Methadone Deaths: Risk Factors in Pain and Addicted Populations

Vania Modesto-Lowe, MD, MPH[1,3], Donna Brooks, MS[1], and Nancy Petry, PhD[2]

[1]Addiction Services Division, Connecticut Valley Hospital, Middletown, CT, USA; [2]Calhoun Cardiology Center, University of Connecticut Health Center, Farmington, CT, USA; [3]Connecticut Valley Hospital, Middletown, CT, USA.

Methadone is highly effective in treating opioid dependence, and it is also used as an analgesic for second-line management of chronic pain. However, recent increases in methadone-related deaths have instigated controversy about the use of this medication. In this paper, we evaluate risk factors for methadone mortality in opioid dependent and pain populations and present guidelines for initiating methadone treatment in these two populations to minimize the risk of death. Early research with methadone-maintained patients revealed that methadone fatalities occur primarily due to respiratory arrest during methadone induction and in the context of polysubstance use. Recent reports of methadone deaths emphasize chronic pain populations, methadone-related QTc prolongation, and the possibility of inducing Torsade de pointes (TdP), a potentially fatal ventricular arrhythmia. Retrospective analyses of these deaths show that patients who develop TdP often present with multiple risk factors, including high methadone doses, use of other medications that cause QTc prolongation, and electrolyte abnormalities. To minimize fatalities, guidelines are presented for initiating methadone in opioid treatment and pain populations that consider the drug's pharmacology along with behavioral, medical and psychiatric risk factors.

KEY WORDS: methadone; mortality; opioid dependence; chronic pain.
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INTRODUCTION

Methadone has two therapeutic uses: treating opioid dependence and alleviating chronic pain. Methadone maintenance treatment (MMT) for opioid dependence reduces crime, HIV seroconversion, and heroin deaths.[1–3] In recent years, methadone treatment for chronic pain has increased because of its long half-life, affordability, and efficacy among patients intolerant or unresponsive to other opioid analgesics.[4,5]

Despite these benefits, there are substantial risks associated with methadone. Methadone ranks as the third most often apprehended analgesic by law enforcement agencies in the United States (US).[6] Between 1999 and 2004, deaths attributed to methadone increased by 390%,[6] an effect primarily related to increased utilization in pain clinics , as well as diversion.[6,7] Methadone-related deaths also occur in MMT, particularly amongst polysubstance users.[8] The two clinical uses of methadone appear associated with different risk factors. Methadone clinics serve relatively young patients with antisocial traits (e.g. lying, stealing) who are prone to misuse multiple substances, increasing risks for lethal interactions with methadone.[9] Conversely, chronic pain appears overrepresented in older individuals in poor health taking multiple medications and experiencing high levels of depression and anxiety.[5] MMT programs are subject to stringent federal and state regulations, but pain treatment settings are in the naissance stages of devising mechanisms to decrease diversion without compromising pain control.[9] MMT and pain clinics employ distinct dosing regimens[5,8] that may contribute differently to toxicity. Early studies, largely from MMT clinics, found mortality primarily from respiratory depression.[10,11] In recent years, Torsade de Pointes (TdP), a serious ventricular arrhythmia, has been implicated in methadone-related deaths. The putative mechanism for the development of TdP is QTc prolongation, an ECG measure that includes myocardium depolarization and repolarization.[12] Recognizing the lethality of TdP, the Food and Drug Administration[13] revised methadone labeling to include these risks, and media and scientific reports fuel debate over methadone's safety.[14]

In this paper, we examine pharmacological properties of methadone and explore how these pharmacological profiles relate to risk factors for methadone deaths in MMT and pain populations. We also describe methods for preventing methadone deaths.

