Systematic Evidence Review on Methadone Harms and Comparative Harms

Roger Chou, MD
Melissa Weimer, DO
Tracy Dana, MLS
Miranda Walker, MA
Jennifer Priest Mitchell, BA

CLINICAL GUIDELINES PROJECT | AMERICAN PAIN SOCIETY

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EXECUTIVE SUMMARY

Purpose of this report

In 2010, the American Pain Society (APS) partnered with the College on Problems of Drug Dependence (CPDD), in collaboration with the Heart Rhythm Society (HRS), to develop a clinical practice guideline on safer prescribing of methadone. As part of the guideline development process, the APS commissioned a systematic review on methadone safety. The purpose of this systematic review is to summarize the evidence on various aspects related to the safety of methadone use, including overdose deaths, cardiac effects, and other harms. The systematic review will be used by the guideline development group convened by the sponsoring organizations to develop recommendations on safer methadone prescribing practices.

Scope

The populations addressed by the systematic review are adults (including pregnant women) and children (younger than 13 years of age) or adolescents (13 to 18 years of age) prescribed methadone for chronic pain or for treatment of opioid dependence. Comparisons of interest were methadone (oral or intravenous) versus placebo, other opioids, or non-opioid analgesics. In addition, studies that compared methadone use alone to methadone plus another intervention were included. The panel requested that the review assess evidence on various harms associated with methadone, 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 panel also requested that the systematic review address how the risks of harms associated with methadone are affected by use of concomitant medications.

The evidence review focused on the following harms:

- Mortality or overdose related to methadone use (including sudden death)
- Cardiovascular events, syncope, arrhythmias, and QT prolongation
- Withdrawal due to adverse events
- Gastrointestinal side effects, such as constipation, nausea, and vomiting
- Respiratory depression and sleep apnea
- Cognitive function, sedation, and psychiatric adverse events
- Abuse, addiction, or hyperalgesia related to methadone use
- Endocrinologic or immunologic effects
- Pregnancy outcomes and neonatal withdrawal syndrome

Methods

We searched the Cochrane Library, Ovid® MEDLINE and PsychInfo through July 2012 for relevant studies using broad terms for harms of methadone use. An update search was performed in January 2014 for new studies on methadone-related overdose and arrhythmia. Reviews of

reference lists supplemented the electronic searches. Studies that met predefined inclusion criteria, based on dual review, were abstracted and quality rated. We used Cochrane Back Review Group criteria to assess the quality of primary studies and Assessment of Multiple Systematic Reviews (AMSTAR) criteria to quality rate systematic reviews. We synthesized evidence using methods adapted from the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group and the Agency for Healthcare Research and Quality Effective Health Care Program. Factors considered when grading the evidence included the type, number, size, and quality of studies and consistency between studies.

Summary of evidence

We assessed the evidence in order to answer 17 separate Key Questions. The Key Questions focused on the harms of methadone use, and on identifying subgroups in whom harms of methadone use may vary.

Key Question 1: In populations prescribed methadone, what is the risk of adverse events compared to non-use of methadone?

- Methadone maintenance therapy was associated with a trend towards lower risk of all-cause mortality in a systematic review of four RCTs (pooled RR 0.48; CI 0.10 to 2.4), but results are difficult to interpret due to the imprecision of estimates and because the studies did not distinguish deaths related to prescribed methadone use from deaths related to other causes (such as illicit drug use) (strength of evidence: low).

- A significantly higher proportion of cases of sudden death in methadone users was associated with no structural heart abnormalities compared to sudden death in non-methadone users (77% versus 40%, p=0.003), but the study had methodological shortcomings (strength of evidence: low).

- The proportion of patients on methadone with QTc prolongation (variably defined as duration >430 to >500 ms), ranged from 0-37% with methadone use and 0-14% with non-use in eleven cross-sectional or before-after studies. Torsades de pointes was reported in 4% of methadone patients and 0% of control patients in one study, with no cases in either methadone or control patients in one before-after study (n=160) (strength of evidence: moderate).

- Methadone maintenance therapy was associated with increased risk of central sleep apnea compared to controls (no opioids) in one cross-sectional study (strength of evidence: low).

- One RCT and some observational studies found methadone associated with worse outcomes related to cognition or mood compared to no methadone use, but results are difficult to interpret because of methodological shortcomings, use of different outcome measures, and uncertain clinical significance (strength of evidence: low).

- Two studies found no difference in sexual function or hormone levels between methadone use versus non-use (strength of evidence: low).

- No study evaluated risk of opioid abuse or addiction in persons prescribed methadone for chronic pain.

- In series of infants of women treated with methadone, almost all studies found that over three-quarters had symptoms of neonatal abstinence syndrome; treatment rates in most studies ranged from 40% to 50% (strength of evidence: low).

- Some observational studies found maternal methadone use associated with increased risk of sudden infant death syndrome compared to non-use, but results are highly subject to confounding effects (strength of evidence: low).

- Effects of methadone on other neonatal outcomes are difficult to assess due to confounding effects related to selection of the control group (ongoing heroin use or drug-free controls), failure of most studies to adjust for potential confounders, and inconsistent results (strength of evidence: low).

Key Question 2: What are the comparative risks of adverse events for methadone compared to other opioids or medications?

- Methadone was not associated with increased risk of mortality compared to other opioids in two large cohort studies (one study found methadone associated with decreased risk compared to morphine). RCTs of methadone versus other opioids were not designed to assess mortality and reported few events. Epidemiological 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 (such as dispensing or sales rates) to estimate risk, and were not designed to distinguish adverse events associated with prescribed versus illicit use of opioids (strength of evidence: low).

- One RCT and three cross-sectional studies found methadone for treatment of opioid dependence associated with increased risk of variably-defined QTc prolongation compared to buprenorphine; one cohort study found no cases of QTc prolongation following intitiation of methadone or buprenorphine (strength of evidence: moderate).

- Cardiac events associated with methadone use were infrequently reported. One cross-sectional study found a non-statistically significant trend towards retrospectively self-reported syncope with methadone compared to buprenorphine (strength of evidence: low).

- There was no difference between methadone and other opioids in incidence of gastrointestinal adverse events, including constipation, in seven RCTs and two observational studies (strength of evidence: moderate).

- One cross-sectional study found methadone but not other opioids associated with higher central apnea index (strength of evidence: low).

- Evidence on comparative effects of methadone versus other opioids on cognitive functioning and psychiatric adverse events found no clear differences (strength of evidence: low).

- One study found methadone associated with increased risk of erectile dysfunction and lower total serum testosterone levels versus buprenorphine (strength of evidence: low).

- No study compared risk of methadone abuse or addiction versus risk of abuse or addiction of other opioids in persons prescribed those medications (no evidence).

- Four RCTS and four cohort studies of methadone versus buprenorphine found no difference in incidence of preterm birth or cesarean delivery. Results related to incidence, severity, or time course of neonatal abstinence syndrome did not show consistent, statistically significant differences between methadone and buprenorphine (strength of evidence: moderate).

Key Question 3: In populations prescribed methadone, what factors predict increased risk of adverse events?

- 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 (strength of evidence: moderate).

- Studies that analyzed methadone overdose case series found a high proportion of cases associated with benzodiazepine co-prescription, benzodiazepine in blood toxicology, use of other concomitant medications, or an illicit source of methadone (quality of evidence: low).

- Factors associated with increased risk of QTc prolongation in cross-sectional studies of patients prescribed methadone include use of other QTc prolonging medications, altered liver function, elevated hemoglobin A1c level, congestive heart failure, male sex, hypokalemia, or use of cocaine or amphetamines, though findings were not consistent across studies (strength of evidence: low).

- In case series of QTc prolongation or torsades de pointes associated with use of methadone, one-half or more of cases had at least one risk factor for QTc prolongation or torsades de pointes other than methadone use (e.g. interacting medications, hypokalemia, hypomagnesemia, or structural heart disease (strength of evidence: low).

- One study found breastfeeding associated with decreased risk of neonatal abstinence syndrome after adjustment for potential confounders, and one found an association between breastfeeding and duration of neonatal abstinence syndrome (no adjustment) (quality of evidence: low).

Key Question 4: In populations prescribed methadone, what are the effects of different dosing strategies on adverse events?

- Methadone rotation was associated with a similar risk of discontinuation compared to initiation of opioids with methadone in one fair-quality cohort study of patients with cancer pain (strength of evidence: low).

Key Question 5: In populations prescribed methadone, what is the accuracy of baseline or follow-up ECGs for predicting adverse cardiac events?

- No studies met inclusion criteria (no evidence).

Key Question 6: In populations prescribed methadone, what are the benefits and harms of baseline or follow-up ECGs?

- No studies met inclusion criteria (no evidence).

Key Question 7: In populations prescribed methadone with evidence of QTc prolongation, what are the benefits of correcting conditions associated with QTc prolongation?

- No studies met inclusion criteria (no evidence).

Key Question 8: In populations prescribed methadone with evidence of QTc prolongation, what are the benefits and harms of continued use of methadone versus switching to another opioid agonist or discontinuation of methadone?

- No studies met inclusion criteria. Case reports and small case series report normalization of QTc intervals and no recurrence of arrhythmias following a switch to buprenorphine or reduction in methadone dose in patients with QTc interval prolongation and ventricular arrhythmia on methadone.

Key Question 9: In populations prescribed methadone at higher risk for adverse events, what are the benefits of methods for reducing risk?

- No studies met inclusion criteria (no evidence).

Key Question 10: In populations prescribed methadone, what is the effectiveness of methods for reducing risk of diversion or non-prescribed use?

- One study randomly allocated patients to take-home methadone privileges, but reported no cases of diversion (strength of evidence: low).

Key Question 11: How does risk of adverse events associated with methadone vary according to dose or duration of therapy?

- Recent initiation or shorter duration of methadone use appeared to be associated with an increased risk of mortality in five observational studies, though risk estimates were close to 1 in one of the studies (strength of evidence: moderate).

- Two studies found no association between higher methadone dose and risk of mortality, but were not designed to distinguish deaths related to methadone use versus deaths due to other causes (strength of evidence: low).

- Higher methadone dose was consistently associated with greater QTc interval prolongation in six studies of patients prescribed higher doses of methadone after controlling for other risk factors, accounting for 1-28% of the observed QTc variability. Case series of patients with torsades de pointes reported high (>200 mg/day) daily methadone doses (strength of evidence: moderate).

- One cross-sectional study of patients with chronic pain found higher methadone doses associated with higher central apnea index (strength of evidence: low).

- Evidence was limited and found no clear association between higher methadone dose and increase risk or severity of gastrointestinal adverse events, endocrinologic effects, cognitive functioning, sedation and psychiatric effects (strength of evidence: low).

- Most studies found no association between higher maternal methadone dose and increased risk of neonatal outcomes (strength of evidence: moderate).

- A systematic review of cohort studies found no association between higher maternal methadone dose and increased risk of neonatal abstinence syndrome when the analysis was restricted to studies that utilized a prospective design or applied objective criteria to identify neonatal abstinence syndrome (strength of evidence: moderate).

Key Question 12: How are risks of methadone affected by the indication for treatment?

- Evidence on differential risks of methadone based on the indication for prescribing are very limited and found no clear differences (strength of evidence: low).

Key Question 13: How are risks of methadone affected by the addition of concomitant medications?

- Several RCTs evaluated risks associated with adding concomitant medications (doxepin, fluconazole, dextromethorphan, or acetaminophen) to methadone, but were not designed to assess serious harms (such as mortality or cardiac events) and found no clear differences in other adverse events (strength of evidence: low).

Key Question 14: How do differences in adherence and access to care affect risk of adverse events associated with methadone?

- No studies met inclusion criteria (no evidence).

Key Question 15: In populations prescribed methadone, what is the accuracy of urine drug testing or prescription drug monitoring for predicting adverse events?

- No studies met inclusion criteria (no evidence).

Key Question 16: In populations prescribed methadone, what are the benefits and harms of urine drug testing or prescription drug monitoring?

- One large cohort study found having at least one urine drug test associated with decreased risk of all-cause mortality. The study did not report urine drug test results or clinician responses to the drug tests (strength of evidence: low).

Key Question 17: In populations prescribed methadone, what are the benefits and harms of different methods for structuring and managing care?

- One cohort study found earning take-home methadone privileges associated with increased survival compared to never earning take-home privileges, though results were not adjusted for confounders and confounding could explain the observed effects (strength of evidence: low).

Discussion

Methadone has become widely prescribed for treatment of chronic pain as well as a 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 well as on the usefulness of methods for predicting and reducing those risks.

INTRODUCTION

Methadone is a synthetic opioid used for the treatment of opioid dependence and for chronic pain.[1, 2] For treatment of opioid dependence, methadone maintenance therapy is associated with decreased risk of illicit opioid use and decreased mortality compared to not using methadone.[3-5] There is less evidence on benefits and harms of methadone as a treatment for chronic pain,[6] despite marked increases in use for this purpose. From 1997 to 2002, methadone prescribing for chronic pain increased nearly four-fold.[7] Recently, methadone has come under increasing scrutiny due to data indicating large increases in the number of methadone-associated overdose deaths.[8] This increase appears largely related to the dramatic rise in the use of methadone for chronic pain, though a small proportion of deaths occur in patients treated for opioid addiction.[9-14] Methadone poisoning deaths in the United States (U.S.) increased steadily from about 800 in 1999 to a high of about 5,500 in 2007; there was a decrease to about 4,900 in 2008.[15] The rate of increase in mortality has been substantially larger than for any other opioid.[16] About 1 of every 3 opioid-related deaths is associated with methadone ingestion, a substantially higher proportion than any other opioid.[17]

The interpretation of data on methadone-associated deaths is complicated by a number of factors, including increased surveillance, differentiating prescribed vs. non-prescribed use of methadone, effects of other potential contributing factors (such as use of other medications and substances), and uncertainty regarding the degree to which increases in deaths are proportionate to increased prescribing. Ascribing cause of methadone-associated death is a particular challenge. In the vast majority of cases, it is not possible to determine whether the death occurred as a result of respiratory depression related to overdose or to other factors, such as arrhythmia. Nonetheless, it is widely acknowledged that the pharmacology of methadone may be associated with unique safety concerns. Methadone differs from other opioids in several aspects. Unlike most opioids, it has N-methyl-D-aspartate (NMDA) antagonist activity at clinical doses.[18] In addition, studies suggest an association between methadone use and widening of the ECG QT interval, which can predispose to arrhythmias, such as the potentially life-threatening torsades de pointes, a type of ventricular tachycardia.[19] Data from the Food and Drug Administration's Adverse Event Reporting System indicate that since 2000, methadone was the second most commonly suspected primary cause of drug-related arrhythmia, after dofetilide.[20] 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.[21] The long half-life of methadone may result in increased potential for unintentional overdoses or other dose-dependent harms, as serum levels of methadone may continue to accumulate for weeks in new users or when changing doses. In a patient for whom the half-life is 60 hours, it would take almost 12 days on a stable dose to reach a steady-state (five half-lives). Unintentional overdoses may be of particular concern in patients who are methadone-naïve, non-adherent to dosing regimens, prescribed dose increases at short intervals, taking other medications that interact with methadone or undergo metabolism through the CYP450 pathway, or have liver dysfunction (the primary site of metabolism).[22] Another factor that complicates use of methadone is that morphine dose equivalent ratios are thought to increase at higher doses, and incomplete cross-tolerance to other opioids may occur, which could affect safety when switching or rotating patients from another opioid to methadone.[23-25]

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[26] and lowered the recommended starting dose of methadone for opioid-naïve patients from a maximum initial dose of 80 mg/day (2.5 to 10 mg every 3 to 4 hours) to a maximum initial dose of 30 mg/day (2.5 to 10 mg every 8 to 12 hours).[27] In 2009, a guideline from the American Pain Society (APS) and the American Academy of Pain Medicine issued recommendations on use of chronic opioid therapy for chronic non-cancer pain. Based on panel consensus (given the lack of evidence on comparative safety of different methadone doses), it recommended starting methadone at 2.5 mg every 8 hours and increasing the dose no more frequently than weekly. It also recommended that in persons being switched to methadone from another opioid, that starting doses should not exceed 30 to 40 mg/day, even in persons on high doses of other opioids. Another guideline published in 2009 focused on prevention of cardiac arrhythmias in persons prescribed methadone.[28] It recommended routine baseline and follow-up ECG monitoring for all patients prescribed methadone. Some aspects of the guideline development process, as well as the recommendations themselves, have been critiqued.[29] The guideline was not endorsed by a professional society or by the federal Center for Substance Abuse Treatment, which convened the guideline group. In addition, some members of the guideline panel declined to be acknowledged in the published article. The strength of the recommendations and the quality of the evidence supporting them was not graded, and it was unclear how trade-offs between potential benefits of routine ECGs and potential harms, costs, and burdens were weighed when formulating the recommendations.[29] A number of persons on that guideline committee were authors on a subsequent guideline funded by the Substance Abuse and Mental Health Services Administration that recommended a cardiac risk management plan including clinical risk assessment of all patients in opioid treatment programs including a routine ECG within the first 30 days in persons with risk factors for QT prolongation, as well as when the methadone dose exceeds 120 mg/day.[30] It also did not grade the strength of the recommendations or the quality of the supporting evidence. Another guideline targeted at use of intravenous methadone for palliative care recommended ECG prior to initiation of methadone, four days after initiation, following dose escalations, and with any clinical changes associated with increased risk of arrhythmia, but was not sponsored by any professional society or governmental entity, did not report being based on a systematic review of the evidence, and did not grade the recommendations or the evidence supporting them.[31]

In 2010, APS partnered with the College on Problems of Drug Dependence (CPDD), in collaboration with the Heart Rhythm Society (HRS), to develop a clinical practice guideline on safer prescribing of methadone. As part of the guideline development process, APS commissioned a systematic review on methadone safety. The purpose of this systematic review is to summarize the evidence on various aspects related to safety of methadone, including overdose deaths, cardiac effects, and other harms. The systematic review will be used by the guideline development group convened by the sponsoring organizations to develop recommendations on safer methadone prescribing practices.

Scope of evidence review and key questions

APS and CPDD each selected a co-chair (R Cruciani and D Fiellin, respectively) to lead a 17 member multidisciplinary expert panel (Appendix A). Panel members had expertise in the areas

of pain, addiction medicine, cardiology, primary care, nursing, palliative care, pharmacology, pediatrics and adolescent medicine, obstetrics and gynecology, epidemiology, and social work. The panel defined the scope of the evidence review, including the Populations, Interventions, Comparators, and Outcomes (PICO) to be addressed (Appendix B). Based on the PICO, the panel formulated 17 Key Questions used to guide the evidence review. The Key Questions addressed critical areas that the panel felt needed to be answered in order to formulate clinical recommendations on methadone safety.

The populations addressed by the evidence review are adults (including pregnant women) and children prescribed methadone for chronic pain or for treatment of opioid dependence. The panel requested that the evidence review assess evidence on various harms associated with methadone, 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 panel also requested that the evidence review address how the risks of harms associated with methadone are affected by use of concomitant medications.

The evidence review focused on the following harms:

- Mortality or overdose related to methadone use (including sudden death)
- Cardiovascular events, syncope, arrhythmias, and QT prolongation
- Withdrawal due to adverse events
- Gastrointestinal side effects, such as constipation, nausea, and vomiting
- Respiratory depression and sleep apnea
- Cognitive function, sedation, and psychiatric adverse events
- Abuse, addiction, or hyperalgesia related to methadone use
- Endocrinologic or immunologic effects
- Pregnancy outcomes and neonatal withdrawal syndrome

Comparisons of interest were methadone (oral or intravenous) versus placebo, other opioids, or non-opioid analgesics. In addition, studies that compared methadone use alone to methadone plus another intervention were included. We excluded studies of patients receiving methadone for management of acute pain. We also excluded studies of persons using unprescribed methadone. Studies that did not clearly distinguish prescribed from unprescribed use of methadone were excluded unless they provided important contextual 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. We included studies that focused on reduction in illicit drug use as an outcome (an intended beneficial effect of methadone maintenance therapy used for opioid dependence) only if they reported included harms. We restricted inclusion to fully published (i.e., not available only as a conference or journal abstract), English language articles.

The Key Questions used to guide this review are listed below:

Key Question 1: In populations prescribed methadone, what is the risk of adverse events compared to non-use of methadone?

Key Question 2: What are the comparative risks of adverse events for methadone compared to other opioids or medications?

Key Question 3: In populations prescribed methadone, what factors predict increased risk of adverse events?

Key Question 4: In populations prescribed methadone, what are the effects of different dosing strategies on adverse events?

Key Question 5: In populations prescribed methadone, what is the accuracy of baseline or follow-up ECGs for predicting adverse cardiac events?

Key Question 6: In populations prescribed methadone, what are the benefits and harms of baseline or follow-up ECGs?

Key Question 7: In populations prescribed methadone with evidence of QTc prolongation, what are the benefits of correcting conditions associated with QTc prolongation?

Key Question 8: In populations prescribed methadone with evidence of QTc prolongation, what are the benefits and harms of continued use of methadone versus switching to another opioid agonist or discontinuation of methadone?

Key Question 9: In populations prescribed methadone at higher risk for adverse events, what are the benefits of methods for reducing risk?

Key Question 10: In populations prescribed methadone, what is the effectiveness of methods for reducing risk of diversion or non-prescribed use?

Key Question 11: How does risk of adverse events associated with methadone vary according to dose or duration of therapy?

Key Question 12: How are risks of methadone affected by the indication for treatment?

Key Question 13: How are risks of methadone affected by the addition of concomitant medications?

Key Question 14: How do differences in adherence and access to care affect risk of adverse events associated with methadone?

Key Question 15: In populations prescribed methadone, what is the accuracy of urine drug testing or prescription drug monitoring for predicting adverse events?

Key Question 16: In populations prescribed methadone, what are the benefits and harms of urine drug testing or prescription drug monitoring?

Key Question 17: In populations prescribed methadone, what are the benefits and harms of different methods for structuring and managing care?

Conflict of interest disclosure

The evidence review was conducted at the Oregon Evidence-based Practice Center with funding from the APS. None of the investigators conducting this review had conflicts of interest to disclose.

METHODS

Literature search and strategy

We searched the Cochrane Library, Ovid® MEDLINE, and PsychInfo through July 2012 for studies assessing harms associated with methadone use (detailed search strategies are shown in (Appendix C). An update search was performed in January 2014 for new studies on methadone-related overdose and arrhythmia. Reviews of reference lists supplemented the electronic searches.

Inclusion and exclusion criteria

All identified citations were imported into an electronic database (EndNote® X1) and reviewed for inclusion. One investigator reviewed potential citations for inclusion and a second investigator checked excluded citations to identify potentially relevant citations not selected by the first reviewer. We included studies that met all of the following criteria:

- Evaluated children or adults prescribed oral or intravenous methadone or infants whose mothers were methadone users
- Were relevant to a Key Question (KQ)
- Reported harms associated with methadone use
- For all Key Questions and harms: Were systematic reviews, randomized or quasi-randomized trials, cohort studies, cross-sectional studies, or case-control studies.
- For mortality, overdose, cardiac events, ECG changes, and pregnancy-related harms, as well as for Key Questions that addressed risk factors for methadone-associated harms: We also included prevalence studies, before-after studies, and case series.

We excluded studies only published as conference abstracts. We excluded non-English language studies. Other reviews, policy statements, and articles without original data were obtained for background and contextual information, but were not included as evidence.

Data extraction and synthesis

Randomized trials

For randomized trials, we abstracted the following information:

- Inclusion and exclusion criteria
- Number of patients enrolled
- Demographics and baseline characteristics
- Setting
- Funding source
- Interventions evaluated
- Duration of follow-up
- Loss to follow-up
- Compliance to treatment
- Adverse events

We assessed the internal validity (quality) of randomized clinical trials (RCTs) using 11 predefined criteria developed by the Cochrane Back Review Group (see Appendix D for details on how we operationalized the criteria).[32] We rated the internal validity of each trial based on the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; the use of co-interventions; compliance to allocated therapy; adequate reporting of dropouts and loss to follow-up; degree of loss to follow-up; non-differential timing of outcome assessment; and the use of intention-to-treat analysis.

We assigned an overall quality grade based on the type, number and seriousness of methodological flaws. We graded trials with no or only minor flaws good-quality, those with serious flaws poor-quality, and all others fair-quality, as described in further detail below.[33]

Studies rated "good" have the least risk of bias and results are considered valid. Good-quality studies include clear descriptions of the population, setting, interventions, and comparison groups; a valid method for allocation of patients to treatment; low dropout rates, and clear reporting of dropouts; appropriate means for preventing bias; appropriate measurement of outcomes, and reporting results.

Studies rated "fair" are susceptible to some bias, but it is not sufficient to invalidate the results. These studies do not meet all the criteria for a rating of good-quality because they have some deficiencies, but no flaw is likely to cause major bias. The study may be missing

information, making it difficult to assess limitations and potential problems. The "fair" quality category is broad, and studies with this rating vary in their strengths and weaknesses: the results of some fair-quality studies are likely to be valid, while others are only probably valid.

Studies rated "poor" have significant flaws that imply biases of various types that may invalidate the results. They have a serious or "fatal" flaw in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting. The results of these studies are at least as likely to reflect flaws in the study design as the true difference between the compared medications. We did not exclude studies rated poor-quality a priori, but poor-quality studies were considered to be less reliable than higher quality studies when synthesizing the evidence, particularly when discrepancies between studies were present.

Observational studies

For observational studies, we abstracted the following information:

- Study design (cohort, case-control, cross-sectional, before-after, case series, prevalence, or other)
- Inclusion and exclusion criteria
- Number of patients eligible and included
- Demographics and baseline characteristics
- Country and setting
- Funding source
- Interventions evaluated
- Duration of follow-up (for studies using a longitudinal design)
- Loss to follow-up (for studies using a longitudinal design) or proportion of patients meeting inclusion criteria who were analyzed
- Adverse events

We assessed the internal validity (quality) of observational studies using predefined criteria based on those developed by Downs and Black and the US Preventive Services Task Force (Appendix D).[34, 35] We rated the internal validity of each study based on the methods used to select patients for inclusion (ideally, enrollment of consecutive or a random sample patients meeting inclusion criteria, with matching if appropriate for the study design); similarity of compared groups at baseline (for comparative studies); accuracy of methods for ascertaining exposures, confounders, and outcomes; blinding of outcomes assessors; adequate reporting of drop-outs (for longitudinal studies) or the proportion of patients meeting inclusion criteria who were analyzed (for non-longitudinal studies); degree of loss to follow-up or proportion meeting

inclusion criteria who were analyzed; and statistical analyses on potential confounders. As with randomized trials, we assigned an overall quality grade based on the type, number and seriousness of methodological flaws (see above). We graded studies with no or only minor flaws good-quality, those with serious flaws poor-quality, and all others fair-quality

In general, a good-quality observational study is considered less reliable than a good-quality randomized trial. Among the observational studies, evidence hierarchies typically place a good-cohort study at the top, followed by case-control studies, cross-sectional studies, before-after studies, and other uncontrolled studies (e.g., case series and prevalence studies).

