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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.*

***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?

7. In populations prescribed methadone with evidence of QTc interval prolongation, what are the benefits of correcting conditions associated with QTc interval prolongation?
8. In populations prescribed methadone with evidence of QTc interval prolongation, what are the benefits and harms of continued use of methadone versus switching to another opioid agonist or discontinuation of methadone?

Detailed methods and data for the review, including search strategies, detailed inclusion criteria, data abstraction tables, and tables with quality ratings of individual studies, are available in the full report, which includes additional key questions and other harms.[14]

Data Sources and Searches

We searched the Cochrane Library, Ovid MEDLINE, and PsycINFO through January 2014 for studies assessing harms associated with methadone use. Reviews of reference lists supplemented the electronic searches.

Evidence Selection

Two reviewers (R.C., M.W., or T.D.) independently evaluated each study to determine inclusion eligibility. Papers were selected for full review if they were relevant to a key question and met the predefined inclusion criteria. This article focuses on use of methadone in nonpregnant adults. Evidence on methadone in pregnancy and in children and on other harms associated with methadone is addressed in the full report.[14] Comparisons of interest were methadone (oral or intravenous) versus placebo, other opioids, or nonopioid analgesics. In addition, we included studies that compared methadone use alone to methadone plus another intervention. We excluded studies of patients receiving methadone for management of acute pain and studies of persons using nonprescribed methadone. Studies that did not clearly distinguish prescribed from nonprescribed use of methadone were excluded unless they provided information not available from studies that evaluated prescribed use. We excluded studies that compared methadone to medications not available in the United States, cost-effectiveness studies, and modeling studies. Clinical outcomes were mortality, overdose, arrhythmia, and ECG changes.

We included systematic reviews, controlled clinical trials, and observational studies. We excluded studies only published as conference abstracts; non–English language studies; and reviews, policy statements, and other articles without original data.

Data Extraction and Quality Assessment

One investigator (R.C., M.W., or T.D.) abstracted details about the study design, patient population, setting, medications, analysis, follow-up, and results. A second investigator (R.C., M.W., or T.D.) reviewed data for accuracy. Two investigators (R.C., M.W., or T.D.) independently applied predefined criteria based on methods developed by the Cochrane Back Review Group,[101] Downs and Black,[22] the U.S. Preventive Services Task Force,[41] and the Assessment of Multiple Systematic Reviews (AMSTAR) tool[95] to assess the quality of each study. Discrepancies were resolved through a consensus process. We graded studies with no or only minor flaws as good quality, those with serious flaws as poor quality, and all others as fair quality.[77] We also ranked the strength of study designs based on an evidence hierarchy (Table 1). Good-quality studies based on designs high on the evidence hierarchy receive higher weight than good-quality studies based on designs lower on the hierarchy. We did not formally assess the quality of case series and retrospective, uncontrolled database studies, though important methodologic shortcomings are discussed. Such studies rank low on the evidence hierarchy, and reliable and validated quality assessment methods for these types of studies are lacking.

Table 1. Strength of Study Designs

We considered the strength of study designs according to the following evidence hierarchy (from highest to lowest):

- Randomized controlled trial
- Nonrandomized controlled clinical trial
- Cohort study
- Case-control study
- Cross-sectional study
- Before-after study
- Prevalence study, case series, other descriptive observational studies

Data Synthesis

We qualitatively synthesized and assessed the overall strength of evidence for a body of literature in accordance with methods adapted from the Grades of Recommendation Assessment, Development and Evaluation (GRADE) Working Group[35,38] and the Agency for Healthcare Research and Quality's (AHRQ's) Methods Guide for Comparative Effectiveness Reviews.[77] To determine the overall strength of evidence, we considered the risk of bias (based on the type and quality of studies), the consistency of results within and between study designs, the directness of the evidence linking the intervention and health outcomes, the precision of the estimate of effect (based on the number and size of studies and confidence intervals for the estimates), strength of association (magnitude of effect), and the possibility for publication bias.

We rated the strength of evidence for each key question using the 4 categories recommended in the Agency for Healthcare Research and Quality guide: A "high" grade indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effect; a "moderate" grade indicates moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of effect and may change the estimate; a "low" grade indicates low confidence that the evidence reflects the true effect and that further research is likely to change the confidence in the estimate of effect and is likely to change the estimate; an "insufficient" grade indicates that evidence either is unavailable or does not permit a conclusion.

Role of the Funding Source and Conflict of Interest Disclosure

None of the investigators conducting this review had conflicts of interest to disclose. This research was funded by the APS, but the APS had no role in study selection quality assessment, synthesis, or development of conclusions. The investigators are solely responsible for the content of the manuscript and the decision to submit for publication.

Results

Size of Literature Reviewed

Investigators reviewed 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 judged 71 studies to be relevant and to meet inclusion criteria for the key questions and outcomes addressed in this article. These included 1 systematic review, 13 randomized trials (4 of which were included in the systematic review), 32 observational studies (in 35 publications), and 25 case series.

Risk of Adverse Events With Methadone Use Compared to Nonuse

Mortality and Overdose

A good-quality systematic review of 4 randomized controlled trials (n = 576)[37,49,76,109] found methadone for treatment of opioid dependence associated with a nonstatistically significant trend toward lower risk of all-cause mortality compared to no methadone maintenance therapy (relative risk [RR] .48; confidence interval [CI] .10–2.4),[65] but results are difficult to interpret because of the imprecision of estimates, because of methodologic shortcomings in the trials, and because the studies were not designed to distinguish deaths related to methadone use from deaths related to other causes (such as illicit or nonprescribed drug use).

One fair-quality case-control study evaluated prospectively identified cases of sudden death involving methadone at "therapeutic" levels (defined as <1 mg/L) compared to sudden death not involving methadone (Table 2).[15] It found that a higher proportion of cases involving methadone had no structural heart abnormalities compared to cases not involving methadone (77% [17/22] vs 40% [42/106], $P = .003$), suggesting a possible causal role of methadone in the sudden deaths. Limitations of this study include no statistical adjustment for potential confounders and not accounting for factors such as tolerance to methadone to define "therapeutic" methadone use, potentially resulting in misclassification of some overdose cases.[75]

Three other observational studies also evaluated the association between methadone maintenance therapy and mortality (Table 2).[18,33,100] Each found methadone maintenance therapy to be associated with either similar or decreased mortality compared with nonuse in patients with opioid addiction[18,100] or compared with expected mortality among the general population.[33]

No study was designed to evaluate mortality associated with methadone use versus nonuse in patients with chronic pain.

Cardiovascular Events

One before-after study (n = 160) reported no cases of torsades de pointes following methadone initiation, despite a relatively high frequency of QTc interval prolongation (Table 3).[51,62] A fair-quality cross-sectional study found that 4% (6/167) of methadone users had torsades de pointes with no cases (0/80) in injection drug users not using methadone, though results may have been confounded by differential concomitant medication use (Table 3).[24]

ECG Changes

The proportion of patients on methadone with QTc interval prolongation ranged from 0 to 37% with methadone use and from 0 to 14% with nonuse in studies of patients on methadone maintenance therapy (Tables 3 and 4).[12,24,43,51,55,59,62,85,86,91,96] Methodologic limitations of the studies included failure to perform adjustment on potential confounding variables or the use of a relatively weak before-after or cross-sectional study designs. In addition, the threshold for defining abnormal QTc intervals varied among studies from >430 to >500 ms. In the methadone arm of a randomized trial, the proportion of patients that developed QTc interval prolongation (defined as >470 ms in men and >490 ms in women) was 23%, with 12% experiencing an increase in >60 ms from baseline.[105] The highest (fair) quality cross-sectional study found that 16% of patients on methadone maintenance therapy had a QTc interval >500 ms, compared to 0% in nonmethadone controls.[24] In before-after analyses of the same or overlapping series of patients, the proportion of patients with QTc interval prolongation based on a threshold of >430 ms in men and >450 ms in women was 31% 6 months after initiating methadone compared to 14% at baseline, and based on a threshold of >500 ms was 2% after 6 months compared to 0% at baseline.[51,55,62]

Two poor-quality, before-after studies found no QTc interval prolongation in persons prescribed oral methadone for cancer pain, but evaluated lower median daily methadone doses (23 and 30 mg) than in studies of ECG changes in persons on methadone maintenance therapy (Table 3).[85,86]

In case series of patients on methadone therapy (including the methadone arm of cross-sectional studies of methadone vs buprenorphine), the prevalence of QTc interval prolongation ranged from .5% to 31% in 5 studies based on a threshold of >430 to 450 ms in men and >460 to >470 ms in women[3,27,28,61,66] to 32% in a study that applied a threshold of >430 ms in men and >450 ms in women (Tables 3 and 4).[20] In 6 studies, the proportion of patients who exceeded a QTc threshold of >500 ms ranged from 0% to 6%.[1,20,28,48,83,90]

Table 2. Mortality and Overdose With Methadone Use Versus Nonuse

Author, Year	Study Design	Inclusion Criteria	Population Characteristics	Interventions	Results	Quality
Chugh, 2008[15]	Case-control	Sudden cardiac death between 2002 and 2006 in the Portland, OR, metro area	Total cohort: n = 128 Mean age 41 years 69% male Cases: n = 22 Mean age 37 years 68% male Mean methadone dose .48 mg/L; Controls: n = 106 Mean age 42 years 69% male	Methadone (route unknown; determined by blood toxicology screen): mean .48 mg/L	Sudden death in absence of underlying cardiac disease, methadone users vs nonmethadone users: 17/22 (77%) vs 42/106 (40%); $P = .003$	Fair
Cornish, 2010[18]	Prospective cohort	Diagnosis of substance misuse, at least 1 prescription of methadone or buprenorphine	n = 5,577 Mean age not reported; 85% 20–39 years of age 69% male	Methadone Methadone plus another opioid Buprenorphine without methadone Mean doses not reported	Mortality, off treatment vs on treatment: 1.32 vs .69 per 100 person-years, adjusted rate ratio 2.3 (95% CI 1.7–3.1)	Fair
Gearing, 1974[33]	Prospective cohort	Volunteer methadone maintenance patients	n = 17,550 Mean age 30 years 79% male, 34% white, 41% black, 24% Hispanic, 1% other	Oral methadone, mean dose not reported (range 80–120 mg)	Mortality rate: methadone 7.6/1,000 vs expected rate, general population age 20–54 years 5.6/1,000	Poor
van Ameijden, 1999[100]	Prospective cohort	Methadone maintenance patients	n = 498 Mean age 33 years 33% female	Oral methadone, mean dose 49 mg (77% of enrolled population)	All-cause mortality, methadone vs no methadone use: RR .83 (CI, *P*-value not reported) Death due to overdose, methadone use vs nonuse: RR .35 (CI not reported; $P = .05$)	Fair