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PHARMACOLOGY

Methadone is a full μ-opioid agonist that also inhibits N-methyl-D-aspartate receptors and monoamine reuptake. Following oral administration, methadone is detectable in the serum within 30 minutes, with a bioavailability between 70–90%. It takes 2–4 hours to achieve peak plasma levels.[15]

Methadone is metabolized primarily in the liver into inactive metabolites by the P450, CYP 3A4 enzymes that are also used by several QTc prolonging medications.[16,17] Methadone is a weak inhibitor of the 3A4 system and a minor weak substrate of 2C89, 2C19 and 2D6.[16] In methadone-naïve persons, it takes approximately two weeks for enzymatic systems to convert methadone into its inactive metabolites.[8] Individual differences in methadone metabolism by CYP 3A4 and 2D6 suggest the possibility of drug interactions that may influence sensitivity and risk, especially when methadone is taken in conjunction with drugs that prolong QTc or have respiratory depressive effects on their own.

Methadone's pharmacokinetics varies widely across individuals perhaps related to genetic polymorphisms of the P450 3A4 enzymatic system. Elimination half-lives range from 5 to 59 hours,[17] and in slow metabolizers, methadone levels can accumulate, perhaps relating to risk for respiratory depression and death.

RESPIRATORY DEPRESSION

Methadone accumulation can lead to sedation, respiratory depression, respiratory arrest and even death. Lethal respiratory depressive effects can occur in doses as low as 30 mg in non-tolerant persons.[16] These effects can also emerge in persons tolerant to opioids, albeit usually at higher doses. Individual differences in the ability to metabolize methadone, along with imperfect cross-tolerance, may heighten risks of respiratory depression during the methadone induction period.

Importantly, methadone's peak respiratory depressant effects usually appear later and persist longer than its peak analgesic effects, especially early in treatment. Thus, individuals prescribed methadone for pain generally experience relief for 4–8 hours, but methadone remains pharmacologically active for much longer periods, potentially leading to toxicity.[15] Although individuals receiving MMT typically take methadone only once daily,[8] its pharmacologic properties may interact with relatively rapid titration regimens to cause increases in serum levels in opioid dependent patients.

RISK FACTORS FOR RESPIRATORY DEPRESSION

Initial efforts to characterize risk factors derive largely from Australia, where deaths related to methadone tablets prescribed for chronic pain increased markedly between 1984 and 1994.[18] Diversion of methadone tablets accounted for about half the deaths, whereas deaths from prescribed methadone declined over this period. Caplehorn[10] examined Australian health department records in 1994, and identified all deaths occurring during the first two weeks of methadone dosing. Most of these deaths were ascribed to overestimation of tolerance and iatrogenic respiratory depression resulting from rapid titration. Subsequent studies similarly found high death rates during induction of MMT.[19,20]

Some studies of MMT patients explored circumstances in which fatalities occurred. A cross-sectional Australian study[19] revealed 238 patients died between 1990–1995, mostly related to drug use (44%) and medical illness (24%). A high percentage of the deaths (21%) occurred in the first week of MMT, and 88% of these were related to polysubstance abuse; only 10% of the patients who died in the first week of MMT tested positive for methadone alone. In another study, Zador and Sunjic[20] reviewed 87 methadone deaths that occurred during the induction period to MMT, and 62 (71%) involved illicit drug-consumption. These studies suggest that overdoses attributed to methadone often occur during the MMT induction period and relate to polydrug use.[19–21] These findings are consistent with reports in the US, in which the number of methadone-related deaths have risen markedly.[6,7,22] Opioid-dependent patients with polysubstance use appear most vulnerable to methadone fatalities,[23] and the role of polysubstance use in methadone overdoses underscores the potential role of pharmacological interactions in these fatalities.