Systematic reviews

We included recent, higher-quality systematic reviews on mortality risk associated with use of methadone.[36] We defined systematic reviews as studies that at a minimum described systematic methods for identifying and selecting studies and synthesizing evidence.[37] For each systematic review, we abstracted the following information:

- Databases searched
- Dates of the searches
- Language restrictions, if any
- Number of studies included
- Criteria used to include studies
- Limitations of the included studies
- Methods for rating the quality of included studies
- Methods for synthesizing the evidence
- Interventions evaluated
- Number of treatment and control subjects
- Adverse event outcomes (including number and quality of studies for each comparison and outcome, and pooled results if available)

The reliability of systematic reviews depends on how well they are conducted. We used predefined criteria adapted from the Assessment of Multiple Systematic Reviews (AMSTAR) tool to assess the internal validity of systematic reviews (Appendix D).[37] Each study was evaluated on the following criteria: comprehensiveness of search strategy; application of pre-defined inclusion criteria to select studies, dual selection of studies, dual extraction of data, adequate explanation of included studies, appropriate assessment of validity and use of appropriate methods to synthesize the evidence. We assigned an overall quality grade based on

the type, number and seriousness of methodological flaws. Systematic reviews with major flaws are more likely to produce positive conclusions about the effectiveness of interventions.[38, 39] We graded systematic reviews with no or only minor flaws good-quality, those with serious flaws poor-quality, and all others fair-quality.

Dual review

Two reviewers independently rated the quality of each systematic review and primary study. Discrepancies were resolved via a consensus process.

Rating a body of evidence

We 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[40, 41] and the Agency for Healthcare Research and Quality's (AHRQ) Methods Guide for Comparative Effectiveness Reviews.[33] 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 considered the strength of study designs according to the following evidence hierarchy (from highest to lowest):

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

We rated the strength of evidence for each key question using the four categories recommended in the AHRQ 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 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 further research is likely to change the confidence in the estimate of effect and is likely to change the estimate; an "insufficient" grade indicates evidence either is unavailable or does not permit a conclusion.

Consistent results from higher-quality studies across a broad range of populations suggest a high degree of certainty that the results of the studies are true, and would be assigned a "high" grade. For a body of evidence given a "moderate" grade, consistent results could be due to true effects, or indicate biases operating across studies. Inconsistent results between higher-quality studies can lower confidence that the results of any particular study are true, or reflect diversity between studies in the populations or interventions evaluated. For a body of evidence given a "low" grade, there is low certainty that the results are not due to bias or other methodologic shortcomings in the studies.

Sparse data (small numbers of trials or small sample sizes) lowers confidence in conclusions from a body of evidence because of imprecise estimates, lack of statistical power, and a higher likelihood that conclusions will be changed by new evidence. If the body of evidence for an intervention consisted of a single study, we generally rated the strength of evidence as low, even if the study itself was rated higher-quality. In exceptional cases, a large, very high-quality randomized trial might receive a "moderate" strength of evidence rating.

For a list of abbreviations and acronyms used in this review see Appendix E.

Peer review

A draft version of this report underwent external peer view by over 20 persons from multiple clinical and scientific disciplines and professional societies. The report was revised based on peer review comments prior to finalization.

RESULTS

Size of literature reviewed

Investigators reviewed 3,750 potentially relevant citations. Of these, we retrieved 1,107 full-text articles to review for inclusion. After review of full-text articles, we judged 161 studies to be relevant to one or more key questions and to meet inclusion criteria. The most common reasons for study exclusion were: wrong outcomes (did not address included harms); wrong study design (pharmacokinetics, case reports, pharmacodynamics); and wrong publication type (editorial, opinion, letters, guidelines, narrative, or non-systematic review).

We identified two systematic reviews and 169 primary studies that were relevant for at least one key question and met inclusion criteria. These included 34 randomized trials (four of which were included in one of the systematic reviews), 108 observational studies (in 111 publications) and 27 case series. Quality ratings for the included studies are shown in Appendix F (for systematic reviews), Appendix G (for randomized trials) and Appendix H (for observational studies). We did not formally assess the quality of some types of observational studies, such as case series and retrospective, uncontrolled database studies, as reliable and validated quality assessment methods for these type of studies are lacking and studies using these designs already rank low on the evidence hierarchy.[42] Full details and data abstraction of included studies are found in Appendix I (for systematic reviews) and J (for RCTs and observational studies).

Key Question 1: In populations prescribed methadone, what is the risk of adverse events compared to non-use of methadone?

Mortality and overdose

A number of studies have evaluated the association between methadone use and risk of all-cause mortality. These data are of limited usefulness for understanding risks associated with methadone, since all-cause mortality does not distinguish between increased mortality related to prescribed methadone overdose or use (a harmful effect of methadone) versus decreased mortality related to reduction in illicit drug use (a beneficial effect of methadone, and not the focus of this review), and the studies were not designed to determine the cause of death.

A good-quality systematic review of four RCTs found methadone for treatment of opioid dependence associated with a non-statistically significant trend towards lower risk of all-cause mortality compared to no methadone maintenance therapy (RR 0.48; CI 0.10 to 2.4; Table 1).[2] The trials enrolled a total of 287 methadone maintenance therapy patients and 289 controls. All had methodological shortcomings, including inadequate reporting of randomization and allocation concealment methods. Results are also difficult to interpret due to the imprecision of estimates and because the studies were not designed to distinguish deaths related to methadone use from deaths related to other causes (such as illicit or non-prescribed drug use). One RCT reported a higher risk of mortality in patients on methadone maintenance versus no methadone maintenance, but the number of events was small and the difference was not statistically significant (3/50 [6%] versus 1/50 [2%]; RR 3.0, CI 0.32 to 28).[43] In the other three RCTs, methadone maintenance therapy was associated with lower mortality risk.[44-46] Longer-term follow-up of one of the studies, published subsequent to the systematic review, reported two deaths among 140 methadone maintained patients (1%; neither were related to overdose) compared to six deaths among 64 non-methadone use patients (9%; RR 0.15; CI 0.03 to 0.73).[47] Four of the six deaths in non-methadone patients were determined to be opioid-related overdoses.

Three fair-quality and one poor-quality controlled observational studies also evaluated the association between methadone use and mortality (Table 2).[48-51] One fair-quality cohort study found no difference between methadone maintenance therapy and no methadone maintenance therapy in all-cause mortality (RR 0.83, CI not reported), though methadone maintenance was associated with decreased risk of overdose death (RR 0.35, CI not reported, p=0.05).[51]Another fair-quality cohort study of patients with a diagnosis of substance misuse in the UK General Practice Research Database found being off opioid substitution treatment associated with higher risk of mortality than being on treatment (76% received methadone, 12% buprenorphine, and 13% both; adjusted rate ratio 2.3, 95% CI 1.7 to 3.1).[49] 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.[48] It found a higher proportion of cases involving methadone had no structural heart abnormalities (77%; 17/22) compared to cases not involving methadone (40%; 42/106, p=0.003), suggesting a causal role of methadone in the sudden deaths. Results of this study are difficult to interpret, as no statistical adjustment was performed for potential confounders. In addition, the blood concentration levels used to define "therapeutic" methadone use did not account for factors such

as tolerance to methadone, and could have resulted in misclassification of some overdose cases.[52] An older, poor-quality prospective cohort study reported a similar mortality rate for 3000 patients undergoing methadone maintenance treatment (7.6/1000) compared to the expected rate among adults 20-54 years of age in New York City in 1969-1970 (5.6/1000 +/- 5.2).[50] The study had a number of important methodological shortcomings, including baseline group differences and no statistical analyses of potential confounders.

Several uncontrolled studies reported mortality associated with methadone (Table 2).[53-58] A before-after study (n=160[53] and 149[54] in two publications) primarily designed to assess ECG changes following initiation of methadone reported no cases of sudden death. One study (n=138) that was primarily designed as a prevalence study of QTc prolongation in persons prescribed methadone maintenance therapy reported two deaths at 2-year follow-up in persons with QTc duration >500 ms at baseline.[55] Neither death was attributed to cardiac causes. Another study (n=41) reported one sudden death in a subject enrolled in a methadone maintenance program, though there was no methadone present in blood toxicology at the time of death.[56] One study estimated a maximum mortality associated with methadone maintenance therapy of 0.06 per 100 patient-years (four deaths per 6450 patient-years), based on the number of deaths in which QTc prolongation could not be excluded as the cause of death based on post-mortem examination, history of trauma, evidence of drug overdose, or attribution to other clinical conditions.[57] A retrospective study found that eight of 12 methadone-related deaths occurred within 3 days of starting methadone. [58]

Cardiovascular events

Two fair-quality studies (in three publications) reported incidence of torsades de pointes in methadone patients (Table 3).[53, 54, 59] A before-after study (reported in two publications) reported no cases of torsades de pointes (n=160) following initiation of methadone, despite the relatively high frequency of QTc prolongation.[53, 54] A 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.[59] Subjects with torsades de pointes had a higher rate of concomitant medication use, suggesting possible confounding factors.

ECG changes

Three cross-sectional studies (two fair-quality[59, 60] and one poor quality[56]) compared QTc interval durations with prescribed methadone use versus non-use, and nine before-after studies (one good-quality,[61] six fair-quality[53, 54, 62-65]and two poor quality,[66, 67] reported in six publications) evaluated ECG changes associated following initiation of methadone use versus baseline (Tables 3 and 10). The before-after studies include patients prescribed methadone in a randomized trial[61] and a cohort study[65]of methadone versus buprenorphine (Table 10). Sample sizes ranged from 14 to 247 participants, and mean oral methadone doses from 20 to 100 mg. Mean ages ranged from 33 to 43 years in patients on methadone maintenance therapy[53, 54, 56, 59, 61, 62, 64, 65]; and were 51 and 56 years in two studies of patients prescribed methadone for chronic pain[60, 67] (mean age was not reported in a third study[66]).

Most studies found an association between methadone use versus non-use and increased QTc interval, though a challenge in interpreting results is use of a relatively weak cross-sectional or before-after study design, failure to adjust for potential confounding variables, and reporting of abnormal QTc intervals using different thresholds. Studies reported prolongation based on a QTc interval of >450 ms,[60, 65] >460 ms,[59] >500 ms,[59, 62, 66, 67] >430 ms in men or >450 ms in women,[54, 67] >450 ms in men or >470 ms in women,[53] or >470 ms in men or >490 ms in women.[61] Two studies did not report criteria used to define for QTc prolongation.[56, 64]

The proportion of patients on methadone with QTc prolongation ranged from 0-37% with methadone use and from 0-14% with non-use in studies of patients on methadone maintenance therapy or chronic pain (Tables 3 and 10).[53, 54, 56, 59, 60, 62-67] In the methadone arm of a randomized trial of methadone versus buprenorphine, the proportion of patients that developed QTc prolongation (defined as >470 ms in men and >490 ms in women) was 23%, with 12% experiencing an increased in >60 ms from baseline.[61] The highest (fair) quality cross-sectional study found 16% of patients on methadone maintenance therapy had a QTc interval >500 ms, compared to 0% in non-methadone controls.[59]

Several reports evaluated the same series of patients at baseline and at 6- or 12-months after starting methadone maintenance therapy.[53, 54, 63] The baseline prevalence of QTc prolongation for these studies, defined as at least >430 ms in men and >450 ms in women, ranged from 3-14%[53, 54, 63]. The incidence of QTc prolongation (based on these thresholds) at 6 months ranged from seven to 31% . The study that assessed QTc prolongation (defined as >450 ms in men and >470ms in women) at 12 months reported an incidence of 13%[53]. In one report, after 6 months of methadone use, 31% of subjects had QTc prolongation (defined as >430 ms for men, and >450 ms for women), compared to 14% prior to initiation of methadone (p=0.2).[54] In a second report, the proportion of patients with QTc interval >450 ms increased from 7% at baseline to 19% at 6 months and the proportion with QTc interval >500 ms increased from 0% at baseline to 2%. Eighteen percent of subjects had an increase in QTc interval of 30 to 60 ms, and 3% had an increase >60 ms.[63] A third report from the same population found that 67% of subjects had an increase of any amount in QTc interval following methadone initiation.[53] QTc prolongation (defined as >450 ms in men and >470 ms in women) was reported in 3% prior to initiation of methadone, 12% 6 months after initiation of methadone, and 13% after 12 months.[53]

Two poor-quality, before-after studies evaluated ECG changes in persons prescribed oral methadone for cancer pain (Table 3).[66, 67] One study found that in 56 patients with ECG data, there was no difference between mean QTc duration prior to methadone use and up to 3 months following initiation (mean 413 versus 413 ms; p=0.99). Four percent (2/56) of patients started on methadone for cancer pain had QTc duration >500 ms at baseline; in both subjects the QTc interval decreased to <500 ms following methadone initiation.[66] The other study of 100 patients found 28% had QTc prolongation (>430 ms in males or >450 ms in females) at baseline, but only one patient (1/64; 2.6%) had QTc >500 ms at week 2, and none at weeks 4 or 8. Eight percent of patients (5/64) had a QTc interval >10% above baseline at week 2, and none had QTc interval >25% above baseline.[67] The median daily methadone doses of 23 and 30 mg in these studies were lower than in most studies of ECG changes in persons on methadone maintenance therapy.[53, 54, 56, 59, 61, 63-65]

Eleven studies[55, 57, 68-76] reported the prevalence of QTc prolongation in persons prescribed methadone (including the methadone arm from three cross-sectional studies of methadone versus buprenorphine[57, 68, 69]), without a non-methadone or buprenorphine control group (Tables 3 and 10). Mean dose of methadone in these studies ranged from 69 to 171 mg/day. All of the studies exclusively enrolled methadone maintenance therapy patients except for one, which also included patients prescribed methadone for pain.[70] Mean age ranged from 33 to 45 years, and about one-quarter to one-third of the subjects were women. One VA study was somewhat of a demographic outlier and evaluated a mostly (93%) male population with mean age 56 years.[71] As with the studies that compared methadone use to non-use, there was variability in how QTc prolongation was defined (range >430 to 450 ms in men and >450 to 470 ms in women). The prevalence of QTc prolongation ranged from 0.5% to 32% in five studies based on a threshold of >430 to 450 ms in men and >430 to >470 ms in women;[68, 69, 71, 72, 74, 75] the study reporting the highest prevalence (32%) applied a threshold of >430 ms in men and >450 ms in women (Table 3).[70] In six studies, the proportion of patients who exceeded a QTc threshold of >500 ms ranged from 0% to 6%.[55, 57, 70, 71, 73, 76]

Two before-after studies of the same patient population reported no change from baseline (non-use) in QRS duration following 6- and 12-months of methadone use (Table 3).[53, 54]

The effect of prenatal exposure to methadone and subsequent QTc prolongation in newborns has not been well studied. One fair-quality, prospective cohort study evaluated ECG changes in 26 infants born to mothers on methadone maintenance treatment compared to 26 healthy term infants born to mothers not taking medications during pregnancy and without any medical conditions (Table 3).[77] QTc prolongation (defined as >460 ms) 2 days after birth was present in 15% (4/26) of infants with prenatal methadone exposure, compared to none of the healthy infants. All four cases resolved to normal levels within a week following birth.

Several case series have evaluated features commonly present in persons with torsades de pointes and are discussed elsewhere (see Key Questions 3 and 11).[19, 78, 79]

Withdrawal due to adverse events

We identified no trials that compared risk of withdrawal due to adverse events (a marker for more severe or intolerable adverse events) in persons prescribed chronic methadone compared to placebo or no methadone. One randomized trial compared methadone versus placebo for chronic neuropathic pain, but was excluded because methadone was only administered every other day, with no study medication on alternate days.[80]

Gastrointestinal adverse events

No study compared rates of nausea, vomiting, or constipation in persons prescribed methadone versus no methadone or placebo.

Respiratory depression and sleep apnea

One fair-quality cross-sectional study (reported in three publications) compared sleep apnea and ventilatory response parameters in patients in a methadone maintenance therapy program for

≥2 months on stable doses of methadone compared to age-, sex-, and body mass index-matched control subjects with no history of substance abuse and not receiving opioids (Table 4).[81-83] The methadone maintenance therapy patients had a higher Apnea/Hypopnea Index (AHI) compared with controls (median 13 versus 8 events per hour, p<0.05), with a significantly higher Central Apnea Index (CAI) (median 1.7 versus 0.15 events per hour, p<0.001), but no difference in Obstructive Apnea Index (OAI).[81] Thirty percent of the methadone maintenance therapy patients had a CAI >5 and 20% had a CAI >10, compared to no control subjects at either threshold. Methadone maintenance therapy was also associated with worse scores on the Epworth Sleepiness Scale (7.1 versus 2.0, p<0.0001), though few subjects had scores >11 (8% versus 0%).[82] A subsequent analysis found that scores on the Beck Depression Inventory was the strongest predictor of daytime sleepiness, with no significant association with blood methadone concentration.[82] Methadone maintenance therapy was also associated with decreased hypercapnic ventilatory response and increased hypoxic ventilatory response.[83]

Cognitive functioning, sedation, and psychiatric outcomes

One fair-quality RCT[84], three fair-[85-87] and six poor-quality[82, 88-93], cross-sectional studies (in ten publications) and five cohort studies(four fair-quality[94-97] and one poor-quality[98]) evaluated cognitive and neurological outcomes in patients maintained on methadone compared to placebo or no-treatment controls (Table 5).

The RCT compared scores on various measures of cognition and mood before and after administration of placebo and various doses of methadone in patients acutely stabilized for opioid withdrawal, using different patterns of administration in a crossover design.[84] Results were difficult to interpret because pre-administration scores on cognition and mood varied in the different intervention groups, though the study concluded that delayed recall was impaired following administration of higher (full stabilization) doses of methadone.

Nine cross-sectional studies (in ten publications) evaluated cognitive and neurological outcomes in patients maintained on methadone compared to control subjects not taking opioids (Table 5).[82, 85-93] Four studies found chronic methadone maintenance therapy associated with lower scores on various tests of information processing, attention, and short- and long-term memory compared to age-, sex-, and education-matched controls.[86, 90, 91, 93] Two cross-sectional studies (by the same first author) reported similar attention scores in working patients on methadone maintenance treatment compared to an unmatched control group of former heroin addicts not on methadone or individuals with no history of opioid medication dependence, though nonworking persons on methadone had worse scores.[88, 89] A cross-sectional study with unmatched controls found methadone initiated recently (within 6 weeks) associated with worse scores on various measures of attention and memory compared to unmatched controls.[92] Another cross-sectional study found no increased risk of abnormalities on neurological examination or electroencephalogram in persons on methadone maintenance therapy versus unmatched controls, but results were only described qualitatively.[85]

A cross-sectional study found patients on methadone maintenance therapy had higher scores on the Beck Depression Inventory (15 versus 2.0, p<0.001, reference normal values ≤9)

compared to age-, sex-, and body mass index-matched controls. There was no difference between groups in Mini Mental State Examination Scores (Table 5).[82]

Three cohort studies found methadone maintenance associated with lower scores on various tests of information processing, attention, and short- and long-term memory compared to controls (Table 5).[95, 97, 98] One found no differences between groups,[96] while another found higher scores on verbal learning and intelligence tests.[94]

No study compared sedation in persons prescribed methadone versus no methadone or placebo.

Abuse, addiction, and hyperalgesia

One cross-sectional study found that patients on chronic methadone maintenance therapy had lower pain tolerance thresholds on cold pressor tests compared to age- and sex-matched controls.[99] However, the importance of this finding is unclear, as no study evaluated clinical outcomes associated with greater hyperalgesic responses to pain provocation.

No study evaluated risk of methadone abuse or addiction in persons prescribed the medication for treatment of chronic pain.

Endocrinologic and immunologic adverse events

Two fair-quality observational studies evaluated effects of methadone versus non-use on male sexual hormones and function (Table 6).[100, 101] One before-after study (n=19) found no change in testosterone levels prior to initiation of methadone maintenance therapy through 12 months after initiation, and improvement in sexual function over time.[101] The study also performed a cross-sectional analysis which found no significant differences between persons on methadone maintenance therapy for an average of 22 months compared to normal controls, untreated heroin addicts, or abstinent former addicts. Another cross-sectional study (n=92) found no difference between patients recently (<7 days) entered into a methadone maintenance program and those on treatment for >60 days in testosterone, prolactin, or thyroid stimulating hormone levels.[100] A before-after analysis from this study of a subgroup of 11 patients evaluated on entry into the program and after 60 days also found no differences in these hormones or in various sexual dysfunction scores.[100]

One poor-quality cross-sectional study found patients on chronic methadone maintenance therapy had higher T4 (140 versus 97) and T3 (2.7 versus 2.2) levels compared to euthyroid controls (blood bank donors), though clinical effects of this finding were not evaluated (Table 6).[102]

Pregnancy outcomes and outcomes in children exposed in utero

No RCT compared methadone maintenance treatment versus placebo in opioid dependent addicted pregnant women. A fair-quality prospective cohort study found no differences between infants of women prescribed methadone for opioid dependence compared to infants of heroin-using women (matched on extent of prenatal care, maternal age, race, and socioeconomic status)

not receiving treatment in gestational age, birth weight, birth head circumference, or risk of neonatal withdrawal syndrome (88% versus 68%; Table 7).[103] There were also no differences in weight, height, and head circumference at 3 years of age, and no clear differences in mean scores on the General Cognitive Index, though infants born to heroin-using mothers were more likely to have more substantial deficits on cognitive testing.

Several poor-quality cohort studies (major shortcomings included failure to perform matching or adjustment) also evaluated outcomes following methadone maintenance treatment during pregnancy versus no methadone maintenance and ongoing heroin use (Table 7). One study found a non-statistically significant trend in risk of perinatal mortality in the heroin group (11% [7/66]) compared to the methadone group (3.3% [3/89]).[104] Three poor-quality cohort studies found no differences between infants of methadone-treated women and those of women using heroin or methadone outside a treatment program in Apgar scores.[105-107] In two poor-quality cohort studies, neonatal withdrawal symptoms were more frequent or severe in the infants of methadone-treated women compared to infants of women using heroin or methadone outside a treatment program,[105, 106] but two others[104, 107] found no differences in risk. Three poor-quality cohort studies found methadone treatment in pregnancy associated with younger gestational age at delivery compared to ongoing heroin use,[107-109] and mixed effects on infant birth weight, with two studies reporting somewhat higher birth weight in infants of methadone-treated women[107, 109] and one study reported no differences.[108] A poor-quality RCT of pregnant heroin-addicted women randomized to methadone or buprenorphine substitution therapy also included a control group not receiving substitution therapy, but it was unclear if allocation to no treatment was randomized.[110] Compared to no substitution therapy, methadone was associated with lower risk of preterm labor after 34 weeks (22% versus 30%, p=0.04) and higher birth weight (2900 versus 2601 g, p=0.007), but higher severity of neonatal abstinence syndrome based on Finnegan score (18 versus 9.2, p<0.000001), longer duration of treatment, and more delayed onset of withdrawal symptoms after birth.

Many observational studies compared pregnancy outcomes in women on methadone maintenance treatment compared to drug free controls (Table 7).[103-105, 107, 109, 111-125] All but four[103, 117, 120, 125] of these were rated poor-quality and their usefulness for evaluating adverse outcomes associated with methadone use in pregnancy is limited because such outcomes are likely to be highly confounded by presence of other risk factors associated with opioid addiction. In addition, most studies did not attempt to match methadone-treated women and drug-free controls on important sociodemographic and clinical variables.

One fair-quality cohort study that used data from linked health databases in New South Wales, Australia found an increased risk of death in infants born to mothers prescribed methadone compared to mothers not prescribed methadone (24 versus 4.0 per 1000 live born infants; RR 6.2,CI 4.0 to 9.6; Table 7).[126] The most common cause of death was sudden infant death syndrome, accounting for 38% of deaths in infants in the methadone group and 10% in the non-methadone group. Results are likely to have been confounded by marked differences between groups on a variety of characteristics, including maternal demographics, smoking status, obstetric history, and receipt of prenatal care. One poor-quality study (no matching or adjustment) found no difference in risk of perinatal mortality between infants of mothers prescribed methadone (3.3% [3/89]) and infants of drug-free controls (3.0% [2/66]) or ex-addicts

no longer using opioids (0% [0/33]; Table 7).[104] One study found higher incidence of sudden infant death syndrome associated with use of methadone during pregnancy compared with no methadone exposure, after adjustment for race, age, parity, maternal smoking status, and low birth weight (0.96% versus 0.14%, adjusted RR 3.6, CI 2.5 to 5.1; Table 7).[118] However, the study did not describe whether methadone was prescribed or used illicitly. A longitudinal study found use of high doses of methadone (defined as ≥59 mg/day) in pregnancy associated with higher risk of sudden infant death syndrome compared to drug-free controls, though no cases were observed with lower doses (19% [high-dose] versus 0% [low-dose] versus 0% [drug-free control], p=0.003; Table 7).[125] Matching and adjustment for confounders were not performed.

In general, most observational studies found infants of methadone-treated mothers had lower birth weight and height, and smaller head circumference compared to infants born to non-heroin addicted mothers. Effects on mean gestational age at delivery were mixed, with most studies showing no association with earlier birth.[103, 107, 112, 115, 124] Most studies that assessed Apgar scores found no differences between infants of methadone-treated mothers and infants of drug-free controls (Table 7).[105, 111, 115, 120, 121] One poor-quality study found that infants of mothers treated with methadone had higher incidence of minor neurological abnormalities and lower scores on developmental evaluations compared to infants born to drug-free mothers through the first 3 years;[121] another found no difference in mean preschool age cognitive tests scores between preschoolers exposed to methadone in utero and those born to drug-free mothers, though a somewhat higher proportion of methadone-exposed children had scores 1 standard deviation below the population mean.[103]

Studies of infants born to methadone treated mothers generally reported rates of neonatal abstinence syndrome of three-quarters or more (range 71% to 96%) (Table 8).[103-105, 117, 119, 121, 127-131] The exception was one study that reported a rate of 50%.[132] The proportion of infants born to methadone treated mothers who received treatment for neonatal abstinence syndrome was generally lower, ranging from 37% to 58% in seven studies[127, 131-136] though two studies reported higher rates of 77% and 88%.[103, 104] Some of the variability in treatment rates could have been due to different methods for defining, assessing, and treating neonatal abstinence syndrome.

Summary of evidence

- Methadone maintenance therapy was associated with a trend towards lower risk of all-cause mortality in a systematic review of four RCTs (pooled RR 0.48; CI 0.10 to 2.4), but results are difficult to interpret due to the imprecision of estimates and because the studies did not distinguish deaths related to methadone use from deaths related to other causes (strength of evidence: low).

- A significantly higher proportion of cases of sudden death in methadone users was associated with no structural heart abnormalities compared to sudden death in non-methadone users (77% versus 40%, p=0.003), but the study had methodological shortcomings (strength of evidence: low).

- The proportion of patients on methadone with QTc prolongation (variably defined as duration >430 to >500 ms), ranged from 0-37% with methadone use and 0-14% with

non-use in eleven cross-sectional or before-after studies. Torsades de pointes was reported in 4% of methadone patients and 0% of control patients in one study, with no cases in either methadone or control patients in one before-after study (n=160) (strength of evidence: moderate).

