Journal of Addictive Diseases
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/wjad20

Methadone Induction Doses

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Version of record first published: 23 Sep 2008.

To cite this article: Anita Srivastava MD & Meldon Kahan MD (2006): Methadone Induction Doses, Journal of Addictive Diseases, 25:3, 5-13

To link to this article: http://dx.doi.org/10.1300/J069v25n03_02

Methadone Induction Doses: Are Our Current Practices Safe?

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ABSTRACT. Purpose: To review the literature on methadone deaths and propose evidence-based dosing guidelines.

Methods: A literature search was conducted on overdose deaths during the induction phase. Data on methadone deaths from the Ontario coroner's office, as well as prescribing guidelines from different countries and jurisdictions, were reviewed. The information was collectively considered and, using the best available evidence, translated into safe dosing guidelines for methadone induction.

Results: A literature review found high death rates during the methadone induction period. Data from the Ontario coroner's office revealed that of deaths that were felt to be attributable to methadone overdose, the majority occurred in those who had consumed diverted methadone: of those deaths within a registered program, the majority occurred during the initial dosing phase. Despite high death rates during induction onto methadone treatment, many jurisdictions do not have prescribing guidelines that take this evidence into account.

Conclusions: Safer prescribing guidelines are needed to reduce deaths during induction onto methadone treatment. Recommendations are made for safe methadone induction doses.

KEYWORDS. Methadone, overdose, guidelines, literature search, induction dose

INTRODUCTION

This article reviews the literature on methadone deaths during the induction phase, reviews current dosing guidelines, and makes recommendations to improve patient safety. These recommendations will be incorporated into an upcoming edition of methadone maintenance guidelines for the physician regulatory body in Ontario.[1]

Background

Methadone treatment is remarkably effective at reducing morbidity and mortality from heroin dependence. While the annual mortality rate of heroin users is 2-3%, with overdose being the primary cause of death,[2,3] the rate among methadone patients is one quarter this rate, due primarily to fewer deaths from overdose and suicide.[4] The overall mortality rate of

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The authors wish to acknowledge Jonathon Kahan, Student, University of Western Ontario.

Journal of Addictive Diseases, Vol. 25(3) 2006
Available online at http://jad.haworthpress.com

doi:10.1300/J069v25n03_02

heroin users declines sharply with entry into treatment, and climbs again with discharge.[5-7]

Despite its success as a treatment for heroin dependence, however, mortality from methadone overdose remains disturbingly high.[8-11] While the majority of deaths are due to street methadone (which has usually been diverted from patients with take home doses),[8,12] a significant number of deaths occur among registered methadone patients. Of these deaths, the majority occur during the initial phases of methadone treatment.[7,9,11,13]

The high death rate during the initial titration phase of methadone treatment likely is a result of its pharmacokinetics and metabolism. Methadone is tightly bound to tissue proteins and has a long half-life, averaging 22-24 hours.[14] Furthermore, the clearance of methadone (as measured by elimination half life) is two to three times longer during initial titration, because it takes several weeks for the induction of hepatic enzymes that convert methadone to inactive metabolites.[15] Also, individuals vary greatly in their genetic capacity to metabolize methadone: the elimination half-life has been reported to range from 5 to 130 hours.[16]

For these reasons, methadone can accumulate rapidly and unpredictably in the serum. Although death usually occurs within a few hours after ingestion of methadone,[17] symptoms of overdose can have an insidious onset with a variable time course. A dose that does not control withdrawal on the first day may be fatal by the third or fourth day, making it difficult for clinicians and their patients to detect early signs of toxicity. Case reports suggest that patients can appear relatively alert when engaged in conversation or activity, succumbing to the overdose during a nap or at night.[18] Sedation may not be perceived as serious or even as undesirable by the patient or their family, since this is what they experienced with their previous opioid use. Patients may be far more frightened of withdrawal than of overdose, pressuring their physician to increase the dose quickly so they won't experience withdrawal symptoms.