THE METHADONE-QTc-TdP LINK

In addition to its respiratory depressive effects, methadone appears to be associated with QTc prolongation. The QTc interval is an ECG measure of myocardium depolarization (Q wave) and repolarization (T wave), with normal values ranging from 400–440 milliseconds (ms) in males and up to 450 ms in females. TdP refers to a distinct pattern of polymorphic ventricular tachycardia, manifested by syncope or sudden death,[24] and it is typically associated with prolongation of the QTc interval. Specifically, increases in QTc intervals greater than 40 ms from baseline or QTc intervals above 500 ms are indicative of risk for TdP.[25] However, prediction of TdP risk is imperfect as many patients with TdP have normal QTc intervals, and most individuals with prolonged QTc never experience TdP.[24] Moreover, some medications (e.g., Amiodarone) are associated with QTc prolongation and rarely with TdP.[25]

In 1973, a series of opioid-dependent patients were evaluated for risk factors of sudden cardiac death.[26] Findings revealed that QTc interval prolongation occurred among individuals with urine toxicologies positive for methadone, but other drugs of abuse were also present, raising questions about the specificity of the association. In 2002, a retrospective case series[27] described 17 MMT and pain patients who experienced QTc prolongation and TdP while receiving high methadone doses (mean=397 mg/day); 12 received either another QTc prolonging medication or had hypokalemia. Subsequent case reports and case series indicating a possible relationship between methadone, QTc prolongation, TdP and sudden deaths led the FDA to issue a public health advisory on methadone.[13]

In reviewing the methadone and QTc literature, Cruciani[12] identified 21 studies. Among these, seven were case reports, two were retrospective studies, seven were cross-sectional analyses, and five were prospective reports. Although QTc prolongation was noted in all the prospective studies with methadone doses ranging from 30 to 180 mg/day, there was no clear dose-dependent relationship between methadone and QTc prolongation. In two studies, plasma levels of methadone were correlated with degree of QTC prolongation, but another found no correlation; the other two did not report dose-dependency data. None of the studies noted TdP. Taken together, available data including that derived from prospective studies indicate the potential for small prolongation of the QTc interval (<40 ms), but not necessarily TdP, with methadone use.

Identification of patient-specific factors that contribute to an intrinsic vulnerability to TdP may prevent toxicity, especially during early stages of methadone treatment. In retrospective case reports of methadone-induced TdP, deaths occurred mostly, but not exclusively, in patients with other risk factors for TdP.[28] Specifically, TdP appears to occur with high daily methadone doses and medications that cause QTc prolongation or inhibit the CYP3A4 enzymatic system. Electrolyte imbalances, such as hypomagnesemia or hypokalemia, were also identified as risk factors.[28] A history of unexplained syncope or seizures should also be considered because these symptoms may reflect underlying cardiac problems which predispose to TdP.[29] Further, women appear to have a greater risk of developing methadone-induced TdP. In a literature

review, Markar et al.[30] found that about 70% of medication-induced TdP cases involved women, irrespective of other risk factors. Although the reasons for this disparity are unclear, women tend to have slightly longer QTc intervals than men.[31]

In high-risk circumstances, conducting a risk-benefit analysis for methadone use is important.[32] Current recommendations[31] to reduce the risk of TdP include: 1) notifying patients of arrhythmia risk when prescribing methadone, 2) inquiring about history of arrhythmia, syncope, and structural heart disease, 3) obtaining a pre-treatment ECG to measure the QTc interval and follow-up ECGs within 30 days and annually, and 4) evaluating additional ECGs if methadone dose exceeds 100 mg/day or if syncope or seizures occur. If the QTc interval is greater than 450 ms but less than 500 ms, review risks/benefits and monitor closely. If the QTc interval exceeds 500 ms, consider discontinuing methadone, reducing the dose and/or eliminating modifiable risk factors. These recommendations underscore the potential for interactions between methadone and drugs that prolong the QTc interval or slow elimination of methadone. Additional considerations for methadone induction strategies are outlined below.