- Methadone maintenance therapy was associated with increased risk of central sleep apnea compared to controls (no opioids) in one cross-sectional study (strength of evidence: low).

- One RCT and some observational studies found methadone associated with worse outcomes related to cognition or mood compared to no methadone use, but results are difficult to interpret because of methodological shortcomings, use of different outcome measures, and uncertain clinical significance (strength of evidence: low).

- Two studies found no difference in sexual function or hormone levels between methadone use versus non-use (strength of evidence: low).

- No study evaluated risk of opioid abuse or addiction in persons prescribed methadone for chronic pain.

- In series of infants of women treated with methadone, almost all studies found that over three-quarters had symptoms of neonatal abstinence syndrome; treatment rates in most studies ranged from 40% to 50% (strength of evidence: low).

- Some observational studies found maternal methadone use associated with increased risk of sudden infant death syndrome compared to non-use, but results are highly subject to confounding effects (strength of evidence: low).

- Effects of methadone on other neonatal outcomes are difficult to assess due to confounding effects related to selection of the control group (ongoing heroin use or drug-free controls) and failure of most studies to adjust for potential confounders, and inconsistent results (strength of evidence: low).

Key Question 2: What are the comparative risks of adverse events for methadone compared to other opioids or medications?

Mortality and overdose

Several RCTs compared methadone versus sustained-release morphine for cancer pain,[137-140] methadone versus buprenorphine for opioid dependence,[141,142] or methadone versus buprenorphine/naloxone for non-cancer pain (Appendix J).[143]All were fair-quality apart from one study[140] rated poor-quality (Appendix G). These studies were not designed or powered to evaluate mortality risk, and most trials reported no deaths. One trial reported two deaths, which were both attributed to disease progression.[137]

A fair-quality retrospective cohort study based on Oregon Medicaid administrative data (n=5,684) compared rates of adverse events in patients with cancer or non-cancer pain with at least one new 28-day prescription of methadone, sustained-release oxycodone, sustained-release morphine, or transdermal fentanyl over a 4-year timeframe, after adjusting for opioid dose (based on morphine equivalents), co-morbidities, concomitant medications, and other potential confounders (Table 9).[144] Adverse events were defined as emergency department (ED) visits or hospitalization for opioid-related events (based on International Statistical Classification of Diseases and Related Health Problems [ICD]-9 codes), all-cause ED visits or hospitalizations, constipation, opioid poisoning (based on ICD-9 codes), overdose symptoms (defined as alteration of consciousness, malaise, fatigue, lethargy, and respiratory failure), and death. Those prescribed fentanyl were significantly older (71 years) than those prescribed other opioids (mean ages ranging from 51-59 years). Those prescribed methadone received the highest morphine-equivalent dosage per day and had a higher prevalence of back pain, fibromyalgia, osteoarthritis, and substance abuse or dependence compared to the other opioids. There were no significant differences between methadone and long-acting morphine in risk of mortality (adjusted HR 0.71, 95% CI 0.46 to 1.08) 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 0.60 to 17.25). The study did not directly compare methadone to fentanyl or oxycodone, but the point estimates for fentanyl and oxycodone versus morphine all overlapped with the 95% confidence intervals of the estimates for methadone versus morphine, with one exception. The overdose risk for fentanyl was lower (adjusted HR 0.46; 95% CI 0.04 to 5.1) than for methadone (adjusted HR 3.2; 95% CI 0.60 to 17), though only one opioid poisoning was detected in the fentanyl group and six in the methadone group, and the confidence intervals for both medications were very wide. Some limitations of this study include clinically relevant, statistically significant differences in baseline characteristics between patients prescribed different long-acting opioids and analysis of outcomes not necessarily specific for opioid-related adverse events. For example, overdose symptoms were defined as alteration of consciousness, malaise, fatigue, lethargy, or respiratory failure.[144]

A fair-quality retrospective cohort study based on national Veterans Affairs system pharmacy data compared all-cause mortality for patients (n=98,068) newly prescribed ≥28 days methadone versus those prescribed long-acting morphine (Table 9).[145] The study excluded patients prescribed methadone for opioid dependence, terminal cancer pain, and palliative care. The mean daily dose of long-acting morphine was 67.5 mg and the mean daily dose of methadone was 25.4 mg. Compared to the morphine cohort, the methadone group was younger and had fewer co-morbid medical conditions, but higher rates of psychiatric conditions, substance use, and pain disorders. To help control for these differences, the study analyzed patients based on their propensity for being prescribed methadone. The baseline characteristics in each propensity quintile were very similar across the two groups. In both groups, all-cause mortality was highest in propensity quintile 1 (patients with the least propensity to receive methadone and most medically ill) and least in quintile 5 (highest propensity to receive methadone). In the propensity-stratified analysis, overall risk of mortality was lower with methadone than morphine (adjusted HR 0.56, 95% CI 0.51 to 0.62). For propensity quintile 1, the adjusted HR was 0.36 (95% CI 0.26 to 0.49); similar trends were observed for quintiles 2-4. For quintile 5, there was no difference between methadone and morphine in risk of all-cause mortality (adjusted HR 0.92,

95% CI 0.74 to 1.2).[145] The main limitation of this study is the possibility of residual confounding by indication. Although the study stratified patients based on their propensity for being prescribed methadone and performed adjustment on potential confounders, unmeasured confounders could still have been present. The likely effects of residual confounding on estimates is difficult to predict, since persons prescribed methadone had features associated both with decreased risk of mortality (younger age and fewer co-morbid medical conditions) as well as with increased risk (more psychiatric conditions and substance abuse).

Four epidemiological studies reported increasing rates of methadone-related overdose deaths since 1990, though the most recent study showed that the number of deaths appeared to peak in 2007 (Table 9).[146-149] Three of these studies evaluated the increase in opioid-related deaths relative to changes in opioid prescription sales.[147-149] One study which used sales of opioids (in grams) per state as a surrogate marker for opioid consumption found an association between higher rates of sales and higher rates of opioid-related poisoning deaths, with the correlation strongest for oxycodone and methadone.[148] Another study by the same lead author found that methadone-related poisoning in the U.S. increased by 213% from 1999 to 2002.[147] Concurrently, methadone sales for chronic pain increased by 175% and for opioid replacement therapy by 43%. By comparison, there was a 104% increase in synthetic-opioid related deaths (fentanyl or meperidine) and a 118% increase in sales and a 57% increase in deaths associated with other opioids like oxycodone, codeine, hydrocodone, morphine, and hydromorphone, with a 70% increase in their sales.[147] The most recent study found that methadone accounted for 9.0% (in morphine milligram equivalents) of prescribed opioids in 2009, but 31% of deaths. 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 opioids (9.7 versus 0.1 to 3.8 deaths per 100 kg morphine milligram equivalents for single drug deaths, and 33.6 versus 0.8 to 20.2 for all deaths).[149]These studies are difficult to interpret due to the lack of true inception cohorts of patients prescribed different opioids, use of indirect and surrogate denominators (opioid sales) to compare risks of different opioids, and inability to distinguish adverse events associated with prescribed versus illicit use of opioids.

Three forensic case series reported the proportion of deaths associated with methadone and buprenorphine, though it was not clear whether patients were prescribed either of these medications or if they included patients taking them illicitly (Table 9).[150-152] Two studies found methadone present in a higher proportion of deaths than buprenorphine (90% versus 10%)[150] and (35% versus 0.4%).[151] The third study found methadone and buprenorphine present in approximately the same number of deaths (9% versus 12%).[152] These studies are of limited usefulness for understanding the comparative risks of methadone and buprenorphine because they do not include information about the number of persons prescribed each medication, making it impossible to estimate rates of events.

Cardiovascular events

One fair-quality cross-sectional study reported a non-statistically significant trend towards increased one-year risk of retrospectively self-reported syncope in patients on methadone compared to buprenorphine for heroin dependence (21% versus 9%, RR 2.3, 95% CI 0.87 to 5.8, Table 10).[69] Interpretation of this study is a challenge because of the high frequency of syncope

of undetermined etiology and unclear causality between methadone use and subsequent syncope, particularly syncope evaluated based on retrospective recall. No other study reported cardiovascular events in persons prescribed methadone versus other opioids, including studies of ECG changes associated with methadone compared to buprenorphine (see below).[57, 61, 68, 69]

A small (n=12) case series of patients on methadone maintenance treatment (mean dose 135 mg) reported on hospitalizations for arrhythmias and QT prolongation (range 480 to 742 ms; Table 10).[153] Among three patients who successfully transitioned to buprenorphine, all had resolution of QT prolongation on no further incidence of arrhythmia at follow-up (mean 8 months, range 1-11 months.) Five patients who reduced methadone doses also had reduced QT duration and no further incidence of arrhythmia. Of the remaining four patients with follow-up data who did not reduce methadone dose or switch to buprenorphine, two had recurrent hospitalizations for ICD storms and/or torsades de pointes.

ECG changes

One good-quality RCT,[61] one fair-quality cohort study,[65] and three fair-quality cross-sectional studies[57, 68, 69] compared the incidence of QTc prolongation in patients prescribed methadone versus buprenorphine (Table 10). Patients in these studies were primarily men treated for opioid addiction. Methodological shortcomings included failure to report methods for ascertaining exposures and potential confounders,[57, 65, 68] and failure to report blinding of outcome assessors.[65, 69] In the five studies, a total of 713 participants received methadone (mean doses ranged from 69 to 111 mg) and 166 received buprenorphine (range 5 to 19 mg). The RCT and cohort study assessed QTc prior to treatment initiation and at follow-up;[61, 65] the cross-sectional studies performed a single ECG in patients already taking methadone or buprenorphine.

The RCT, which only included patients with a normal ECG at baseline, found that 23% (12/53) of those randomized to methadone 60-100 mg/day developed QTc prolongation (defined as >470 ms for men or >490 ms for females), compared to no cases in 54 patients allocated to buprenorphine 16-32 mg/day (OR 14, CI 1.9 to 110; p=0.01).[61] Twelve percent of patients in the methadone group developed an increase in QTc from baseline of greater than 60 ms, compared to 2% with buprenorphine.

The cohort study (n=80) found no cases of QTc prolongation >450 ms with either methadone (mean dose 88-96 mg) or buprenorphine (16-19 mg) at baseline or at 1 or 6 months after initiation of therapy.[65]

Thresholds for abnormal QTc prolongation varied in the cross-sectional studies, ranging from >430 to >500 ms. Incidence ranged from 5-31% in the methadone groups, with no cases reported in the buprenorphine groups.[57, 68, 69] Differences in the threshold used to define abnormal QTc prolongation did not appear to explain the differences in estimates. The study that reported the highest proportion of patients with QTc prolongation with methadone (31% [127/407]) used a value of >440 ms to define prolongation,[69] while a study that used a slightly lower threshold (>430 ms) reported a much lower proportion (6% [2/35]).[68]

An observational study that compared ECG findings on and off intravenous opioids in hospitalized patients with cancer pain found methadone associated with a larger increase in QTc interval compared to morphine (42 versus 9.0 ms), though findings may have been confounded by QTc interval-prolonging effects of the carrier agent chlrobutanol.[154]

Effects of methadone dose on QTc duration are discussed elsewhere (see Key Question 11).

One of the cross-sectional studies reported increased risk of U waves in patients on methadone compared to buprenorphine, though the difference was not statistically significant (31% [11/35] versus 0% [0/19], p=0.26).[68]

Withdrawal due to adverse events

One fair-quality RCT (n=103) found methadone (7.5 mg every 12 hours plus 5 mg as needed for breakthrough pain) associated with higher risk of withdrawal due to adverse events compared to sustained-release morphine (15 mg every 12 hours plus immediate release morphine every 4 hours as needed for breakthrough pain) in patients with poorly controlled cancer pain (22% versus 6%; RR 4.0, 95% CI 1.3-13, Table 11).[137] Two other fair-quality RCTs reported few withdrawals due to adverse events and no clear differences between various doses of methadone and buprenorphine (Table 11).[141, 155] Other RCTs of methadone versus another opioid or medication did not report withdrawals due to adverse events.

Gastrointestinal adverse events

Four RCTs (three fair-quality[137-139] and one poor-quality[140]) of patients with cancer pain found no differences between oral methadone and sustained-release morphine[137-140] in gastrointestinal adverse events (including nausea, vomiting, and constipation, Table 12). Three fair-quality trials of patients treated for opioid dependence found no differences between methadone and buprenorphine in risk of constipation, nausea, or vomiting (Table 12).[141, 142, 156] Two other trials of methadone versus buprenorphine for treatment of opioid dependence stated there were no differences in adverse events, but did not provide data or report on specific adverse events (including gastrointestinal adverse events).[157, 158] The results from the RCTs were consistent with a fair-quality cohort study, which found no difference in risk of constipation between methadone and buprenorphine in opioid-dependent persons (Table 12).[159]

A fair-quality retrospective cohort study based on Oregon Medicaid administrative data (n=5,684) of patients with cancer or non-cancer pain found no differences between methadone, sustained-release oxycodone, sustained-release morphine, or transdermal fentanyl in risk of constipation (Table 12).[144]

Respiratory depression and sleep apnea

A poor-quality cross-sectional study of patients with chronic pain who underwent polysomnography found an association between methadone use and a higher apnea-hypopnea index (p=0.007) and central apnea index (p=0.004), but no association between measures of sleep apnea and use of other around-the-clock opioids (Table 13).[160]

An older, poor-quality trial reported no difference in incidence of respiratory depression among patients with severe pain taking 10 mg methadone (7% or 2/30) versus 100 mg pethidine (7% or 2/30; Table 13).[161]

Abuse, addiction, and hyperalgesia

No study compared abuse or addiction of prescribed methadone compared to abuse or addiction of other prescribed opioids.

Cognitive functioning, sedation, and psychiatric outcomes

One fair-quality RCT found no differences in psychiatric outcomes between patients randomized to methadone or morphine for treatment of opioid dependence during an initial (pre-crossover) 6-week treatment period (Table 14).[162] Following crossover and 6 additional weeks of treatment, methadone was associated with higher (worse) scores on the Beck Depression Inventory (15 versus 7) and the State Trait Anxiety Index (46 versus 39). A poor-quality RCT also conducted in persons with opioid dependence found no differences between oral methadone and sublingual buprenorphine in tests of cognitive function.[163] However, another poor-quality study found patients randomized to methadone performed worse on a battery of cognitive tests compared to those randomized to buprenorphine, or matched opioid-free controls (Table 14).[164]

A poor-quality cohort study found no differences between methadone maintenance and levomethadyl acetate prescribed for opioid addiction on short- and long-term memory (Table 14).[165]

A poor-quality cross-sectional study of patients recently (within 6 weeks) started on opioid substitution therapy found methadone associated with slower attention compared to buprenorphine/naloxone, based on the simple Reaction Time ($p<0.01$), though there were no differences between groups in other tests of attention and memory (Table 14).[92] In a prospective study (by the same lead author) of patients within 2 months of initiation of methadone or buprenorphine (with or without naloxone) that were also using benzodiazepines found no clear differences between the opioids in tests of memory over time (Table 14).[166]

Four RCTs (two fair-quality[137, 139] and two poor-quality[138, 140]) of persons with cancer pain found no clear differences between oral methadone and oral morphine or transdermal fentanylin outcomes related to sedation or confusion (Table 14). A fair-quality RCT of patients being treated for opioid addiction found no difference between methadone and buprenorphine in risk of insomnia, anxiety, somnolence, or depression (Table 14).[142]

Endocrinologic and immunologic adverse events

One fair-quality study (reported in two publications) found methadone associated with increased risk of erectile dysfunction versus buprenorphine (53% vs. 21% $p=0.048$), lower (worse) scores on the International Index of Erectile Dysfunction, and lower serum total testosterone.[167, 168]

Pregnancy outcomes and outcomes in children exposed in utero

Four RCTs (three fair-quality[132, 169, 170] and one poor-quality[110]) compared methadone (doses 20-140 mg/day) versus buprenorphine (doses 2-32 mg/day) for treatment of opioid dependence in pregnant women (Table 15). All of the trials found no statistically significant differences between methadone and buprenorphine in incidence of preterm birth or cesarean delivery. One of the four trials found methadone associated with a significantly lower mean birth weight than buprenorphine (2878 versus 3094 g, p=0.005);[169] the other three trials found no differences between groups in birth weight.

Results related to incidence, severity, or time course of neonatal abstinence syndrome were somewhat inconsistent (Table 15). Two fair-quality trials found methadone associated with non-statistically significant trends towards increased risk of treatment for neonatal abstinence syndrome compared to buprenorphine (45% versus 20%, p=0.23.[132] and 57% versus 47%, p=0.26[169]). One of the trials reported a greater amount of medication used to treat neonatal abstinence syndrome (10 versus 1.1 mg of morphine, p<0.0091), length of treatment (9.9 versus 4.1 days, p<0.003), and length of hospital stay (18 versus 10 days, p<0.0091), and lower gestational age at delivery (38 vs. 39 weeks, p=0.007) in infants of methadone- vs. buprenorphine-treated women.[169] The other trial found methadone associated with a non-statistically significant, 3-fold increase in the amount of medication used to treat neonatal abstinence syndrome (p=0.13).[132] However, a third fair-quality trial found no differences between neonates of methadone- versus buprenorphine-treated mothers in incidence or duration of neonatal abstinence syndrome, time to initiate treatment, or total amount of morphine used, though methadone was associated with longer hospital stay (difference 1.3 days, p=0.02).[170] One poor-quality trial found methadone associated with more severe neonatal abstinence syndrome (Finnegan score 18 versus 9.2, p<0.001), more delayed onset (about half of the cases manifested after 48 hours, compared to none after 48 hours with buprenorphine), and longer duration of treatment.[110] Important methodological shortcomings in this trial include a large number of post-randomization exclusions, unclear use of blinding, and unclear methods of randomization and allocation concealment. None of the trials reported congenital abnormalities, and the trials were not designed to assess child developmental outcomes.

One good-[171] and three fair-quality[127, 133, 135] cohort studies found no differences between methadone and buprenorphine in incidence of cesarean delivery, gestational age at delivery, mean head circumference, and/or incidence of preterm (<37 weeks gestation) birth (Table 15). Two studies (one good- and one fair-quality) found significantly increased incidence of neonatal abstinence syndrome with methadone use compared to buprenorphine (78% vs. 40%; p<0.001 and 63% vs. 41%; p=0.03). Both studies also found that neonatal abstinence syndrome tended to be more severe in babies born to methadone-treated mothers, with 53% and 80% requiring treatment, compared to 15% and 57% (p<0.001 and 0.03) of babies born to buprenorphine-treated mothers. One of the studies found maternal methadone use associated with lower birth weight (25% versus 6.4% with birth weight <2500 g, p=0.03) and longer duration of hospitalization (20 versus 9.4 days, p=0.0009), after adjustment for maternal age,[127] but the other two found no differences.[133, 135] Two studies evaluated Apgar scores and found no differences.[127, 135] One study also found no difference in incidence of stillbirth (4% vs. 1%; p=0.5) or congenital malformations (3% vs. 5%; p=0.9).[171]

One fair-quality trial of methadone (mean dose at delivery 53 mg/day) versus morphine (mean dose at delivery 300 mg/day) found no differences between groups in incidence of cesarean delivery, mean birth weight, and incidence or severity of neonatal abstinence syndrome (Table 15).[172]

Summary of evidence

- Methadone was not associated with increased risk of mortality compared to other opioids in two large cohort studies (one study found methadone associated with decreased risk compared to morphine). RCTs of methadone versus other opioids were not designed to assess mortality and reported few events. Epidemiological 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 (such as dispensing or sales rates) to estimate risk, and were not designed to distinguish adverse events associated with prescribed versus illicit use of opioids (strength of evidence: low).

- One RCT and three cross-sectional studies found methadone for treatment of opioid dependence associated with increased risk of variably-defined QTc prolongation compared to buprenorphine; one cohort study found no cases of QTc prolongation following initiation of methadone or buprenorphine (strength of evidence: moderate).

- Cardiac events associated with methadone use were infrequently reported. One cross-sectional study found a non-statistically significant trend towards retrospectively self-reported syncope with methadone compared to buprenorphine (strength of evidence: low).

- There was no difference between methadone and other opioids in incidence of gastrointestinal adverse events, including constipation, in seven RCTs and two observational studies (strength of evidence: moderate).

- One cross-sectional study found methadone but not other opioids associated with higher central apnea index (strength of evidence: low).

- Evidence on comparative effects of methadone versus other opioids on cognitive functioning and psychiatric adverse events found no clear differences (strength of evidence: low).

- One study found methadone associated with increased risk of erectile dysfunction and lower total serum testosterone levels versus buprenorphine (strength of evidence: low).

- No study compared risk of methadone abuse or addiction versus risk of abuse or addiction of other opioids in persons prescribed those medications.

- Four RCTS and four cohort studies of methadone versus buprenorphine found no differences in incidence of preterm birth or cesarean delivery. Results related to

incidence, severity, or time course of neonatal abstinence syndrome did not show consistent, statistically significant differences between methadone and buprenorphine (strength of evidence: moderate).

Key Question 3: In populations prescribed methadone, what factors predict increased risk of adverse events?

Most studies that evaluated factors associated with increased risk of adverse events in persons prescribed methadone focused on dose effects, which are discussed elsewhere (see Key Question 11).

Mortality and overdose

One fair-quality, 12-year retrospective cohort study (n=2378) evaluated risk factors for all-cause and drug-related mortality in patients prescribed methadone maintenance therapy (median 4.4 years) by primary care physicians in Tayside, Scotland (Table 16).[173] Most of the cohort was male (67%), under 30 years old (65%), of low socioeconomic status (50%), had a low (0) Charlson Comorbidity index (87%), were prescribed a mean dose of methadone less than 60 mg (85%), had at least one urine drug test (78%), and were co-prescribed benzodiazepines (75%). Twenty-one percent of patients were prescribed methadone for less than 6 months, 36% for 6 months to 3 years, and 42% for ≥3 years. Fifty-two percent were on treatment at the end of the study or had died. During the study, 181 (8%) patients died, with 60 (3%) deaths related to drug use. Cause of death was available from medical examiner records for 92% of patients.[173]

Risk factors for all-cause mortality included higher Charlson Comorbidity Index score (for score 1-2 versus 0, AHR 1.1, 95% CI 1.0 to 1.1; for score ≥3 versus 0, AHR 1.2, 95% CI 1.2 to 1.3), overuse of methadone (relative to non-overuse, AHR 1.7, 95% CI 1.0 to 2.7), and history of psychiatric admission (relative to no history of psychiatric admission, AHR 2.5, 95% CI 1.7 to 3.7). Protective factors included time since last methadone prescription filled (for 4-6 months compared to ≤1 month since last fill, AHR 0.91, 95% CI 0.84 to 0.99; for ≥6 months compared to ≤1 month since last fill, AHR 0.70, 95% CI 0.66 to 0.73), and having at least one urine drug test (relative to no urine drug tests, AHR 0.33, 95% CI 0.22 to 0.49). Age, methadone breaks of more than 90 days, mean methadone dose >60 mg, and co-prescribing of benzodiazepines, antipsychotics, antidepressants, or opioid analgesics were not associated with differential risks of all-cause mortality. Risk factors for drug-related deaths included history of psychiatric admission (relative to no history of psychiatric admission, AHR 2.4, 95% CI 1.2 to 4.6) and co-prescription of benzodiazepines (relative to no co-prescription, AHR 4.4, 95% CI 1.3 to 14). Protective factors for drug-related deaths were 6 months or longer since last methadone prescription (relative to ≤1 month, AHR 0.02, 95% CI 0.00 to 0.05), co-prescription with an antipsychotic (relative to no co-prescription, AHR 0.27, 95% CI 0.08 to 0.89), and co-prescription with an antidepressant (relative to no co-prescription, AHR 0.51, 95% CI 0.30 to 0.98). Age, overuse of methadone, methadone breaks of more than 90 days, having at least one urine drug test, and co-prescription of other opioids were not associated with differential risks of drug-related death.[173]

Some issues made results of this study difficult to interpret. There were important baseline differences between those prescribed methadone maintenance therapy who died compared to

those alive, suggesting an increased likelihood of residual confounding. More importantly, it was unclear if methadone was prescribed at the time of almost half of the deaths. In addition, drug-related deaths could be attributed to any substance, not just methadone.

Another 12-year, retrospective cohort study evaluated risk factors for overdose mortality in a cohort of patients (n=5,200) in Amsterdam during methadone maintenance therapy and within 1 year of leaving methadone maintenance therapy (Table 16).[174] The majority of patients were male (77%), aged 30-39 years (71%), and almost all experienced a temporary discontinuation of methadone maintenance therapy (99%). There were 68 overdose deaths (1.3%) during the study. Increased mortality was associated with male sex (ARR 3.3 relative to female sex, 95% CI 1.5 to 7.2), and being born in the Netherlands (ARR 5.0 relative to ethnic minority, 95% CI 2.3 to11). Methodological shortcomings included unclear assembly of an inception cohort and unclear reporting of attrition.

Five other studies analyzing methadone overdose and associated risk factors reported mixed results (Table 16). A database study of 250 overdose deaths in West Virginia found patients with methadone-related overdose less frequently had a documented prescription for the medication (38%) compared to oxycodone or hydrocodone overdose patients (69% and 87%).[11] An separate analysis of the same database found that of 295 opioid-related overdoses, methadone was a contributing factor in 112 deaths; 32% of these decedents had been prescribed methadone.[175] There was no difference between methadone overdose deaths compared to overdose deaths associated with other opioids in likelihood of presence of any non-opioid prescription medications (AOR 1.2, 95% CI 0.70 to 2.0), benzodiazepines (AOR 0.71, 95% CI 0.4 to1.2), illicit drugs (AOR 0.65, 95% CI 0.31 to1.4), over the counter medications (AOR 2.8, 95% CI 0.84 to 9.6), or alcohol (AOR 0.66, 95% CI 0.29 to 1.5), though some estimates were imprecise.[11] One study evaluated risk factors for methadone overdose deaths compared to other types of overdose deaths and found no statistically significant associations with sex, race, or age in adjusted analysis.[14] Another study found that compared to decedents who used methadone illicitly, decedents prescribed methadone were older (OR 1.2, 95% CI 1.1 to 1.3) and more likely to have antidepressants in their toxicology at death (OR 8.8,95% CI 2.3 to 33).[9] A retrospective study of 3,162 Scottish methadone maintenance patients found a history of psychiatric admissions (adjusted HR 7.0, 95% CI 3.5 to 14) and prescription for benzodiazepines (adjusted HR 1.4, 95% CI 1.2 to 1.7) associated with increased risk of drug-related mortality.[176]

Fourteen case series reported characteristics associated with adverse outcomes in persons prescribed methadone,[12, 14, 177-187] though they are of limited usefulness because they utilized a cross-sectional design and did not report risks in relation to comparison groups of patients without methadone-related overdose or using methadone illicitly (Table 16). Five studies reported benzodiazepines and methadone were both present in blood toxicology in 36-67% of methadone overdose deaths.[9, 12, 180, 183, 184] Five studies reported concomitant use of methadone and multiple prescription or non-prescription medications in 61-92% of deaths.[9, 178, 183-185] Four studies reported an illicit source of methadone in 25-67% of overdose deaths.[9, 177, 184, 186] In three studies, methadone-related death during the induction of methadone maintenance therapy occurred at a rate of 8.6/10,000 inductions, or methadone-related deaths during induction accounted for 3-28% of the deaths in the study population.[12, 181, 187]

One study found white race (OR 4.3,95% CI 2.6 to 7.1), tricyclic antidepressant use (OR 2.1 ,95% CI 1.2 to 3.8), cocaine use (OR 3.2,95% CI 1.4 to 7.4), morphine use (OR 2.1,95% CI 1.0 to 4.3), opiate use (OR 2.8,95% 1.4 to 5.8), benzodiazepine use (OR 1.7, 95% CI 1.1 to 2.4) and concomitant tricyclic antidepressants and benzodiazepine use (OR 4.3, 95% CI 2.0 to 9.6) associated with increased risk of methadone related overdose death compared to risk of death from all other causes, though it was not clear whether the methadone was prescribed.[180] Use of citalopram was protective (OR 0.31;95% CI 0.10 to 0.92). Another study of overdose deaths in New York city found methadone-associated overdose deaths less likely in men compared to women (AOR 0.6, 95% CI 0.52 to 0.70), though it was also unclear whether methadone was prescribed.[179] Presence of cocaine (AOR 0.56, 95% CI 0.49 to 0.64), heroin (AOR 0.46, 95% CI 0.40 to 0.53), or alcohol (AOR 0.78, 95% CI 0.68 to 0.91) in blood at death were also associated with lower risk of methadone overdose death compared to absence of these substances. Persons older than 24 years were more likely to experience a methadone-overdose death compared to those aged 15-25 (AOR range 1.7-3.0 for age groups from 25 to 64 years).