Methadone deaths can be minimized through careful prescribing, close monitoring and patient education. The first step is the development of detailed and comprehensive clinical guidelines. There is evidence that national guidelines can affect major change in prescribing patterns: a British study demonstrated significant improvement in prescribing patterns following the widespread dissemination of national methadone prescribing guidelines.[19] Evidence-based guidelines could help to ensure the safety of patients and to thus preserve the credibility and viability of methadone treatment programs.

METHODS

A MedLine search was performed to identify case series and epidemiological studies on methadone-related deaths. The search terms used were "methadone," "deaths," "toxicity," "overdose," "mortality," "starting doses," "induction," "dose," and "fatality," studies were selected for review if they were primarily concerned with methadone deaths during the induction phase, methadone dosing issues, and methadone-related deaths. Information was extracted on death rates and changes over time, initial methadone doses, number of days to death and contributing factors.

Secondly, unpublished data on deaths attributed to methadone toxicity between 1996 and 2000 inclusive in Ontario were reviewed, with the cooperation of the Ontario Coroner's office. Information was extracted on death rates and changes over time, initial methadone doses, time to death and contributing factors.

Methadone dosing guidelines were reviewed, where available, for provincial, state and national jurisdictions in the US, Canada, Britain and Australia. The search of guidelines was conducted through internet searches of NIDA and other sites, review of addiction textbooks and telephone interviews with the registrars' offices at Canadian provincial medical colleges (Table 1).

RESULTS

Literature Review

Methadone Deaths During the Induction Phase

There is little published on death rates during the initial phases of methadone treatment and

TABLE 1. Responses from Canadian Provincial Physician Licensing Bodies§

Province	Methadone Starting Dose Recommendations	Dose Increment Policy	Policy on Take Home Doses	Training Requirements for Physicians
British Colombia	Up to 40 mg	* NA	-no carry (except weekends) for patients on > 100 mg/day -4 days of take home doses or 400 mg whichever is least	NA
Alberta	20-40 mg	NA	-none in the first three months -can carry for up to 6 days, but up to 3 weeks if proof of employment	NA
Manitoba	NA	NA	NA	NA
Ontario	10-30 mg	Increase q3-4 days by 5-15 mg	-none 1st 2 months -1 additional take home dose/ month up to a max of 6	1 day training course followed by four practicum sessions
Quebec	20-40 mg	5-20 mg weekly dose increases with reassessment at 120 mg/ day	-none 1st 2 months -1 additional take home dose/ month up to a max of 6	One day training in opioid dependence
Nova Scotia	10-30 mg	NA	NA	NA
Newfoundland	Stated 10-30 mg	NA	NA	NA

§ Responses are quoted as they were received from provincial colleges. Provinces and Territories that are not listed did not respond.
* NA = "Not Available"–means that either the College was unaware of an existing policy or did not have an official policy in place.

much of the data is retrospective. One retrospective study by Caplehorn[20] found a mortality rate of 2.2 per thousand admissions to methadone maintenance in the first two weeks of treatment in New South Wales in 1994. The author concluded that prescribed methadone was either responsible for or contributed to the deaths of at least ten of the thirteen patients. In another study, Caplehorn and Drummer[9] found that the relative risk of fatal accidental drug toxicity for patients in the first two weeks of MMT induction was 6.7 times higher than that of heroin addicts not in treatment, and 98 times higher than that of patients on longer-term MMT. An Amsterdam study found a death rate of 6.0/1000 py (person-years) during the first two weeks after (re)entering treatment which was higher than the rate of 2.2/1000 py observed during maintenance treatment.[7]

Initial Dose

Again, there are very limited publications on the initial induction doses that may have led to overdose deaths. According to one paper, a single methadone dose of 50-100 mg can be lethal to non-tolerant adults.[21] In another study of ten new methadone patients' deaths, the mean methadone dose was 53 mg with a mean time to death of three days and a mean final dose of 57 mg.[22] An analysis of 238 deaths during methadone maintenance from 1990-1995 in New South Wales[11] found that of all deaths that were felt to be drug-related, 42% occurred during the first week of methadone treatment in patients whose physicians had followed the recommended guidelines of starting methadone doses of 20-40 mg, with a maximum increase of 5-10 mg in any one day or 30 mg in the first week. The mean starting doses were 40 mg (with a range of 20-40 mg) and the mean number of days in treatment until time of death was 3.3 days.