METHADONE INDUCTION FOR OPIOID DEPENDENCE

Observations in MMT clinics suggest potential difficulties in initiating methadone to avoid TdP, respiratory depression, and death. Specifically, the relatively high death rates documented during methadone induction may relate in part to methadone's long half-life, extensive bioavailability, tendency to accumulate with continuous dosing, and low elimination.[10,11] Individual pharmacokinetic differences, combined with relatively rapid titration during the induction period, may also predispose to methadone intoxication and its respiratory depressive effects.[8]

Physicians may find it challenging to determine initial methadone dosing, especially when MMT patients may overstate their use or supplement methadone with street opioids. Initial assessment should include a substance abuse history along with identification of psychosocial (e.g. living environment), medical (e.g. sleep apnea, liver or pulmonary disease), and psychiatric (e.g. depression) factors that may influence risks as well as compliance status.[8,33,34] Although these factors, and their relative associations with risk, are not fully explored empirically, potential risk factors for QTc and respiratory depression during methadone treatment are outlined in the right-hand column of Table 1

Table 1. Potential Risk Factors in Methadone Deaths

Potential risk factors for respiratory depression	Potential risk factors for TdP
Advancing age[5,32]	Female gender[30]
Medically compromised[34]	Electrolyte imbalance[27,28]
Liver or pulmonary pathology[8]	Liver or cardiac pathology[8]
Sleep apnea[33]	Unexplained syncope or seizures[29]
Polysubstance use[19,21]	Other drug and medication use, especially those that impact QTc or inhibit CYP 3A428[28,30]
Opioid-naïve/low tolerance[32]	Prolonged QTc[24]
High doses of methadone[34]	High doses of methadone[27,28]
Rapid titration of methadone dosing[34]	

However, obtaining accurate information from patients about potential risk factors is not easy.[35] Even in the context of an adequate history, the patient's level of tolerance to illicit opioids may not translate into initial adequate methadone dosing due to incomplete cross-tolerance among opioids and genetic variability among μ-opioid receptors.

Resisting pressures to raise the dose too frequently may constitute a major challenge. Individuals differ significantly in how long it takes for methadone to achieve steady state and maximum effect, and it may take seven days or longer to realize full therapeutic actions.[15] Meanwhile, strong cravings to use opioids may persist and elicit in patients a sense of urgency to increase the dose or resort to street heroin. Drinking heavily or using benzodiazepines may also result in accidental overdoses.[23] It is important for MMT patients to be aware of potentially lethal interactions, especially with central nervous system (CNS) depressants. In MMT settings, patients are required to attend daily appointments, during which methadone ingestion and clinical status can be monitored and dosage adjusted accordingly.[8]

Because 30 mg of methadone can cause fatal respiratory depression in opioid-naïve individuals, consensus now exists that methadone induction protocols should initiate doses under 30 mg.[15] Most guidelines propose increases of 5–10 mg every 3–5 days, until cravings are reduced and, if taken, euphorigenic effects of illicit opioids are blocked.[8] Although these guidelines exist, empirical data demonstrating dose-response relationships and safe dosing levels in these contexts are lacking. The relative risk of death at different starting or incremental dosing levels is unknown.[8]

Nevertheless, therapeutic doses of methadone should be neither intoxicating nor sedating, and they should curb opioid cravings and narcotic withdrawal for 24 to 36 hours.[36] A subgroup of patients will continue to use benzodiazepines, alcohol and other drugs while maintained on methadone. Assessments should be conducted frequently and education provided, especially related to the possibility of lethal interaction with CNS depressants.

METHADONE INDUCTION FOR CHRONIC PAIN

Methadone accumulation during early stages of treatment has been implicated in deaths of chronic pain patients as well,[7,13] but MMT and chronic pain patients differ with regards to behavioral, physiological and psychological characteristics that impact risk.[37] Older adults, an important subgroup of the chronic pain population, have medical comorbidities that result in taking multiple medications and potential for drug interactions (e.g. diuretics and methadone) distinct from those typically seen in MMT patients.[37,38] Moreover, older adults often experience physiological (decline in hepatic functioning) and cognitive (forgetfulness) changes that may heighten risk for complications with methadone.[38] Further, pain patients receive multiple methadone doses each day, with average total daily doses generally higher than those used in MMT.[32,39] Although MMT clinics require that patients demonstrate the ability to use methadone responsibly before take-home privileges are granted,[8] pain patients tend to self-administer methadone at the outset of treatment. This less stringent methadone monitoring combined with the complexities of dosing regimens may increase iatrogenic risks. Another com-

plication of less intense supervision of methadone in pain settings is the increased potential for misuse.[37]