Cardiovascular events and ECG changes

A fair-quality RCT that compared methadone to buprenorphine for treatment of opioid dependence found no association between sex and magnitude of QTc interval changes (Table 17).[61] Too few patients had other risk factors for QTc prolongation (use of medications associated with QTc interval prolongation, hypokalemia, or increased creatinine) to assess their effects.

Several cross-sectional studies evaluated the association between various risk factors and risk of QTc prolongation or torsades in patients prescribed methadone (Table 17). Although some studies found use of other QTc prolonging medications associated with increased risk of QTc prolongation in patients prescribed methadone,[59, 60] others found no association.[53, 70] Some studies also found an association between altered liver function,[59] elevated hemoglobin A1c level,[188] congestive heart failure,[188] male sex,[53, 62, 70] hypokalemia,[59, 65] or use of cocaine or amphetamines[75, 188] and increased risk of QTc prolongation in patients prescribed methadone.

In case series of QTc prolongation or torsades de pointes associated with use of methadone, one-half or more of cases had at least one risk factor for QTc prolongation or torsades de pointes other than methadone use (e.g. interacting medications, hypokalemia, hypomagnesemia, or structural heart disease) (Table 17).[19, 78, 79, 189]However, because these studies did not evaluate inception cohorts of patients prescribed methadone, they are not able to demonstrate causality between the adverse events and the evaluated risk factors, or the magnitude of any such associations. A review of adverse events reported to the FDA's MedWatch program identified 59 cases of QTc prolongation or torsades de pointes associated with use of methadone.[79] About one-half of cases had at least one risk factor for QTc prolongation or torsades de pointes other than methadone use (interacting medications, hypokalemia, hypomagnesemia, or structural heart disease). A second review of 40 published cases of torsades de pointes associated with methadone found high frequency of use of an interacting medication (55%), heart disease (22%), liver cirrhosis/renal failure (28%), or hypokalemia (35%).[78] A third review (n=31) of adult cases of methadone-associated tQTc interval prolongation and/or torsade de pointes found that 77% (24/31) of patients had multiple risk factors besides methadone, including heart disease (35%),

hypokalemia (23%), hypomagnesemia (13%), use of medications associated with QTc prolongation (45%), or hepatic impairment (19%).[189] A smaller (n=17) case series of torsades de pointes in patients prescribed high doses of methadone for outpatient treatment of pain or methadone maintenance (mean daily dose 397 mg/day) found that 82% (14/17) were taking a medication associated with QT interval prolongation (10 patients), had hypokalemia (7 patients), or structural heart disease (3 patients).[19] However, a multiple linear regression analysis found no association between age, sex, use of other QT-interval prolonging medications, structural heart disease, or hypokalemia and the QTc interval (minimum p=0.28).[190]

Sleep apnea

A fair-quality cross-sectional study of persons on methadone maintenance therapy and subjective sleep complaints found no association between severity of obstructive or central sleep apnea and age, cigarettes/day, sex, Beck Depression Inventory score, use of other opioids, cocaine use, marijuana use, or benzodiazepine use, based on univariate analysis.[191] Obstructive hypopnea-apnea index scores were higher in persons with higher body mass index and lower in non-Hispanic Caucasians.

Cognitive functioning and psychiatric outcomes

One small (n=18) fair-quality prospective cohort study found smokers on methadone maintenance therapy performed worse than non-smokers on methadone maintenance therapy on the Gambling Task, but there was no significant difference in the Wisconsin Card Sorting test (Table 18).[192] There were no differences in cognitive performance between non-smokers versus smokers on methadone.

Pregnancy outcomes and outcomes in children exposed in utero

Few studies evaluated predictors of neonatal abstinence syndrome in infants of women prescribed methadone other than dose of maternal methadone (see Key Question 11). The only study that performed multivariate analysis found breastfeeding ≥72 hours the only factor other than methadone dose associated with risk of receiving treatment for neonatal abstinence syndrome, decreasing the odds by about half (adjusted OR 0.55, 95% CI 0.34 to 0.88, Table 19).[134] Although this good-quality study and one fair-quality other study[193] found an association between maternal use of benzodiazepines and risk of neonatal abstinence syndrome in univariate analyses, there was no association in the one study that adjusted for other risk factors (Table 19).[134] One study found a trend towards shorter duration of neonatal abstinence syndrome in breastfed infants, by about 8 days (p=0.06), based on univariate analysis.[194] One fair-quality study found a higher number of cigarettes consumed per day by the mother associated with increased duration of treatment for neonatal withdrawal syndrome,(Table 19)[133] while another fair-quality study found heavy smokers had a higher peak neonatal abstinence syndrome score compared with light smokers (9.8 versus 5.6, p=0.014; Table 19).[195] One poor-quality study found no association between risk of neonatal withdrawal syndrome and mode of feeding or maternal use of other medications (Table 19).[196]

Summary of evidence

- 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 (strength of evidence: moderate).

- Studies that analyzed methadone overdose case series found a high proportion of cases associated with benzodiazepine co-prescription, benzodiazepine in blood toxicology, use of other concomitant medications, or an illicit source of methadone (strength of evidence: low).

- Factors associated with increased risk of QTc prolongation in cross-sectional studies of patients prescribed methadone include use of other QTc prolonging medications, altered liver function, elevated hemoglobin A1c level, congestive heart failure, male sex, hypokalemia, or use of cocaine or amphetamines, though findings were not consistent across studies (strength of evidence: low).

- In case series of QTc prolongation or torsades de pointes associated with use of methadone, one-half or more of cases had at least one risk factor for QTc prolongation or torsades de pointes other than methadone use (e.g. interacting medications, hypokalemia, hypomagnesemia, or structural heart disease (strength of evidence: low).One study found breastfeeding associated with decreased risk of neonatal abstinence syndrome after adjustment for potential confounders, and one found an association between breastfeeding and duration of neonatal abstinence syndrome (no adjustment) (strength of evidence: low).

Key Question 4: In populations prescribed methadone, what are the effects of different dosing strategies on adverse events?

Few studies have evaluated the effects of different methadone dosing strategies on adverse events. One fair-quality cohort study of patients with cancer pain compared effects of methadone rotation from other opioids to initiation of opioids with methadone on risk of discontinuation due to side effects (Table 20).[197] Those that rotated to methadone from another opioid discontinued due to side effects at a similar rate as the group that initiated their opioid use with methadone (3% [3/100] versus 3% [3/89]). A good-quality cohort study of pregnant women compared a taper withdrawal program (either 3 or 7 days) with a methadone maintenance program or the combination of both on maternal and neonatal outcomes (Table 20).[198] There was no difference in incidence or treatment of neonatal abstinence syndrome between the groups, however those in the groups that combined a taper withdrawal program and a maintenance program had lower neonatal intensive care unit admissions (30% for 3-day taper, 36% for 7-day taper, 46% for maintenance only versus 13% for 3-day taper with maintenance and 0 for 7-day taper with maintenance, p=0.003). A cohort study in pregnant women evaluated a single daily dose (in the morning) versus a split dose (twice daily), but didn't evaluate clinical outcomes.[199]

- Methadone rotation was associated with a similar risk of discontinuation compared to initiation of opioids with methadone in one fair-quality cohort study of patients with cancer pain (strength of evidence: low).

Key Question 5: In populations prescribed methadone, what is the accuracy of baseline or follow-up ECGs for predicting adverse cardiac events?

Although some groups recommend baseline or follow-up ECGs in persons prescribed methadone,[26, 28] we identified no studies that assessed the accuracy of baseline or follow-up ECGs for predicting adverse cardiac events.

- No studies met inclusion criteria (no evidence).

Key Question 6: In populations prescribed methadone, what are the benefits and harms of baseline or follow-up ECGs?

We identified no studies that assessed benefits or harms associated with baseline or follow-up ECGs in patients prescribed methadone, either directly as a result of performing the ECG itself, or indirectly as a result of subsequent clinical actions.

- No studies met inclusion criteria (no evidence).

Key Question 7: In populations prescribed methadone with evidence of QTc prolongation, what are the benefits of correcting conditions associated with QTc prolongation?

Treatable conditions associated with QTc prolongation include use of other medications associated with QTc prolongation, electrolyte abnormalities (hypokalemia, hypomagnesemia, and hypocalcemia), and hypothyroidism. We identified no studies that assessed benefits associated with correcting conditions associated with QTc prolongation in populations prescribed methadone.

- No studies met inclusion criteria (no evidence).

Key Question 8: In populations prescribed methadone with evidence of QTc prolongation, what are the benefits and harms of continued use of methadone versus switching to another opioid agonist or discontinuation of methadone?

We identified no studies that assessed benefits or harms of continued use of methadone compared with switching to another opioid, discontinuation of methadone, or reduced doses of methadone in patients prescribed methadone with evidence of QTc interval prolongation. Two case reports and one case series (n=3) that did not meet inclusion criteria reported no recurrence of arrhythmias and normalization of QTc intervals in patients prescribed methadone with evidence of QTc prolongation or ventricular arrhythmias following a switch to buprenorphine.[153, 200, 201] One of these studies also reported improvement in prolongation of QTc interval and no recurrence of arrhythmias in four patients following reduction of methadone dose.[153]

- No studies met inclusion criteria. Case reports and small case series report normalization of QTc intervals and no recurrence of arrhythmias following a switch to buprenorphine or reduction in methadone dose in patients with QTc interval prolongation and ventricular arrhythmia on methadone.

Key Question 9: In populations prescribed methadone at higher risk for adverse events, what are the benefits of methods for reducing risk?

We identified no studies that addressed the benefits of methods for reducing risk for those at higher risk for adverse events.

- No studies met inclusion criteria (no evidence).

Key Question 10: In populations prescribed methadone, what is the effectiveness of methods for reducing risk of diversion or non-prescribed use?

Evidence on the effectiveness of methods for reducing risk of diversion or non-prescribed use of methadone is extremely sparse. One RCT reported no cases of diversion in 69 patients on methadone maintenance therapy who were randomly allocated to receive take-home methadone privileges.[202] In addition to reporting no events, the trial did not explain how diversion was defined or monitored. One other study of patients prescribed methadone maintenance with take home allowances described methadone storage practices and compared the storage practices of people with children compared to those without children, but did not evaluate the association between different methadone storage practices and risk of diversion or non-prescribed use.[203]

- One study randomly allocated patients to take-home methadone privileges, but reported no cases of diversion (strength of evidence: low).

Key Question 11: How does risk of adverse events associated with methadone vary according to dose or duration of therapy

Many studies have assessed the effect of methadone dose or duration of therapy on adverse events, though most did not make statistical adjustments for potential confounders.

Mortality and overdose

Few studies have evaluated whether risk of mortality varies according to dose of methadone (Table 21). One fair-quality cohort study found higher doses of methadone maintenance therapy associated with lower risk of overdose death, but was not designed to distinguish overdoses related to methadone (the outcome of interest for this review) from overdoses related to drugs (an efficacy outcome not included for this review).[51] There was no association between higher methadone maintenance therapy doses and all-cause mortality. A second fair-quality retrospective study of 64 deaths in 3,162 methadone maintenance therapy patients also found no significant association between methadone dose and likelihood of drug-related death (<60 vs. ≥60 mg/day HR 0.98, 95% CI 0.44 to 2.2).[176]

A number of retrospective studies found recent initiation or shorter duration of methadone use appeared to be associated with an increased risk of mortality (Table 21).[145, 173, 174, 176, 204] A Veterans Affairs system study found that about two-thirds of 515 deaths in patients prescribed methadone for chronic pain occurred in the first 30 days of treatment.[145] An Australian study of methadone maintenance patients found 21% (50/238) of deaths reported in a 5-year period occurred in the first week of treatment.[204] Nearly all (88%) of the first-week deaths were classified as drug-related, compared with just under half (44%) of deaths that occurred at any time. A study of 3,152 methadone maintenance therapy patients in Scotland found the first 2 weeks of methadone use associated with increased risk of death versus non-use for <30 days (adjusted HR 2.6, 95% CI 1.0 to 6.6).[176] Compared with 1-2 weeks of treatment, treatment for 3-10 weeks and >10 weeks were associated with lower risk of drug-related mortality (adjusted HR 0.40, 95% CI 0.17 to 0.95 and 0.10, 95% CI 0.03 to 0.35, respectively). Two European studies of patients receiving methadone maintenance therapy found longer duration of methadone treatment associated with slightly decreased risk of all-cause mortality (AHR 0.95 per year, 95% CI 0.94 to 0.96[173]) and drug-related death (AHR 0.93 per year of use, 95% CI 0.92 to 0.95 in one study,[173] and RR 0.21 for >11 years versus <11 years in the other[174]). One of the studies also found recent initiation of methadone maintenance therapy associated with increased risk compared to continued use (ARR 2.9, 95% CI 1.4 to 5.8).[174]

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 (OR 1.2 per 50 mg of methadone, 95% CI 1.1 to 1.4; Table 21).[69]

Six studies found higher methadone doses or higher methadone serum concentration associated with longer QTc interval or greater QTc increase from baseline after controlling for other risk factors associated with QTc interval prolongation (Table 21)[53, 59, 69, 73, 75, 190] In these studies, the amount of QTc variability explained by the methadone dose varied from about 1-28%, including one study that found a greater proportional effect between methadone dose and QTc prolongation in men (28%) compared with women (12%).[69] Other studies found higher methadone dose associated with QTc prolongation in a specific subgroup (e.g. men treated for <12 months[70]) or based on univariate analyses.[57, 68] One cohort study found more pronounced QTc interval prolongation (>500 ms) only in patients prescribed 120 mg/day or more of methadone.[57] Studies that found no association between methadone dose and QTc interval prolongation tended to evaluate populations on relatively low (e.g., <50 or <100 mg/day) mean doses of methadone.[60, 65, 68]

Case series of 17[190] and 40[78] reported high daily methadone doses (mean dose 231 mg/day[78] and 397 mg/day[190]) in patients prescribed methadone with torsades de pointes.

Sleep apnea

A cross-sectional study of patients with chronic pain who underwent polysomnography found an association between higher methadone use and higher apnea-hypopnea index (p=0.002) and central apnea index (p=0.008) (Table 21).[160] No such association was found with other (non-

methadone) opioids. A fair-quality prevalence study of patients on methadone maintenance therapy, subjective sleep complaints, and sleep-disordered breathing found no association between methadone dose and obstructive apnea-hypopnea or central apnea index (Table 21).[191] There was also no association between duration of methadone maintenance therapy and central apnea index, though higher dose was associated with greater obstructive apnea-hypopnea index (Somers $D_{y,x}$ 0.24 for months of methadone treatment, 95% CI 0.11 to 0.37; Somers $D_{y,x}$ is a nonparametric measure of association that gives t he proportionate reduction of error in predicting rank-order on y given knowledge of rank-order on x).

Gastrointestinal adverse events

A poor-quality longitudinal study (n=51) found no differences in the proportion of patients reporting diarrhea, nausea, vomiting, or constipation at 3 compared to 9 months following the initiation of methadone maintenance therapy (Table 21).[205] A poor-quality cross-sectional study found no difference in risk of constipation between patients recently (within the last 5 months) started on methadone maintenance therapy versus those on therapy for 2 or more years (Table 21).[206]

Endocrinologic effects

Two before-after studies found no duration-dependent effects of methadone on testosterone levels through 12 months[101] or 60 days[100] after initiation of maintenance therapy (Table 21). In one of the studies (n=19), the proportion of men reporting sexual dysfunction decreased over time after starting methadone.[101] It also found no clear association between higher methadone doses and lower testosterone levels.[101] The other study found no differences in testosterone levels shortly (within 7 days) following initiation of therapy compared to re-evaluation after 60 days, even though the average dose had increased from 38 to 83 mg/day.[100]

A poor-quality longitudinal study (n=51) found no differences in the proportion of patients reporting decreased libido or anorgasmia at 3 compared to 9 months following the initiation of methadone maintenance therapy (Table 21).[205] A poor-quality cross-sectional study found no difference in risk of impotence or delayed ejaculation between patients recently (within the last 5 months) started on methadone maintenance therapy versus those on therapy for 2 or more years.[206]

Cognitive functioning, sedation, and psychiatric effects

Two fair-quality studies evaluated effects of methadone maintenance duration on measures of cognitive function or psychiatric effects. One prospective cohort study found lower depression with longer duration (through 4 weeks) of methadone maintenance ($p<0.001$, Table 21).[207] A cross-sectional study found longer (at least 6 months) methadone use associated with better cognitive function on a cognitive battery of fluency tests ($p<0.03$ on all measures, Table 21).[208]

Two poor-quality studies evaluated effects of methadone dose or duration on measures of cognitive function or psychiatric effects (Table 21). One trial (unclear if randomized) found no

differences in cognitive function in patients on stable doses of 50 versus 80 mg/day of methadone maintenance therapy or shortly after persons in the 80 mg/day group were titrated down to 50 mg/day on the Wechsler Adult Intelligence Scale.[209] A cross-sectional study found a trend towards lower anxiety and depression with longer duration (through up to 12 months) of methadone maintenance, though results were not statistically significant.[210]

A poor-quality longitudinal study (n=51) found no differences in the proportion of patients reporting drowsiness, anxiety, irritability, depression, or tiredness at 3 compared to 9 months following the initiation of methadone maintenance therapy (Table 21).[205] A poor-quality cross-sectional study found no difference in risk of sleepiness between patients recently (within the last 5 months) started on methadone maintenance therapy versus those on therapy for 2 or more years (Table 21).[206]

Pregnancy outcomes and outcomes in children exposed in utero

No trial randomized women to different doses of methadone and compared risk of neonatal abstinence syndrome associated with different doses. A good-quality systematic review of 65 cohort studies evaluated the association between maternal methadone dose and risk of neonatal abstinence syndrome (Table 1).[211] When all studies reporting incidence of neonatal abstinence syndrome at different doses were included, there was a significantly lower incidence of neonatal abstinence syndrome at lower doses (for ≤20 vs. >20 mg, RR 0.52; 95% CI 0.33 to 0.81, risk difference 48%, 10 studies and for ≤40 vs. >40 mg, RR 0.69; 95% CI 0.51 to 0.94, risk difference 31%, 9 studies). However, when the analysis was restricted to studies that used a prospective design or applied objective criteria to identify neonatal abstinence syndrome, there was no association between dose and incidence.

Three studies evaluated the association between methadone dose and other outcomes in children exposed to methadone in utero and adjusted for potential confounders (Table 21).[125, 134, 212] One prospective study found higher maternal methadone doses associated with younger gestational age, longer hospitalization, lower birth weight, longer birth length, and greater birth head circumference in adjusted models (p=0.001 for all based on adjusted estimates).[125] However, a retrospective study found no association between maternal methadone dose and birth weight after adjusting for number of prenatal visits and gestational duration at first prenatal visit.[212] Another retrospective study found doses of ≥90 mg/day associated with increased risk of receiving treatment for neonatal abstinence syndrome compared to doses of <30 mg/day (adjusted OR 4.8, 95% CI 2.2 to 11).[134] Doses of 30 to <90 mg/day were associated with a non-statistically significant trend towards increased risk compared to the doses <30 mg/day.

Other studies did not attempt to adjust for confounders in their analyses. Studies that evaluated the relationship between methadone dose and birth weight reported inconsistent results, ranging from a positive correlation (higher methadone dose associated with higher birth weight),[121, 213] no association,[112, 214, 215] and even an inverse correlation (higher methadone dose associated with lower birth weight).[125]

Summary of evidence

- Recent initiation or shorter duration of methadone use appeared to be associated with an increased risk of mortality in five observational studies, though risk estimates were close to 1 in one of the studies (strength of evidence: moderate).

- Two studies found no association between higher methadone dose and risk of mortality, but were not designed to distinguish deaths related to methadone use versus deaths due to other causes (strength of evidence: low).

- Higher methadone dose was consistently associated with greater QTc interval prolongation in six studies of patients prescribed higher doses of methadone after controlling for other risk factors, accounting for 1-28% of the observed QTc variability. Case series of patients with torsades de pointes reported high (>200 mg/day) daily methadone doses (strength of evidence: moderate).

- One cross-sectional study of patients with chronic pain found higher methadone doses associated with higher central apnea index (strength of evidence: low).

- Evidence was limited and found no clear association between higher methadone dose and increase risk or severity of gastrointestinal adverse events, endocrinologic effects, cognitive functioning, sedation and psychiatric effects (strength of evidence: low).

- Most studies found no association between higher maternal methadone dose and increased risk of neonatal outcomes (strength of evidence: moderate).

- A systematic review of cohort studies found no association between higher maternal methadone dose and increased risk of neonatal abstinence syndrome when the analysis was restricted to studies that utilized a prospective design or applied objective criteria to identify neonatal abstinence syndrome (strength of evidence: moderate).

Key Question 12: How are risks of methadone affected by the indication for treatment?

Few studies have evaluated whether risks of methadone vary depending on the indication for treatment (e.g., treatment for opioid addiction versus chronic pain, or cancer pain versus non-cancer pain). Rather, the great majority of studies focused on patients with a specific indication for methadone.

A previously described (see Key Question 2) fair-quality, retrospective cohort study based on Oregon Medicaid administrative data that compared rates of adverse events of methadone stratified according to whether patients had cancer or non-cancer pain.[144] In subjects with cancer pain (but not those with non-cancer pain), methadone was associated with less likelihood for ED/hospital encounter for an opioid-related adverse event (AHR 0.24, 95% CI 0.05 to 1.1) compared to the morphine cohort. In subjects with non-cancer pain (but not those with cancer pain), methadone was associated with increased risk of overdose symptoms compared to the

morphine cohort (AHR 1.6, 95% CI 1.0 to 2.4). However, the confidence intervals for the two subgroups overlapped for these two outcomes, indicating no clear difference in risk. In both subgroups, methadone was not associated with increased risk of constipation, opioid poisoning (based on ICD-9 codes), or death compared to morphine.

A fair-quality retrospective cohort study found no difference in risk of neonatal abstinence syndrome in infants of mothers prescribed methadone for pain versus those prescribed methadone for opioid addiction (Table 22).[216] However, infants of mothers prescribed methadone for opioid addiction were more likely to require treatment for neonatal abstinence syndrome (58% versus 10%, p=0.002) and were of older gestational age at delivery (39 versus 36 weeks, p=0.0002).[216] Results are likely to be confounded because women with pain used a lower maximum dose of methadone (median: 40 versus 60 mg, p=0.004), and used methadone for a shorter duration during pregnancy (5 versus 36 weeks; p<0.0001).

Summary of evidence

- Evidence on differential risks of methadone based on the indication for prescribing are very limited and found no clear differences (strength of evidence: low).

Key Question 13: How are risks of methadone affected by the addition of concomitant medications?

Although a number of studies evaluated concomitant medication use as a risk factor for methadone-associated harms (see Key Question 3), few studies prospectively evaluated risks associated with adding concomitant medications to methadone. Five RCTs (sample sizes ranged from 15 to 50 subjects) compared use of doxepin,[217, 218] fluconazole,[219] dextromethorphan,[220] or acetaminophen[221] plus methadone versus methadone alone (Table 23). The studies were rated fair-[217, 218, 221] or poor-quality;[219] methodological shortcomings included unclear randomization, allocation concealment, and lack of description of co-interventions. The only trial to evaluate risk of symptoms associated with overdose (defined as lightheadedness, drowsiness, and diaphoresis) found addition of fluconazole resulted in higher serum levels of methadone, but was not associated with increased risk of overdose symptoms (2/15 versus 0/12).[219] Trials of the combination of doxepin plus methadone reported no difference in risk of various adverse events, but methods used to assess adverse events were not well described.[217, 218] Absolute incidence of adverse events was higher in patients taking methadone plus dextromethorphan compared to placebo (171 events versus 13 events) though none were serious and most (63%) occurred in patients taking >240 mg of dextromethorphan.[220] One fair-quality trial of patients with cancer pain being switched from morphine found the combination of acetaminophen plus methadone associated with worsening somnolence compared to methadone alone (42% versus 10%, p=0.04), with no differences in constipation, nausea, or vomiting.[221] The trial did not report whether the doses of methadone received in the two groups differed.

Summary of evidence

- Several RCTs evaluated risks associated with adding concomitant medications (doxepin, fluconazole, dextromethorphan, or acetaminophen) to methadone, but were

not designed to assess serious harms (such as mortality or cardiac events) and found no clear differences in other adverse events (strength of evidence: low).

Key Question 14: How do differences in adherence and access to care affect risk of adverse events associated with methadone?

We identified no studies that addressed how differences in adherence and access to care affected risk of adverse events.

Summary of evidence

- No studies met inclusion criteria (no evidence).

Key Question 15: In populations prescribed methadone, what is the accuracy of urine drug testing or prescription drug monitoring for predicting adverse events?

No study evaluated the accuracy of urine drug testing or prescription monitoring programs for predicting adverse events in persons prescribed methadone. One study of patients in methadone maintenance therapy found urine drug test results more concordant with self-reported illicit drug use (an outcome outside the scope of this review) in older patients and patients with less history of illicit drug use during treatment.[222] Another study of patients with chronic pain treated who were routinely urine drug tested estimated noncompliance in 9% of 1,563 patients prescribed methadone.[223]

- No studies met inclusion criteria (no evidence).

Key Question 16: In populations prescribed methadone, what are the benefits and harms of urine drug testing or prescription drug monitoring?

