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Methadone Overdose and Cardiac Arrhythmia Potential: Findings From a Review of the Evidence for an American Pain Society and College on Problems of Drug Dependence Clinical Practice Guideline

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Abstract: The number of deaths associated with methadone use increased dramatically in parallel with marked increases in its use, particularly for treatment of chronic pain. To develop a clinical guideline on methadone prescribing to reduce potential harms, the American Pain Society commissioned a review of various aspects related to methadone safety. This article summarizes evidence related to unintentional overdose due to methadone and harms related to cardiac arrhythmia potential. We searched Ovid MEDLINE, the Cochrane Library, and PsycINFO databases through January 2014 for studies assessing harms associated with methadone use; we judged 70 studies to be relevant and to meet inclusion criteria. The majority of studies on overdose and cardiac arrhythmia risk are observational and provide weak evidence on which to base clinical guidelines. In patients prescribed methadone for treatment of opioid dependence, data suggest that mortality benefits related to reduction in illicit drug use outweigh harms. Despite epidemiologic data showing marked increases in the numbers of methadone-related deaths that have been primarily attributed to increased use of methadone for chronic pain, evidence on methadone and mortality risk in this population has been somewhat contradictory. There is some evidence that recent initiation of methadone, psychiatric admissions, and concomitant use of benzodiazepines are associated with a higher risk for overdose. Evidence on cardiac risks is primarily limited to case reports of torsades de pointes, primarily in patients on high doses of methadone, and to studies showing an association between methadone use and prolongation of QTc intervals. Research is needed to understand the effectiveness of dosing methods, electrocardiogram monitoring, and other risk mitigation strategies in patients prescribed methadone.

***Perspective:** This systematic review synthesizes the evidence related to methadone use and risk for overdose and cardiac arrhythmia. Findings regarding the association between methadone use and QTc interval prolongation and risk factors for methadone-associated overdose suggest potential targets for risk mitigation strategies, though research is needed to determine the effectiveness of such strategies at reducing adverse outcomes.*

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***Key words:** Methadone, evidence-based medicine, harms, systematic review.*

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Dear Reader,

The development of guidelines is a complex and costly enterprise. Funding is increasingly reliant on providing impact and outcome data. The American Pain Society requests your assistance in evaluating the impact of the Methadone Safety Guideline. Please follow this link

(http://www.surveygizmo.com/s3/1548754/APS-Methadone-Survey) to complete a brief questionnaire before reading the guideline. The survey consists of 11 multiple-choice questions and should take no more than a few minutes.

We also seek readers willing to take a follow-up survey (see instructions at the end of this survey). These data will assist the APS in developing data on guideline impact and thus assist us in securing and determining allocation of funding in the future. We are offering a token incentive for your participation.

Thank you for your cooperation.

Clinical Practice Guidelines Committee
American Pain Society

Methadone is a synthetic opioid used for the treatment of opioid dependence and for chronic pain. For treatment of opioid dependence, methadone maintenance therapy is subject to specific federal regulations and is associated with decreased risk of illicit opioid use and associated complications, including drug-related overdose.[9,36,72] There is less evidence on the benefits and harms of methadone as a treatment for chronic pain,[13] despite marked increases in use for this purpose.[99] Recently, methadone has come under increasing scrutiny because of data indicating large increases in the number of methadone-associated deaths.[34] From 1999 to 2008, cases of methadone poisoning in the United States increased by 600%, compared to an increase in poisoning deaths due to heroin of 2.4%, and an increase in deaths due to other synthetic opioids of 138%.[10,30] Although the number of methadone overdose deaths peaked in 2007, methadone remains associated with a disproportionately large number of opioid-related overdose deaths.[10] Challenges in interpreting the data on methadone-associated mortality include the difficulty in separating out methadone deaths associated with prescribed versus nonprescribed use, understanding potential contributing factors to overdose deaths (such as the duration of use, dose, medical comorbidities, and medication interactions), determining whether observed increased deaths are due to riskier prescribing practices or are proportionate to increased use, and understanding the comparative safety of methadone relative to other opioids.

Methadone differs from other opioids in several aspects. Unlike most opioids, it has *N*-methyl-D-aspartate antagonist activity at clinical doses.[88] In addition, studies suggest an association between methadone use and prolongation of the corrected electrocardiographic QT (QTc) interval, which can predispose to arrhythmias, such as the potentially life-threatening torsades de pointes, a type of ventricular tachycardia.[54] Methadone also has a long and variable half-life. Although the half-life is usually estimated at 15 to 60 hours, it can be as long as 120 hours.[60] A long half-life may result in increased potential for unintentional overdoses or other dose-dependent harms. Assuming 5 half-lives to reach steady state, in a patient for whom the half-life is 60 hours, it would take almost 12 days on a stable dose to reach peak serum levels. In addition, methadone to morphine dose equivalent ratios are thought to increase at morphine equivalent doses (eg, 1:2 methadone to morphine at low doses, to as high as 1:20 at high doses), and incomplete cross-tolerance to other opioids may occur, which could affect safety when switching patients from another opioid to methadone.[2,44,87]

In 2006, the U.S. Food and Drug Administration (FDA) issued a safety alert regarding the association between methadone and risk of death and cardiac arrhythmias,[89] and lowered the recommended starting dose of methadone to a maximum initial dose of 30 mg/day (2.5–10 mg every 8–12 hours).[21] In 2009, a guideline from the American Pain Society (APS) and the American Academy of Pain Medicine recommended starting methadone at 2.5 mg every 8 hours and increasing the dose no more frequently than weekly. Three subsequent guidelines that were limited in scope to prevention of cardiac arrhythmias each recommended risk assessment and electrocardiographic (ECG) monitoring in patients prescribed methadone.[56,63,94]

This article reviews the evidence related to unintentional overdose due to methadone and harms related to cardiac arrhythmia potential. It is part of a larger review[14] commissioned by the APS and the College on Problems of Drug Dependence (CPDD), in conjunction with the Heart Rhythm Society, to develop a clinical practice guideline on safer prescribing of methadone.

Methods

With the input of a 17-member multidisciplinary panel convened by the APS and the College on Problems of Drug Dependence (Appendix 1), we developed a review protocol and analytic framework for this review. The panel requested that the evidence review assess evidence on various harms associated with prescribed methadone use, risk factors for those harms (based on demographics, presence of medical and psychiatric comorbidities, prescribing characteristics such as dose or duration of therapy, and other factors), and methods for reducing or mitigating risks associated with use of methadone. The review included the following key questions related to overdose deaths and cardiac risks:

1. In populations prescribed methadone, what is the risk of adverse events compared to nonuse of methadone?
2. What are the comparative risks of adverse events for methadone compared to other opioids or medications?
3. How does risk of adverse events associated with methadone vary according to dose or duration of therapy?
4. In populations prescribed methadone, what factors predict increased risk of adverse events?
5. In populations prescribed methadone, what is the accuracy of baseline or follow-up ECGs for predicting adverse cardiac events?
6. In populations prescribed methadone, what are the benefits and harms of baseline or follow-up ECGs?

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