Changes Over Time

Higher death rates at the start or expansion of methadone programs have been described. In 1972, with the introduction of maintenance methadone therapy in the United States there were many methadone-related deaths: in an 18 month period there were 1504 cases of methadone overdose deaths in New York City.[23] Similarly, the expansion of methadone treatment in the West of Scotland was also accompanied by an increase in methadone-related deaths from 1991-1997.[10] However, from 1997 to 2001, following inquiry and an educational program, methadone-related deaths decreased by nearly 48% despite a three-fold increase in the number

of patients on methadone treatment during the same period.

Polysubstance Use

Polysubstance use is another major contributing factor to methadone-related deaths. The review of methadone-related deaths in New South Wales found evidence of polysubstance use in 92% of drug-related deaths that occurred during the first week of methadone maintenance treatment; in nearly half of these cases, there was a known history of polydrug use.[11] Another study found that benzodiazepines were a co-intoxicant in the majority of methadone-related deaths in an Alabama county,[24] and benzodiazepine use has been reported to cause a five-fold increase in risk of fatal overdose.[25] The Drug Abuse Warning Network confirmed that most methadone-related deaths for eight metropolitan areas in the United States involved other substances, including alcohol, other opioids, benzodiazepines and antidepressants.[26] Animal studies confirm that benzodiazepines increase the lethality of methadone.[27]

Another contributing factor to methadone-related deaths may be low opioid tolerance. This is becoming an increasingly important issue as a higher proportion of patients are being initiated on methadone for prescription opioid dependence, and it seems probable that these patients will have a wider range of baseline tolerance than heroin users. A patient's degree of opioid tolerance cannot be reliably established by history or urine drug screening. Even patients who are highly tolerant to large doses of opioids will have incomplete tolerance when started on methadone, due to the heterogeneity of opioid receptors. Moreover, respiratory tolerance develops much more slowly and less completely than psychoactive tolerance.[28] Other risk factors for methadone overdose include respiratory illness, age, and medications that inhibit methadone metabolism (such as quinolone or macrolide antibiotics, fluconazole, and fluvoxamine).[29-32] Severe hepatic dysfunction may also prolong methadone metabolism.

Review of Ontario Coroners' Data

In Ontario, 194 methadone-related deaths occurred between the years 1996-2000. Of these, 43 (23%) were enrolled in a methadone program. The death rate (per 1000) for those enrolled in a program was 4.2 in the year 1996, declining steadily to a low of 1.7 by the year 2000. The higher death rate in the earlier period could potentially be attributed to a rapid rise in the number of newly trained physicians prescribing methadone in the mid-90s although this has not been formally evaluated.

Of those enrolled in a methadone program, the lowest dose at the time of death was 30 mg, with the majority of doses between 60 and 90 mg. The shortest duration on methadone was three days and the average duration was 3-8 days suggesting that the majority who died while on a methadone program did so during the induction phase. Sixty percent had benzodiazepines and 30% had alcohol on their toxicology screen.[33]

Guidelines Review

Our review of guidelines from five different provinces in Canada (Newfoundland, Quebec, Ontario, British Columbia, Alberta) revealed that recommendations for the initial methadone dose varied from 15-40 mg, with varying recommendations for frequency and amount of increments (see Table 1). Ontario, British Columbia and Quebec used their own provincial guidelines, whereas the registrars of the other provincial colleges indicated that they either followed Ontario guidelines or the Health Canada Best Practices guidelines (Newfoundland, Nova Scotia). Manitoba and Alberta had no published guidelines, and we did not receive a response from Prince Edward Island.