We identified only one study that evaluated associations between the use of urine drug testing on harms associated with use of methadone. A previously described (see Key Question 3), fair-quality, retrospective cohort study of patients (n=2,378) prescribed methadone maintenance therapy by primary care physicians in Tayside, Scotland found having had at least one urine drug test (irrespective of the result) associated with decreased risk of all-cause mortality (relative to no urine drug test, AHR 0.33, 95% CI 0.22 to 0.49), though effects on risk of drug-related death did not reach statistical significance (AHR 0.52, 95% CI 0.26 to 1.04). The type of urine drug test used, urine drug test results, and clinician responses to urine drug test results were not reported or analyzed.[173] Some issues that make interpretation of this study difficult, including the possibility of residual confounding, unclear use of methadone at the time of almost half of the deaths, and attribution of drug-related deaths to any substance, are discussed in more detail elsewhere (see Key Question 3).

No study evaluated benefits or harms of prescription drug monitoring in persons prescribed methadone.

Summary of evidence

- One large cohort study found having at least one urine drug test associated with decreased risk of all-cause mortality. The study did not report urine drug test results or clinician responses to the drug tests (strength of evidence: low).

Key Question 17: In populations prescribed methadone, what are the benefits and harms of different methods for structuring and managing care?

A good-quality retrospective cohort study comparing outcomes of individuals in a methadone maintenance clinic allowed to take-home methadone compared to those not allowed to take home methadone (Table 24).[224] Individuals allowed to take-home methadone had to demonstrate satisfactory adherence to program rules and regulations and show substantial progress in treatment, including no drug abuse for at least 3 months, regular program or clinic attendance, demonstrated ability to responsibly self-medicate, absence of serious behavioral problems, absence of known recent criminal activity, stable home environment, and ability to safely and securely store and handle methadone. Compared to the group allowed to take-home methadone, the group never allowed to take-home methadone was significantly younger at onset of opiate addiction (mean age: 22 versus 23 years, p=0.03), were addicted for a longer duration before admission to maintenance treatment (mean16 versus 15 years, p=0.04) and were more likely to use amphetamines on admission (12% versus 6.2%, p=0.20).

The study found take-home methadone privileges associated with increased survival (time from methadone maintenance treatment to death) compared with those who never earned privileges (mean 13 versus 12 years, p=0.04), though results were not adjusted for potential confounders. Among those allowed to take-home methadone, survival time was longer in those allowed to take-home methadone 3 or more months 3-6 months after starting treatment compared to those allowed to take-home methadone less than 3 months after starting treatment (mean 13 to 14 versus 10 years). There were no differences between groups in the risk of hospitalizations while in methadone maintenance treatment.

Summary of evidence

- One cohort study found earning take-home methadone privileges associated with increased survival compared to never earning take-home privileges, though results were not adjusted for confounders and confounding could explain the observed effects (strength of evidence: low).

DISCUSSION

This report systematically summarizes the evidence on the magnitude of 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 methadone-associated harms.

It is difficult to interpret the evidence on methadone-associated mortality. Although epidemiologic studies show marked trends showing increasing numbers of methadone-related

deaths, such studies were not based on inception cohorts of patients prescribed methadone (so it was not possible to directly estimate risks), used surrogate denominators (e.g., dispensing or sales rates) to enable risk estimates, and were frequently unable to distinguish deaths associated with prescribed versus illicit use of methadone.[146-148, 225] Randomized trials of methadone versus placebo were typically conducted in patients treated for opioid dependence and were not designed to specifically assess for risks of methadone-associated mortality,[43-46] and randomized trials of methadone versus buprenorphine or morphine were not designed or powered to adequately evaluate mortality risk.[137-142] In two large observational studies, methadone was either associated with lower risk of death compared to morphine or there was no clear difference in risk between methadone and other long-acting opioids, in persons with chronic pain.[144, 145] Studies suggest that risk factors for deaths associated with methadone include presence of medical or psychiatric comorbidities, overuse of methadone, concomitant use of benzodiazepines or other medications, and recent initiation of methadone.[173-175] In case series,[9, 12, 178, 180, 183-185] a high proportion of methadone-associated deaths were associated with concomitant use of benzodiazepines or other prescription medications.

A number of observational studies, including prospective before-after studies, found methadone associated with risk of QTc interval prolongation compared to no methadone[53, 54, 56, 59, 63, 64] or buprenorphine.[57, 61, 68, 69] Higher methadone dose appeared to be associated with increased risk for or greater magnitude of QTc interval prolongation.[53, 59, 69, 190] Evidence on the association between presence of other risk factors (such as use of concomitant medications, presence of heart disease, liver cirrhosis or renal failure, and electrolyte abnormalities) was sparse or inconsistent.[53, 59, 70] Despite the evidence showing an association between methadone use and QTc interval prolongation, the clinical importance of these findings are less clear. Although one case-control study found methadone associated-cases of sudden death less likely to be associated with structural heart abnormalities than other cases of sudden death, the study had methodological limitations, including failure to perform adjustment on potential confounders and potential misclassification of "therapeutic" methadone use.[48] Prospective studies have been too small to adequately assess risk of arrhythmia in persons prescribed methadone, though one study found a non-statistically significant trend towards increased risk of retrospectively self-reported syncope compared to buprenorphine.[69] Nonetheless, the dose-response association between QTc interval prolongation and torsades de pointes is well-established for sotalol and dofetilide, and there is no known reason why a similar association would not occur for QTc prolongation associated with methadone.

Methadone use during pregnancy is associated with a high frequency of neonatal withdrawal syndrome.[103-105, 117, 119, 121, 127-131] Observational studies that compared other neonatal and infant outcomes (such as mortality, birth weight, or preterm labor) between infants exposed to methadone compared to those not exposed are difficult to interpret, as most studies evaluated women on methadone maintenance therapy and comparisons to control groups (non-addicted women, or those continuing to use illicit opioids) are subject to substantial confounding and reported inconsistent results. Randomized trials of methadone versus buprenorphine during pregnancy found no clear differences or inconsistent results in neonatal outcomes.[110, 132, 170] There is no clear association between maternal methadone dose and risk of neonatal abstinence syndrome.[211]

Evidence on other harms associated with methadone is limited, particularly for risks of methadone compared with other opioids. An exception is gastrointestinal adverse events, which appear similar in persons treated with methadone and sustained-release morphine or buprenorphine.[137-142] One cross-sectional study found methadone, but not other around-the-clock opioids, associated with increased risk of sleep apnea.[160] No studies were designed to evaluate risk of abuse, addiction, or hyperalgesia in persons prescribed methadone, compared to risks in persons prescribed other opioids. Although a number of medications are known to interact with methadone, few randomized trials evaluated the incremental risks of adding medications to methadone, and were not designed to adequately evaluate risks of serious harms.[217-221]

Evidence on methods for reducing or mitigating risks associated with methadone is extremely sparse, in part because of the large sample sizes that would be needed to demonstrate beneficial effects on clinical outcomes. No studies have 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 studies have 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 situation is common for medications associated with QTc interval prolongation, including those for which risk mitigation strategies are recommended as routine practice. Some evidence suggests that (R)-methadone may have less of an effect on QTc interval prolongation compared to the racemic (R, S)-methadone available in the U.S., but it is not FDA-approved and was therefore excluded from this review.[226] However, further research appears warranted. No studies have 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 methods.

Methadone has become widely prescribed for treatment of chronic pain as well as a 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 electrocardiographic abnormalities and cardiac arrhythmias have raised important concerns regarding the safety of methadone, yet many critical research gaps related to harms. Research is urgently needed to better characterize the risks associated with methadone, particularly in comparison with other opioids, as well as on the usefulness of methods for predicting and reducing those risks.

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Table 1. Systematic reviews of adverse events of methadone use

Author, year	Number of studies	Number of patients (treatment and control)	Interventions	Results	Quality
Cleary, 2010[211]	67 studies 29 included in meta-analysis	n=5139 (treatment vs control results not reported)	Methadone Comparisons not reported Mean dose of studies that showed a relationship between methadone use and neonatal abstinence syndrome (19 studies): 39.4 mg, SD 25.2 Mean dose of studies that did not show a relationship between methadone use and neonatal abstinence syndrome (18 studies): 64.6 mg, SD 30.1, p=0.06	<u>Neonatal abstinence syndrome</u> ≤20 mg vs. >20 mg (10 studies, n=558): RR 0.52 (95% CI 0.33 to 0.81); 48% risk difference (0.56 vs. 0.27) ≤40 mg vs. >40 mg (9 studies, n=773): RR 0.69 (95% CI 0.51 to 0.94), 31% risk difference (0.73 vs. 0.43)	Good
Mattick, 2009[2]	11 studies (4 reported mortality outcomes)	Among 4 studies reporting mortality n=537 (Methadone n=287; controls n=289)	Among studies reporting mortality Methadone doses 60 and 97 mg (2 studies), variable (1 study) or not reported (1 study)	<u>Mortality</u> Methadone use vs non-use (4 studies, n=576): RR 0.48 (CI 0.10 to 2.39)	Good

Table 2. Mortality and overdose outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Anchersen, 2009[57]	Pro-spective cohort	Oral methadone maintenance therapy patients willing to participate	Total cohort: n=200 Mean age 41 years, 31% female Methadone: n=173 Mean age 42 years 31% female Buprenorphine: n=27 Mean age 37 years 33% female	Oral methadone: mean dose 111 mg (SD 35) Sublingual buprenorphine: mean dose 19 mg (SD 5)	Maximum estimated mortality associated with methadone maintenance therapy: 0.06/100 patient-years (4 deaths/6450 patient-years)	Fair
Chugh, 2008[48]	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 0.48 mg/L; Controls: n=106 Mean age 42 years 69% male	Methadone (route unknown; determined by blood toxicology screen): mean 0.48 mg/L	Sudden death in absence of underlying cardiac disease, methadone users vs. non-methadone users: 17/22 (77%) vs. 42/106 (40%); p=0.003	Fair
Cornish, 2010[49]	Pro-spective cohort	Diagnosis of substance misuse, at least one prescription of methadone or buprenorphine	n=5577 Mean age not reported; 85% 20 to 39 years of age 69% male	Methadone Methadone plus another opioid Buprenoprhine without methadone Mean doses not reported	Mortality, off treatment vs. on treatment: 1.32 vs. 0.69 per 100 person-years, adjusted rate ratio 2.3 (95% CI 1.7 to 3.1)	Fair

Table 2. Mortality and overdose outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Gearing, 1974[50]	Pro-spective 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 7.6/1000 versus expected rate, general population age 20-54 years 5.6/1000	Poor
Krantz, 2005[54]	Pro-spective before-after	Age >18 years with opioid addiction duration of at least 1 year and at least 1 previous attempt at detoxification	n=149 Mean age 43 years 37% female	Oral methadone, mean dose, 6 months: 80 mg qd (SD 32, range 20-120 mg)	No cases of sudden death during study	Fair
Lipski, 1973[56]	Cross-sectional	Asymptomatic (not described) MMT patients	Total cohort: n=107 Mean age 32 years Approx. 25% female Methadone: n=41 Mean age 33 years No methadone: n=32, Mean age 34 years	Methadone, mean dose and route not reported No methadone *(results for heroin group [n=34] not included)*	One sudden death reported in methadone patient	Poor
Martell, 2005[53]	Pro-spective before-after	Age >18 years with opioid addiction duration of at least 1 year and at least 1 previous attempt at detoxification	n=233 Mean age 43 years 37% female □	Mean dose, 6 months: 80 mg qd (range 20-120 mg) Mean dose, 12 months: 90 mg qd (range 20-200 mg)	All-cause mortality: 3/160 (1.9%) No incidence of torsades de pointes, cardiac arrhythmia, syncope or sudden death	Fair
Peles, 2007[55]	Cross-sectional	Methadone maintenance for at least 100 days	n=138 Mean age 41 years Duration of MMT 4.4 years 29% female	Oral methadone, mean dose 171 mg	Mortality, mean follow-up 1.2 years: 2/138 (2%)	Fair

Table 2. Mortality and overdose outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
van Ameijden, 1999[51]	Pro-spective 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 0.83 (CI, p-value not reported) Death due to overdose, methadone use vs nonuse: RR 0.35 (CI not reported; p=0.05)	Fair
Wagner-Servais, 2003[58]	Retro-spective cohort	All deaths occurring at the institution between 1994 and 1998 that were related to methadone	n=19 Mean age 29 years 32% female	Methadone in blood at time of death: 200-1000 µg/l	8/12 (66.6%) prescribed methadone died within 3 days of initial dose	Fair

Table 3. Cardiovascular events and ECG changes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Chang, 2012[62]	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[70]	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 (men: >430 ms; women: >450 ms): 33/104 (32%)	Not rated
Ehret, 2006[59]	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[71] Other publications: Fareed, 2013[188]	Case series	Methadone maintenance, treated at clinic for at least 6 months	n=55 Mean age 56 years 7% female 64% non-white	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[72]	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 to 1.27)	Not rated

Table 3. Cardiovascular events and ECG changes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Huh, 2010[60]	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. non-use Mean QTc interval: 443 vs. 408 ms QTc >450 ms: 33/90 (37%) vs. 3/40 (7.5%)	Fair
Katz, 2013[73]	Case series	Methadone maintenance, participating in cardiac safety program	n=531 Mean age 41 years 43% female 36% non-white	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[54]	Pro-spective 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=0.2 Mean QRS duration: 92.8 ms vs. 92.6 ms, mean difference -0.2; p=0.76 No incidence of TdP, arrhythmia	Fair
Lipski, 1973[56]	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[74]	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 pathological 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. Cardiovascular events and ECG changes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Martell, 2005[53] other publications: Krantz, 2008[63]	Pro-spective 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 >450ms (men) or >470ms (women): 5/160 (3%) vs. 18/149 (12%) QRS interval: 93 (SD 8) ms vs. 93 (SD 8); magnitude of change -0.2 (SD 6); p=0.7 Methadone use, baseline vs. 12 months: Proportion with QTc interval >450ms (men) or >470ms (women): 5/160 (3%) vs. 14/108 (13%) QRS interval: 93 (SD 8) ms vs. 91 (SD 8); magnitude of change -0.8 (SD 3); p=0.4 No incidence of torsades de pointes, cardiac arrhythmia or syncope	Fair
Mayet, 2011[75]	Case series	Opioid dependence, receiving stable dose of methadone for ≥4 weeks	n=83 Mean age 40 years 29% female 12% non-white	Oral methadone: mean dose 75 mg/day	Mean QTc interval: 429 ms Proportion with QTc interval ≥450ms (men) or ≥470ms (women): 18% (15/83) Proportion with QTc interval >500 ms: 0% (0/83)	Not rated
Peles, 2007[224]	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[66]	Retro-spective 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. Cardiovascular events and ECG changes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Reddy, 2010[67]	Pro-spective 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% non-white	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[76]	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 (0.5%) Proportion with QTc >500 ms: 0%	Not rated
Schmittner, 2009[64]	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)	Three-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

Table 4. Respiratory depression and sleep apnea with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Teichtahl, 2005[83] Other publications: Wang, 2005[65]; Wang 2008[82]	Cross-sectional	Patients on methadone maintenance treatment ≥2 months	n=70 (50 methadone, 20 non-opioid-using controls) Mean age 35 years 50% female Race not reported	Mean methadone serum level 0.34 mg/L (SD 0.34, range 0.09 to 1.70 mg/L)	Methadone vs. control Hypercapnic Ventilatory Response: 1.3 vs. 1.64, p=0.01 Hypoxic Ventilatory Response: 2.1 vs. 1.12, p=0.008	Fair
Wang, 2005[65] Other publications: Teichtahl 2005[83]; Wang 2008[82]	Cross-sectional	Patients on methadone maintenance treatment ≥2 months	n=70 (50 methadone, 20 non-opioid-using controls) Mean age 35 years 50% female Race not reported	Mean methadone serum level 0.34 mg/L (SD 0.34, range 0.09 to 1.70 mg/L)	Methadone vs. control Apnea/Hypopnea Index events per hour: 13 vs. 8 (p<0.05) Central Apnea Index events per hour: 1.7 vs. 0.15 (p<0.001) Obstructive Apnea Index: No significant differences reported	Fair
Wang, 2008[82] Other publications: Teichtahl, 2005[83]; Wang, 2005[65]	Cross-sectional	Patients on methadone maintenance treatment ≥2 months	n=70 (50 methadone, 20 non-opioid-using controls) Mean age 35 years 50% female Race not reported	Mean methadone serum level 0.34 mg/L (SD 0.34, range 0.09 to 1.70 mg/L)	Methadone vs. control Beck Depression Inventory: 4.6 vs. 2.1 p<0.001 Epworth Sleepiness Scale: 7.1 vs. 2.0, p<0.0001); score >11: 8% (4/50) vs. 0% (0/20)	Fair

Table 5. Cognitive functioning and psychiatric outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Appel, 1976[88] and Appel, 1982[89]	Cross-sectional	Methadone patients working or attending school and drug-free former heroin addicts with >=2 years of addiction; matched controls	n=96 Mean age 31 years 100% male 35% White 45% Black 20% Hispanic	Methadone: range 70-120 mg (mean not reported) Non-use	No significant differences on Digit-Symbol Substitution Task or modified Continuous Performance Test between working methadone patients vs. drug-free former heroin addicts vs. opioid-naïve working patients Means of each group significantly higher than non-working methadone patients (p<0.05)	Poor
Curran, 2001[84]	Cross-over RCT	Opiate dependence > 6 months with no major illness	n=24 Mean age 33 years 67% male; Race not reported Mean duration of opiate use: 10 years	Methadone split dose (50% in am and 50% in pm) or single dose (100% in am and placebo in pm) Placebo	Single dose vs. split dose vs. placebo: no differences between groups Prose recall, immediate: 8.8 vs. 8.1 vs. 9.6 Prose recall, delayed: 5.9 vs. 7.4 vs. 7.6 Cancellation, single (seconds): 1.4 vs. 1.8 vs. 2.2 Cancellation, double (seconds): 4.3 vs. 6.6 vs. 4.9 DSST: 52.0 vs. 49.0 vs. 51.0 Tapping (number): 187.3 vs. 174.4 vs. 180.5 Simple reaction time (ms): 307.6 vs. 308.0 vs. 336.0 No significant differences between groups for any results	Fair
Darke, 2000[90]	Cross-sectional	Methadone maintenance subjects enrolled >3 months; matched controls using heroin <3 times	n=60 (30 methadone, 30 controls) Mean age 36 years 60% male Race not reported	Methadone: mean dose 77 mg Non-use	Methadone vs. control (mean raw scores) Digital symbol: 53.5 vs. 70.4 Symbol search: 24.7 vs. 31.4 Digit span: 14.4 vs. 17.3 WCST (CLR): -0.28 vs. 0.28 COWAT: 31.6 vs. 36.4 CFT-copy: 29.1 vs. 31.1	Poor

Table 5. Cognitive functioning and psychiatric outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Gordon, 1970[98]	Pro-spective cohort	Not reported	n=95 (methadone n=27, non-user n=29, 14-day detox n=20, 4-day detox n=19) Mean age 30 years 81% male	Methadone: 100 mg average dose Non-use	Methadone vs. non-use Simple reaction time (mean, msec): 226 vs. 294 (p<0.01) for males, 288 vs. 348 (p<0.01) for females Multiple-discrimination-single-response task (mean, msec): 250 vs. 313 (p<0.05) for males, 305 vs. 336 (p<0.01) for females	Poor
Gritz, 1975[87]	Cross-sectional	Ex-heroin addicts from the methadone maintenace outpatient program and the total abstience colony at the Brentwood VA Hospital, Los Angeles	n=25 (methadone n=10, abstinent n=10, controls n=5) Median age: Methadone 31 years Abstient 25 years Controls 22 years 100% male Median duration methadone use: 5 months Median duration abstinence: 2 months	Methadone, median dose: 65 mg/day (quartile range: 35 to 85 mg)	Methadone vs. abstinent vs. controls Peak EEG left alpha (Hz): 8.3 vs. 8.8 vs. 9.6 (p<0.02 for methadone vs. control) Peak EEG right alpha (Hz): 8.4 vs. 8.5 vs. 9.5 (p<0.03 for methadone vs. control) Mean Wechler pairs total score (0 to 20 score): 18.4 (SD: 1.6) vs. 15.6 (SD: 2.8) vs. NR (p=0.01) Mean hidden word test (scale NR): 19.3 (SD: 3.9) vs. 14.7 (SD: 4.8) vs. NR (p=0.03) Mean story recall (scale NR): 13.2 (SD: 0.8) vs. 10.0 (SD: 2.5) vs. NR (p=0.003) Mean verbal learning (0 to 8 score): 5.6 (SD: 1.3) vs. 4.2 (1.1) vs. NR (p=002)	Poor

Table 5. Cognitive functioning and psychiatric outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Gruber, 2006[94]	Pro-spective cohort	Subjects enrolled in a methadone maintenance program, ages 18 to 45 years, met DSM–IV criteria for opiate dependence, and were beginning methadone maintenance treatment, subjects were excluded if they were pregnant, had an organic mental disorder, seizure disorder, or central nervous system disease (e.g., multiple sclerosis or cerebral vascular incident), or if they had a history of head trauma or loss of consciousness	n=17 Mean age 41 years 35.2% female Race not reported	Methadone, mean dose: 68 mg/kg	Baseline vs. 2 month follow-up Mean Rey Auditory Verbal Learing (words recalled): 40.9 vs. 47.4 (p=0.004) Mean WAIS-R: 42.9 vs. 49.2 (p=0.03) Mean Rey-Osterrieth Complex Figure Test (delay condition): 11.0 vs. 14.03 (p=0.03)	Fair
Lenn, 1976[85]	Cross-sectional	Methadone maintenance; abstained from illicit drug use for previous 6 months; urinalysis positive for methadone, negative for morphine, quinine, codeine, and other drugs	n=50 (methadone n=25; heroin or methadone abstinent controls n=25); Mean age 34 years 52% male Race not reported	Methadone: 0-50 mg Non-use	Methadone use vs. non-use, proposition of patients History of headache: 8/25 (32%) vs. 4/25 (16%) History of tremor: 8/25 (32%) vs. 2/25 (8%) History of vertigo: 1/25 (4%) vs. 0/25 (0%) Tremor on exam: 3/25 (12%) vs. 0/25 (0%) Abnormal exam: 0/25 (0%) vs. 2/25 (8%) Abnormal EEG: 2/25 (8%) vs. 3/25 (12%)	Poor

Table 5. Cognitive functioning and psychiatric outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Mintzer, 2002[95]	Cohort	Enrolled in outpatient methadone maintenance programs free of significant medical problems or Axis I psychiatric disorders; healthy matched controls	n=39 (methadone n=18, healthy controls n=21); Mean age: Methadone 38 years Control 35 years Methadone: 39% male Control: 48% male Black race: Methadone 72% Control 67%	Methadone: mean dose not reported Non-use	Methadone vs. control DSST (mean number correct): 20.17 vs. 28.86 (p=0.004) DSST (mean number attempted): 21.17 vs. 30.57 (p=0.002) Trail-making A (mean seconds): 77.61 vs. 56.17 (p=0.007) Trail-making B (mean seconds): 136.09 vs. 94.73 (p=0.014)	Fair
Mintzer, 2005[86]	Cross-sectional	Opioid-dependent methadone maintenance patients; matched controls; compared with currently abstinent former opioid abusers	n=59 (18 methadone, 21 matched controls, 20 abstinent former users) Mean age: Methadone 38 years Controls 35 years Abstinent former users 40 years Methadone 39% male Controls 48% male Abstinent former users 65% male Black race: Methadone 72% Controls 67% Abstinent former users 95%	Methadone: mean dose not reported Non-use	Methadone vs. non-use vs. former abuser - DSST (mean correct): 20.17 vs. 28.86 vs. 24.05 (p<0.005 methadone vs. non-use) - Trail-making A (mean total time, seconds): 77.61 vs. 56.17 vs. 106.52 (p<0.05 methadone vs. others) - Trail-making B (mean total time, seconds): 136.09 vs. 94.73 vs. 131.88 (p<0.05 non-use vs. others) - Two-back task (mean sensitivity): 1.70 vs. 2.20 vs. 2.08 (p<0.05 methadone vs. non-use)	Fair

Table 5. Cognitive functioning and psychiatric outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Moskowitz, 1985[96]	Pro-spective cohort	Former heroin addicts enrolled in methadone maintenance programs for at least 6 month and considered stabilized in treatment; healthy controls	Study 1: n=24 (methadone n=12, non-users n=12) 100% male Study 2: n=30 (methadone n=15, former users n=15) 100% male Race not reported	Methadone: mean dose not reported Non-use	There were no differences between groups in either study on any of the cognitive test	Poor
Pirastu, 2006[164]	RCT	Opiate-dependent patients attending local drug addiction clinic for at least 12 months, with no central nervous system pathology or axis 1 disorder, no head trauma or dementia, no medication known to affect cognitive functioning, no past or present alcohol or other illicit substance dependencies	n=69 (methadone n=30, buprenorphine n=18, matched controls n=21); Mean age 34 years Methadone 97% male Buprenorphine 94% male Controls 67% male Race not reported	-Methadone, mean dose not reported -Buprenorphine, mean dose not reported -No methadone (healthy controls)	Methadone vs. buprenorphine vs. controls - Gambling task net scores (mean): 2.93 vs. 19.67 vs. 15.33 (p<0.05 methadone vs. buprenorphine) - Wisconsin card sorting task preservative errors (mean): 28.7 vs. 22.8 vs. 12.6 (p<0.05 methadone vs. controls) - WAIS (mean): 85 vs. 89.3 vs. 104 (p<0.05 controls vs. others) - BVRT correct (mean): 5.67 vs. 6.06 vs. 7.90 (p<0.05 controls vs. others) - BVRT errors (mean): 6.5 vs. 5.22 vs. 2.57 (NS)	Fair

Table 5. Cognitive functioning and psychiatric outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Prosser, 2006[93]	Cross-sectional	Healthy patients 21-55 years, either opiate-dependent currently receiving methadone maintenance therapy or opiate-dependent who have received methadone maintenance therapy and currently abstinent or controls without a history of opiate-dependence	n=85 (29 methadone maintenance therapy, 27 former users, 29 controls) Mean age: Methadone 38 years Former users 43 years Controls 34 years Methadone 79% male Former users 74% male Controls 72% male Black race: Methadone 21% Former users 41% Controls 35% White race: Methadone 38% vs. Former users 26% Controls 41%; Hispanic: Methadone 41% Former users 26% Controls 10%;	Methadone, mean dose not reported; max dose 74 mg/day Non-use	Methadone vs. former users vs. controls WAIS (mean): 8.05 vs. 8.6 vs. 12.16 (p<0.001 controls vs. others) BVRT correct (mean): 6.7 vs. 4.65 vs. 7.63 (p=0.001 former users vs. others) BVRT errors (mean): 5.4 vs. 7.82 vs. 2.36 (p<0.001 controls vs. others) BVRT right errors (mean): 2.55 vs. 3.96 vs. 1.05 (p<0.001 former users vs. controls) BVRT left errors (mean): 2.4 vs. 3.22 vs. 1.21 (p=0.011 former users vs. controls)	Poor
Rapeli, 2007[92]	Cross-sectional	Opioid dependence and start of opioid substitution treatment in last 6 weeks; matched controls	n=50 (16 methadone, 17 buprenorphine/ naloxone, 17 controls) Mean age 30 years 50% male Race not reported	Methadone, mean dose 53 mg Buprenorphine, mean dose 16 mg Naloxone, mean dose 4 mg Non-use	Methadone vs. buprenorphine/naloxone vs. control Tonic alertness: 256 vs. 228 vs. 244 Phasic alertness: 245.6 vs. 227.4 vs. 230.3 TAP Go/No-go reaction time: 528.3 vs. 496.9 vs. 465.5 TAP Go/No-go errors: 0.6 vs. 1.2 vs. 0.5 Wechsler Memory Scale (WMS), logical memory recall:12.5 vs. 14.3 vs. 16.3 WMS, logical memory, delayed recall: 11.1 vs. 13.4 vs. 14.5	Poor