Prevention models to minimize mortality in pain settings should start with appropriate selection of candidates based on medical and behavioral stability. Methadone should not be used, or used very cautiously, in individuals with QTc prolongation higher than 500 ms or cardiopulmonary abnormalities.[33,40,41] Additional risk factors for TdP are highlighted in the right-hand column of the table and include a history of unexplained syncope or seizures and other medication usage that affect QTc or CYP 3A4. Pain patients likely to "doctor shop," misuse methadone, or mix it with CNS depressants are not good candidates for methadone.[32,35] Because a subgroup of pain patients experience substance use disorders, it is critically important to assess for a history of substance use before initiating methadone treatment for pain.[35] Although risk factors should be carefully considered, circumstances exist (e.g. end of life) in which benefits of improving refractory pain may outweigh risks associated with methadone.[39]

Elderly, medically compromised, and opioid-naïve individuals starting on methadone require special dosing considerations. According to Canadian guidelines,[32] initial methadone doses for opioid-naïve patients should not exceed 15–30 mg a day for the first three days, and it may be as low as 1–2 mg in medically vulnerable patients. In the US, the current package insert recommends starting methadone at 2.5–10 mg every 8–12 hours, with gradual titration, depending on efficacy and tolerability.[5] Despite some variation in initial dosing, both guidelines advocate for a "start low and go slow" approach, vigilance in assessing signs of toxicity, and slow titrations upward when necessary. If pain persists, rescue doses may be required to improve analgesia during initial stages of treatment.[42] Patients are encouraged to monitor pain states, doses taken, quality of sleep, mood, and activity level.

Methadone is seldom employed as a first-line analgesic,[39] and transitioning from another opioid analgesic to methadone can be fraught with difficulties. The "3-day" and "stop-and-go" approaches are two commonly employed strategies.[39] In the "3-day" method, the dose of the first opioid is reduced over 3 days (one-third reduction daily) and replaced with the equianalgesic dose of methadone. Using the "stop-and-go" method, the initial opioid is discontinued and immediately substituted with an equianalgesic dose of methadone. However, most equianalgesic tables derive from single dose studies and do not reflect methadone's tendency to accumulate over time, and patients tolerant to other opioids may not be tolerant to methadone due to the heterogeneity of opioid receptor systems. Several guidelines recommend a 75–95% reduction from the calculated methadone dose (and no more than 40 mg) as the initial dose, short-acting opioids for breakthrough pain, and close monitoring to ensure adequate analgesia and minimal side effects.[32,38,39] To avoid fatalities, the family should be cognizant of, and alert to, sedation and respiratory depression.

CONCLUSIONS

Early studies indicate that methadone-related fatalities were primarily related to respiratory depression during initial treatment along with polysubstance use. Recent research extends these factors to pain clinic patients, and also include cardiac pathology especially as relates to QTc prolongation and TdP. Potentially modifiable pharmacologic risk factors in both MMT and pain populations include high methadone doses, concomitant use of medications that cause QTc prolongation, electrolyte abnormalities, or inhibition of the CYP3A4 enzymatic system.

Efforts to address difficulties in initiating methadone have resulted in developing context specific guidelines. These protocols imply that safe usage of methadone requires an appreciation of its pharmacology as well as individual medical, psychiatric, and behavioral factors that may affect the use of, or response to, methadone. Early identification of risk factors, conservative dose titration, and vigilance for adverse medication interactions may reduce methadone-associated mortality in both MMT and pain populations.

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Corresponding Author: *Vania Modesto-Lowe, MD, MPH; Connecticut Valley Hospital, P.O. Box 351, Silver Street, Middletown, CT 06457, USA (e-mail: Vania.Modesto-Lowe@po.state.ct.us).*

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