Ontario and Newfoundland recommend a starting dose of 15-30 mg, Alberta and Quebec recommend 20-40 mg, and British Columbia recommends a maximum of 40 mg. Ontario guidelines recommend an increase of 5-15 mg every three to four days during the first two weeks of methadone treatment and 5-10 mg every 7-14 days thereafter. Quebec guidelines recommend weekly increases of 5-20 mg. None of the provinces provided guidelines on how to choose between the low and high ends of the suggested dosing range, although they did caution against the use of benzodiazepines and other sedating drugs. Recommendations regarding take-home doses also varied, although all provinces recommended no take-home doses in the first two months of treatment.

By comparison, Australia's guidelines are conservative and state that "a dose less than or equal to 20 mg for a 70 kg person can be presumed safe," while recommending caution in "starting doses of 30 mg or more" and "extreme care" with starting doses of 40 mg or more. The guidelines also recommend dose increments of 5-10 mg every 3 days with a maximum weekly dose increase of 20 mg and a maximum dose of 40 mg at the end of the first week. Guidelines from the United Kingdom recommend starting doses of 10-40 mg, or 10-20 mg for opiate-naïve patients,[34] with dose increases of no more than 5-10 mg on any given day with a maximum weekly 30 mg dose increase.

The American Society of Addiction Medicine recommends no more than 40 mg on the first day.[35] The "State Methadone Treatment Guidelines" treatment improvement protocol series (TIPS) published by CSAT (Centre for Substance Abuse Treatment, Substance Abuse Mental Health Services Administration, USA) is out of print, but a prior edition from 1998-1999 also recommended a starting dose of up to 40 mg on the first day of treatment. While we were not able to find guidelines for each state, we did find detailed guidelines published by the California Society for Addiction Medicine, which recommended up to 30 mg as an initial dose, with an additional 10 mg that day for patients in severe withdrawal. Daily assessment was recommended, with an increase of 5-10 mg per day if withdrawal is not completely suppressed for at least 2-4 hours. Those guidelines recommend that if withdrawal is completely suppressed for 2-4 hours but then returns, the increase should be delayed for one to two days.

A review of guidelines from 17 countries[36] found initial recommended doses for five countries, ranging from 30 mg per day (Belgium) to 55-60 mg per day (Ireland and Spain). The European methadone network (Euromethwork)[37] recommends a starting dose of 10-30 mg for most patients, with 25-40 mg for patients with higher tolerance and with dose increases of 10-20 mg per dose.

DISCUSSION

Studies on methadone-related deaths should be interpreted with caution as they are based on retrospective chart audits and toxicology samples and may be subject to hindsight bias. The presence of methadone in a post-mortem blood sample does not prove causality,[38] although it is reasonable to assume that methadone contributed to an overdose death especially for those occurring during initial methadone titration. Moreover, while it is possible that deaths may be erroneously attributed primarily to methadone rather than to a mixed overdose, the reverse is also possible. In Caplehorn's[20] review of deaths in a methadone program in New South Wales, there were differences between the official causes of death and those that the author and an independent forensic pathologist determined were the cause of death, with the latter attributing a greater number of deaths to methadone than to mixed drug toxicity. From a clinical perspective, while many of the deaths are associated with polysubstance use, the fact that many patients abuse and use other substances must be taken into consideration and accounted for when developing safe induction dose guidelines. Dose-response relationships and safe dosing levels cannot be determined from the studies to date. The relative risk of death at different starting or incremental doses is not known, either for methadone alone or for methadone combined with benzodiazepines or other drugs.

Nonetheless, the literature suggests that methadone is a potentially dangerous drug with a narrow margin of safety during the initial titration. The ratio between the maximum recommended initial dose in Ontario (30 mg) and a potentially fatal single dose (50-70 mg) is approximately 2:1. The ratios for phenytoin, acetaminophen, and desipramine are 6:1, and 10:1 and 20:1, respectively,[39] offering considerably wider safety margins for overdose.

While caution is necessary with methadone induction doses, this must be balanced against treatment needs. Higher methadone doses have been shown to reduce opioid use and increase treatment retention.[40] A lower initial dose will extend the time required to reach the optimal dose by one to two weeks. The early weeks of methadone treatment are often associated with the highest drop-out rate, and it is possible that a lower dose will push the drop-out rate even further. A lower initial dose might also prolong the patient's substance use, increasing the risk of

overdose. Thus, changes in methadone dosing protocols should be accompanied by an evaluation of not only methadone deaths but also of treatment retention and substance use during initial titration.