Table 3. Cardiovascular Events and ECG Changes With Methadone Use Versus Nonuse

Author, Year	Study Design	Inclusion Criteria	Population Characteristics	Interventions	Results	Quality
Chang, 2012[12]	Before-after	Methadone maintenance with opioids addiction >1 year	n = 150 Mean age 37 years 16% female Race not reported (study conducted in China)	Oral methadone: mean dose 40 mg/day	Baseline vs follow-up ECG Mean QTc interval: 422 vs 430 ms QTc interval increased >30 ms above baseline at 6 months: 27/150 (18%) QTc >500 ms: 0%	Fair
Cruciani, 2005[20]	Case series	Adults receiving ≥20 mg/day for more than 2 weeks	n = 110 Mean age 45 years 39% female, 82% white, 14% black, 5% other	Oral methadone: mean dose 110 mg/day	Proportion of patients with QTc prolongation: 33/104 (32%)	Not rated
Ehret, 2006[24]	Cross- sectional	Active or former injection drug users hospitalized between January 1999 and December 2003	n = 247 Mean age 37 years 34% female Race not reported	Oral methadone: 4–300 mg/day; median dose 100 mg/day Control group: no methadone	Methadone use vs no use QTc ≥500 ms: 27/167 (16%) vs 0/80 (0%) QTc ≥460 ms: 50/167 (30%) vs 8/80 (10%) Torsades de pointes: 6/167 (4%) vs 0/80 (0%)	Fair
Fareed, 2010[28] Other publications: Fareed, 2013[29]	Case series	Methadone maintenance, treated at clinic for at least 6 months	n = 55 Mean age 56 years 7% female 64% nonwhite	Oral methadone: mean dose 90 mg/day	Baseline (already on methadone) vs follow-up ECG Mean QTc interval: 417 vs 442 ms QTc >450 ms on most recent ECG: 14/52 (27%) QTc >500 ms on most recent ECG: 3/52 (5.8%)	Not rated
Fonseca, 2009[31]	Case series	Methadone maintenance with stable dose for at least 2 months	n = 109 Mean age 38 years 32% female 92% Caucasian	Oral methadone: mean dose 64 mg	QTc duration >440 ms (men) or >450 ms (women): 10/109 (9.2%; 7 men, 3 women) Older age was the only variable associated with significantly increased risk of prolonged QTc interval in multivariate analysis (OR 1.15; CI 1.03–1.27)	Not rated

Table 3. Continued

Author, Year	Study Design	Inclusion Criteria	Population Characteristics	Interventions	Results	Quality
Huh, 2010[43]	Cross-sectional	Methadone for chronic pain	n = 130 Mean age 51 years 55% female Race not reported (study conducted in Korea)	Oral methadone: mean dose 30 mg/day	Methadone use vs nonuse Mean QTc interval: 443 vs 408 ms QTc >450 ms: 33/90 (37%) vs 3/40 (7.5%)	Fair
Katz, 2013[48]	Case series	Methadone maintenance, participating in cardiac safety program	n = 531 Mean age 41 years 43% female 36% nonwhite	Oral methadone: mean dose 44 mg/day	Proportion with QTc >500 ms at some point during study: 21/588 (3.7%)	Not rated
Krantz, 2005[55]	Prospective before-after	Age >18 years with opioid addiction duration of at least 1 year and at least 1 previous attempt at detoxification	n = 118 Mean age 43 years 37% female Race not reported	Oral methadone: mean dose, 6 months 80 mg (range 20–120 mg)	Methadone use, baseline vs 6 months Proportion of patients with increased QTc (>430 ms for men; >450 ms for women): 14% (17/118) vs 31% (37/118); $P = .2$ Mean QRS duration: 92.8 ms vs 92.6 ms, mean difference –.2; $P = .76$ No incidence of torsades de pointes, arrhythmia	Fair
Lipski, 1973[59]	Cross- sectional	Asymptomatic (not described) MMT patients	n = 75 (41 methadone patients) Mean age 33 years Approximately 25% female Race not reported	Oral methadone: mean dose 87 mg (range 10–600; median 70)	Methadone vs no intervention QTc prolongation (not defined) 14/41 (34%) vs 0/32 (0%)	Poor
Maremmani, 2005[61]	Case series	Methadone treatment for at least 6 months, steady methadone dose for at least 4 months, active clinic participation	n = 83 Mean age 34 years 24% female Race not reported	Oral methadone: mean dose 87 mg, range 10–600 mg	Proportion of patients with pathologic QTc duration (>470 ms in men, >480 ms in women): 2% (2/83; both male) Methadone dose, gender not associated with prolongation	Not rated

Table 3. Continued

Author, Year	Study Design	Inclusion Criteria	Population Characteristics	Interventions	Results	Quality
Martell, 2005[62] Other publications: Krantz, 2008[51]	Prospective before-after	Age >18 years with opioid addiction duration of at least 1 year and at least 1 previous attempt at detoxification	n = 160 Mean age 43 years 37% female Race not reported	Oral methadone: mean dose, 6 months: 80 mg, range 20–120 mg); mean dose, 12 months 90 mg, range 20–200 mg)	Methadone use, baseline vs 6 months Proportion with QTc interval >450 ms (men) or >470 ms (women): 5/160 (3%) vs 18/149 (12%) QRS interval: 93 (SD 8) ms vs 93 (SD 8); magnitude of change –.2 (SD 6); $P = .7$ Methadone use, baseline vs 12 months: Proportion with QTc interval >450 ms (men) or >470 ms (women): 5/160 (3%) vs 14/108 (13%) QRS interval: 93 (SD 8) ms vs 91 (SD 8); magnitude of change –.8 (SD 3); $P = .4$ No incidence of torsades de pointes, cardiac arrhythmia, or syncope	Fair
Mayet, 2011[66]	Case series	Opioid dependence, receiving stable dose of methadone for ≥4 weeks	n = 83 Mean age 40 years 29% female 12% nonwhite	Oral methadone: mean dose 75 mg/day	Mean QTc interval: 429 ms Proportion with QTc interval ≥450 ms (men) or ≥470 ms (women): 18% (15/83) Proportion with QTc interval >500 ms: 0% (0/83)	Not rated
Peles, 2007[83]	Case series	Methadone maintenance for at least 100 days	n = 138 Mean age 41 years 29% female Race not reported	Oral methadone: mean dose 171 mg/day	QTc interval 450–460 ms: 12/138 (9%) 461–500 ms: 7/138 (5%) >500 ms: 3/138 (2%) Mortality, mean follow-up 1.2 years: 2/138 (2%)	Not rated
Reddy, 2004[85]	Retrospective before-after	Outpatients treated with methadone for cancer pain, based on prescription data, with ECG data	n = 56 No demographic data reported	Oral methadone: median dose 30 mg/day, range 2–480 mg/day	Baseline vs follow-up QTc >500 ms: 2/56 (4%) vs 0/56 (0%) Mean QTc interval: 413 ms (SD 30) vs 413 ms (SD 26)	Poor

Table 3. Continued

Author, Year	Study Design	Inclusion Criteria	Population Characteristics	Interventions	Results	Quality
Reddy, 2010[86]	Prospective before-after	Cancer diagnosis, no prior history of methadone use, started on methadone for pain management	n = 100 Median age 56 years 54% female 30% nonwhite	Oral methadone: median dose 23 mg/day, range 3–90 mg/day	Baseline vs 2-week follow-up Median QTc interval: 429 vs 429 ms QTc > upper limit of normal (>430 ms for males, >450 ms for females): 28% (28/100) vs 31% (20/64) QTc >500 ms: 0% (0/100) vs 1.6% (1/64) QTc >10% above baseline: 7.8% (5/64) at 2 weeks QTc >25% above baseline: 0% (0/64) at 2 weeks	Poor
Roy, 2012[90]	Case series	Stable methadone maintenance for >3 months	n = 180 Mean age 33 years 31% female Race not reported	Oral methadone: mean dose 80 mg/day	Proportion of men with QTc >450: 15/125 (8.3%) Proportion of women with QTc >470: 1/55 (.5%) Proportion with QTc >500 ms: 0%	Not rated
Schmittner, 2009[91]	Before-after	Age 18–45 years; opioid dependent according to DSM-IV criteria; self-report at least 30 day use; willing to undergo urine toxicology screening	n = 14 Mean age 35 years 43% female 57% black (other races not reported)	3-week oral methadone 30–80 mg/day	Methadone use, baseline vs follow-up No statistically significant differences in PR, QRS, or QTc intervals reported in text; data not shown	Fair

Abbreviations: DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; MMT, methadone maintenance treatment; OMT, oral methadone treatment; OR, odds ratio; SD, standard deviation; SE, standard error.

Table 4. Cardiovascular Events and ECG Changes With Methadone Use Compared With Another Opioid

Author, Year	Study Design	Inclusion Criteria	Population Characteristics	Interventions	Results	Quality
Anchersen, 2009[1]	Cross-sectional	OMT patients willing to participate (all subjects were recruited)	Total cohort: n = 200 Mean age 41 years 69% male	Oral methadone: mean dose 111 mg (SD 35) Sublingual buprenorphine: 19 mg (SD 5)	Methadone vs buprenorphine QTc interval >500 ms: 5% (8/173) vs 0% (0/27)	Fair
Athanasos, 2008[3]	Cross- sectional	Methadone or buprenorphine dependent	n = 54 Mean age 35 years 63% male Race not reported	Methadone: mean dose 69 mg (SD 29) Buprenorphine: mean dose 11 mg (SD 5)	Methadone vs buprenorphine Mean QTc duration: 407 ms vs 407 ms; $P = .27$ Prolonged (>430 in men) QTc interval: 6% (2/35) vs 0% (0/19); all subjects with prolonged QTc interval were men Presence of U-waves: 31% (11/35) vs 0% (0/19)	Fair
Fanoe, 2007[27]	Cross-sectional	Age >18 years treated with methadone or buprenorphine on a daily basis	n = 450 Mean age 41 years 74% male Race not reported 30% self-reported illicit opioid use within week prior to study interview	Oral methadone: 100 mg median dose Oral buprenorphine: mean dose 5.4 mg	Methadone vs buprenorphine QTc interval >440 ms: 127/407 (31%) vs 0/34 (0%) Self-report syncope: 21% vs 9%, RR 2.3, 95% CI .87–5.8	Fair
Kornick, 2003[50]	Cross-sectional	Patients receiving IV methadone or morphine at Memorial Sloan Kettering Cancer Center between July 1999 and March 2001	n = 82 Demographic data not reported	IV methadone, mean dose 17.8 mg/hour (range .1–97.1; SE 20.6) IV morphine, mean dose 9.8 mg (range .7–35; SE 7.9)	Methadone vs no methadone: mean difference QTc interval, 41.7 ms (SE 7.8 ms); $P < .0001$ Morphine vs no morphine: mean difference QTc interval: 9.0 ms (SE 6.1 ms); $P = .15$	Good
Stallvik, 2013[96]	Cohort	OMT patients on methadone or buprenorphine in Norway	n = 80 Mean age 36 years Race not reported	Oral methadone: mean dose 88–96 mg/day Oral buprenorphine: mean dose 16–19 mg/day	Methadone vs buprenorphine Mean QTc duration: 408 ms vs 398 ms ($P > .05$) QTc >450 ms: 0/45 (0%) vs 0/35 (0%)	Fair
Wedam, 2007[105] Other publications: Johnson, 2000[45]	Randomized controlled trial	Age 21–55 years; DSM-IV opioid-dependent; evidence of recent opioid use on toxicology screen	n = 154 Mean age 36 years 62% male 60% nonwhite (not described) Mean heart rate 64 beats/minute	Methadone 60–100 mg Buprenorphine 16–32 mg	Methadone vs buprenorphine QTc >470 (men)/490 (women) ms: 12/53 (23%) vs 0/54 (0%); OR 14.4 (95% CI 1.9–109.5; $P = .01$) >60 ms change in QTc from baseline: 12% vs 2%; OR 8.4 (95% CI 1.9–36.4)	Good

Abbreviations: DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; OMT, oral methadone treatment; OR, odds ratio; SD, standard deviation; SE, standard error.