Table 5. Cognitive functioning and psychiatric outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Specka, 2000[91]	Cross-sectional	Methadone maintenance >=4 months, with stable dose >=6 weeks; matched healthy controls	n=108 (54 methadone; 54 healthy controls) Mean age 29 years 65% male Race not reported	Methadone, mean dose 93 mg (range 10-240 mg) Non-use	Methadone use vs. non-use Labyrinth of lines, number of responses: 26.4 vs. 29.3; Simple Choice Reaction decision errors: 2.1 vs.1.6 Mean decision time, ms: 369 vs. 386 Mean reaction time, ms: 509 vs. 546 Attention, number of responses: 456.6 vs.503.2	Poor
Verdejo, 2005[97]	Pro-spective cohort	Abstinent heroin abusers with a minimumabstinence period of 15 days for any substance, or methadone maintenance patients involved in a formal methadone maintenance treatment, being stabilized in their current methadone dose for at least 15 days and a minimum abstinence period of 48 hours from any drug except methadone, those who hadpreviously been diagnosed with any other disorder from Axis 1 or 2 of the DSM-IV were excluded	n=41 (methadone n=18, abstinent n=23) Mean age (years) Methadone 35 years Abstinent: 32 years	Methadone dose, mean: 83.82 mg	Methadone vs. abstinent Mean WCST (percentage perseverative errors): 15.00 vs. 18.98; p=NS Mean WCST (percentage conceptual level responses): 54.52 vs. 46.81; p=NS Mean letter number sequencing (raw score): 6.93 vs. 8.30; p=NS Mean animal recognition task (number recognized): 19.46 vs. 19.43; p=NS Mean fruit recognition task (number recognized): 12.40 vs. 13.00; p=NS Mean FAS word recognition task (number recognized): 29.20 vs. 31.95; p=NS Mean digit test, group 1 (time of performance): 22.64 vs. 19.30; p=0.009 Mean digit test, group 2 (time of performance): 22.64 vs. 20.91; p=NS Mean digit test, group 3 (time of performance): 36.50 vs. 31.65; p=0.044 Mean digit test, group 4 (time of performance): 51.21 vs. 44.00; p=NS) Mean oral trails test, group 1 (time of performance): 56.53 vs. 40.91; p=0.003 Mean oral traits test, group 2 (time of performance): 92.90 vs. 62.39; p=0.003 Mean oral traits, interference (time part 2-time part 1): 36.07 vs. 21.48; p=0.044	Fair

Table 5. Cognitive functioning and psychiatric outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Wang, 2008[82]	Cross-sectional	Patients on stable dose methadone maintenance treatment >=2 months; matched healthy controls	n=70 (50 methadone, 20 healthy controls) Mean age 35 years 50% male Race not reported	Methadone, mean dose not reported (mean serum concentration level 0.34 mg/l) Non-use	Methadone use vs. non-use Obstructive Sleep Apnea-Hypopnea Index:10.8 hours vs. 9.4 hours; p=0.59 Central Apnea Index: 6.7 hours vs. 0.25 hours; p<0.001 Mini Mental State Exam: 28.66 vs. 29.35, p=0.09 BDI: 14.64 vs. 2.05; p<0.001	Poor

Table 6. Endocrinologic and immunologic outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Brown, 2005[100]	Cross-sectional	Men enrolled in methadone maintenance clinic	n=92 Mean age 42 years 100% male 80% White 18% Black, 1% Hispanic	Methadone: new users mean dose 38 mg; mean dose continuous users 100 mg	New use vs. continuous use Mean thyroid stimulating hormone, μIU/ml: 1.3 vs. 2.0 Mean testosterone, ng/mL: 5.8 vs. 4.6 Mean prolactin, ng/mL: 8.8 vs. 9.8	Fair
Cushman, 1973[101]	Before-after	Methadone-maintained patients attending the St. Luke's Hospital Center methadone maintenance clinic	n=19 Mean age 34% 100% male 36% Black (other races not reported)	Methadone: mean dose not reported	Methadone, baseline vs. 12-month follow-up No change in mean testosterone levels observed with methadone use Normal LH levels before and during methadone use	Fair
English, 1988[102]	Cross-sectional	Methadone maintenance therapy; healthy controls	n=195 (Methadone n=145; healthy controls n=50); Mean age 32 years 54% male (methadone group only; gender not reported for controls) Race not reported	Methadone: mean dose not reported (range 15-45 mg)	Methadone vs. controls T4 nmol/L: 139.8 vs. 97.4; p<0.001 T3 nmol/L: 2.7 vs. 2.15; p<0.001	Poor

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Intervention	Results	Quality
Anyaegbunam, 1997[111]	Case-control	Not reported	n=48 (methadone n=24, control n=24); Mean maternal age 30 years Race not reported	Methadone: mean dose 60 mg (range 20-70 mg) Non-use	Methadone vs. controls Mean birth weight (g): 2985 vs. 3010 Meconium: 13% (3/24) vs. 17% (4/24) Apgar <7 at 1min: 17% (4/24) vs. 13% (3/24) Apgar <7 at 5min: 8% (2/24) vs. 4% (1/24)	Poor
Binder, 2008[110]	RCT	Participation in substitution program by 12th week of pregnancy, <30 years old, dependence on opiates for 3-5 years, HIV and BWR negative, no active B or C hepatitis, no history of thromboembolism, primigravidity or second gravidity with uneventful course of pregnancy, absence any other chronic conditions, not a current smoker, no presence of other addictive substances	n=117 (methadone n=32, heroin/No treatment n=47; study included buprenorphine arm [n=38], results not abstracted) Mean maternal age 27 years Race not reported Mean duration of addiction 4 years	Methadone: mean dose 80 mg Heroin without treatment (no treatment group)	Methadone vs. no treatment Preterm labor: 22% (7/32) vs. 30% (14/47); p=0.04 Mean birth weight (g): 2900 vs. 2601; p=0.007 Severity of NAS (Finnegan score): 18 vs. 9.2; p<0.000001 Duration of NAS treatment (days): 30 vs. 11, p<0.000001 Delayed onset of withdrawal symptoms (days): 0 vs. 1, p<0.000001	Poor
Brown, 1998[112]	Cross-sectional	Pregnant women followed up at methadone clinic	n=96 (methadone n=32, controls n=32; study included cocaine arm [n=32], results not abstracted) Mean maternal age 27 years 42% Black (other races not reported)	Methadone: mean dose not reported Controls (no methadone)	Methadone vs. control Mean birth weight (g): 2748 vs. 3032 Mean head circumference (cm): 32.4 vs. 33.5 (p<0.05) Mean gestational age (weeks): 37.8 vs. 38.0	Poor

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year
Anyaegbunam, 1997[111]
Binder, 2008[110]
Brown, 1998[112]

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Intervention	Results	Quality
Burns, 2010[126]	Cross-sectional	Women in New South Wales health databases with live births, women on a methadone program with infants who died or did not die and comparison group of women not on methadone program with infants who died and who did not die	n=675,310 (methadone n=865; general population n=674,445) Mean maternal age not reported; 93% ages 20-39 years Race not reported	Methadone: mean dose not reported Non-use	Methadone vs. control Infant deaths: 2.42% (21/865) vs. 0.4% (2698/674445) Infant mortality rate: 24.3/1,000 live births vs. 4.0/1,000 live births; RR: 6.2 (95% CI: 4.0 to 9.6) Neonatal death rate: 12.71/1,000 live births vs. 2.8/1,000 live births; RR: 4.5 Late infant death rate: 11.6/1,000 live births vs. 1.2/1,000 live births; RR: 9.7 SIDS: 38% (n=8) of deaths vs. 10% (n=278) of deaths	Fair
Chasnoff, 1982[114] Other publications: Chasnoff 1984[113]	Cross-sectional	Women enrolled in the Perinatal Addiction Project during the first or early second trimester of pregnancy and completed a course of intensive prenatal care	n=85 (methadone n=39, no methadone n=27; study included polydrug arm [n=19], results not abstracted) Mean maternal age 23 years 48% White 38% Black 14% Hispanic	Methadone: mean dose 15 mg (range 5-40 mg) Non-use	Methadone vs. no methadone Mean birth weight (g): 2815 vs. 3492 (p<0.05) Mean length (cm): 47.9 vs. 51.1 (p<0.05) Mean head circumference (cm): 32.5 vs. 34.6 (p<0.05)	Poor

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year
Burns, 2010[126]
Chasnoff, 1982[114] Other publications: Chasnoff 1984[113]

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Intervention	Results	Quality
Chasnoff, 1984[114] Other publications: Chasnoff, 1982[113]	Cross-sectional	Women enrolled in the Perinatal Addiction Project during the first or early second trimester of pregnancy and completed a course of intensive prenatal care	n=122 (methadone n=51, drug-free n=27; other comparisons not abstracted: sedative/ stimulant n=22, pentazocine and tripelennamine n=13, PCP n=9) Mean maternal age 23 years 48% White 38% Black, 14% Hispanic	Methadone: mean dose 15 mg (range 5-40 mg) Non-use	Methadone vs. drug-free Mean birth weight (g): 2840 vs. 3479 (p<0.01) Mean length (cm): 48.2 vs. 51.1 (p<0.01) Mean head circumference (cm): 32.2 vs. 34.7 (p<0.01)	Poor
Connaughton, 1977[105]	Pro-spective cohort	Drug-dependent women giving birth between 1969-1974	n=428 (methadone n=135, heroin and no counseling/prenatal care n=63, drug dependent and minimal counseling/prenatal care n=80; nonclinic control n=75, clinic control n=75) Demographic data not reported	Methadone: mean dose not reported Heroin: addicted women with no prenatal care Drug dependent: women with minimal prenatal care Nonclinic control: nonaddicted patients with no prenatal care Clinic control: nonaddicted patients with prenatal care	Methadone vs. heroin vs. drug dependent vs nonclinic control vs. clinic control Low birth weight: 19% (26/135) vs. 48% (30/63) vs. 39% (31/80) vs 20% (15/75) vs. 16% (12/75) Incidence of neonatal morbidity: 70% (93/133) vs. 75% (47/63) vs. 82% (64/78) vs 25% (19/75) vs. 32% (24/75) Incidence of intrauterine growth retardation: 8% (10/133) vs. 13% (8/63) vs 8% (6/78) vs. 3% (2/75) vs. 9% (7/75) Withdrawal symptoms: 91% (116/128) vs. 95% (57/60) vs. 93% (67/73) vs 0% (0/75) vs. 0% (0/75) Severe withdrawal symptoms: 13% (16/128) vs. 25% (15/60) vs. 13% (9/72) vs 0% (0/75) vs 0% (0/75) Mean apgar at 1 min: 7.6 vs. 7.0 vs. 7.3 vs 7.9 vs. 8.2 Mean apgar at 5 min: 8.9 vs. 8.3 vs. 8.4 vs 9.2 vs. 9.4	Poor

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year
Chasnoff, 1984[114] Other publications: Chasnoff, 1982[113]
Connaughton, 1977[105]

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Intervention	Results	Quality
Davis, 1973[106]	Pro-spective cohort	Mothers being maintained on methadone and gave birth during a 17 month period (9/1971-2/1973)	n=70 (low-dose methadone n=31, high-dose methadone n=18, heroin n=21) Mean maternal age 23 years Race not reported	Low-dose methadone: ≤50 mg, mean dose not reported High-dose methadone: ≥60 mg, mean dose not reported No methadone treatment (heroin addicts not receiving methadone)	Low-dose methadone vs. high-dose methadone vs. no methadone Mean gestational age (weeks): 38.61 vs. 39.61 vs. 39.81 Mean birth weight (pounds): 5.90 vs. 6.45 vs. 6.52 Mean apgar at 1min: 8.12 vs. 7.08 vs. 7.45 Mean apgar at 5min: 9.07 vs. 8.59 vs. 8.60 % infants with mod-severe withdrawal symptoms: 45% (14/31) vs. 61% (11/18) vs. 29% (6/21), p=0.05	Poor
Dinges, 1980[115]	Cross-sectional	Pregnant women participating in an urban methadone treatment program and pregnant women not drug-dependent	n=58 (methadone n=28, no methadone controls n=30) Demographic data not reported	Methadone: mean dose 18 mg No methadone treatment (categorized as optimal or nonoptimal based on neonate delivery)	Light opiate vs. heavy opiate vs. heavy opiate and non-opiate vs. optimal vs. nonoptimal Mean birth weight (g): 2956 vs. 2927 vs. 2783 vs. 3358 vs. 3309 ($p<0.05$) Mean gestational age (weeks): 39.1 vs. 38.9 vs. 38.2 vs. 40.1 vs. 39.1 ($p<0.06$) Mean apgar at 1min: 6.6 vs. 7.7 vs. 8.2 vs. 8.7 vs. 8.1 Mean apgar at 5min: 7.4 vs. 8.7 vs. 8.9 vs. 9.3 vs. 8.6	Poor

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year
Davis, 1973[106]
Dinges, 1980[115]

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Intervention	Results	Quality
Doberczak, 1987[116]	Cross-sectional	Cases were drug-dependent mothers enrolled in methadone treatment programs in New York Controls were mothers at the same clinic seen immediately after cases	n=300 (methadone n=150, controls n=150); Mean maternal age 28 years 32% White 23% Black 44% Hispanic	Methadone: mean in 3rd trimester dose 41.2 mg/day (range: 2.5-100 mg/day) Non-use	Methadone vs. controls Mean birth weight (g): 2800 vs. 3248 (p<0.001) Mean birth weight percentile: 25 vs. 50-75 (p<0.001) Mean gestational age (weeks): 38.9 vs. 39.3 (NS) Intrauterine growth retardation: 20% (30/150) vs. 4% (6/150); p<0.001 Mean head circumference (cm): 32.6 vs. 33.8 (p<0.001) Head circumference percentile: 25 vs. 50-75 (p<0.001)	Poor
Dryden, 2009[134]	Pre-valence	Singleton infants born to drug abusing women prescribed substitute methadone	n=440 Median maternal age 28 years (range 15-41) Race not reported	Methadone: mean dose not reported; 22% 1-29 mg; 38% 30-59 mg; 30% 60-89 mg; 10% >=90 mg	Factors predictive of treatment for neonatal abstinence syndrome Methadone dose >90 mg vs. 1-29 mg: OR: 4.82 (95% CI: 2.18 to 10.64); p<0.001 Breastfeeding >72 hours (unclear is vs no breastfeeding and/or breastfeeding < 72 hours): OR: 0.52 (95% CI: 0.33 to 0.83); p=0.006	Good
Fajemirokun-Odudeyi, 2006[108]	Retro-spective cohort	Women who used heroin or methadone and who gave birth to babies with possible withdrawal symptoms	n=108 (methadone n=52, heroin n=47, unknown n=9) Mean maternal age 25 years Race not reported	Methadone: mean dose 32 mg No methadone (pregnant women abusing IV drugs, not enrolled in methadone substitution program)	Methadone vs. no methadone Mean gestational age (weeks): 38.2 vs. 38.4 Mean birth weight (g): 2784 vs. 2803 Premature delivery (<37 weeks): 30% (16/54) vs. 23% (11/47) Neonatal death: 2% (1/54) vs. 2% (1/47) Apgar <7 at 1min: 0 vs. 5 (11%); p=0.01 Apgar <7 at 5min: 0 vs. 2 (4%) Maximum NAS score: 4.7 vs. 5.8; p=0.004	Poor

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year
Doberczak, 1987[116]
Dryden, 2009[134]
Fajemirokun-Odudeyi, 2006[108]

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Intervention	Results	Quality
Harper, 1977[117]	Cross-sectional	>=18 years old <=29 weeks pregnant; planning to continue the pregnancy to term; free of pre-existing medical diseases and/or obstetric complications during pregnancy; willing to have blood drawn periodically and urine screened periodically	n=41 (methadone n=22, controls n=19) Demographic data not reported	Methadone: mean dose not reported	Methadone vs. controls Mean birth weight (g): 2946 vs. 3423 (p<0.05) Below 50th birth weight percentile: 77% (17/22) vs. 32% (6/19); p<0.05 Infants with withdrawal symptoms: 96% (21/22) vs. 11% (2/19) Severity of withdrawal positively correlated with total methadone dose during last 12 weeks of pregnancy (p<0.02) and maternal daily dose at time of delivery (p<0.01)	Fair
Kandall, 1976[93]	Cross-sectional	Mothers with histories of past or present narcotic usage and controls	n=365 (106 methadone n=106, specific methadone program during entire pregnancy n=40, heroin n=61, methadone + heroin n=59, ex-addicts n=33, control n=66,) Demographic data not reported	Mean dose not reported for any group	Methadone vs. methadone + heroin vs. methadone specific program vs. ex-addicts vs. controls vs. heroin Mean birth weight (g): 2961 vs. 2535 vs.3032 vs. 2615 vs. 3176 vs. 2490 (p<0.01 for methadone vs. control) Mean gestational age (wks): 39.4 vs. 38.3 vs. 39.6 vs. 38.6 vs. 40.0 vs. 38.0 (p<0.05 for methadone vs. control) Within methadone group Mean birth weight (g) White: 3147; Black: 2510; Puerto Rican: 2638 (p<0.001 White vs. others)	Poor

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year
Harper, 1977[117]
Kandall, 1976[93]

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Intervention	Results	Quality
Kandall, 1977[104]	Retro-spective cohort	Infants born to mothers with past illicit drug histories	n=316 (methadone n=89, 61 methadone + heroin n=61, ex-addicts n=34, controls n=66, heroin only n=66) Mean maternal age not reported 12% White 56% Black 32% Hispanic	Methadone only Methadone + heroin Former addicts (non-use) Healthy controls Heroin only	Methadone vs. methadone + heroin vs. non-use vs. controls vs. heroin alone Mean gestational age (weeks): 39.2 vs. 38.3 vs. 38.6 vs. 40.0 vs. 38.0 (p<0.001 for methadone + heroin vs. controls; p<0.01 for methadone and non-use vs. controls; p<0.01 for heroin vs. methadone) Methadone vs methadone + heroin vs heroin alone Perinatal mortality: 4% (3/89) vs. 5% (3/62) 8% (5/66) Infants with withdrawal symptoms: 83% (74/89) vs. 81% (50/62) vs. 79% (48/66) Infants treatment for withdrawal: 77% (66/86) vs. 68% (40/59) vs. 43% (26/61); p<0.001	Poor
Kandall, 1993[118]	Retro-spective cohort	All live-born infants between 1/1979-2/1989	n=1,209,534 total births (methadone n=3,416, no methadone n=1,193,079) Demographic data not reported	Methadone: mean dose not reported	Methadone vs. no methadone SIDS deaths: 1% (33/3,416) vs. 0.1% (1,664/1,193,079); p<0.01 Adjusted RR: 3.6 (95% CI: 2.5 to 51)	Poor
Lifschitz, 1985[103] Other publications: Lifschitz, 1983	Pro-spective cohort	Mothers enrolled in a methadone treatment program for at least 2 consecutive months during pregnancy	n=67 (methadone n=26, drug-free=41, heroin n=25) Mean age not reported 41% White 31% Black 28% Hispanic	Methadone: mean dose not reported Non-use Heroin use	Methadone vs. non-use vs. heroin Mean gestational age (weeks): 38.8 vs. 39.2 vs. 38.4 Mean birth weight (g): 2910 vs. 3289 vs. 2759; p<0.01 methadone vs. non-use Mean birth length (cm): 47.8 vs. 49.7 vs. 47.4; p<0.01 methadone vs. non-use Mean head circumference (cm): 33.2 vs. 34.5 vs. 33.0; p<0.01 methadone vs. non-use Treated for NAS: 88% (23/26) vs. 0% (0/41) vs. 68% (17/25)	Fair

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year
Kandall, 1977[104]
Kandall, 1993[118]
Lifschitz, 1985[103] Other publications: Lifschitz, 1983

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Intervention	Results	Quality
Newman, 1975[128]	Pre-valence	Enrolled in New York City methadone maintenance treatment program	n=313 Mean maternal age 25 years (range 18-42) 26% White 50% Black 24% Hispanic	Methadone: mean dose not reported (range <40 to >100 mg; 39% 40-60 mg)	Methadone <40mg vs. 40-60mg vs. 70-90mg vs. 100mg vs. >100mg Infants with withdrawal symptoms: 71% (31/44) vs. 77% (94/122) vs. 81% (58/72) vs. 81% (38/47) vs. 85% (24/28) 7 infants died, distribution by dose not reported	Poor
Quick, 2009[119]	Case-control	Sub-sample of case-control study	n=20 (methadone n=10, non-methadone n=10) Mean maternal age not reported Race not reported	Methadone: mean dose varied by trimester; range 53 mg (1st trimester) - 62 mg (3rd trimester) Non-use	Methadone vs. non-methadone Mean gestational age (weeks): 39.08 vs. 39.09 Mean birth weight (g): 3238 vs. 3438 Mean length (cm): 51.60 vs. 52.20 Mean head circumference (cm): 34.80 vs. 34.65 Mean length of stay (days): 17.40 vs. 2.90 (p=0.005) Mean highest Finnegan score: 13.20 vs. 0.20 (p<0.0001) Mean NNNS stress abstinence score: 0.17 vs. 0.10 (p=0.04) Neonatal abstience syndrome: 80% (8/10) vs. 0% (0/10); p<0.0001	Poor
Rajegowda, 1972[129]	Cross-sectional	Not reported	n=53 (methadone n=15, no treatment n=38) Demographic data not reported	Methadone: mean dose not reported Non-use	Methadone vs. non-use Newborns with NAS: 87% (13/15) vs. 39.5% (15/38); p<0.005	Poor
Ramirez-Cacho, 2006[120]	Retro-spective cohort	Pregnant women consecutively enrolled from January 2001 to December 2003 in prenatal methadone maintenance program.	n=107 (methadone n=56, control n=51); Mean maternal age 28 years 27% White 67% Hispanic 6% other	Methadone: median dose 70 mg/day (range: 20-130 mg) Non-use	Methadone vs. non-use Apgar at 1min: 8 vs. 9 Apgar at 5 min: 9 vs. 9	Fair

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year
Newman, 1975[128]
Quick, 2009[119]
Rajegowda, 1972[129]
Ramirez-Cacho, 2006[120]

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Intervention	Results	Quality
Rosen, 1975[130]	Pre-valence	Mothers entering the labor-delivery suite who was on methadone maintenance	n=31 Demographic data not reported	Methadone: mean dose 38.1 mg/day	Maternal methadone dosage Severe symptoms: 10 to 100mg/day Moderate symptoms: 10 to 65mg/day Absent or mild symptoms: 20 to 60mg/day No correlation between dose and neonatal abstinence syndrome	Poor
Rosen, 1985[121]	Pro-spective cohort	Pregnant women on methadone maintenance from the High Risk Perinatal Clinic and various methadone clinics	n=88 (methadone n=57, drug-free n=31) Mean maternal age 25 years 6% White 78% Black 16% Hispanic	Methadone: mean dose 42 mg Non-use	Methadone vs. non-use Mean apgar score 1 min: 7.4 vs. 8.1 Mean apgar score 5 min: 8.5 vs. 9.0 Infants with withdrawal syndrome: 75% (46/61) vs. 0% (0/32) Infants with severe withdrawal: 23% (14/61) vs. 0% (0/32) Infants with moderate withdrawal: 52% (32/61) vs. 0% (0/32) Infants with none/mild withdrawal: 24.9% (15/61) vs. 0% (0.32)	Poor
Shaw, 1994[136]	Pro-spective cohort	Women receiving methadone replacement at the local drug dependency unit	n=64 (methadone n=32, control n=32) Demographic data not reported	Methadone: median dose 35 mg (range 5-80) Non-use	Methadone vs. non-use Median gestational age (weeks): 40 vs. 40 Preterm birth (<36 weeks): 6% (2/32) vs. 3% (1/32) Median birth weight (kg): 2.83 vs. 3.52 (p<0.001) 37% (12/32) in methadone group received treatment for NAS	Poor

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year
Rosen, 1975[130]
Rosen, 1985[121]
Shaw, 1994[136]

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Intervention	Results	Quality
Stimmel, 1976[107]	Retro-spective cohort	Women who gave birth while enrolled in the methadone maintenance program from March 1968 to May 1974 at The Mount Sinai Hospital and a comparison group selected from the population of women whose infants were delivered in the obstetrical service from January through October 1972 without a recorded history of drug abuse	n=115 (methadone n=28, comparison n=30, no treatment n=57) Mean maternal age 24 years 14% White 35% Black 51% Hispanic	Methadone: mean dose not reported Comparison (drug-free controls) No treatment (heroin or methadone users)	Methadone vs. comparison vs. no treatment Mean gestational age (weeks): 39.2 vs. 39.6 vs. 36.7 Fetal distress: 16.1% vs. 23.3% vs. 42.1% (p<0.05) Birth weight <2,500g: 22.6% vs. 3.3% (p<0.01) Mean birth weight (g): 2933 vs. 3309 vs. 2763 Mean apgar at 1min: 8.5 vs. 8.3 vs. 8.4 Mean apgar at 5min: 9.7 vs. 9.8 vs. 9.6 Narcotic withdrawal: 58.1% (16/28) vs. 0% (0/30) vs. 50.9% (29/57)	Poor
Strauss, 1974[122]	Cross-sectional	Not reported	n=144 (methadone n=72, control n=36, high-risk control n=36) Mean maternal age 23 years Race not reported	Methadone: low-dose ≤60 mg/day; Methadone: high-dose 80-150 mg/day Non-use	Methadone vs. control vs. high-risk non-use Mean birth weight (g): 2897.6 vs. 3002.8 vs. 3016.6 Mean gestational age (weeks): 38.9 vs. 39.3 vs. 39.1 Mean apgar at 1min: 7.5 vs. 7.8 vs. 7.6 Mean apgar at 5min: 8.7 vs. 8.6 vs. 8.9 Length of stay (days): 11.4 vs. 4.9 vs. 5.1 (p<0.001)	Poor
van Baar, 1989[123]	Pro-spective cohort	Drug-dependent women giving birth between 6/1983-7/1985 and comparison group of same area	n=72 (methadone n=35, control n=37) Mean maternal age 28 years Race not reported	Methadone: mean dose range not reported (5-80 mg/day) Non-use	Methadone vs. non-use Mean gestational age (weeks): 38.0 vs. 39.7 Mean birth weight (g): 2880.8 vs. 3428.8 Birth weight <2.3% growth curve: 11% (4/35) vs. 0% (0/37) Apgar score <7 at 1min: 11% (4/35) vs. 5% (2/37) Apgar score <7 at 5min: 3% (1/35) vs. 0% (0/37)	Poor