While delays in reaching an optimal dose are a concern, longitudinal mortality studies suggest that cautious prescribing results in decreased mortality. Iatrogenic methadone toxicity often occurs in the context of polysubstance users receiving methadone from inexperienced physicians.[41] Studies in both Ontario and West of Scotland demonstrated a marked drop in methadone-related deaths from the mid to late 90s; in both cases, the changes may reflect better physician education and more careful prescribing.

Methadone overdose deaths are tragic in themselves, but they also have serious consequences for the viability and expansion of methadone programs. In Ontario, community physicians largely provide methadone treatment. Recently, the coroner's office organized a large public inquest into several methadone-related deaths; physicians have been named in newspaper reports; and several physicians have had their license to prescribe methadone suspended by the provincial medical college (CPSO). This could do enormous harm to methadone programs by discouraging physician participation, disrupting patient access, and damaging community and government support. Thus, guidelines must balance the concerns of overdose deaths, public safety, treatment retention, and program viability.

Our review of the literature and the Ontario coroner's data suggest that the induction period is particularly fraught with danger, that deaths have occurred in patients where the initial doses were within the recommended guidelines of up to 40 mg for starting doses, and that deaths can occur even several days after treatment initiation and are often associated with polysubstance use. Our review of the existing guidelines found that several jurisdictions allow for initial methadone doses of up to or even greater than 40 mg despite reported deaths at these doses.

Thus, taking into consideration the limited evidence on methadone-related deaths, we have developed guidelines that incorporate the best available evidence to date, balance the need for safety with the need to retain patients, and allow for the reality that many patients use other substances that could contribute to fatal overdoses in combination with methadone. These preliminary guidelines were disseminated to all physicians with a methadone license in the province of Ontario and suggestions for revision were solicited. Clinical consensus indicated that the following initial dosing guidelines were felt to be reasonable and in keeping with the collective clinical experience of the several hundred licensed physicians in Ontario.

The following proposed guidelines take into consideration that higher initial doses (as several existing guidelines allow), lack of opioid tolerance, poor general patient health, and polysubstance use, have all been associated with overdose deaths.

Suggested Guidelines

An initial methadone dose of no more than 30 mg is recommended, or 10-20 mg for high risk (see below) patients (Table 2). Dose increases should be no more than 5-15 mg every three to five days, with a total weekly increase of no more than 20 mg for high-risk patients. The higher increases in the 10-15 mg range should be made only every three to five days and should be reserved for patients who remain in withdrawal for much or most of the day.

Definition of Higher Risk

High-risk patients include those over 65, those with underlying respiratory disease or severe hepatic dysfunction, and patients on cytochrome CYP3A4 inhibitors (such as quinolone or macrolide antibiotics, fluconazole, and some SSRIs). Also at high risk are patients on any sedating medication, including benzodiazepines, antidepressants, sedating antihistamines, and antipsychotics. Patients who have a lower baseline opioid tolerance are also at high risk (see below).

Missed Doses

Patients who miss a dose during the initial titration may lose some tolerance to methadone, and their current dose should not be increased