Table 5. Methadone Dose and Duration and Adverse Events

Author, Year (Sample Size)	Prospective Design	Adjustment for Confounders	Method of Analyzing Methadone Dose	Findings
Anchersen, 2009[1] (n = 200)	Yes	No	Continuous variable	Methadone dose and QTc prolongation: correlation coefficient .367 (95% CI .22–.51)
Athanasos, 2008[3] (n = 54)	Yes	No	<60 vs >60 mg/day	No correlation between methadone dose and QTc prolongation
Buster, 2002[8] (n = 5,200)	No	Yes	Recent methadone use vs continuous use	Recent initiation of methadone associated with increased risk compared to continued use: adjusted RR 2.9 (95% CI 1.4–5.8)
Chang, 2012[12] (n = 283)	No	Yes	Continuous variable	Methadone dose and QTc prolongation: correlation coefficient .210 (P = .0014) in males and .164 (P = .2363) in females
Cousins, 2011[19] (n = 3,162)	No	Yes	<60 vs ≥60 mg/day	Drug-related mortality: adjusted HR .98 (95% CI .44–2.18)
Cruciani, 2005[20] (n = 110)	Yes	No	Continuous variable	Effect size .03, P = .89 for methadone dose
Ehret, 2006[24] (n = 247)	No	Yes	Continuous variable	Correlation between daily methadone dose and QTc prolongation, rs = .20; P < .01
Fanoe, 2007[27] (n = 450)	No	No	Continuous variable	Higher rate of self-reported syncope per 50 mg/day increase in methadone dose: OR 1.2 (95% CI 1.1–1.4)
Huh, 2010[43] (n = 90)	No	No	Continuous variable	No association between methadone dose and QTc interval (average dose 30 mg/day)
Justo, 2006[47] (n = 40)	No	No	Continuous variable	High-dose methadone commonly associated with TdP (98% of patients)
Katz, 2013[48] (n = 531)	No	Yes	Continuous variable	Higher methadone dose associated with greater magnitude of increase in the QTc interval from baseline (P = .009)
Krantz, 2003[53] (n = 17)	No	Yes	Continuous variable	Higher methadone dose associated with increased risk of TdP (r = .51; P = .03)
Krebs, 2011[57] (n = 108,492)	No	Yes	Continuous variable	Mortality risk lower for methadone compared to morphine; dose-adjusted HR .58 (95% CI .52–.64). Most deaths occurred during the first 30 days of use in both groups
Martell, 2005[62] (n = 160)	Yes	Yes	Continuous variable	Higher serum methadone level significantly associated with QTc prolongation at 6 and 12 months
Mayet, 2011[66] (n = 83)	Yes	Yes	Continuous variable	Methadone dose predicted longer QTc duration (β .318; P = .003)
McCowan, 2009[68] (n = 2,378)	No	Yes	Continuous variable	Increased duration of treatment associated with decreased risk of all-cause mortality: HR .95 (95% CI .94–.96)
Roy, 2011[90] (n = 180)	No	Yes	Continuous variable	No association between methadone dose and degree of QTc prolongation (average dose ~80 mg/day)
Stallvik, 2013[96] (n = 45)	No	Yes	Continuous variable	No association between methadone dose and degree of QTc prolongation (average dose 88–96 mg/day)
van Ameijden, 1999[100] (n = 498)	Yes	Yes	5–55 mg/day; 55–75 mg/day; >75 mg/day	Higher methadone dose associated with lower rate of death due to overdose
Zador, 2000[110] (n = 238)	No	Yes	Daily dose of 266 mg	Higher dose associated with more severe sleep apnea (P = .002 for apnea-hypopnea; P = .008 for central apnea)

Abbreviations: OR, odds ratio; TdP, Torsades de pointes.

Risks of Adverse Events With Methadone Compared to Other Opioids

Mortality and Overdose

Methadone was not associated with increased risk of all-cause mortality versus morphine in 1 fair-quality cohort study (n = 5,684) based on Oregon Medicaid administrative data of patients with chronic noncancer or cancer pain (adjusted hazard ratio [HR] .71, 95% CI .46–1.08).[42] There was also no difference in risk of emergency department encounters or overdose symptoms. Although methadone was associated with increased risk of opioid poisoning, the difference was not statistically significant (adjusted HR 3.22, 95% CI .60–17.25), and this

outcome was defined using nonspecific symptoms such as alteration of consciousness, malaise, fatigue, lethargy, or respiratory failure. In another fair-quality cohort study (n = 98,068) based on national Veterans Affairs administrative data, methadone was associated with decreased all-cause mortality risk compared to morphine based on an analysis stratified according to propensity to be prescribed methadone (adjusted HR .56, 95% CI .51–.62).[57]

Randomized trials of methadone versus other opioids were not designed to assess mortality and reported few or no events.[6,45,64,69,70,74,102] Epidemiologic studies found methadone to be associated with higher risk of overdose than other opioids, but they did not evaluate true inception cohorts of patients prescribed different opioids, they used surrogate denominators (such as dispensing or sales rates) to estimate risk, and they were not designed to distinguish adverse events associated with prescribed versus illicit use of opioids.[10,79-81] One recent study found that methadone accounted for 9.0% (in morphine milligram equivalents) of prescribed opioids in 2009 but 31% of deaths.[10] Using kilograms sold as the denominator, the rate of methadone deaths (9.7 deaths per 100 kg morphine milligram equivalents) was higher than for any other opioid (9.7 vs .1–3.8 deaths per 100 kg morphine milligram equivalents for single-drug deaths, and 33.6 vs .8–20.2 for all deaths).

Cardiovascular Events

Cardiac events associated with methadone use were infrequently reported. One fair-quality cross-sectional study found a nonstatistically significant trend in syncope with methadone compared to buprenorphine in patients treated for opioid addiction (RR 2.3, 95% CI .87–5.8) but relied on retrospective recall of syncopal episodes.[27]

ECG Changes

One good-quality randomized controlled trial[105] and 3 fair-quality cross-sectional studies[1,3,27] found methadone for treatment of opioid dependence to be associated with increased risk of QTc interval prolongation compared to buprenorphine (Table 4). In the 4 studies, a total of 668 participants received methadone (mean doses ranged from 69 to 111 mg), and 131 received buprenorphine (range 5–19 mg). One cohort study (n = 80) found no cases of QTc interval prolongation >450 ms with either methadone (mean dose 88–96 mg) or buprenorphine (16–19 mg).[96]

The randomized controlled trial found that 23% (12/53) of patients with a normal ECG at baseline randomized to methadone developed QTc interval prolongation (>470 ms for men or >490 ms for females) compared to no cases in 54 patients randomized to buprenorphine (odds ratio 14, CI 1.9–110).[105] Twelve percent of patients on methadone had an increase in QTc interval >60 ms compared with 2% with buprenorphine. In the cross-sectional studies, the incidence of QTc interval prolongation (variably defined) ranged from 5 to 31% in the methadone groups, with no cases reported in the buprenorphine groups.[1,3,27] An observational study that compared ECG findings on and off intravenous opioids in hospitalized patients with cancer pain found methadone to be associated with a larger increase in QTc interval compared to morphine (42 vs 9.0 ms), though findings may have been confounded by QTc-prolonging effects of the carrier agent chlorobutanol.[50]

Effects of Dose or Duration on Methadone-Associated Adverse Events

Mortality and Overdose

Two fair-quality cohort studies found no clear association between higher doses of methadone maintenance therapy and risk of overdose death or all-cause mortality.[19,100] No study specifically evaluated the association between methadone dose and overdose risk in patients with chronic pain, although 2 observational studies found an association between higher doses (based on morphine equivalents) of opioids in general and increased risk of mortality.[19,100]

Recent initiation or shorter duration of methadone use was associated with increased risk of mortality in 5 observational studies (Table 5).[8,19,57,68,110] Two studies found that a high proportion of methadone-associated deaths occurred soon after methadone initiation for chronic pain (about two-thirds of deaths occurred within the first 30 days of therapy)[57] or methadone maintenance therapy (about 21% of deaths occurred within the first week).[110] Three studies found the period soon after initiation of methadone maintenance therapy associated with increased mortality risk,[8,19,68] though risk estimates were close to 1 in 1 of the studies.[68] In the 2 other studies, treatment for 3 to 10 weeks and >10 weeks was associated with lower risk of drug-related mortality than treatment for 1 to 2 weeks (adjusted HR .40, 95% CI .17–.95, and .10, 95% CI .03–.35, respectively)[19] and recent initiation associated with increased risk compared to continued use (adjusted RR 2.9, 95% CI 1.4–5.8).[8]

Cardiovascular Events and ECG Changes

One cross-sectional study found higher doses of methadone maintenance therapy associated with increased risk of self-reported syncope in the last year (odds ratio 1.2 per 50 mg of methadone, 95% CI 1.1–1.4; Table 5).[27]

Six studies found higher methadone doses or higher methadone serum concentrations associated with greater QTc interval prolongation after controlling for other factors associated with QTc interval prolongation.[24,27,48,53,62,66] In these studies, the amount of QTc variability explained by differences in methadone dose ranged from 1 to 28%. Other studies found higher methadone dose associated with QTc interval prolongation in a specific subgroup (eg, men[12,20]) or based on univariate analyses.[1,3] One cohort study found QTc intervals of >500 ms only in patients prescribed 120 mg/day or more of methadone.[1] Studies that found no association between methadone dose and QTc interval prolongation tended to evaluate populations on relatively low (eg, <50 or <100 mg/day) mean doses of methadone.[3,43,96]

Case series (n = 17 patients[53] and 40 patients[47]) reported high daily methadone doses (mean dose

