone induction is a high-risk period, with prior research demonstrating all-cause mortality is higher during the first 4 weeks of methadone treatment.
- Adverse events were seen in our study, but overall low rates (overdose <1% and oversedation events were mild). All reported deaths in early autopsy studies occurred in outpatient settings
- However, this risk needs to be weighed against with the high mortality rates of ongoing use or discontinuation of therapy.
- Majority of studies were identified to be a high risk of bias, or case reports/case series

CONCLUSIONS

- Our review identified a wide range of rapid methadone titration protocols in inpatient and outpatient settings.
- There were low rates of adverse events in an inpatient setting and fentanyl era
- Initial methadone induction phase is a high-risk period, but rapid methadone titration may be applied safely in specific populations with an appropriately monitored context.
- Future higher quality studies and prospective research are needed to assess longer term follow up

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