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year
Stimmel, 1976[107]
Strauss, 1974[122]
van Baar, 1989[123]

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year	Study design	Inclusion criteria	Population characteristics	Intervention	Results	Quality
Wouldes, 2004[124]	Pro-spective cohort	Agreeable to undergoing 2 further ultrasounds during the 3rd trimester of pregnancy; gestational age confirmed by ultrasound scan prior to 20 weeks gestation; no evidence of preterm labor within 48 hours of scheduled ultrasounds	n=34 (methadone n=17, controls n=17) Mean maternal age 30 years Race not reported	Methadone: mean dose 52 mg Non-use	Methadone vs. non-use Mean gestational age (weeks): 39.22 vs. 40.66 (p=0.003) Mean birth weight (g): 3033.24 vs. 3656.76 (p=0.0005) Mean birth length (cm): 49.14 vs. 52.24 (p=0.0005) Mean head circumference (cm): 33.99 vs. 35.79 (p=0.001)	Poor
Wouldes, 2010[125]	Cross-sectional	Women seen at the women's hospital or in the same region	n=74 (low-dose methadone n=16, high-dose methadone n=16, non-use n=42) Demographic data not reported	Methadone: mean dose 64 mg Non-use	High-dose methadone vs. low-dose methadone vs. non-use Mean adjusted gestation age (weeks): 36.21 vs. 39.36 vs. 40.41 (p=0.001) Mean adjusted birth weight (g): 2870.27 vs. 3137.50 vs. 3419.42 (p=0.001) Mean adjusted birth length (cm): 48.49 vs. 49.23 vs. 50.75 (p=0.001) Mean adjusted head circumference (cm): 32.86 vs. 33.84 vs. 35.52 (p=0.001) Preterm (<37 complete weeks): 56% (9/16) vs. 19% (3/16) vs. 2% (1/42); p=0.001 SIDs: 19% (3/16) vs. 0% (0/16) vs. 0% (0/42); p=0.003 Treated for NAS: 50% (8/16) vs. 19% (3/16) vs. 0% (0.42); p=0.264	Fair
Zelson, 1973[131]	Cross-sectional	Not reported	n=76 (methadone n=42, non-use n=34) Mean maternal age 22 years Race not reported	Methadone, mean dose not reported (range 10-160 mg) Non-use (heroin use)	Methadone vs. non-use Mean birth weight (g): 2625 vs. 2464 Infant mortality: 2% (1/42) vs 3% (1/34) Treated for withdrawal: 48% (20/42) vs. 18% (6/34)	Poor

Table 7. Adverse pregnancy outcomes with methadone use versus non-use

Author, year
Wouldes, 2004[124]
Wouldes, 2010[125]
Zelson, 1973[131]

Table 8. Rates of neonatal abstinence syndrome in infants of women treated with methadone

Author, year	Symptoms of neonatal abstinence syndrome	Treatment for neonatal abstinence syndrome
Bakstad, 2009[133]	Not reported	58%
Connaughton, 1977[105]	91%	Not reported
Dryden, 2009[134]	Not reported	46%
Fischer, 2006[132]	50%	45%
Harper, 1977[117]	96%	Not reported
Kakko, 2008[127]	78%	53%
Kandall, 1977[104]	83%	77%
Lejeune, 2006[135]	Not reported	49%
Lifschitz, 1985[103]	Not reported	88%
Newman, 1975[128]	71-85%	Not reported
Quick, 2009[119]	80%	Not reported
Rajegowda, 1972[129]	80%	Not reported
Rosen, 1975[130]	86%	Not reported
Rosen, 1985[121]	75%	Not reported
Shaw, 1994[136]	Not reported	37%
Zelson, 1973[131]	76%	48%

Table 9. Mortality and overdose outcomes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Bell, 2009[150]	Case series	Deaths in New South Wales, Australia reported between April 2006 and December 2006 in which post-mortem toxicological screening was positive for methadone or buprenorphine	n=67 Mean age 39 years 76% male Race not reported	Methadone: mean dose not reported Buprenorphine: mean dose not reported	Methadone vs. buprenorphine Death: 90% (60/67) vs. 10% (7/67) Overdose death: 72% (43/60) vs. 29% (2/7); p<0.05	Not rated
Bruera, 2004[137]	RCT	Patients with advanced cancer and poor control of pain requiring initiation of strong opioids; normal renal function; life expectancy of at least 4 weeks; normal cognition	n=103 Median age 60 years 36% male	Oral methadone: 7.5mg and methadone 5mg for breakthrough pain Morphine: slow-release morphine 15mg and immediate-release morphine 5mg for breakthrough pain	Methadone vs. morphine Death: 0% (0/49) vs. 2% (1/54)	Fair
Hartung, 2007[144]	Retro-spective cohort study	≥1 prescription of ≥28 days supply filled between January 1, 2000, and December 31, 2004, and at least 180 days of continuous Medicaid fee for service program eligibility prior to their first (index) fill. Continuous exposure was defined as successive LAO prescriptions at a maximum interval of 31 days from the last prescription's days' supply.	n=5,684 Mean age: Methadone 51 years Fentanyl 71 years Oxycodone 57 years Morphine 59 years Methadone 63% male Fentanyl 74% male Oxycodone 64% male Morphine 65% male	Methadone Transdermal fentanyl Extended-release oxycodone Extended-release morphine (mean doses not reported)	Methadone vs. morphine (reference group) Opioid poisoning: HR 3.22 (95% CI: 0.60 to 17.25)	Fair

Table 9. Mortality and overdose outcomes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Krebs, 2011[145]	Retro-spective cohort	n=98,068 New prescription for >=28 days' supply of oral methadone or long-acting morphine from a VA outpatient pharmacy between January 1, 2000 and December 31, 2007; >=30-day window free of long-acting opioid prescriptions before the index prescription date to avoid contamination	n=98,068 Mean age: Methadone 56 years. Morphine 59 years Methadone 93% male Morphine 95% male Methdaone 52% non-white Morphine 49% non-white	Oral methadone or oral morphine (mean doses not reported)	Methadone vs. morphine, all-cause mortality Propensity-adjusted mortality HR 0.56 (95% CI 0.51 to 0.62) Quintile 1 HR 0.36 (95% CI 0.26 to 0.49) Quintile 2 HR 0.46 (95% CI 0.37 to 0.56) Quintile 3 HR 0.50 (95% CI 0.41 to 0.61) Quintile 4 HR 0.66 (95% CI 0.54 to 0.81) Quintile 5 HR 0.92 (95% CI 0.74 to 1.61)	Fair
Paulozzi, 2006[147]	Epidem-iological study	Deaths due to drug poisoning (NCHS coded to poisoning from 'drugs, medicaments, or biological substances')	Population characteristics not reported	Methadone, codeine, oxycodone, hydrocodone, morphine, hydromorphone, fentanyl, and meperidine (mean doses not reported)	1999 to 2002, 213% increase in methadone poisoning 40-49 year olds represented the majority of deaths Males represented 69.2% of opioid analgesic alone group and 72.9% of decedents in heroin or cocaine-alone group	Not rated
Paulozzi, 2006[146]	Epidem-iological study	Deaths reported in the Drug abuse Warning Network (DAWN) between 1997 and 2002	Age 6-97 years mean age not reported; Other population characteristics not reported	-Cocaine, heroin, morphine, opioid analgesics (mean doses not reported)	The number of deaths from all drugs increased 27% between 1997 and 2002 The number of reports of opioid analgesics deaths increased 97% Methadone-related deaths increased 185% vs. oxycodone-related deaths increased 728% vs. fentanyl-related deaths increased 678% vs. hydrocodone-related deaths increased 175%	Not rated

Table 9. Mortality and overdose outcomes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Paulozzi, 2006[147]	Epidem-iological study	Not reported	Population characteristics not reported	Methadone, codeine, fentanyl, hydrocodone, hydromorphone, meperidine, morphine, oxycodone	Rates of death due to any opioid were lowest in the Midwest and highest in the Southwest, Mid-Atlantic region, and New England. Methadone distribution ranged 13-fold, from 236g/100,000 in Nebraska to 3,030g/100,000 in Alaska. Drug poisoning mortality correlated most strongly opioid sales for immediate release oxycodone (r=0.73, R2= 0.52, p<0.0001), total oxycodone (r=0.68, R2= 0.46, p<0.0001), and total methadone (r=0.66, R2= 0.43, p<0.0001) in multivariate analysis.	Not rated
Paulozzi, 2012[225]	Epidem-iological study	Methadone deaths, as reported in the Drug Abuse Warning Network	Population characteristics not reported	Methadone Other opioids (buprenorphine, fentanyl, hydrocodone, hydromorphone, morphine, oxycodone)	Deaths: 9.7 versus 0.1 to 3.8 deaths per 100 kg morphine milligram equivalents for single drug deaths; 33.6 versus 0.8 to 20.2 for all deaths	Not rated
Pirnay, 2004[152]	Case series	Deaths with toxicological analysis available and identified presence of buprenorphine or methadone performed at the Laboratory of Toxicology of the Paris (France) Police Department from June 1997 to June 2002	n=69 cases (35 methadone and 34 buprenorphine) Median age 33 years, range 20-48 72% male	Methadone, buprenorphine (mean doses not reported)	Methadone was directly implicated in 9% (3/35) of deaths and strongly plausible in 31% (11/35) deaths Buprenorphine was directly implicated in 12% (4/34) of deaths and strongly plausible in 24% (8/34) deaths	Not rated

Table 9. Mortality and overdose outcomes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Soyka, 2006[151]	Case series	Suspected non-natural deaths in the Munich (Germany) and upper Bavaria region in 2002 and 2003 with autopsy, toxicology and/or police reports available	n=272 cases Mean age 30 years 82% male	Methadone, heroin, buprenorphine (mean doses not reported)	Methadone was found in 35% of cases (96/272) vs. buprenorphine in 0.4% (1/272) 55% (53/272) of deaths were in methadone maintenance patients 16 deaths due to methadone occurred during the first days of adaptation or after discontinuation of methadone	Not rated

Table 10. Cardiovascular events and ECG changes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Anchersen, 2009[57]	Cross-sectional	OMT patients willing to participate (all subjects were recruited)	Total cohort: n=200 Mean age 41 years 69% male Methadone cohort n=173 Mean age 42 years 69% male Buprenorphine cohort n=27 Mean age 37 years 67% 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[68]	Cross-sectional	Methadone or buprenorphine dependant; a healthy control group was also included	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=0.27 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)	Poor
Fanoe, 2007	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 0.87 to 5.8	Fair
Hanon, 2010[153]	Case series	All methadone maintenance patients with QT prolongation and ventricular arrhythmias admitted between July 2007 and April 2009	n=12 Mean age 54 years 75% male	Methadone: mean dose 135 mg (range 35 to 250 mg)	Patients (n=3) who transitioned to buprenorphine had resolution of QT prolongation on no further incidence of arrhythmia at follow-up (mean 8 months, range 1-11 months.) Patients who reduced methadone doses (n=5) had reduced QT duration and no further incidence of arrhythmia.	Not rated

Table 10. Cardiovascular events and ECG changes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Kornick, 2003[154]	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/hr (range 0.1 to 97.1; SE 20.6) IV morphine, mean dose 9.8 mg (range 0.7 to 35; SE 7.9)	Methadone vs. no methadone Mean difference QTc interval, 41.7 ms (SE 7.8 ms); p<0.0001 Morphine vs. no morphine Mean difference QTc interval: 9.0 ms (SE 6.1 ms); p=0.15	Good
Wedam, 2007[61] Other publications: Johnson, 2000[125]	RCT	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% non-white (not described) Mean HR 64 bpm	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 to 109.5; p=0.01) >60 ms change in QTc from baseline: 12% vs. 2%; OR 8.4 (95% CI: 1.9 to 36.4)	Fair

Table 11. Withdrawal due to adverse events with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Bruera, 2004[137]	RCT	Patients with advanced cancer and poorly controlled pain requiring initiation of strong opioids, normal renal function, life expectancy of at least 4 weeks, and normal cognition	n=103 Median age 60 years 46% male	Oral methadone: 7.5mg Morphine: slow-release morphine 15mg	Methadone vs. morphine Withdrawals due to AEs: 22% (11/49) versus 6% (3/54); RR 4.0, 95% CI 1.3 to 13	Fair
Johnson, 2000[141]	RCT	Age 21-55 years; opioid dependent; evidence of recent opioid use	n=220 Mean age 36 years 68% male 62% non-white	Low-dose oral methadone: mean dose 20 mg High-dose oral methadone: mean dose 90 mg Buprenorphine: mean dose 27 mg	Low-dose methadone vs. high-dose methadone vs. buprenorphine Withdrawals due to AEs: 0% (0/55) vs. 2% (1/55) vs. 2% (1/55)	Fair
Schottenfeld, 1997[155]	RCT	Methadone maintenance patients meeting DSM-III-R criteria for opioid and cocaine dependence	n=116 Mean age 33 years; 69% fmale 22% non-white	Oral methadone: 20 mg and 65 mg Buprenorphine: 4 and 12 mg	No withdrawals in any group (methadone 20 mg, methadone 65 mg, buprenorphine 4 mg or buprenorphine 12 mg) due to adverse events	Fair

Table 12. Gastrointestinal outcomes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Bruera, 2004[137]	RCT	Poor control of pain caused by advanced cancer necessitating initiation of strong opioids; normal renal function; life expectancy >4 weeks; normal cognition; written informed consent	n=103 (methadone n=49, morphine n=54) Median age 60 years 36% male Race not reported	Methadone: mean dose 7.5 mg every 12 hours and 5 mg every 4 hours Morphine: mean dose 15 mg sustained release every 12 hours and 5 mg every 4 hours	No significant differences between groups for sedation, nausea, confusion or constipation	Fair
Giacomuzzi, 2003[159]	Pro-spective cohort	Confirmed diagnosis of opioid dependence	n=67 Mean age 28 years 27% female Race not reported	Methadone: mean dose 25 mg (range 5-160) Sublingual buprenorphine: mean dose 10 mg (range 2-32 mg)	Methadone vs. buprenorphine No significant differences at baseline vs. follow-up or between groups Proportion of patients reporting constipation at baseline: 48% (11/23) vs. 33% (10/30) At follow-up: 22% (2/23) vs. 20% (6/30)	Fair
Hartung, et al. 2007[144]	Retro-spective cohort study	≥1 prescription of ≥28 days supply filled between January 1, 2000, and December 31, 2004, and at least 180 days of continuous Medicaid fee for service program eligibility prior to their first (index) fill.	n=5,684 Mean age: Methadone 51 years Fentanyl 71 years Oxycodone 57 years Morphine 59 years Methadone 27% male Fentanyl 26% male Oxycodone 36% male Morphine 35% male	Methadone Transdermal fentanyl Extended release oxycodone Extended release morphine (mean doses not reported)	Methadone vs. morphine (reference group) Opioid poisoning: HR 3.22 (95% CI 0.60 to 17.25) CIs for other outcomes, including mortality, hospitalizations, and overdose symptoms overlapped for methadone, oxycodone and fentanyl vs. morphine	Fair

Table 12. Gastrointestinal outcomes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Johnson, 1992[157]	Con-trolled trial	Age 21-50 years; self-report addiction at least 4 months in duration; >= episodes heroin use/day; heroin cost >$50/day; self-rated score of >= 4 on withdrawal scale (0 [no withdrawal] to 9 [worst withdrawal ever]); positive opioid urine screening	n=162 Mean age 33 years 70% male 58% White 40% Black 2% other	Oral methadone: 20 mg Buprenorphine: 8 mg	No significant differences between groups for adverse effects (loss of appetite, difficulty urinating, anxiety, sedation, constipation)	Poor
Johnson, 2000[141]	RCT	Age 21-55 years; opioid dependent; evidence of recent opioid use	n=220 Mean age 36 years 68% male 62% non-white	Low-dose oral methadone: mean dose 20 mg High-dose oral methadone: mean dose 90 mg (range 60-100) Buprenorphine: mean dose 27 mg (range 16-32 mg)	Low-dose methadone vs. high-dose methadone vs. buprenorphine Withdrawals due to AEs: 0% (0/55) vs. 2% (1/55) vs. 2% (1/55)	Fair
Ling, 1996[158]	RCT	Age 18-65 years; competent to give informed consent; in good general health; met DSM-III-R criteria for diagnosis of opioid dependence and methadone maintenance treatment	n=225 Mean age 41 years 80% male 14% White 20% Black 65% Hispanic <1% other	Oral methadone: 30 mg/day or 80 mg/day Buprenorphine: 8 mg/day	No significant differences among non-specific AEs described as equally represented in all groups	Fair

Table 12. Gastrointestinal outcomes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Lofwall, 2005[156]	RCT	18 to 50 years old, DSM-III-R criteria for opioid dependence, at least 1 year of intravenous opioid dependence	n=165 Mean age 33 years 70% male 51% Black (other races not reported)	Methadone: mean 54 mg/day Buprenorphine: mean 8.9 mg/day	No differences between groups in liver function tests, vital signs, or reported side effects including GI side effects	Fair
Mattick, 2003[142]	RCT	Opioid dependent; age 18 or older; live in commuting distance of clinic; competent to give consent; signed consent.	n=405 Mean age 30 years 70% male	Flexible dose regime: Weeks 1-6, patients dosed daily Weeks 7-13, buprenorphine group received double the week 6 dose on alternate days	No significant differences between groups for constipation, nauseas, or vomiting	Fair
Mercadante, 2008[139]	RCT	Pain requiring strong opioids; use of opioids for mild to moderate pain	n=108 Mean age 59 years 51% male	Morphine: sustained-release morphine using initial doses of 60mg/day Fentanyl: transdermal fentanyl 0.6mg/day Methadone: oral methadone 15mg/day divided in 3 doses	No significant differences between groups for scores on nausea, vomiting, drowsiness, constipation, or confusion	Fair

Table 12. Gastrointestinal outcomes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Mercadante, 1998[138]	RCT	Required strong opioids for pain management	n=40 Median age 63 years 95% male	Morphine: sustained-release 10, 30, 60, and 100mg or morphine q8-12h as needed Methadone: oral liquid preparation of 0.1% methadone 2-3 times per day as needed	No significant differences between groups for scores on nausea, vomiting, drowsiness, constipation, or confusion	Poor
Ventafridda, 1986[140]	RCT	Not reported	n=66 Mean age not reported 66% male	Morphine: 1st day 4mg q4h titrated up to a max of 24mg q4h Methadone: 1st day 8-28mg q6h for 3 days then q8h	No significant differences between groups for % of days side effects were present (constipation, nausea, vomiting)	Poor

Table 13. Respiratory depression and sleep apnea outcomes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Intervention	Results	Quality
Matts, 1964[161]	RCT	Patients in severe pain; other criteria not reported	n=90 Demographic data not reported	Methadone: 5 mg (range 5 to 10 mg) Pethidine: 50 mg (range 50-100) Dextromoramide: 5 mg (range 5 to 10 mg)	Methadone vs. pethidine vs. dextromoramide Incidence of respiratory depression: 7% (2/30) vs. 7% (2/30) vs. 0% (0/30)	Poor
Webster, 2008[160]	Cohort	Chronic pain, on around-the-clock opioid therapy, had undergone polysomnography between February 2004-July 2005.	n=140 Mean age 51 years (22-84)	Median daily dosage of all opioids was 266 mg of morphine equivalents (range 15–5,985 mg).	Methadone vs. NSAIDs Effect of medications on apnea-hypopnea (correlation coefficient): 0.139 (SE 0.051); p=0.007 vs. 0.042 (SE 0.075); p=0.571 Effect of medications on central apnea indices (correlation coefficient): 0.164 (SE 0.056); p=0.004 vs. 0.044 (SE 0.083); p=0.598 Methadone vs. non-methadone opioids Dose response relations for apnea-hypopnea (correlation coefficient): 0.138 (SE 0.044); p=0.002 vs. 0.113 (SE 0.076); p=0.140 Dose response relations for central apnea index (correlation coefficient): 0.130 (SE 0.049); p=0.008 vs. 0.073 (SE 0.083); p=0.385	Poor

Table 14. Cognitive functioning, sedation, and psychiatric outcomes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Bruera, 2004[137]	RCT	Patients with advanced cancer and poor control of pain requiring initiation of strong opioids, normal renal function, life expectancy of at least 4 weeks, and normal cognition	n=103 Median age 60 years 36% male Race not reported	Methadone: median dose 20 mg at study conclusion (range 8-40 mg) Morphine: median dose 45 mg at study conclusion (range 15-150 mg)	Methadone vs. morphine No significant differences between groups for sedation or confusion	Fair
Eder, 2005[162]	Cross-over RCT	Between ages 19-60 years; had to have diagnosis of opioid dependence according to DSM-IV	n=64 Mean age 29 years; 88% male Race not reported	Methadone: mean dose, 85 mg Slow-release morphine: mean dose 680 mg	Methadone vs. morphine No significant differences among groups for psychiatric outcomes but methadone associated with worse scores (higher): Beck Depression Inventory: 15 vs. 7 State Trait Anxiety Inventory: 46 vs. 39	Fair

Table 14. Cognitive functioning, sedation, and psychiatric outcomes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Grevert, 1977[165]	Pro-spective cohort	Methadone subjects in methadone maintenance program, levomethadyl acetate subjects from the Addiction Research Foundation Clinic, and matched controls receiving unemployment from the California Employment Development Department, no other criteria reported	n=124 (methadone n=42, LAAM n=42, control n=40); Median age: Methadone 28 years Levomethadyl acetate 26 years Control 26 years Methadone 76% male Levomethadyl acetate 91% male White race Methadone 50% Levomethadyl acetate 71% Control 62% Black race	Methadone, mean dose: 52 mg/day (range: 20 to 80) Levomethadyl acetate, mean dose: 54 mg at 2nd session and 60 mg at final session (range: 15 to 100)	Methadone vs. levomethadyl acetate vs. control Reported decrease in memory function: 30% vs. 39% vs. 42% (NS) Mean memory score at final test (estimated from graph, 0 to 25 score): 19 vs. 19 vs.18 (NS) Mean number of guesses on memory test (estimated from graph, 0 to 50 score): 43 vs. 39 vs. 35 (NS) Mean number score on memory test at final test (estimated from graph, 0 to 50): 59 vs. 59 vs. 64 (NS)	Poor
Mattick, 2003[142]	RCT	Opioid dependent; age 18 or older; live in commuting distance of clinic; competent to give consent; signed consent.	n=405 (methadone n=205, buprenorphine n=200) Mean age 30 years; 69% male Race not reported	Methadone: mean dose not reported (range 20-150 mg) Buprenorphine: mean dose not reported (range 2-32 mg)	Methadone vs. buprenorphine Insomnia: 10% (20/202) vs. 13% (25/192) Anxiety: 7% (15/202) vs. 5% (9/192) Somnolence: 9% (18/202) vs. 5% (9/192) Depression: 5% (9/202) vs. 6% (12/192)	Fair
Mercadante, 2008[139]	RCT	Pain requiring strong opioids;had received opioids for mild to moderate pain	n=108 enrolled (methadone n=36, morphine n=36, fentanyl n=36) Mean age 59 years 51% male Race not reported	Methadone: initial dose15 mg Morphine: initial dose 60 mg Fentanyl: initial dose 0.6 mg	Methadone vs. fentanyl vs. morphine No differences between groups for scores on drowsiness or confusion	Fair
Mercadante, 1998[138]	RCT	Required strong opioids for pain management	n=40 enrolled (methadone n=20, morphine n=20); Mean age 63 years 48% male Race not reported	Methadone liquid: 0.1% Sustained-release morphine: mean dose not reported (range 10-100mg)	Methadone vs. morphine No significant differences between groups for scores on drowsiness or confusion	Poor

Table 14. Cognitive functioning, sedation, and psychiatric outcomes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Pirastu, 2006[164]	RCT	Opiate-dependent patients attending local drug addiction clinic for at least 12 months, with no central nervous system pathology or axis 1 disorder, no head trauma or dementia, no medication known to affect cognitive functioning, no past or present alcohol or other illicit substance dependencies	n=69 (methadone n=30, buprenorphine n=18, matched controls n=21) Mean age (years): Methadone 35 years Buprenorphine 33 years Controls 34 years Methadone 96% male Buprenorphine 94% male Controls 67% male	Methadone: mean dose not reported Buprenorphine: mean dose not reported No methadone (healthy controls)	Methadone vs. buprenorphine vs. controls Gambling task net scores (mean): 2.93 vs. 19.67 vs. 15.33 (p<0.05 methadone vs. buprenorphine) Wisconsin card sorting task preservative errors (mean): 28.7 vs. 22.8 vs. 12.6 (p<0.05 methadone vs. controls) WAIS (mean): 85 vs. 89.3 vs. 104 (p<0.05 controls vs. others) BVRT correct (mean): 5.67 vs. 6.06 vs. 7.90 (p<0.05 controls vs. others) BVRT errors (mean): 6.5 vs. 5.22 vs. 2.57 (NS)	Fair
Rapeli, 2007[92]	Cross-sectional	Age 18-50; for OST patients, opioid dependence according to DSM-IV and start of OST in last 6 weeks	n=50 (methadone n=16, buprenorphine/naloxone n=17, controls n=17) Mean age 30 years 50% male Race not reported	Methadone: mean dose 53 mg (range 30-105 mg) Buprenorphine: mean dose 16 mg Naloxone: mean dose 4 mg No methadone (controls)	Methadone vs. buprenorphine/ naloxone vs. controls Tonic alertness, simple reaction time 257.6 vs. 228.0 vs. 244.4	Poor

Table 14. Cognitive functioning, sedation, and psychiatric outcomes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Rapeli, 2009[166]	Pro-spective cohort	Participants with opioid dependence were volunteers admitted for standard OST in addiction clinics; and had an opioid dependence diagnosis, benzodiazepine dependence or abuse diagnosis, start of OST in last 2 months, and treatment of opioid dependence with either methadone, buprenorphine, or buprenorphine/naloxone. All participants	n=43 (methadone n=13, buprenorphine/naloxone n=15, control n=15) Mean age 29 years 56% male Race not reported	Methadone: mean dose 126 mg Buprenorphine: mean dose 23 mg No methadone (healthy controls)	Methadone vs. buprenorphine vs. controls No significant difference among groups in tests of memory over time	Poor
Soyka, 2008[163]	RCT	No confirmed subjective memory complaints or history of organic brain syndrome or seizures; no measurable cognitive and memory impairment; IQ of 85 or greater; neither neurological nor psychiatric diagnosis or history apart from the opioid dependence in the patient group	n=70 (methadone n=24, buprenorphine n=22, healthy controls n=24); Demographic data not reported	Methadone: mean dose not reported Buprenorphine: mean dose not reported No methadone (healthy controls)	Methadone vs. buprenorphine vs. controls No difference between treatment groups on any cognitive functioning tests	Poor
Ventafridda, 1986[140]	RCT	Not reported	n=66 (methadone n=36, morphine n=30) Mean age not reported 57% male Race not reported	Methadone: mean dose not reported (maximum dose 28 mg) Morphine: mean dose not reported (maximum dose 24 mg)	Methadone vs. morphine, proportion of days with side effects Drowsiness: 47% vs. 54% Restlessness: 19% vs. 20%	Poor