Table 6. Risk Factors for Mortality and Overdose Outcomes With Methadone Use

Author, Year	Study Design	Inclusion Criteria	Population Characteristics	Interventions	Results	Quality
Ballesteros, 2003[4]	Case series	Accidental death with methadone as primary cause	n = 198 Mean age 39 years 64% male 98% white 75% cases methadone was the only drug contributing to death; 49% (97 cases) the source of methadone was known	Methadone; mean dose not reported	Source in methadone-related overdose deaths (available for 97 cases): 75% (73/97) prescribed by a physician 25% (24/97) obtained illicitly In opiate treatment program in North Carolina at time of death (available for 198 cases): 4% (8/198) identified as in treatment 96% (190/198) not identified as in treatment	Not rated
Barrett, 1996[5]	Case series	Medical examiner cases where drug screen was performed and there was evidence of methadone	n = 91 Median age 35 years 67% male 85% white	Methadone; mean dose not reported	Death due to methadone toxicity: 12% (11/91) Death due to polydrug toxicity: 37% (34/91)	Not rated
Bryant, 2004[7]	Case series	Accidental overdose deaths from methadone or heroin	n = 7,451 (1,024 methadone overdoses, 4,627 heroin overdoses, 408 both) Mean age not reported: age 15–24 years: 5%; age 24–34 years: 29%; age 35–44 years: 43%; age 45–54 years: 19%; age 55–64 years: 4% 79% male 34% white, 36% black, 30% Hispanic 81% methadone detected	Methadone, heroin	Methadone-induced overdose deaths, risk factors: Men vs women, AOR .6 (CI .52–.70) Age 15–24 vs: age 25–34 years, AOR 1.69 (CI 1.08–2.64); age 35–44 years, AOR 3.03 (CI 1.97–4.67); age 45–54 years, AOR 2.79 (CI 1.78–4.35); age 55–64 years, AOR 2.34 (95% CI 1.37–4.01) Cocaine detected vs no cocaine detected in toxicology, AOR .56 (CI .49–.64) Heroin vs no heroin detected in toxicology, AOR .46 (CI .40–.53) Alcohol vs no alcohol present in toxicology, AOR .78 (CI .68–.91) Deaths in 1990 vs: 1997, AOR .58 (CI .42–.82); 1998, AOR .69 (CI .50–.96)	Not rated
Buster, 2002[8]	Retrospective cohort study	Current and former methadone patients (within 1 year of leaving treatment) in Amsterdam, The Netherlands, between January 1, 1986, and December 1998	n = 5,200 Mean age not reported; 71% age 30–39 years 77% male Race not reported	Methadone; mean dose not reported	1% (68/5,200) overdose deaths Risk of mortality: Men vs women: ARR 3.3 (95% CI 1.5–7.2), and being born native of The Netherlands vs other countries: ARR 5.0 (95% CI 2.3 to11)	Fair

Table 6. Continued

Author, Year	Study Design	Inclusion Criteria	Population Characteristics	Interventions	Results	Quality
Chan, 2006[11]	Case series	Decedents with methadone found in their toxicologic analyses at death, hospitalized patients	n = 500 Mean age 46 years 76% male 31% white, 27% black, 41% Hispanic Subjects in the accidental overdose group were significantly younger (44 vs 48 years; $P < .001$) and were more likely to be white race (41% vs 23%; $P < .01$) compared to the death for all causes group	Methadone; mean dose not reported	Overdose due to methadone vs death from other cause Concomitant benzodiazepines, OR 1.66 (CI 1.12–2.45) Concomitant tricyclic antidepressant and benzodiazepine, OR 4.34 (CI 1.97–9.56) Risk factors associated with a methadone overdose vs death from another cause: White race, OR 4.27 (CI 2.57–7.12) Amitriptyline use, OR 2.12 (CI 1.17–3.85) Cocaine use, OR 3.16 (CI 1.35–7.40) Morphine use, OR 2.13 (CI 1.05–4.33) Opiate use, OR 2.84 (CI 1.38–5.85) Citalopram use, OR .31 (.10–.92)	Not rated
Cousins, 2011[19]	Retrospective cohort study	Residents of Tayside, Scotland, receiving prescribed methadone between January 1993 and February 2004	n = 3,162 Mean age not reported; 46% age 20–29 years; 26% age 30–39 years 65% male Race not reported	Methadone: mean dose not reported; 74% of patients had a last methadone dose of <60 mg	Mortality risk: Psychiatric admission vs no psychiatric admission: adjusted HR 7.0 (95% CI 3.5–14) Prescription for benzodiazepines vs no prescription: adjusted HR (1.4, 95% CI 1.2–1.7)	Fair
Ernst, 2002[25]	Case series	Methadone-related deaths with methadone in toxicologic analysis between 1993 and 1999	n = 84 deaths Mean age 31 years 68% male 48% prescribed methadone 90% prescribed were enrolled in MMT; 30% had chronic pain 44% were depressed and/or suicidal 27% had history of drug overdose 19% had schizophrenia or other psychotic disorder	Methadone: mean dose not reported	64% (54/84) died from accidental causes 74% (40/54) of accidental cause of death was combination of drug effects Among MMT patients (n = 36), 28% (10/36) died within <1 week of methadone initiation, 72% (26/36) died after the first week of MMT	Not rated
Gagajewski, 2003[32]	Case series	Intentional and unintentional deaths associated with methadone as found in toxicologic analysis during autopsy between 1992 and 2002	n = 96 cases (MMT cases n = 33) Mean age 45 years 77% male 91% white	Methadone: mean dose not reported	9% (3/33) MMT patients died during the first week of methadone induction Benzodiazepines were found in 67% (22/33) of the MMT group For those who were prescribed methadone for pain (n = 15), 47% (7/15) died from overdose vs 53% (8/15) from natural causes	Not rated

Table 6. Continued

Author, Year	Study Design	Inclusion Criteria	Population Characteristics	Interventions	Results	Quality
McCowan, 2009[68]	Retrospective cohort study	Registered with a Tayside, Scotland, general practitioner; prescribed and dispensed methadone between January 1993 and February 2004	n = 2,378 Mean age not reported (range 16–60 years) 55% of population aged 20–29 years 67% male Race not reported	Methadone: mean dose not reported, 85% mean dose <60 mg	Incidence All-cause mortality 8% (181/2,378) Death due to drug dependence 3% (60/2,378) Charlson Comorbidity Index 1–2: AHR 1.08 (95% CI 1.02–1.14) Charlson Comorbidity Index >3: AHR 1.20 (95% CI 1.15–1.26) Overusing methadone: AHR 1.67 (95% CI 1.05–2.67) Duration of methadone treatment (years): AHR .95 (95% CI .94–.96) Time since last prescription filled (4–6 months): AHR .91 (95% CI .84–.99) Time since last prescription filled (>6 months): AHR .70 (95% CI .66–.73) Having urine tested: AHR .33 (95% CI .22–.49) Duration of treatment years: AHR .93 (95% CI .92–.95) >6 months since prescription: AHR .02 (95% CI .00–.05) History of psychiatric admission: AHR 2.41 (95% CI 1.25–4.64) Use of benzodiazepines: AHR 4.35 (95% CI 1.32–14.30) Antipsychotic use: AHR .27 (95% CI .08–.89) Antidepressant use: AHR .51 (95% CI .30–.98)	Fair
Neale, 2000[73]	Case series	Nonfatal overdose treated in the hospital or emergency department and current methadone prescription, use of methadone prior to overdose, or desire for methadone at the time of the interview	n = 33 Mean age 26 years (range 18–36 years) 64% male 97% white	Methadone: mean dose for 64% of population 65 mg (range 30–110)	Reported dose of methadone taken prior to overdose was 35–1,000 mg (median 110 mg) Accidental overdose 12% (4/33) Diversion 9% (3/33)	Not rated

Table 6. Continued

Author, Year	Study Design	Inclusion Criteria	Population Characteristics	Interventions	Results	Quality
Seymour, 2003[92]	Case series	Methadone found on toxicologic analyses at death and found to contribute to cause of death	n = 270 (187 methadone related) Mean age 27 years (range 15–58) 79% male Race not reported 97% history of substance abuse 68% active IV drug users 43% in MMT 37% prescribed methadone 55% obtained illicit methadone	Methadone: mean dose not reported	85% (230/270) of deaths were polydrug related 65% (176/270) decedents died with concomitant diazepam 31% (84/270) decedents died with concomitant temazepam 34% (95/270) decedents died with concomitant heroin 55% (149/270) of deaths occurred over the weekend 46% (124/270) of weekend deaths were in MMT No association between timing of death and MMT (P = .13)	Not rated
Shah, 2005[93]	Case series	New Mexico residents with unintentional drug overdose between 1998 and 2002 based on cause of death determination and finding methadone in the toxicologic analyses at death	n = 1,120 Median age 40 years 75% male 53% Hispanic; 42% White; 5% Black, American Indian, or Asian	Methadone: mean dose not reported	Overdose due to methadone vs other drugs: no statistically significant associations with sex, race, or age in adjusted analysis	Not rated
Sunjic, 1997[98]	Case series	Medical examiner methadone-related deaths	n = 25 deaths Mean age 30 years; range 17–53 76% male Race not reported	Methadone: mean dose not reported	92% (23/25) died from polydrug toxicity 44% (11/25) died with alcohol 53% (13/25) died with benzodiazepines 50% (13/25) of these were taking methadone for pain 14% (4/25) of these were in MMT 40% (10/25) injected methadone prior to death	Not rated
Ward, 2001[104]	Case series	Opioid-related deaths examined by the medical examiner	n = 84 (45 methadone-related deaths; 15 prescribed methadone) Mean age 30 years 93% male Race not reported ≥2 drugs on toxicologic analysis (n = 73, 87%)	Methadone: mean dose not reported	Presence of methadone or morphine 86% (72/84) Presence of other opioids 17% (14/84) Presence of benzodiazepines 62% (51/84) Presence of 2 or more drugs 87% (73/84)	Not rated

Table 6. Continued

Author, Year	Study Design	Inclusion Criteria	Population Characteristics	Interventions	Results	Quality
Weimer, 2011[106]	Case series	All deaths where methadone was found on the toxicology at death	n = 203 Mean age 36 years 64% male 95% white 54% history of substance abuse 61% died of polysubstance overdose	Methadone: mean dose not reported	Methadone source: 67% (41/61) obtained illicitly 28% (17/61) prescribed by a physician for analgesia 5% (3/61) obtained from an OTP Prescribed methadone vs illicit source: older age, OR 1.16 (CI 1.06–1.26) Antidepressant use, OR 8.78 (CI 2.3–33.2) Illicit methadone vs prescription or MMT source: younger age, OR .92 (CI .86–.97) Less likely to have antidepressants, OR .17 (CI .05–.61)	Not rated
Williamson, 1997[107]	Case series	Decedents with methadone in toxicologic analyses at death and cause of death drug overdose	n = 47 Mean age 30 years 64% male Race not reported 36% prescribed methadone tablets for pain; 19% MMT	Methadone: mean dose not reported	Mortality, methadone for pain vs MMT: RR 7.29 (95% CI 2.15–31.48)	Not rated
Zador, 2002[111]	Case series	Deaths with methadone in blood at autopsy	n = 87 (methadone tablet deaths n = 16, methadone syrup deaths n = 63) Mean age 38 years 53% male Methadone syrup deaths: Mean age 32 years 76% male Race not reported	Methadone: mean dose not reported	Methadone tablet deaths: 29% (5/16) suicide death 47% (8/16) died of drug-related causes 24% (4/16) died of medically related causes 75% (12/16) history of chronic pain Methadone syrup deaths: 78% (49/63) died of drug-related causes 11% (7/63) died of trauma 2% (1/63) died of medically related causes 5% (3/63) died of a combination of causes 54% (47/87) were enrolled in methadone maintenance Mortality: methadone maintenance 72% (34/47) 15% (7/47) deaths during induction (first 7 days) 86% (6/7) of induction deaths were drug-related Overall mortality rate during induction 8.6 deaths/10,000 inductions (95% CI 2.2–15.0)	Not rated

Abbreviations: AHR, adjusted HR; AOR, adjusted OR; ARR, adjusted RR; MMT, methadone maintenance treatment; OR, odds ratio.

