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Research Gaps on Methadone Harms and Comparative Harms: 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: Methadone-associated overdose deaths have dramatically increased. In order to inform an evidence-based clinical practice guideline to improve safety of methadone prescribing, the American Pain Society commissioned a systematic review on various aspects related to methadone safety. We searched Ovid MEDLINE, Cochrane Library, and PsycINFO databases through July 2012 to identify studies that addressed 1 or more of 17 Key Questions related to methadone safety; an update search was performed in 2014 for new studies related to methadone-related overdose and risks related to cardiac arrhythmias. A total of 168 studies met inclusion criteria for the review. The purpose of this article is to highlight critical research gaps in the literature related to methadone safety. These include lack of evidence on risk factors associated with methadone-overdose deaths and adverse events, limited evidence to evaluate the comparative mortality of methadone versus other opioids, insufficient evidence to fully understand the harms associated with methadone use during pregnancy, and insufficient evidence to determine effects of risk mitigation strategies such as electrocardiogram monitoring, strategies for managing patients with prolonged QTc intervals on screening, urine drug testing, alternative dosing regimens for initiation and titration of therapy, and timing of follow-up. Therefore, most guideline recommendations are based on weak evidence. More research is needed to guide safe methadone prescribing practices and decrease the adverse events associated with methadone.

***Perspective:** This article summarizes critical research gaps in the literature related to methadone safety, based on a systematic review commissioned by the American Pain Society. Critical research gaps were identified in a number of areas, highlighting the need for additional research to guide safer prescribing and risk mitigation strategies.*

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

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

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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 chronic pain. Recently, use of methadone for management of chronic pain has increased dramatically,[16,21,52,84] but this practice has come under increasing scrutiny because of data indicating precipitous increases in the number of methadone-associated overdose deaths[44] and the potential for methadone to prolong corrected electrocardiographic QT (QTc) intervals and lead to a life-threatening cardiac arrhythmia, torsades de pointes.

Ideally, clinical guidelines to manage methadone's complexities and mitigate risks should be informed by high-quality evidence. In 2010, the American Pain Society (APS) partnered with the College on Problems of Drug Dependence (CPDD), in conjunction with the Heart Rhythm Society, to develop a clinical practice guideline on safer methadone prescribing. As part of this process, the APS/CPDD commissioned a systemic evidence review addressing 17 Key Questions related to methadone safety, as determined by a multidisciplinary panel (Table 1).[25] The purpose of this article is to identify and summarize critical weaknesses ("research gaps")—defined as areas in which the evidence base inadequately addressed a Key Question—related to methadone safety and harms.

Methods

A systematic review protocol and analytic framework were developed with the input of a 17-member multidisciplinary panel convened by APS and CPDD. The panel requested that the review assess evidence on the risk of various harms associated with prescribed methadone use, risk factors for those harms, and methods for reducing or mitigating the risks associated with use of methadone, and developed the Key Questions to guide the review. Detailed methods for the systematic review, including full search strategies, detailed inclusion criteria (including the populations, interventions, comparisons, outcomes, study designs, and settings evaluated), data abstraction tables, and tables with quality ratings of individual studies, are presented in the full report.[25] Separate articles in this issue summarize evidence on harms related to overdose and cardiac arrhythmia[24] and present the Guideline developed from the review.[23]

Data Sources and Searches

We searched the Cochrane Library, Ovid MEDLINE, and PsycINFO through July 2012 for relevant studies using broad terms for harms of methadone use. An update search was performed in January 2014 for new studies on methadone overdose and cardiac arrhythmia potential. Reviews of reference lists supplemented the electronic searches.

Evidence Selection

We included randomized trials and observational studies that evaluated adults (including pregnant women) and children (younger than 13 years of age) or adolescents (13–18 years of age) prescribed methadone for chronic pain or for treatment of opioid dependence. Comparisons of interest were methadone (oral or intravenous) versus placebo or no methadone, other opioids, or nonopioid analgesics. Studies that compared methadone use alone to methadone plus another intervention were also included. The review assessed evidence on various harms associated with methadone, including mortality or overdose related to methadone, cardiovascular events (eg, syncope, arrhythmias, and QTc prolongation), gastrointestinal side effects, respiratory depression and sleep apnea, hyperalgesia, endocrinologic effects, cognitive dysfunction, and psychiatric disorders, abuse, addiction, and pregnancy and neonatal outcomes. The review also assessed evidence on 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 systematic review also addressed how the risks of harms associated with methadone are affected by use of concomitant medications.