TABLE 2. Recommended Procedures for Methadone Induction

Initial dose–low risk:	Maximum 30 mg
Initial dose–high risk	10-20 mg
Dose increase–low risk:	• 5-15 mg q 3-5 days • 15 mg only if withdrawal most of the day
Dose increase–high risk	• 5-15 mg q 3-5 days • 15 mg increase only if withdrawal most of the day • Maximum 20 mg per week
Definition of high risk	• Over 65 • Respiratory disease or hepatic dysfunction • On CYP 3A4 inhibitors • On sedating medications such as benzodiazepines, antidepressants, antihistamines, antipsychotics • Lower baseline opioid tolerance
Estimation of baseline opioid tolerance	Lower tolerance possible if: Non-daily use of opioids, or oral opioid use of codeine, or < 200 mg morphine equivalent/day
Take home doses	No take-home doses in first two weeks
Monitoring	Assessed by physician at least twice per week, several hours after dosing
Missed doses	• Don't increase current dose for one or two days. • Restart at initial dose if 2 consecutive doses missed
Patient education	• Take methadone in morning • Avoid alcohol, sedating drugs, and triggers • Have family member call clinic or ED at first sign of toxicity • Don't take substances to relieve withdrawal symptoms, but if you do, take 10 hrs after last methadone dose • Check with a physician before discontinuation or initiation of any medications

for one or two days. Titration should be restarted at the initial dose if two consecutive doses are missed.

Lower Opioid Tolerance

Lower tolerance should be considered in patients who do not use opioids daily or who are on oral opioids at 'moderately high' doses (e.g., codeine, or less than 200 mg of oral morphine or its equivalent). Establishing opioid use can be difficult, as patients might exaggerate their use in order to get on methadone, or they may simply not remember how their use varies from day to day. Physicians can attempt to increase the reliability of their estimate by obtaining corroborating information from other physicians or family members, and by obtaining confirmation of regular opioid use with urine drug testing by chromatography. If the physician is still in doubt regarding the patient's level of tolerance, it is safer to use the lower initial dose.

Take-Home Doses

Under no circumstances should the patient be given take-home bottles of methadone during the initial titration, even if family members agree to dispense it. In fact, this can lead to several other problems including the dangerous possibility that family members may dispense the medication incorrectly, divert it, or use it for personal consumption.

Monitoring

The patient should be assessed by the physician at least twice per week, preferably several hours after the patient's dose. If possible, the patient's family member should be asked to report on the patient's response to methadone. Patients and their families should be educated on symptoms of overdose, and told to contact the clinic or take the patient to the ED at the first sign of toxicity. Higher-risk patients may require closer monitoring (see below).

Patient Education

The patient should be advised to take the methadone in the morning, and to avoid alcohol or sedating drugs. The physician should explain the risks of taking drugs to relieve withdrawal symptoms, and point out that ongoing opioid use will delay the time to reach the optimal dose by building up tolerance. Those who insist on using drugs to relieve withdrawal symptoms should be advised to take the drug only when they are in severe withdrawal, at least ten hours after taking methadone; use only the smallest amount of opioid necessary to relieve withdrawal symptoms, preferably by the oral route; and avoid alcohol, benzodiazepines and street methadone. They should, if possible, stay with supportive friends or family, and avoid contact with drug users and other triggers.

Benzodiazepines and Other Sedatives

Patients should be advised not to drink alcohol, take sedating antihistamines or purchase benzodiazepines during the initial titration. Sedating drugs should not be prescribed unless the patient has already been on a moderate dose of

that medication daily for at least two months and the clinician is confident they are compliant. Such patients should receive a lower initial methadone dose even if they are taking an additional sedating medication for therapeutic reasons. Patients dependent on high daily doses of street benzodiazepines should be tapered off them, preferably in an inpatient setting, prior to initiating methadone.

Patients who binge on alcohol or benzodiazepines are perhaps the most difficult group to manage. It might be necessary to assess and observe the patient before and several hours after each dose, particularly on the third or fourth day after an increase. Inpatient titration should be considered if available.

Drug Interactions

Patients should be advised to check with their methadone physician prior to taking any new prescribed medication, including antibiotics or antidepressants.

CONCLUSION

Evidence suggests that physician training and education, including national guidelines with a dissemination strategy, can lower methadone overdose rates. Given the vulnerability and heterogeneity of patients seeking treatment for opioid dependency, it is important for physicians to exercise caution during the induction phase of methadone treatment. The consistent and wide-spread application of evidence-based guidelines is needed in order to minimize the risk of deaths during the induction phase of methadone maintenance treatment and to consequently maintain the credibility and viability of methadone programs. Future research is needed on the effects of these guidelines on methadone deaths, substance use, and treatment retention.

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