Table 7. Risk Factors for Adverse Cardiovascular Events and ECG Changes With Methadone Use

Author, Year	Study Design	Inclusion Criteria	Population Characteristics	Interventions	Results	Quality
Chang, 2012[12]	Before-after	Methadone maintenance with opioids addiction >1 year	n = 150 Mean age 37 years 16% female Race not reported (study conducted in China)	Oral methadone: mean dose 40 mg/day	Methadone-QTc correlation significant in males (r = .210, *P* = .001) but not females (r = .164, *P* = .23)	Fair
Cruciani, 2005[20]	Cross-sectional	Adults receiving ≥20 mg/day for more than 2 weeks	n = 104 Mean age 45 years 61% male 82% white, 14% black, 5% other History of CHF, CAD, or MI: 7%; probable or definite high risk for QTc prolongation: 24%; possible or probable risk for TdP: 14%; drugs interacting with methadone: 29%; antidepressants, 35%; antiretrovirals, 17%; antimicrobials, 18%	Oral methadone: mean dose 110 mg/day	Relationship between dose and QTc significant for methadone dose and male sex (Spearman rho = .60; *P* = .01, d = 1.5)	Fair
Ehret, 2006[24]	Cross- sectional	Active or former injection drug users hospitalized between January 1999 and December 2003	n = 167 Mean age 37 years 66% male Race not reported 28% HIV, 28% HBV, 29% HCV	Methadone: 4–300 mg/day; median dose 100 mg/day Nonuse	TdP vs no TdP Increased risk based on number of concomitant medications = 9 vs 4	Fair
Fareed, 2013[29]	Case series	Methadone maintenance, treated at clinic for at least 6 months	n = 55 Mean age 56 years 7% female 64% nonwhite	Oral methadone: mean dose 90 mg/day	Factors associated with QTc >500 ms were CHF diagnosis (*P* = .04), HbA1c >6 (*P* = .05), and recent cocaine use (*P* = .03)	Not rated
Justo, 2006[47]	Case series	Not reported	n = 40 Mean age 40 years (range: 20–60 years) Gender not reported Race not reported	Methadone: mean dose 231 mg/day (range: 60–1,000 mg/day)	High-dose methadone was the most common risk factor for TdP, accounting for 98% (39/40) Second most common risk factor being concomitant use of agents that increase serum methadone levels inhibiting liver metabolism or those that trigger TdP, accounting for 55% (22/40)	Not rated

Table 7. Continued

Author, Year	Study Design	Inclusion Criteria	Population Characteristics	Interventions	Results	Quality
Krantz, 2003[53]	Case series	Inclusion: use of methadone, QTc > 500 ms in the setting of polymorphic ventricular tachycardia Exclusion: congenital long QT syndrome, inadequate documentation of arrhythmia	n = 17 Mean age 49 years 41% male Race not reported	Methadone: 283–387 mg	Mean QTc interval was 615 + 77 m Mean heart rate 64 + 15 beats/minute 41% (7/17) hypokalemia 53% (9/17) receiving potential QT-prolonging drugs 18% (3/17) had structural heart disease 82% (14/17) had 1 potential risk factor for arrhythmia 35% (6/17) patients had their methadone dose increased within 1 month prior to QT prolongation 41% (7/17) patients had been receiving methadone therapy for 3 or fewer months	Not rated
Martell, 2005[62]	Prospective cohort (before-after)	Age >18 years with opioid addiction duration of at least 1 year and at least 1 previous attempt at detoxification	n = 160 Mean age 43 years 63% male Race not reported 52% HCV 23% HIV	Methadone: mean dose, 6 months 80 mg qd (range 20–120 mg); mean dose, 12 months 90 mg qd (range 20–200 mg)	Methadone use, baseline (n = 160) vs 6 months (n = 149) Variables predictive of QTc prolongation in multivariate analysis: methadone use, male gender, HIV positive	Fair
Pearson, 2005[82]	Case series	All methadone-associated adverse events reported to the FDA from 1969 to October 2002	n = 59 Mean age 46 years (age not reported in 5 cases) 39% male Race not reported	Methadone: mean dose 410 mg (dose not reported in 17 cases)	49% of cases had at least 1 risk factor for QTc prolongation or torsades de pointes other than methadone use	Not rated
Roy, 2012[90]	Case series	Stable methadone maintenance for >3 months	n = 180 Mean age 33 years 31% female Race not reported	Oral methadone: mean dose 80 mg/day	No association between QTc prolongation and presence of cocaine metabolites in urine ($P = .13$)	Poor
Stallvik, 2013[96]	Cohort	OMT patients on methadone in Norway	n = 45 Mean age 36 years Race not reported	Oral methadone: mean dose 88–96 mg/day	QTc interval associated with serum potassium concentration ($P = .04$), no association with female sex	Fair
Viewig, 2013[103]	Review of case reports	Case reports of methadone and TdP published before January 2012	n = 31 Mean age: 45 years 61% male Race not reported	Methadone: mean dose 265 mg (dose not reported in 2 cases)	77% of cases had multiple risk factors for QTc prolongation or TdP other than methadone use	Not rated
Wedam et al, 2007[105] Other publications: Johnson, 2000[45]	Randomized controlled trial	Age 21–55 years; DSM-IV opioid dependent; evidence of recent opioid use on toxicologic screen	n = 165 Mean age 36 years 62% male 60% nonwhite (not described) Mean heart rate 64 beats/minute	Methadone: 60–100 mg Buprenorphine: 16–32 mg Levomethadyl: 75–155 mg	No association between sex and magnitude of QTc interval changes	Fair

Abbreviations: CHF, congestive heart failure; CAD, coronary artery disease; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; HbA1c, hemoglobin A1c; HBV, hepatitis B virus; HCV, hepatitis C virus; MI, myocardial infarction; OMT, oral methadone treatment; TdP, torsades de pointes.

Table 8. Summary of Evidence

Outcomes	Number and Type of Studies	Summary of Findings	Limitations	Precision	Consistency	Strength of Evidence
Adverse events: methadone use vs nonuse						
Mortality and overdose	9 studies: 1 SR (including 4 RCTs); 4 observational studies	Methadone maintenance therapy was associated with a trend toward lower risk of all-cause mortality in a systematic review of 4 RCTs (pooled RR .48, CI .10–2.4). A significantly higher proportion of cases of sudden death in methadone users was associated with no structural heart abnormalities compared to sudden death in nonmethadone users (77% vs 40%, $P = .003$), but the study had methodologic shortcomings.	Risk estimates from RCTs were imprecise; studies did not distinguish deaths related to prescribed methadone use from deaths related to other causes; lack of adjustment for confounders in observational studies	Imprecise	Inconsistent	Low
Cardiovascular events	2 observational studies	One before-after study reported no cases of torsades de pointes following methadone initiation and 1 fair-quality cross-sectional study found that 4% (6/167) of methadone users had torsades de pointes on ECG, with no cases (0/80) in injection drug users not using methadone.	No RCTs; lack of adjustment for confounders in observational studies	Imprecise	Inconsistent	Low
ECG changes	19 observational studies	The proportion of patients on methadone with QTc prolongation ranged from 0 to 37% with methadone use and 0–14%. Prevalence of QTc prolongation ranged from 0 to 32%, depending on threshold; prevalence of QTc >500 ms ranged from 0 to 6%.	No RCTs; lack of adjustment for confounders in observational studies; prevalence data from uncontrolled observational studies used inconsistent QTc thresholds	Imprecise	Consistent	Moderate
Adverse events: methadone vs other opioids						
Mortality and overdose	12 studies: 6 RCTs; 6 observational studies	Methadone was not associated with increased risk of mortality compared to other opioids in 2 large cohort studies. RCTs of methadone vs other opioids were not designed to assess mortality and reported few events. Epidemiologic studies found methadone associated with higher risk of overdose than other opioids, but did not evaluate true inception cohorts of patients prescribed different opioids, used indirect and surrogate denominators to estimate risk, and were not designed to distinguish adverse events associated with prescribed vs illicit use of opioids.	RCTs were fair or poor quality and were not powered to evaluate mortality risk; lack of adjustment for confounders in observational studies	Imprecise	Inconsistent	Low
Cardiovascular events	1 observational study	One cross-sectional study found a nonstatistically significant trend toward retrospectively self-reported syncope with methadone compared to buprenorphine.	No RCTs; limited evidence from 1 methodologically flawed observational study	Imprecise	Not applicable	Low

Table 8. Continued

Outcomes	Number and Type of Studies	Summary of Findings	Limitations	Precision	Consistency	Strength of Evidence
ECG changes	4 studies: 1 RCT; 4 observational studies	Methadone for treatment of opioid dependence was associated with increased risk of variably defined QTc prolongation compared to buprenorphine.	All studies flawed due to inadequate reporting methods	Imprecise	Some inconsistency	Moderate
Effects of dose or duration on methadone-associated adverse events						
Mortality and overdose	6 observational studies	Two studies found no association between higher methadone dose and risk of mortality, but were not designed to distinguish deaths related to methadone use vs deaths due to vother causes. Recent initiation or shorter duration of methadone use appeared to be associated with an increased risk of mortality in 5 observational studies.	No RCTs	Imprecise	Consistent	Dose: Low Duration: Moderate
Cardiovascular events and ECG changes	14 studies: 12 observational studies; 2 case series	One cross-sectional study found higher doses of methadone maintenance therapy associated with increased risk of self-reported syncope. Higher methadone dose was consistently associated with greater QTc prolongation in 5 studies after controlling for other risk factors, accounting for 1–32% of the observed QTc variability. Two case series reported high daily methadone doses in patients with torsades de pointes.	No RCTs	Precise	Consistent	Moderate
Risk factors for methadone-associated adverse events						
Mortality and overdose	16 studies: 2 observational studies; 14 case series	A large, retrospective cohort study of patients on methadone maintenance therapy found presence of medical comorbidities, overuse of methadone, and psychiatric admission associated with increased risk of all-cause mortality and psychiatric admission and co-prescription of benzodiazepines associated with increased risk of drug-related deaths. A smaller cohort study also found history of psychiatric admissions and benzodiazepines associated with increased risk of drug-related mortality. Case series of methadone-related deaths commonly reported presence of concomitant benzodiazepines and other medications.	No RCTs or prospective observational evidence	Precise	Consistent	Moderate

Table 8. Continued

Outcomes	Number and Type of Studies	Summary of Findings	Limitations	Precision	Consistency	Strength of Evidence
Cardiovascular events and ECG changes	12 studies: 1 RCT; 7 observational studies; 4 case series	There was no association between sex and magnitude of QTc interval changes in 1 RCT. Some observational studies found an association between use of other QTc-prolonging medications, altered liver function, hypokalemia, and increased risk of QTc prolongation in patients prescribed methadone, but others found no associations. Presence of other risk factors (besides methadone use) for QTc prolongation or torsades de pointes were common in case series.	Limited evidence from RCTs or prospective, well-controlled observational studies	Imprecise	Inconsistent	Low
Accuracy and clinical effects of baseline or follow-up ECG in patient prescribed methadone						
No studies	No studies		No studies	Not applicable	Not applicable	No evidence
Clinical effects of strategies to mitigate risks in patients with QTc prolongation on methadone						
No studies	No studies		No studies	Not applicable	Not applicable	No evidence

Abbreviations: RCTs, randomized controlled trials; SR, systematic review.