Data Extraction and Quality Assessment

Studies that met predefined inclusion criteria, based on dual review, were abstracted and quality rated. Information abstracted from studies included study purpose, design, setting, sample size, population characteristics, interventions evaluated, duration of follow-up, primary and secondary outcomes and results, outcome results, and funding sources. Studies were rated as good, fair, or poor quality based on criteria from the Cochrane Back Review Group for primary studies and Assessment of Multiple Systematic Reviews (AMSTAR) for systematic reviews.

Data Synthesis

We rated the strength of each body of evidence as high, moderate, low, or insufficient using methods adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group[53] and the Agency for Healthcare Research and Quality Effective Health Care Program,[87] based on the type, number, size, and quality of studies; precision of estimates; strength of associations or effects; and consistency between studies. A "low" grade indicates low confidence that the evidence reflects the true effect because of serious methodologic shortcomings in the trials, very imprecise estimates, or serious unexplained inconsistency. An "insufficient" grade indicates that evidence is unavailable or does not permit a conclusion. This article focuses on areas rated low or insufficient, in order to highlight areas in which new research would most likely impact future assessments and clinical recommendations.

Table 1. Key Questions and Related Research Gaps

Key Question	Section Where Research Gaps Summarized
1. In populations prescribed methadone, what is the risk of adverse events compared to nonuse of methadone?	• Mortality associated with methadone use compared to nonuse
2. What are the comparative risks of adverse events for methadone compared to other opioids or drugs?	• Mortality associated with methadone use compared to other opioids
3. In populations prescribed methadone, what factors predict increased risk of adverse events?	• Patient assessment and selection • Risk factors associated with methadone mortality
4. In populations prescribed methadone, what are the effects of different dosing strategies on adverse events?	• Initiation and dosing of methadone
5. In populations prescribed methadone, what is the accuracy of baseline or follow-up ECGs for predicting adverse cardiac events?	• Electrocardiographic QTc interval monitoring
6. In populations prescribed methadone, what are the benefits and harms of baseline or follow-up ECGs?	• Electrocardiographic QTc interval monitoring
7. In populations prescribed methadone with evidence of QTc prolongation, what are the benefits of correcting conditions associated with QTc prolongation?	• Management and treatment of harms
8. In populations prescribed methadone with evidence of QTc prolongation, what are the benefits and harms of continued use of methadone versus switching to another opioid agonist or discontinuation of methadone?	• Management and treatment of harms
9. In populations prescribed methadone at higher risk for adverse events, what are the benefits of methods for reducing risk?	• Patient assessment and selection • Management and treatment of harms
10. In populations prescribed methadone, what is the effectiveness of methods for reducing risk of diversion or nonprescribed use?	• Patient assessment and selection • Management and treatment of harms
11. How does risk of adverse events associated with methadone vary according to dose or duration of therapy?	• Risk factors associated with methadone mortality
12. How are risks of methadone affected by the indication for treatment?	• See full report[24]
13. How are risks of methadone affected by concomitant medications?	• Effects of concomitant medications on methadone-associated harms
14. How do differences in adherence and access to care affect risk of adverse events associated with methadone?	• See full report[24]
15. In populations prescribed methadone, what is the accuracy of urine drug testing or prescription drug monitoring for predicting adverse events?	• Urine drug testing and use of prescription drug monitoring program data
16. In populations prescribed methadone, what are the benefits and harms of urine drug testing or prescription drug monitoring?	• Urine drug testing and use of prescription drug monitoring program data
17. In populations prescribed methadone, what are the benefits and harms of different methods for structuring and managing care?	• See full report[24]

Note: Evidence on methadone use in children and in pregnancy was reviewed for all key questions and summarized in separate sections.

Results

Results of the Literature Search

The literature search yielded a total of 3,746 potentially relevant citations. Of these, we retrieved 1,170 full-text articles to review for inclusion. After review of full-text articles, we included 170 studies (including 168 primary studies and 2 systematic reviews) that were relevant to 1 or more key questions and met inclusion criteria. Although the systematic review was guided by the key questions, we organized our findings on research gaps by clinical area. Table 1 shows the key questions with the corresponding clinical areas.

Patient Assessment and Selection

Evidence regarding the utility of risk stratification instruments for predicting aberrant drug-related behaviors in patients prescribed opioids in general for chronic pain has been previously reviewed.[22] However, no study evaluated the utility of patient assessment and selection instruments for predicting adverse events in patients specifically prescribed methadone for chronic pain or opioid dependence.[22] In addition, no study evaluated clinical outcomes associated with the use of different patient selection or risk stratification approaches in patients prescribed methadone.