231 mg/day[47] and 397 mg/day[53]) in patients prescribed methadone with torsades de pointes.

Risk Factors for Methadone-Associated Adverse Events

Mortality and Overdose

A fair-quality retrospective cohort study (n = 2,378) of patients on methadone maintenance therapy found presence of medical comorbidities, overuse of methadone, and psychiatric admission to be associated with increased risk of all-cause mortality and psychiatric admission, and found co-prescription of benzodiazepines to be associated with increased risk of drug-related deaths (Table 6).[68] Another retrospective study (n = 3,162) of methadone maintenance patients also found a history of psychiatric admissions and prescription for benzodiazepines associated with increased risk of drug-related mortality.[19]

Fourteen case series reported characteristics associated with adverse outcomes in persons prescribed methadone[4,5,7,11,25,32,73,92,93,98,104,106,107,111] (Table 6). Five studies reported that both benzodiazepines and methadone were present in blood toxicology in 36 to 67% of methadone overdose deaths,[11,32,92,98,106] 5 studies reported concomitant use of methadone and multiple prescription or nonprescription medications in 61 to 92% of deaths,[5,92,98,104,106] and 4 studies reported an illicit source of methadone in 25 to 67% of overdose deaths.[4,98,106,107]

Cardiovascular Events and ECG Changes

A fair-quality randomized trial of methadone versus buprenorphine for treatment of opioid dependence found no association between sex and magnitude of QTc interval changes (Table 7).[105]

Several cross-sectional studies evaluated the association between various risk factors and risk of QTc interval prolongation or torsades in patients prescribed methadone (Table 7). Although some studies found use of other QTc-prolonging medications to be associated with increased risk of QTc interval prolongation in patients prescribed methadone,[24,43] others found no association.[20,62] Some studies also found an association between altered liver function,[24] elevated hemoglobin A1c level,[29] congestive heart failure,[29] male sex,[12,20,62] hypokalemia,[24,96] or use of cocaine or amphetamines[29,66] and increased risk of QTc interval prolongation in patients prescribed methadone. In case series of QTc interval prolongation or torsades de pointes associated with use of methadone, one-half or more of cases had at least 1 risk factor for QTc interval prolongation or torsades de pointes other than methadone use (eg, interacting medications, hypokalemia, hypomagnesemia, or structural heart disease; Table 7).[47,53,82,103]

Accuracy and Clinical Effects of Baseline or Follow-Up ECG in Patient Prescribed Methadone

We identified no study on the accuracy or clinical effects of performing a baseline or follow-up ECG in patients prescribed methadone.

Clinical Effects of Strategies to Mitigate Risks in Patients With QTc Interval Prolongation on Methadone

No studies met inclusion criteria. Two case reports and 1 very small (n = 3) case series reported no recurrence of arrhythmias and normalization of QTc intervals in patients prescribed methadone with evidence of QTc interval prolongation or ventricular arrhythmias following a switch to buprenorphine.[26,40,52] One of these studies also reported improvement in prolongation of QTc interval and no recurrence of arrhythmias in 4 patients following reduction of methadone dose.[40]

Discussion

This report summarizes the evidence on the harms associated with use of methadone for chronic pain or for treatment of opioid dependence, risk factors for those harms, and methods for predicting, reducing, or mitigating harms. Our findings are summarized in Table 8.

Interpreting the evidence on methadone-associated mortality remains a challenge. In patients treated for opioid dependence, evidence from randomized trials found methadone associated with a nonstatistically significant trend toward decreased all-cause mortality, suggesting that any methadone-associated harms are outweighed by beneficial effects related to reduction of illicit drug use. For patients treated with methadone for chronic pain, the evidence is less clear. Despite 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 is somewhat contradictory. Although epidemiologic studies found methadone to be associated with higher mortality risk than other opioids, such studies were not based on inception cohorts of patients prescribed methadone, used surrogate denominators (eg, dispensing or sales rates) to calculate risk estimates, and were frequently unable to distinguish deaths associated with prescribed versus illicit use of methadone or identify the indication for treatment.[10,79-81] In addition, in 2 large cohort studies based on administrative data, either methadone was associated with lower risk of death compared to morphine or there was no clear difference in risk between methadone and other opioids.[42,57] In fact, in 1 large study of Veterans Affairs patients, methadone was associated with lower risk of mortality than morphine in patients with pain, after controlling for potential confounders through a propensity-stratified analysis.[57] A potential explanation for these findings is that in the VA, procedures to manage methadone more safely may mitigate potential harms,[71] rather than methadone's being "safer" per se. Evidence indicates that risk factors for methadone-associated deaths include presence of medical or psychiatric comorbidities, overuse of methadone, concomitant use of benzodiazepines or illicit drugs, and recent initiation of methadone, suggesting potential targets for risk mitigation strategies.[8,39,68]

Cardiac arrhythmias have been postulated as a potential mechanism of methadone-associated mortality. Although data to estimate the number of deaths in patients prescribed methadone due to cardiac arrhythmia are sparse, relative to respiratory depression from accidental overdose it is concluded to be low.[1] On the basis of evidence primarily from observational studies, we found methadone to be associated with increased risk of QTc interval prolongation compared to no methadone[12,24,43,51,55,59,62,91] or to buprenorphine.[1,3,27,105] In most studies, higher methadone doses appeared to be associated with increased risk for or greater magnitude of QTc interval prolongation.[24,27,48,53,62] Evidence on the association between various risk factors and severity of QTc interval prolongation in patients prescribed methadone was limited, but it suggests an association with increased dose, use of concomitant QTc-prolonging medications, presence of heart disease, liver cirrhosis or renal failure, and electrolyte abnormalities.[20,24,29,62,96,103] The clinical importance of the observed association between methadone use and QTc interval prolongation is less clear. Although one case-control study found methadone-associated cases of sudden death less likely to be related to structural heart abnormalities than were other cases of sudden death, suggesting a causal role of methadone-induced arrhythmia, the study had methodologic limitations, including failure to adjust for potential confounders and potential misclassification of "therapeutic" methadone use.[15] Prospective studies have been too small to adequately assess risk of arrhythmia in persons prescribed methadone.[27]

Evidence on methods for reducing or mitigating risks associated with methadone is extremely sparse, in part because of the large samples and follow-up that might be required to demonstrate beneficial effects on clinical outcomes. No study evaluated the usefulness of baseline screening ECGs for predicting adverse cardiovascular outcomes in patients being started on methadone, or clinical outcomes associated with use of ECG screening or monitoring compared to no screening or monitoring. No study evaluated effects on clinical outcomes of methods for mitigating risks in persons on methadone found to have prolonged QTc interval, such as dose reductions or discontinuation of methadone, switching to alternative opioids, or addressing other factors associated with QTc interval prolongation. However, this is true for almost all medications associated with QTc interval prolongation, including those for which ECG monitoring is recommended as routine practice.[23] In some cases, medications such as cisapride and terfenadine were removed from the U.S. market because of concerns about risk associated with QTc interval prolongation based on relatively small numbers of cases and very low estimated event rates.[58,108] Some evidence suggests that (*R*)-methadone may have less of an effect on QTc interval prolongation than the racemic (*R*,*S*)-methadone available in the United States, but this form of methadone is not FDA-approved and was excluded from this review.[67] No study evaluated effects of urine drug monitoring, use of information from prescription drug–monitoring programs, different methadone dosing strategies, or different methods for structuring

and monitoring care on risks of adverse events in persons prescribed methadone. Community-based prevention programs involving naloxone could reduce risk of overdose due to methadone and other opioids, but they were outside the scope of this review, with supporting evidence primarily anecdotal and observational.[16,97]

Our findings are in accordance with other recent systematic reviews and guidelines on risks associated with methadone.[17,65,78] Strengths of our review are that we assessed evidence for a number of clinically important harms, included patients prescribed methadone for treatment of opioid dependence as well as those prescribed methadone for chronic pain, and reviewed evidence from observational studies as well as randomized trials. We also utilized standardized methods for grading and synthesizing the evidence. A limitation of our review is that we excluded non–English language articles, which could result in language bias. However, empiric research suggests that exclusion of non–English language articles does not tend to result in biased findings in studies of non–complementary medicine interventions.[46,84] In addition, we had to primarily rely on observational studies, many with important methodologic shortcomings, given the lack of randomized trials addressing the key questions in this review. This is reflected in the strength of evidence ratings, which were primarily low, indicating limited certainty in the conclusions.

Methadone has become widely prescribed for treatment of chronic pain as well as treatment for opioid dependence. Trends that indicate marked increases in the absolute number of methadone-associated deaths and overdoses as well as reports linking methadone with ECG abnormalities and cardiac arrhythmias have raised important concerns regarding the safety of methadone, yet many critical research gaps related to harms remain. Research is urgently needed to better characterize the risks associated with methadone, particularly in comparison with other opioids, as is research on the usefulness of methods for predicting and reducing those risks, the cost-effectiveness of such strategies, and potential barriers to implementing strategies and their impact on patient care.

References

1. Anchersen K, Clausen T, Gossop M, Hansteen V, Waal H: Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: A mortality assessment study. Addiction 104:993-999, 2009

2. Anderson R, Saiers JH, Abram S, Schlicht C: Accuracy in equianalgesic dosing: Conversion dilemmas. J Pain Symptom Manage 21:397-406, 2001

3. Athanasos P, Farquharson AL, Compton P, Psaltis P, Hay J: Electrocardiogram characteristics of methadone and buprenorphine maintained subjects. J Addict Dis 27:31-35, 2008

4. Ballesteros MF, Budnitz DS, Sanford CP, Gilchrist J, Agyekum GA, Butts J: Increase in deaths due to methadone in North Carolina. JAMA 290:40, 2003

5. Barrett DH, Luk AJ, Parrish RG, Jones TS: An investigation of medical examiner cases in which methadone was detected, Harris County, Texas, 1987-1992. J Forensic Sci 41: 442-448, 1996

6. Bruera E, Palmer JL, Bosnjak S, Rico MA, Moyano J, Sweeney C, Strasser F, Willey J, Bertolino M, Mathias C, Spruyt O, Fisch MJ: Methadone versus morphine as a first-line strong opioid for cancer pain: a randomized, double-blind study. J Clin Oncol 22:185-192, 2004

7. Bryant WK, Galea S, Tracy M, Markham Piper T, Tardiff KJ, Vlahov D: Overdose deaths attributed to methadone and heroin in New York City, 1990-1998. Addiction 99:846-854, 2004

8. Buster MCA, van Brussel GHA, van den Brink W: An increase in overdose mortality during the first 2 weeks after entering or re-entering methadone treatment in Amsterdam. Addiction 97:993-1001, 2002

9. Caplehorn JR, Dalton MS, Haldar F, Petrenas AM, Nisbet JG: Methadone maintenance and addicts' risk of fatal heroin overdose. Subst Use Misuse 31:177-196, 1996

10. Centers for Disease Control and Prevention: Vital signs: risk for overdose from methadone used for pain relief—United States, 1999-2010. MMWR Morb Mortal Wkly Rep 61:493-497, 2012

11. Chan GM, Stajic M, Marker EK, Hoffman RS, Nelson LS: Testing positive for methadone and either a tricyclic antidepressant or a benzodiazepine is associated with an accidental overdose death: Analysis of medical examiner data. Acad Emerg Med 13:543-547, 2006

12. Chang KC, Huang CL, Liang HY, Chang SS, Wang YC, Liang WM, Lane HY, Chen CH, Stephen Huang SK: Gender-specific differences in susceptibility to low-dose methadone-associated QTc prolongation in patients with heroin dependence. J Cardiovasc Electrophysiol 23: 527-533, 2012

13. Chou R: Comparative efficacy and safety of long-acting oral opioids for chronic non-cancer pain: A systematic review. J Pain Symptom Manage 26:1026, 2004

14. Chou R, Weimer M, Dana T, Walker M, Mitchell JP: Systematic Evidence Review on Methadone Harms and Comparative Harms. Glenview, IL, American Pain Society, Available at, http://www.americanpainsociety.org/uploads/files/FINAL_Systematic_Evidence_Review_on_Methadone_Harms.pdf. Accessed February 28, 2014

15. Chugh SS, Socoteanu C, Reinier K, Waltz J, Jui J, Gunson K: A community-based evaluation of sudden death associated with therapeutic levels of methadone. Am J Med 121:66-71, 2008

16. Centers for Disease Control and Prevention: Community-based opioid overdose prevention programs providing naloxone—United States, 2010. MMWR Morb Mortal Wkly Rep 61:101-105, 2012

17. Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, Taylor RJ, Fry-Smith A, Day E, Lintzeris N, Roberts T, Burls A, Taylor RS: Methadone and buprenorphine for the management of opioid dependence: A systematic review and economic evaluation. Health Technol Assess 11:1-171, 2007. iii-iv

18. Cornish R, Macleod J, Strang J, Vickerman P, Hickman M: Risk of death during and after opiate substitution treatment in primary care: Prospective observational study in UK General Practice Research Database. BMJ 341:1-8, 2010

19. Cousins G, Teljeur C, Motterlini N, McCowan C, Dimitrov BD, Fahey T: Risk of drug-related mortality during periods of transition in methadone maintenance treatment: A cohort study. J Subst Abuse Treat 41:252-260, 2011

20. Cruciani RA, Sekine R, Homel P, Lussier D, Yap Y, Suzuki Y, Schweitzer P, Yancovitz SR, Lapin JA, Shaiova L, Sheu RG, Portenoy RK: Measurement of QTc in patients receiving chronic methadone therapy. J Pain Symptom Manage 29: 385-391, 2005

21. Dolophine® hydrochloride tablets (methadone hydrochloride tablets USP) prescribing information Nov 2006. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/006134s028lbl.pdf. Accessed January 14, 2014

22. Downs SH, Black N: The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. J Epidemiol Community Health 52:377-384, 1998

23. Drew BJ, Califf RM, Funk M, Kaufman ES, Krucoff MW, Laks MM, Macfarlane PW, Sommargren C, Swiryn S, Van Hare GF, American Heart Association; Councils on Cardiovascular Nursing, Clinical Cardiology, and Cardiovascular Disease in the Young: Practice Standards for Electrocardiographic Monitoring in Hospital Settings: An American Heart Association Scientific Statement From the Councils on Cardiovascular Nursing, Clinical Cardiology, and Cardiovascular Disease in the Young: Endorsed by the International Society of Computerized Electrocardiology and the American Association of Critical-Care Nurses. Circulation 110:2721-2746, 2004

24. Ehret GB, Voide C, Gex-Fabry M, Chabert J, Shah D, Broers B, Piguet V, Musset T, Gaspoz J-M, Perrier A, Dayer P, Desmeules JA: Drug-induced long QT syndrome in injection drug users receiving methadone: High frequency in hospitalized patients and risk factors. Arch Intern Med 166:1280-1287, 2006

25. Ernst E, Bartu A, Popescu A, Ileutt KF, Hansson R, Plumley N: Methadone-related deaths in Western Australia 1993-99. Aust N Z J Public Health 26:364-370, 2002

26. Esses JL, Rosman J, Do LT, Schweitzer P, Hanon S: Successful transition to buprenorphine in a patient with methadone-induced torsades de pointes. J Interv Card Electrophysiol 23:117-119, 2008

27. Fanoe S, Hvidt C, Ege P, Jensen GB: Syncope and QT prolongation among patients treated with methadone for heroin dependence in the city of Copenhagen. Heart 93: 1051-1055, 2007

28. Fareed A, Vayalapalli S, Byrd-Sellers J, Casarella J, Drexler K, Amar R, Smith-Cox J, Lutchman TS: Onsite QTc interval screening for patients in methadone maintenance treatment. J Addict Dis 29:15-22, 2010

29. Fareed A, Vayalapalli S, Scheinberg K, Gale R, Casarella J, Drexler K: QTc interval prolongation for patients in methadone maintenance treatment: A five years follow-up study. Am J Drug Alcohol Abuse 39:235-240, 2013

30. Fingerhut LA: Increases in poisoning and methadone-related deaths: United States, 1999–2005. Available at: http://www.cdc.gov/nchs/data/hestat/poisoning/poisoning.htm. Accessed January 14, 2014

31. Fonseca F, Marti-Almor J, Pastro A, Cladellas M, Farré M, de la Torre R, Torrens M: Prevalence of long QTc interval in methadone maintenance patients. Drug Alcohol Depend 99:327-332, 2009

32. Gagajewski A, Apple FS: Methadone-related deaths in Hennepin County, Minnesota: 1992-2002. J Forensic Sci 48: 668-671, 2003

33. Gearing FR, Schweitzer MD: An epidemiologic evaluation of long-term methadone maintenance treatment for heroin addiction. Am J Epidemiol 100:101-112, 1974

34. General Accountability Office: Methadone-associated overdose deaths: Factors contributing to increased deaths and efforts to prevent them. Available at: http://www.gao.gov/products/GAO-09-341. Accessed January 14, 2014

35. GRADE Working Group: Grading quality of evidence and strength of recommendations. BMJ 328:1490-1494, 2004

36. Gronbladh L, Ohlund LS, Gunne LM: Mortality in heroin addiction: Impact of methadone treatment. Acta Psychiatr Scand 82:223-227, 1990

37. Gunne L-M, Grönbladh L: The Swedish methadone maintenance program: A controlled study. Drug Alcohol Depend 7:249-256, 1981

38. Guyatt G, Gutterman D, Baumann MH, Addrizzo-Harris D, Hylek EM, Phillips B, Raskob G, Lewis SZ, Schunemann H: Grading strength of recommendations and quality of evidence in clinical guidelines: Report from an American College of Chest Physicians Task Force. Chest 129:174-181, 2006

39. Hall AJ, Logan JE, Toblin RL, Kaplan JA, Kraner JC, Bixler D, Crosby AE, Paulozzi LJ: Patterns of abuse among unintentional pharmaceutical overdose fatalities. JAMA 300: 2613-2620, 2008

40. Hanon S, Seewald RM, Yang F, Schweitzer P, Rosman J: Ventricular arrhythmias in patients treated with methadone for opioid dependence. J Interv Card Electrophysiol 28: 19-22, 2010

41. Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D, Methods Work Group, Third US Preventive Services Task Force: Current methods of the U.S. Preventive Services Task Force: A review of the process. Am J Prev Med 20:21-35, 2001

42. Hartung DM, Middleton L, Haxby DG, Koder M, Ketchum KL, Chou R: Rates of adverse events of long-acting opioids in a state Medicaid program [Erratum appears in Ann Pharmacother, 2007 Sep;41(9):1552]. Ann Pharmacother 41:921-928, 2007

43. Huh B, Park CH: Retrospective analysis of low-dose methadone and QTc prolongation in chronic pain patients. Korean J Anesthesiol 58:338-343, 2010

44. Inturrisi CE: Clinical pharmacology of opioids for pain. Clin J Pain 18:S3-S13, 2002

45. Johnson RE, Chutuape MA, Strain EC, Walsh SL, Stitzer ML, Bigelow GE: A comparison of levomethadyl acetate, buprenorphine, and methadone for opioid dependence. N Engl J Med 343:1290-1297, 2000

46. Juni P, Holenstein F, Sterne J, Bartlett C, Egger M: Direction and impact of language bias in meta-analyses of controlled trials: empirical study. Int J Epidemiol 31: 115-123, 2002

47. Justo D, Gal-Oz A, Paran Y, Goldin Y, Zeltser D: Methadone-associated torsades de pointes (polymorphic

ventricular tachycardia) in opioid-dependent patients. Addiction 101:1333-1338, 2006

48. Katz DF, Sun J, Khatri V, Kao D, Bucher-Bartelson B, Traut C, Lundin-Martinez J, Goodman M, Mehler PS, Krantz MJ: QTc interval screening in an opioid treatment program. Am J Cardiol 112:1013-1018, 2013

49. Kinlock TW, Gordon MS, Schwartz RP, O'Grady K, Fitzgerald TT, Wilson M: A randomized clinical trial of methadone maintenance for prisoners: Results at 1-month post-release. Drug Alcohol Depend 91:220-227, 2007

50. Kornick CA, Kilborn MJ, Santiago-Palma J, Schulman G, Thaler HT, Keefe DL, Katchman AN, Pezzullo JC, Ebert SN, Woosley RL, Payne R, Manfredi PL: QTc interval prolongation associated with intravenous methadone. Pain 105: 499-506, 2003

51. Krantz MJ: Heterogeneous impact of methadone on the QTc interval: What are the practical implications? J Addict Dis 27:5-9, 2008

52. Krantz MJ, Garcia JA, Mehler PS: Effects of buprenorphine on cardiac repolarization in a patient with methadone-related torsade de pointes. Pharmacotherapy 25:611-614, 2005

53. Krantz MJ, Kutinsky IB, Robertson AD, Mehler PS: Dose-related effects of methadone on QT prolongation in a series of patients with torsade de pointes. Pharmacotherapy 23: 802-805, 2003

54. Krantz MJ, Lewkowiez L, Hays H, Woodroffe MA, Robertson AD, Mehler PS: Torsade de pointes associated with very-high-dose methadone. Ann Intern Med 137: 501-504, 2002

55. Krantz MJ, Lowery CM, Martell BA, Gourevitch MN, Arnsten JH: Effects of methadone on QT-interval dispersion. Pharmacotherapy 25:1523-1529, 2005

56. Krantz MJ, Martin J, Stimmel B, Mehta D, Haigney MCP: QTc interval screening in methadone treatment. Ann Intern Med 150:387-395, 2009

57. Krebs EE, Becker WC, Zerzan J, Bair MJ, McCoy K, Hui S: Comparative mortality among Department of Veterans Affairs patients prescribed methadone or long-acting morphine for chronic pain. Pain 152:1789-1795, 2011

58. Lindquist M, Edwards IR: Risks of non-sedating antihistamines. Lancet 349:1322, 1997

59. Lipski J, Stimmel B, Donoso E: The effect of heroin and multiple drug abuse on the electrocardiogram. Am Heart J 86:663-668, 1973

60. Lynch ME: A review of the use of methadone for the treatment of chronic noncancer pain. Pain Res Manag 10: 133-144, 2005