Informed Consent and Methadone Management Plan

No study evaluated whether an informed consent process improves clinical outcomes, patient adherence to treatment, or patient satisfaction with regard to treatment of chronic pain or opioid dependence in patients prescribed methadone. No study evaluated effects of different educational strategies to inform patients about the indication for methadone treatment, goals of therapy, or availability of alternative therapies. No study evaluated clinical outcomes or patient satisfaction after instituting plans to monitor therapy, adjust doses, or manage potential adverse effects.

Initiation of Methadone

No study evaluated effects of different dosing strategies for initiation or titration of methadone on risk of harms. Evidence for recommended starting doses or titration of methadone is limited and based on expert opinion, conversion tables (with substantial variability in suggested conversion ratios),[94] and previously published guidelines.[22] Five retrospective studies found recent initiation of methadone use associated with increased risk of all-cause mortality.[15,30,70,80,120,131] No study evaluated how quickly tolerance is lost after stopping methadone.

Mortality Associated With Methadone Use Compared to Nonuse

Although epidemiologic studies found markedly increased numbers of methadone-related deaths,[17,88,89,91] these studies are limited by their failure to enroll inception cohorts of patients being started on opioids, inability to differentiate licit from illicit methadone use, and reliance on surrogate denominators (eg, dispensing or sales rates). Other observational studies were not designed to differentiate mortality as a result of prescribed methadone versus illicit use, were not designed to determine cause of death, or had other important methodologic shortcomings including no statistical analyses for potential confounders or use of an uncontrolled design.[1,26,49,62,69,75,76,92,117,120]

Although randomized trials found methadone for the treatment of opioid dependence associated with a nonstatistically significant trend toward lower risk of all-cause mortality compared to no methadone maintenance treatment,[78] no study was designed to evaluate effects of methadone on mortality or other serious harms in patients prescribed methadone for chronic pain.

Mortality Associated With Methadone Use Compared to Other Opioids

No randomized controlled trial (RCT) was designed or powered to evaluate the comparative mortality of methadone versus other opioids, and most trials reported no deaths.[13,59,77,81,82,119] Two retrospective cohort studies compared mortality in patients prescribed methadone to mortality associated with other opioids prescribed for the treatment of chronic pain[58,70] but had methodologic limitations, including baseline differences in 1 of the studies.[58] The other study unexpectedly found methadone to be associated with decreased risk of mortality versus morphine in a propensity-matched analysis.[70]

Although epidemiologic studies reported increases in rates of methadone-related overdose deaths since 1990, findings are difficult to interpret because of the lack of true inception cohorts of patients prescribed different opioids, use of indirect and surrogate denominators (eg, opioids sales) to generate risk estimates, and inability to distinguish adverse events associated with prescribed from those associated with illicit use of opioids.[17,88,89,91] Although data on the number of deaths associated with methadone and buprenorphine are available from forensic case series, findings are of limited usefulness because it was not possible to determine from these studies whether patients were prescribed the medications or took them illicitly, and denominators were not available to calculate risk estimates.[9,93,110]

Risk Factors Associated With Methadone Mortality

No RCT assessed risk factors for methadone mortality. Although several cohort studies evaluated risk factors for mortality in patients treated with methadone for opioid dependence including time in treatment, methadone dose, comorbidities, and concomitant medications,[15,30,80,117,120] findings were difficult to interpret because of differences in baseline characteristics and unclear prescription of methadone at the time of death. Additionally, the studies were not designed to distinguish overdoses related to methadone from overdoses related to illicit drug use.

Fifteen case series and 2 retrospective cohort studies reported risk factors for methadone-related mortality and overdose.[7,8,14,15,18,42,48,54,70,85,90,106,107,114,123,126,127,132] Studies found a high proportion of cases associated with benzodiazepine co-prescription, benzodiazepine in blood toxicology, use of other concomitant medications, or an illicit source of methadone. Methodologic shortcomings of these studies include use of a cross-sectional design and inability to calculate risk estimates because of the lack of comparison group or denominator data regarding the number of patients prescribed methadone.

Electrocardiographic QTc Interval Monitoring

There is no direct evidence on the effects of screening ECGs versus no screening in patients prescribed methadone on clinical outcomes such as mortality or arrhythmia, or effects of different ECG screening or monitoring strategies (eg, targeted vs universal monitoring, optimal timing or frequency of monitoring) for patients prescribed methadone. Evidence on effects of methadone on QTc interval prolongation is primarily limited to observational studies with relatively weak designs (cross-sectional studies, before-after studies, or case series).[1,5,31,40,43,47,67,69,75,76,92,101,102,105,125] In addition, thresholds for defining an abnormal QTc interval varied across studies, making it difficult to synthesize data. Data on risk factors for QTc interval prolongation are mostly limited to studies evaluating methadone dose-dependent effects,[40,43,62,68,76,79] though no study evaluated the optimal methadone dose threshold for ECG monitoring. Research is also lacking regarding current clinical practice patterns regarding use of screening ECG in patients prescribed methadone, or barriers to its use.