61. Maremmani I, Pacini M, Cesaroni C, Lovrecic M, Perugi G, Tagliamonte A: QTc interval prolongation in patients on long-term methadone maintenance therapy. Eur Addict Res 11:44-49, 2005

62. Martell BA, Arnsten JH, Krantz MJ, Gourevitch MN: Impact of methadone treatment on cardiac repolarization and conduction in opioid users. Am J Cardiol 95:915-918, 2005

63. Martin JA, Campbell A, Killip T, Kotz M, Krantz MJ, Kreek MJ, McCarroll BA, Mehta D, Payte J, Stimmel B, Taylor T, Wilford BB: QT interval screening in methadone maintenance treatment: Report of a SAMHSA expert panel. J Addict Dis 30:283-306, 2011

64. Mattick RP, Ali R, White JM, O'Brien S, Wolk S, Danz C: Buprenorphine versus methadone maintenance therapy: A randomized double-blind trial with 405 opioid-dependent patients. Addiction 98:441-452, 2003

65. Mattick RP, Breen C, Kimber J, Davoli M, Mattick RP, Breen C, Kimber J, Davoli M: Methadone maintenance therapy versus no opioid replacement therapy for opioid dependence. Cochrane Database Syst Rev ;CD002209, 2009

66. Mayet S, Gossop M, Lintzeris N, Markides V, Strang J: Methadone maintenance, QTc and torsade de pointes: Who needs an electrocardiogram and what is the prevalence of QTc prolongation? Drug Alcohol Rev 30:388-396, 2011

67. McCance-Katz EF: (*R*)-Methadone versus racemic methadone: What is best for patient care? Addiction 106:687-688, 2011

68. McCowan C, Kidd B, Fahey T: Factors associated with mortality in Scottish patients receiving methadone in primary care: Retrospective cohort study. BMJ 338:b2225, 2009

69. Mercadante S, Casuccio A, Agnello A, Serretta R, Calderone L, Barresi L: Morphine versus methadone in the pain treatment of advanced-cancer patients followed up at home. J Clin Oncol 16:3656-3661, 1998

70. Mercadante S, Porzio G, Ferrera P, Fulfaro F, Aielli F, Verna L, Villari P, Ficorella C, Gebbia V, Riina S, Casuccio A, Mangione S: Sustained-release oral morphine versus transdermal fentanyl and oral methadone in cancer pain management. Eur J Pain 12:1040-1046, 2008

71. Michel M, Trafton J, Martins S, Wang D, Tu S, Johnson N, Goldstein MK: Improving patient safety using ATHENA-decision support system technology: The opioid therapy for chronic pain experience, in Henriksen K, Battles JB, Keyes MA, Grady ML (eds): Advances in Patient Safety: New Directions and Alternative Approaches (Vol. 4: Technology and Medication Safety). Rockville, MD, Agency for Healthcare Research and Quality, 2008

72. National Institutes of Health: NIH consensus panel recommends expanding access to and improving methadone treatment programs for heroin addiction. Eur Addict Res 5: 50-51, 1999

73. Neale J: Methadone, methadone treatment and non-fatal overdose. Drug Alcohol Depend 58:117-124, 2000

74. Neumann AM, Blondell RD, Jaanimagi U, Giambrone AK, Homish GG, Lozano JR, Kowalik U, Azadfard M: A preliminary study comparing methadone and buprenorphine in patients with chronic pain and coexistent opioid addiction. J Addict Dis 32:68-78, 2013

75. Newman RG: Attributing fatal cardiac effects to methadone: What's the evidence? J Addict Dis 27:1-4, 2008

76. Newman RG, Whitehill WB: Double-blind comparison of methadone and placebo maintenance treatments of narcotic addicts in Hong Kong. Lancet 314:485-488, 1979

77. Owens DK: AHRQ Series Paper 5: Grading the strength of a body of evidence when comparing medical interventions—Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol 63:513-523, 2010

78. Pani PP, Trogu E, Maremmani I, Pacini M: QTc interval screening for cardiac risk in methadone treatment of opioid dependence. Cochrane Database Syst Rev 6:CD008939, 2013

79. Paulozzi LJ: Opioid analgesic involvement in drug abuse deaths in American metropolitan areas. Am J Public Health 96:1755-1757, 2006

80. Paulozzi LJ, Budnitz DS, Xi Y: Increasing deaths from opioid analgesics in the United States. Pharmacoepidemiol Drug Saf 15:618-627, 2006

81. Paulozzi LJ, Ryan GW: Opioid analgesics and rates of fatal drug poisoning in the United States. Am J Prev Med 31:506-511, 2006

82. Pearson EC, Woosley RL: QT prolongation and torsades de pointes among methadone users: Reports to the FDA spontaneous reporting system. Pharmacoepidemiol Drug Saf 14:747-753, 2005

83. Peles E, Bodner G, Kreek MJ, Rados V, Adelson M: Corrected-QT intervals as related to methadone dose and serum level in methadone maintenance treatment (MMT) patients: A cross-sectional study. Addiction 102:289-300, 2007

84. Pham B, Klassen TP, Lawson ML, Moher D: Language of publication restrictions in systematic reviews gave different results depending on whether the intervention was conventional or complementary. J Clin Epidemiol 58:769-776, 2005

85. Reddy S, Fisch MJ, Bruera E: Oral methadone for cancer pain: no indication of Q-T interval prolongation or torsades de pointes. J Pain Symptom Manage 28:301-303, 2004

86. Reddy S, Hui D, El Osta B, de la Cruz M, Walker P, Palmer J, Bruera E: The effect of oral methadone on the QTc interval in advanced cancer patients: A prospective pilot study. J Palliat Med 13:33-38, 2010

87. Ripamonti C, De Conno F, Groff L, Belzile M, Pereira J, Hanson J, Bruera E: Equianalgesic dose/ratio between methadone and other opioid agonists in cancer pain: Comparison of two clinical experiences. Ann Oncol 9:79-83, 1998

88. Ripamonti C, Groff L, Brunelli C, Polastri D, Stavrakis A, De Conno F: Switching from morphine to oral methadone in treating cancer pain: what is the equianalgesic dose ratio? J Clin Oncol 16:3216-3221, 1998

89. Rosemont Pharmaceuticals Limited: Methadone hydrochloride DTF 1mg/1ml oral solution. Available at: http://xpil.medicines.org.uk/ViewPil.aspx?DocID=22767. Accessed January 14, 2014

90. Roy AK, McCarthy C, Kiernan G, McGorrian C, Keenan E, Mahon NG, Sweeney B: Increased incidence of QT interval prolongation in a population receiving lower doses of methadone maintenance therapy. Addiction 107:1132-1139, 2012

91. Schmittner J, Schroeder JR, Epstein DH, Krantz MJ, Eid NC, Preston KL: Electrocardiographic effects of lofexidine and methadone coadministration: secondary findings from a safety study. Pharmacotherapy 29:495-502, 2009

92. Seymour A, Black M, Jay J, Cooper G, Weir C, Oliver J: The role of methadone in drug-related deaths in the west of Scotland. Addiction 98:995-1002, 2003

93. Shah N, Lathrop SL, Landen MG: Unintentional methadone-related overdose death in New Mexico (USA) and implications for surveillance, 1998-2002. Addiction 100:176-188, 2005

94. Shaiova L, Berger A, Blinderman CD, Bruera E, Davis MP, Derby S, Inturrisi C, Kalman J, Mehta D, Pappagallo M, Perlov E: Consensus guideline on parenteral methadone use in pain and palliative care. Palliat Support Care 6:165-176, 2008

95. Shea BJ, Hamel C, Wells GA, Bouter LM, Kristjansson E, Grimshaw J, Henry DA, Boers M: AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. J Clin Epidemiol 62:1013-1020, 2009

96. Stallvik M, Nordstrand B, Kristensen O, Bathen J, Skogvoll E, Spigset O: Corrected QT interval during treatment with methadone and buprenorphine—Relation to doses and serum concentrations. Drug Alcohol Depend 129:88-93, 2013

97. Straus MM, Ghitza UE, Tai B: Preventing deaths from rising opioid overdose in the US—The promise of naloxone antidote in community-based naloxone take-home programs. Subst Abuse Rehabil 4:65, 2013

98. Sunjic S, Zador D: Methadone-related deaths in New South Wales. Med J Aust 166:54-55, 1997

99. U.S. Department of Justice DEA: Automation of reports and consolidation order's system (ARCOS): Retail Drug Summary Reports, 1998–2002. Available at: http://www.deadiversion.usdoj.gov/arcos/retail_drug_summary/index.html. Accessed November 8, 2009

100. Van Ameijden EJC, Langendam MW, Coutinho RA: Dose-effect relationship between overdose mortality and prescribed methadone dosage in low-threshold maintenance programs. Addict Behav 24:559-563, 1999

101. van Tulder M, Furlan A, Bombardier C, Bouter L, Editorial Board of the Cochrane Collaboration Back Review G: Updated method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group. Spine 28:1290-1299, 2003

102. Ventafridda V, Ripamonti C, Bianchi M, Sbanotto A, De Conno E: A randomized study on oral administration of morphine and methadone in the treatment of cancer pain. J Pain Symptom Manage 1:203-207, 1986

103. Vieweg WV, Hasnain M, Howland RH, Clausen T, Koneru JN, Kogut C, Crouse EL, Hancox JC, Fernandez A, Pandurangi AK: Methadone, QTc interval prolongation and torsade de pointes: Case reports offer the best understanding of this problem. Ther Adv Psychopharmacol 3:219-232, 2013

104. Ward M, Barry J: Opiate-related deaths in Dublin. Ir J Med Sci 170:35-37, 2001

105. Wedam EF, Bigelow GE, Johnson RE, Nuzzo PA, Haigney MCP: QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. Arch Intern Med 167:2469-2475, 2007

106. Weimer MB, Korthuis PT, Behonick GS, Wunsch MJ: The source of methadone in overdose deaths in Western Virginia in 2004. J Addict Med 5:188-202, 2011

107. Williamson PA, Foreman KJ, White JM, Anderson G: Methadone-related overdose deaths in South Australia, 1984-1994. How safe is methadone prescribing? Med J Aust 166:302-305, 1997

108. Wysowski DK, Corken A, Gallo-Torres H, Talarico L, Rodriguez EM: Postmarketing reports of QT prolongation and ventricular arrhythmia in association with cisapride and Food and Drug Administration regulatory actions. Am J Gastroenterol 96:1698-1703, 2001

109. Yancovitz SR, Des Jarlais DC, Peyser NP, Drew E, Friedmann P, Trigg HL, Robinson JW: A randomized trial of an interim methadone maintenance clinic. Am J Public Health 81:1185-1191, 1991

110. Zador D, Sunjic S: Deaths in methadone maintenance treatment in New South Wales, Australia 1990-1995. Addiction 95:77-84, 2000

111. Zador DA, Sunjic SD: Methadone-related deaths and mortality rate during induction into methadone maintenance, New South Wales, 1996. Drug Alcohol Rev 21: 131-136, 2002

Appendix 1

List of Panel Members

Cochairs

APS: Ricardo Cruciani, MD
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Panel Members

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