Management and Treatment of Harms

No study evaluated how timing of follow-up after initiation of methadone or during methadone therapy affects adverse outcomes. In persons on methadone found to have QTc interval prolongation on ECG screening, no study evaluated the effect of risk mitigation strategies (eg, dose reduction, discontinuation, switching to an alternative opioid, correcting electrolyte abnormalities, or discontinuation of potentially interacting medications) on clinical outcomes such as development of torsades or sudden death. No study addressed optimal strategies for managing QTc interval prolongation in patients prescribed methadone with impaired liver function or structural heart disease.

Although evidence found no clear differences between methadone and other opioids in risk of constipation, respiratory depression, sleep apnea, sedation, cognitive dysfunction, psychiatric outcomes, and immunologic or endocrinologic adverse events, data were sparse, with frequent methodologic limitations.[3,4,12,13,33-35,38,41,51,55,56,73,77,81,83,95,99,100,108,111,115,119,121,122,124]

Evidence on risk of opioid abuse and addiction with methadone was also sparse. No study evaluated the risk of opioid abuse or addiction in persons prescribed methadone for the treatment of chronic pain or compared risk with methadone versus other prescribed opioids.

Although 1 cross-sectional study found that patients on chronic methadone maintenance therapy had lower pain tolerance thresholds on cold pressor tests compared to matched controls,[38] it was not designed to evaluate effects on clinical outcomes and there are no studies on comparative risks of hyperalgesia with methadone versus other opioids.

Urine Drug Testing and Use of Prescription Drug–Monitoring Program Data

No study evaluated the accuracy of urine drug testing for predicting adverse events in patients prescribed methadone. Although 1 large cohort study of patients prescribed methadone found having undergone at least 1 urine drug test to be associated with decreased risk of all-cause mortality, effects on risk of drug-related death did not reach statistical significance and results were difficult to interpret because of the possibility for residual confounding, unclear use of methadone at the time of almost half of the deaths, and difficulty in attributing drug-related deaths.[80] No study compared effects of different urine drug testing strategies (eg, shorter vs longer intervals between testing, or standardized protocols vs protocols based on individualized risk assessments). Data are also lacking on effects of accessing information from prescription drug–monitoring programs on reducing adverse events associated with methadone. In many states, prescribing of methadone at a licensed opioid treatment facility is not reported to state prescription drug–monitoring programs.

Effects of Concomitant Medications on Methadone-Associated Harms

Evidence on the magnitude of clinical harms associated with the concomitant use of methadone plus potential interacting medications is limited. Although a number of medications are known to interact with methadone, few randomized trials evaluated the incremental risks of adding medications to methadone and were not designed to adequately evaluate risks of serious harms such as mortality or cardiac events.[27,29,32,116,128]

Several case series of methadone overdose cases found a high proportion of cases associated with benzodiazepine co-prescription or benzodiazepine in blood toxicology.[18,30,48,106,114,126] In several of these case series, it was not clear if patients were prescribed methadone or using illicit methadone. Methadone dose, duration of use of methadone, and other risk factors for adverse events were also not clear.

Methadone Use in Pregnancy

One RCT and several observational studies compared pregnancy outcomes in women on methadone maintenance therapy compared to drug-free controls,[2,10,11,19,20,28,36,37,57,64-66,74,96,98,103,112,113,118,129,130] but most were poor-quality and potentially confounded by the presence of other risk factors associated with opioid dependence. Also, most studies did not attempt to match methadone-treated women and drug-free controls on important sociodemographic and clinical variables. No study compared pregnancy outcomes in patients treated with methadone versus placebo for chronic pain. For pregnant women treated for opioid dependence, limited data from RCTs and cohort studies showed no differences in incidence of preterm birth or cesarean delivery between methadone and buprenorphine,[6,10,46,60,61,63,71,72] but data comparing methadone with other opioids was very sparse.[45]

No study evaluated the effect of methadone dose, dosing strategy (eg, divided dose vs single dose), or duration of therapy on pregnancy outcomes.

Neonatal Outcomes

Effects of methadone on neonatal outcomes are difficult to assess because of confounding effects related to selection of the control group (eg, ongoing heroin use or drug-free controls), failure of most studies to adjust for potential confounders, and inconsistent results. Rates of neonatal abstinence syndrome diagnosis in infants of women prescribed methadone were generally 75% or more,[28,57,63,64,74,86,96,97,103,104,133] though rates of treatment for neonatal abstinence syndrome were low in some studies.[6,39,63,72,109,133] Evidence regarding the comparative incidence, severity, or time course of neonatal abstinence syndrome due to methadone compared to buprenorphine were inconsistent in 4 RCTs and 4 cohort studies, preventing strong conclusions.[6,10,46,60,61,63,71,72] Data on effects of methadone use during pregnancy in women treated for chronic pain were extremely sparse.

Methadone Use in Children and Adolescents

Evidence on the use of methadone in children is extremely limited. No study evaluated effects of methadone initiation or dose titration strategies in children. In addition, evidence to determine optimal QTc intervals in children are limited, and there is insufficient evidence to determine rates of QTc interval prolongation or effectiveness of cardiac assessment or ECG screening in children prescribed methadone.

Discussion

Methadone is a widely used long-acting opioid agonist with unique properties that potentially increase risks relative to other opioids. In the last several years, risks associated with methadone have come under greater scrutiny because of reports of increasing methadone-related deaths. Evidence-based clinical recommendations could help prescribers better understand the risks associated with methadone and inform safer prescribing practices, and should be informed by well-conducted RCTs or controlled observational studies. However, for the majority of the research questions developed by the APS/CPDD multidisciplinary expert panel on methadone safety, we found a number of critical research gaps.

Despite evidence from epidemiologic studies showing markedly increased numbers of methadone-related deaths, such data remain difficult to interpret because of a number of factors, including challenges in determining whether methadone was prescribed or used illicitly, potential effects of confounders, and difficulty in calculating risk estimates because of the lack of denominator data for the number of patients prescribed methadone. In addition, evidence from cohort studies on comparative risks of methadone versus other opioids is mixed, with the largest, highest-quality study showing no increased risk of overdose with methadone versus morphine when prescribed for chronic pain.[69] Interpretation of even well-designed observational studies is a challenge because of potential residual confounding related to how patients are selected for methadone therapy or managed versus other opioids. Evidence to understand risk factors for methadone-related deaths are also limited. For example, although concomitant benzodiazepines have been found in a high proportion of methadone-associated deaths, such data are largely from uncontrolled case series and therefore limited in being able to show causality. Rather, such data are largely hypothesis generating, warranting further evaluation in well-designed case-control or cohort studies.

Potential cardiac side effects of methadone use associated with QTc interval prolongation have been the target of risk mitigation strategies. However, evidence to guide optimal approaches to reducing arrhythmogenic risks, such as ECG monitoring, are very limited. To aid in interpretation of future studies, we recommend use of standardized thresholds to define abnormal QTc interval prolongation. Ideally, future research on ECG screening and monitoring will evaluate important clinical outcomes such as mortality or arrhythmia. However, given that the rates of such events appear to be low,[1] requiring large studies with long duration of follow-up, randomized trials would be difficult to design and carry out and might represent an ethical dilemma, given recommendations for routine ECG monitoring for many drugs associated with QTc interval prolongation. Therefore, large observational studies that control well for potential confounders may be more suitable for evaluating the yield and effects of ECG monitoring and alternative ECG-monitoring strategies. Studies that focus on patients at higher risk for QTc interval prolongation, such as those prescribed higher doses of methadone or other QTc interval-prolonging drugs, would probably require smaller samples than studies of patients without risk factors. Better evidence would help improve our understanding of the feasibility, acceptability, and cost-effectiveness of ECG screening and monitoring in both chronic pain settings and opioid treatment centers, given concerns that additional requirements in opioid treatment centers might impede access to methadone maintenance therapy or have other unintended consequences.[50]

Additional research is also needed to guide clinical practice and policy regarding other risk-mitigation strategies in patients prescribed methadone, such as methods for patient risk assessment, selection, and education; optimal dose initiation and titration strategies; follow-up and monitoring intervals; urine drug testing strategies; and use of data from prescription drug–monitoring programs. Research is needed both to understand how such efforts affect rates of harms associated with methadone use and to devise optimal methods for implementing such strategies. Evidence is particularly limited on methods for safely managing pregnant women with chronic pain and on use of methadone in children.

Despite the urgent need to improve safety around use of methadone, important research gaps necessitate that most clinical practice guideline recommendations are currently based on only weak evidence. Research is needed to better guide safe methadone prescribing practices and optimize risk mitigation strategies, in order to decrease the adverse events associated with methadone.

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