Table 15. Adverse pregnancy outcomes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Bakstad, 2009[133]	Pro-spective cohort	Pregnant women enrolled in OMT programs in Norway with delivery between 2005-2007	n=41 (methadone n=26, buprenorphine n=12) Mean maternal age 32 years Race not reported	Methadone: mean dose at delivery: 90 mg (range: 7 to 260 mg) Buprenorphine: mean dose at delivery: 13 mg (range: 3 to 24 mg)	Methadone vs buprenorphine Mean gestational age (weeks) 39.3 vs. 39.2 Mean birth weight (g) 3150 vs. 3130 Mean head circumference (cm) 33.9 vs. 34.3 Preterm birth (<37 weeks) 4% (1/26) vs. 8% (1/12) Cesarean section 31% (8/26) vs. 33% (4/12) Treatment for neonatal abstinence syndrome 58% (15/26) vs. 67% (8/12) Neonatal abstinence syndrome duration: 43 days vs. 37 days	Fair
Binder, 2008[110]	RCT	Participation in substitution program by 12th week of pregnancy, up to 30 year, dependence on IV applied opiates for 3-5 years, HIV negative, primigravidity or second gravidity with uneventful course of the preceding pregnancy, absence of any other chronic conditions	n=117 (methadone n=32, buprenorphine n=38) Mean maternal age 27 years Race not reported Mean duration of addiction 4 years	Methadone, buprenorphine mean doses not reported	Methadone vs buprenorphine Mean birth weight (g): 3050 vs. 2900 IUGR: 9% (3/32) vs. 11% (4/38); Cesarean rate: 6% (2/32) vs. 8% (3/38) No differences between groups in Apgar scores at 1, 5 and 10 minutes Finnegan neonatal abstinence syndrome score: 18 vs. 9.2 (p<0.001) Delayed onset of withdrawal symptoms (days): 0 vs. 1 (p<0.001)	Poor
Fischer, 1999[157]	RCT	Opioid-dependent pregnant females, presented at the drug addiction outpatient clinic, and willing to follow the maintenance program	n=48 (methadone n=24, morphine n=24) Mean maternal age 26 years Race not reported Mean duration of dependence 5 years	Methadone: mean dose at delivery was 53 mg (range 13-200 mg) Morphine: mean dose at delivery was 300 mg (range 60-660 mg)	Methadone vs morphine Vaginal delivery 75% (18/24) vs. 75% (18/24) Mean birth weight (g): 3036.46 vs. 2912.92 No difference in incidence of neonatal abstinence syndrome; p=0.752 No difference in intensity of neonatal abstinence syndrome; p=0.702	Fair

Table 15. Adverse pregnancy outcomes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Fischer, 2006[172]	RCT	Opioid-dependent pregnant women, over 18 years, and willing to follow protocol and avoid use of illegal drugs	n=18 enrolled (14 analyzed - methadone n=6, buprenorphine n=8); Mean maternal age 26 years Race not reported Mean duration of heroin use 5 years	Methadone: mean dose not reported (range 40-100 mg) Buprenorphine: mean dose not reported (range 8-24 mg)	Methadone vs buprenorphine Neonatal abstinence symptoms: 50% (3/6) vs. 63% (5/8) Treatment for neonatal abstinence syndrome: 45% (3/6) vs. 20% (2/8) Mean cumulative dose for treatment for neonatal abstinence syndrome: 2.71 mg vs. 2.00 No difference between groups in birth weights (data not shown)	Fair
Jones, 2005[170]	RCT	21-40 years of age, with estimated gestational age of 6-30 weeks, DSM-IV diagnosis of current opioid dependence, requesting maintenance pharmacology, recent self-reported opioid use, opiate-positive urine specimen at intake	n=30 (methadone n=15, buprenorphine n=15) Mean maternal age 30 years 67% Black 28% White 5% other	Methadone: mean dose not reported (range 20-100 mg) Buprenorphine: mean dose not reported (range 4-24 mg)	Methadone vs buprenorphine Treatment for neonatal abstinence syndrome: 45% (5/11) vs. 22% (2/9); p=0.23 NICU admission: 18% (2/11) vs. 10% (1/9); p=0.453 Total length of stay for neonate (days): 8.1 vs. 6.8 (p=0.021) Mean birth weight (g): 3001.8 vs. 3530.4, (p=0.091) Preterm birth: 9% (1/11) vs. 0%; p=NR Cesarean section: 9% (1/11) vs.11% (1/9); p=NR	Fair

Table 15. Adverse pregnancy outcomes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Jones, 2010[169]	RCT	Opioid-dependent women aged 18-41 years with a singleton pregnancy between 6-30 weeks of gestation, with no medical or other conditions contraindicating participation, not subject to pending legal action, no disorders related to use of benzodiazepines or alcohol	n=175 randomized (methadone n=89, buprenorphine n=86) Mean maternal age 27 years White race - Methadone 85% vs. Buprenorphine 91% Black race - Methadone 14% Buprenorphine 3%	Methadone: mean dose not reported, starting dose not reported, dose adjustments of 50-10 mg as needed, range 20-140 mg Buprenorphine: mean dose not reported, starting dose not reported, dose adjustments of 2 mg as needed, range 2-32 mg	Methadone vs buprenorphine Neonatal abstinence syndrome treatment: 57% (41/73) vs 47% (27/58); OR 0.7 (95% CI 02 to 1.8) Peak score (0 to 42 scale): 12.8 vs. 11.0; p=0.04 Morphine given (mean, mg): 10.4 vs. 1.1; p<0.0091 Duration of treatment (mean, days): 9.9 vs. 4.1; p<0.003125 Infant's hospital stay (mean, days): 17.5 vs. 10.0; p<0.0091 Head circumference (mean, cm): 33.0 vs. 33.8; p=0.03 Birth weight (mean, g): 2878.5 vs. 3093.7; p=0.005 Birth length (mean, cm): 47.8 vs. 49.8; p=0.005 Gestational age (mean, weeks): 37.9 vs. 39.1; p=0.007	Fair

Table 15. Adverse pregnancy outcomes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Kakko, 2008[127]	Pros-pective cohort	Pregnant opiate-dependent women enrolled in either the methadone maintenance treatment (MMT) program from 1982-2006 or the buprenorphine maintenance treatment (BMT) program from 2001-2006	n=65 (methadone n=26, buprenorphine n=39) Mean maternal age 31 years Race not reported	Methadone: mean dose 71 mg (range 20-120 mg) Buprenorphine: mean dose 15.4 mg (range 2-32mg)	Methadone vs buprenorphine Apgar score <4 at 1min: 3 vs. 0 (p=NS) Apgar score <4 at 5min: 0 vs. 0 Preterm infants (30-32 weeks): 0% (0/36) vs. 2.1% (1/47); p=NS Preterm infants (35-37 weeks): 9% (3/36) vs. 6.% (1/47) Cesarean section: 36% (13/36) vs. 21% (10/47); p=0.14 Mean gestational age (weeks): 38.6 vs. 39.5 (p=0.06) Mean birth weight (g): 2941 vs. 3250 (p=0.008) Mean birth height (cm): 47.6 vs. 48.4 (p=0.12) Mean head circumference (cm): 33.8 vs. 34.0 (NS) Birth weight <2500g: 25% vs. 6.4% (p=0.03) Birth weight <-2SD: 30.6% vs. 12.8% (p=NS) Neonatal abstinence syndrome: 78% (28/36) vs. 40% (19/47); p=0.0008 Treated for neonatal abstinence syndrome: 53% (19/36) vs. 15% (7/47); p=0.0004 Length of hospital stay: 20 vs. 9.4 days (p=0.0009)	Fair
Lacroix, 2011[171]	Pros-pective cohort	Pregnant women enrolled in OMT programs in France between January 1, 1998 and December 31, 2006	n=135 Mean age 31 years Race not reported Duration of opioid dependence not reported	Methadone: mean dose 38-42 mg/day Buprenorphine: mean dose 5.1-6.3 mg/day	Methadone vs buprenorphine Live births 89% (40/45) vs 94% (85/90); p=0.42 Stillbirth 4% (2/45) vs 1% (1/90); p=0.5 Premature birth 10% (4/40) vs 19% (16/85); p=0.5 Malformations present at birth 3% (1/40) vs 5% (4/85); p=0.9 Neonatal abstinence syndrome 63% (25/45) vs 41% (35/90); p=0.03 Neonatal abstinence syndrome requiring treatment with hydrochloride 80% vs 57%; p=0.03	Good

Table 15. Adverse pregnancy outcomes with methadone use compared with another intervention

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Lejeune, 2006[135]	Pro-spective cohort	Live births to mothers receiving drug substitution that had started before or during this pregnancy within the framework of a maintenance protocol, continued until delivery	n=259 (n=260 infants) Mean age 29 years Race not reported Mean length of opiate dependence 8 years	Methadone: mean dose at delivery 57 mg (range: 10 to 180 mg) Buprenorphine: mean dose at delivery 5.4 mg (range: 0.4 to 24 mg)	Methadone vs buprenorphine Mean birth weight (g) 2790 vs. 2843 (p=NS) Mean gestational age (weeks) 38.4 vs. 38.8 (p=NS) IUGR 38% (38/101) vs. 31% (49/159); p=NS Premature birth (<37 weeks) 16% (16/101) vs. 10% (16/159); p=NS Mean Apgar at 5 min 9.9 vs. 9.8; p=NS Breastfed 23% (23/101) vs. 21% (33/159); p=NS Lipsitz score >9 for NAS (scale 0 to 20) 30% (30/101) vs. 32% (51/159); p=NS Mean max Lipsitz score 9.13 vs. 9.17; p=NS Treated for NAS 49% (50/101) vs. 52% (83/159); p=NS Mean age at max score (hours) 80 vs. 66; p=0.066 Mean age at recovery of birth weight (day) 13 vs. 10; p=0.001	Fair

Table 16. Risk of mortality and overdose outcomes with methadone use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Ballesteros, 2003[177]	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[178]	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[179]	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: 5%, Age 24-34: 29%, Age 35-44: 43%, Age 45-54: 19%, Age 55-64: 4%; 79% male 34% White 36% Black, 30% Hispanic 81% methadone detected	Methadone, heroin	Methadone-induced overdose deaths, risk factors Men vs. women AOR 0.6 (CI 0.52 to 0.70) Age 15-24 vs.: age 25-34 yrs, AOR 1.69 (CI 1.08 to 2.64); age 35-44 yrs, AOR 3.03 (CI 1.97 to 4.67); age 45-54 yrs AOR 2.79 (CI 1.78 to 4.35); age 55-64yrs, AOR 2.34 (95% CI 1.37 to 4.01) Cocaine detected vs. no cocaine detected in toxicology AOR 0.56 (CI 0.49 to 0.64) Heroin vs. no heroin detected in toxicology AOR 0.46 (CI 0.40 to 0.53) Alcohol vs. no alcohol present in toxicology AOR 0.78 (CI 0.68 to 0.91) Deaths in 1990 vs.: 1997 AOR 0.58 (CI 0.42 to 0.82); 1998 AOR 0.69 (CI 0.50 to 0.96)	Not rated

Table 16. Risk of mortality and overdose outcomes with methadone use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Buster, 2002[174]	Retro-spective 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 to 7.2), and being born in Native of the Netherlands vs other countries: ARR 5.0 (95% CI 2.3 to11).	Fair
Chan, 2006[180]	Case series	Decedents with methadone found in their toxicological 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<0.001) and were more likely to be White race (41% vs. 23%; p<0.01) 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 to 2.45) Concomitant tricyclic antidepressant and benzodiazepine OR 4.34 (CI 1.97 to 9.56) Risk Factors associated with a methadone overdose vs. death from another cause: White race OR 4.27 (CI 2.57 to 7.12) Amitriptyline use OR 2.12 (CI 1.17 to 3.85) Cocaine use OR 3.16 (CI 1.35 to 7.40) Morphine use OR 2.13 (CI 1.05 to 4.33) Opiate use OR 2.84 (CI 1.38 to 5.85) Citalopram use OR 0.31 (0.10 to 0.92)	Not rated
Cousins, 2011[176]	Retro-spective 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 psychiatirc admission: adjusted HR 7.0 (95% CI 3.5 to 14) Prescription for benzodiazepines vs no prescription: adjusted HR (1.4, 95% CI 1.2 to 1.7)	Fair

Table 16. Risk of mortality and overdose outcomes with methadone use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Ernst, 2002[181]	Case series	Methadone-related deaths with methadone in toxicological analysis between 1993-1999	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 <1 week of methadone intiation, 72% (26/36) died after the first week of MMT	Not rated
Gagajewski, 2003[12]	Case series	Intentional and unintentional deaths associated with methadone as found in toxicological analysis during autopsy between 1992-2002	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
Hall, 2008[175]	Case series	Unintentional drug overdoses in West Virginia in 2006, determined by ICD-10 codes X40-X44	n=295 Mean age 39 years 67% male Race not reported	Methadone: mean dose not reported	40% (112/295) methadone associated overdose; 32% (94/295) prescribed methadone	Not rated

Table 16. Risk of mortality and overdose outcomes with methadone use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
McCowan. 2009[173]	Retro-spective cohort study	Registered with a Tayside, Scotland general practitioner; prescribed and dispensed methadone between January 1993 and February 2004	n=2378 Mean age not reported; range 16-60 years, 55% of population age 20-29, 67% male Race not reported	Methadone: mean dose not reported, 85% mean dose <60 mg	Incidence All-cause mortality 8% (181/2378) Death due to drug dependence 3% (60/2378) Charlson Comorbidity Index 1-2: AHR 1.08 (95% CI 1.02 to 1.14) Charlson Comorbidity Index > 3: AHR 1.20 (95% CI 1.15 to 1.26) Overusing methadone: AHR 1.67 (95% CI 1.05 to 2.67) Duration of methadone treatment (years): AHR 0.95 (95% CI 0.94 to 0.96) Time since last prescription filled (4-6 months): AHR 0.91 (95% CI 0.84 to 0.99) Time since last prescription filled (>6 months): AHR 0.70 (95% CI 0.66 to 0.73) Having urine tested: AHR 0.33 (95% CI 0.22 to 0.49) Duration of treatment years: AHR 0.93 (95% CI 0.92 to 0.95) >6 months since prescription: AHR 0.02 (95% CI 0.00 to 0.05), History of psychiatric admission: AHR 2.41 (95% CI 1.25 to 4.64) Use of benzodiazepines : AHR 4.35 (95% CI1.32 to 14.30) Antipsychotic use: AHR 0.27 (95% CI 0.08 to 0.89) Antidepressant use: AHR 0.51 (95% CI 0.30 to 0.98)	Fair

Table 16. Risk of mortality and overdose outcomes with methadone use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Neale, 2000[182]	Case series	Non-fatal over-dose treated in the hospital or ED 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 35-1000mg (median 110mg) Accidental overdose 12% (4/33) Diversion 9% (3/33)	Not rated
Paulozzi, 2009[11]	Case series	Death certificate documented unintentional drug poisoning	n=250 Mean age 34 years (methadone group only; n=87) Gender not reported Race not reported	Methadone: mean dose not reported Other opioid analgesic (most commonly hydrocodone or oxycodone)	Characteristics of unintentional deaths, methadone vs. other opioid analgesic Use any non-medical route AOR 0.34 (95% CI 0.16 to 0.70) Injecting medication AOR 0.21 (95% CI 0.06 to 0.73) Benzodiazepines AOR 0.71 (95% CI 0.40 to 1.25)	Not Rated
Seymour, 2003[183]	Case series	Methadone found on toxicological 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=0.13)	Not rated

Table 16. Risk of mortality and overdose outcomes with methadone use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Shah, 2005[14]	Case series	New Mexico residents with unintentional drug overdose between 1998 and 2002 based on cause of death determination and finding methadone in the toxicological 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[184]	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[185]	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 Two or more drugs on toxicological 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 16. Risk of mortality and overdose outcomes with methadone use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Weimer, 2011[9]	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 to 1.26) Antidepressant use OR 8.78 (CI 2.3 to 33.2) Illicit methadone vs. prescription or MMT source: Younger age OR 0.92 (0.86 to 0.97) Less likely to have antidepressants OR 0.17 (CI 0.05 to 0.61)	Not rated
Williamson, 1997[186]	Case series	Decedents with methadone in toxicological 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 to 31.48)	Not rated

Table 16. Risk of mortality and overdose outcomes with methadone use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Zador, 2002[187]	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 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 to 15.0)	Not rated

Table 17. Risk of adverse cardiovascular events and ECG changes with methadone use and risk factors

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Chang, 2012[62]	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=0.210, p=0.001) but not females (r=0.164, p=0.23)	Fair
Cruciani, 2005[70]	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 probably risk for TdP: 14%; Drugs interacting with methadone: 29%; anti-depressants, 35%; anti-retrovirals, 17%; anti-microbials, 18%	Oral methadone: mean dose 110 mg/day	Relationship between dose and QTc significant for methadone dose and male sex (Spearman rho=0.60; p=0.01, d=1.5)	Fair
Ehret, 2006[59]	Cross-sectional	Active or former injections drugs 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 Non-use	TdP vs. no TdP Increased risk based on number of concomitant medications - 9 vs. 4	Fair
Fareed, 2013[188]	Case series	Methadone maintenance, treated at clinic for at least 6 months	n=55 Mean age 56 years 7% female 64% non-white	Oral methadone: mean dose 90 mg/day	Factors associated with QTc >500 ms were congestive heart failure diagnosis (p=0.04), HbA1c >6 (p=0.05), and recent cocaine use (p=0.03)	Not rated

Table 17. Risk of adverse cardiovascular events and ECG changes with methadone use and risk factors

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Justo, 2006[78]	Case series	Not reported	n=40 Mean age 40 years (range: 20 to 60 years) Gender not reported Race not reported	Methadone: mean dose 231 mg/day (range: 60 to 1000 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
Krantz, 2003[190]	Case series	Inclusion: use of methadone, QTc > 500msec 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 to 387 mg	Mean QTc interval was 615+77msec Mean heart rate 64+15 beats/min 41% (7/17) Hypokalemia 53% (9/17) receiving potential QT prolonging drugs 18% (3/17) had structural heart disease 82% (14/17) had one 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[53]	Pro-spective 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% Hepatitis C 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[79]	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 one risk factor for QTc prolongation or torsades de pointes other than methadone use	Not rated
Roy, 2012[76]	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 interval prolongation and presence of cocaine metabolites in urine (p=0.13)	Poor

Table 17. Risk of adverse cardiovascular events and ECG changes with methadone use and risk factors

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Stallvik, 2013[65]	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 concentraion (p=0.04), no association with female sex	Fair
Vieweg, 2013[189]	Review of case reports	Case reports of methadone and torsades de pointes 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 torsades de pointes other than methadone use	Not rated
Wedam et al, 2007[61] Other publications: Johnson, 2000[141]	RCT	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% non-white (not described) Mean HR 64 bpm	Methadone: 60 to100 mg Buprenorphine: 16 to 32 mg Levomethadyl: 75 to 155 mg	No association between sex and magnitude of QTc interval changes	Fair

Table 18. Risk of adverse cognitive outcomes with methadone use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Rotheram-Fuller, 2004[192]	Pro-spective Cohort	Stable methadone maintenance ≥6 months, healthy controls	n=37 (MMT smokers n=9, MMT non-smokers n=9, control smokers n=9, control non-smokers n=10) Mean age 40 years Gender not reported 36% White 32% Black 32% Latino	Methadone: mean dose 68.0 mg smokers and 55.3 mg non-smokers No methadone (smokers and non-smokers controls)	Methadone smokers vs. methadone non-smokers vs. control smokers vs. control non-smokers Gambling task net score (mean): -30.7 vs. -8.0 vs. 5.8 vs. -1.2 ($p<0.05$ for methadone smokers vs. others)	Fair

Table 19. Risk of adverse pregnancy outcomes with methadone use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results
Bakstad, 2009[133]	Cross-sectional	Pregnant women enrolled in OMT programs in Norway with delivery between 2005-2007	n=41 (methadone n=26, buprenorphine n=12) Mean maternal age 32 years Race not reported	Methadone: mean dose in month preceding delivery 90 mg (range: 7–260 mg) Buprenorphine: mean dose in month preceding delivery 13 mg (range: 3–24 mg)	Methadone vs. buprenorphine Mean cigarettes per day: 9 vs. 13 (duration of NAS correlated with mean cigarettes per day for methadone only: p=0.023)
Berghella, 2003[193]	Prevalence	Maternal and neonatal records of heroin-addicted pregnancies from 9/1996-12/1999	n=100 Mean maternal age 29 years Race not reported 81% smokers	Methadone: mean dose not reported (results stratified to < 80 mg and ≥80 mg) Non-use	Methadone and benzodiazepine use vs. non-use Treatment for neonatal abstinence syndrome: 61% (30/39) vs 77% (30/61) Duration of treatment for neonatal abstinence syndrome: 9.6 vs. 19.5; p=0.01
Choo, 2004[195]	Pro-spective cohort	Women diagnosed with current opiate dependence and trated with methadone pharmacotherapy, ess than 28 weeks pregnant	n=29 Mean maternal age 30 years 88% African American	Methadone: mean dose 77.0 mg/day	Light smokers vs. heavy smokers Mean gestational age (weeks): 36.8 vs. 38.3; p=NS Mean birth weight (g): 2471.9 vs. 2784.6; p=NS Mean head circumference (cm): 31.5 vs. 32.3; p=NS Mean Apgar at 5 min: 8.7 vs. 8.8; p=NS NAS peak score: 5.6 vs. 9.8; p=0.014 Time to NAS peak score (hours): 37.8 vs. 113.8; p=0.016 Adjusted analysis for gestational age and opiate-positive neonatal toxicology, time to NAS peak score still significant: p=0.025 Mean duration of NAS (days): 5.1 vs. 9.5; p=0.054 Subset of term infants Light smokers vs. heavy smokers NAS peak score: 6.8 vs. 11.0; p=0.039 Time to NAS peak score (hours): 42.9 vs. 116.9; p=0.042 Mean duration of NAS (days): 5.9 vs. 10.6; p=NS

Table 19. Risk of adverse pregnancy outcomes with methadone use

Author, year	Quality
Bakstad, 2009[133]	Fair
Berghella, 2003[193]	Fair
Choo, 2004[195]	Fair

Table 19. Risk of adverse pregnancy outcomes with methadone use

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results
Dryden, 2009[134]	Preva-lence	Singleton infants born to drug abusing women prescribed substitute methadone	n=440 Median age 28 years Race not reported 88% smokers 50% HCV antibody positive	Methadone: mean dose not reported (22% 1-29 mg, 38% 30-59 mg, 31% 60-89 mg, 9% ≥90 mg)	Factors predictive of treatment for NAS Methadone dose ≥90 mg vs. 1-29 mg: 43 vs. 98; OR: 5.09 (95% CI: 2.32 to 11.18); p<0.001 Breastfeeding ≥72 hours: OR: 0.52 (95% CI: 0.33 to 0.83); p=0.006 Unadjusted benzodiazepine use: OR: 1.73 (95% CI: 1.17 to 2.55), p=0.006
Lim, 2009[194]	Cross-sectional	Pregnant women receiving methadone therapy	n=66 (low-dose methadone n=23, moderate-dose methadone n=26, high-dose methadone n=17) Mean maternal age 26 years 97% White 3% Black	Methadone: mean dose 97 mg (range 15-240)	Low dose (≤70 mg) vs. moderate dose (71-139 mg) vs. high dose (≥140mg) Cesarean section: 48% (11/23) vs. 35% (9/26) vs. 35% (6/17) Treatment for neonatal abstinence syndrome: 65% (15/23) vs. 73% (19/26) vs. 100% (17/17); p=0.01 for low dose vs. moderate dose and p=0.005 for low dose vs. high dose Length of stay (days): 19.1 vs. 25.6 vs. 27.8 Breastfed: 17% (4/23) vs. 23% (6/26) vs. 41% (7/17)
Malpas, 1995[196]	Cross-sectional	Mothers and babies coded for drug abuse or neonatal withdrawal, respectively, from 1/1987-12/1991 compared with population seen at Christchurch Health and Development Study (longitudinal birth cohort)	n=70 (methadone n=40, non-use n=30) Demographic data not reported	Methadone: mean dose not reported Non-use	Methadone, low-dose (1-10 mg) vs. moderate dose (11-20 mg) vs. high-dose (≥21 mg) vs. no methadone Mean max symptom score: 10.4 vs. 10.7 vs. 12.7 vs. 3.4; p<0.001 for non-use vs. others Mean length of stay (days): 0.6 vs. 16.5 vs. 26.0 vs. 7.9 Neonatal abstinence syndrome requiring treatment: 20% (3/15) vs. 53% (10/19) vs. 67% (4/6) vs. 3% (1/30) Mean duration of treatment (days): 2.4 vs. 7.3 vs. 12.3 vs. 0.9 (p<0.001) Breastfeeding: no relationship found, data not reported

Table 19. Risk of adverse pregnancy outcomes with methadone use

Author, year	Quality
Dryden, 2009[134]	Good
Lim, 2009[194]	Fair
Malpas, 1995[196]	Poor

Table 20. Methadone rotation and adverse events

Author, year	Study design	Inclusion criteria	Population characteristics	Intervention	Results	Quality
Jones, 2008[198]	Retro-spective cohort	Methadone maintained during pregnancy or receiving a prescription for either 3 or 7 days of methadone-assisted withdrawal, with no other concurrently medication-assisted tapers from alcohol or benzodiazepines, and have available maternal medical chart and complete delivery outcome information	n=175 (3-day taper n=67; 3-day taper + maintenance n=8; 7-day taper n=28;. 7-day taper + maintenance n=20; maintenance only n=52) Mean maternal age 26 years 14% White 86% Black or other race	Methadone: 3-day taper withdrawal (20 mg, 10 mg, and 10 mg given days 1 to 3, respectively) Methadone: 7-day taper withdrawal (40 mg, 30 mg, 25 mg, 20 mg, 15 mg, 10 mg, and 5 mg given days 1 to 7, respectively) Methadone maintenance: 30 mg, 40 mg, 50 mg, and 60 mg given days 1 to 4, respectively, then additional increases in 5 mg or 10 mg doses were provided based upon clinical indications	3-day taper vs. 3-day taper + maintenance vs. 7-day taper vs. 7-day taper + maintenance vs. maintenance only Maternal urine toxicology positive for illicit drugs at delivery: 53% (35/67) vs. 33% (2/8) vs. 57% (16/28) vs. 15% (3/20) vs. 23% (12/52) Mean head circumference (cm): 32.9 vs. 33.2 vs. 31.2 vs. 32.8 vs. 31.8 (p=0.06) NICU admission: 30% (20/67) vs. 13% (1/8) vs. 36% (10/28) vs. 0 vs. 46% (23/52) Mean birth weight (g): 2834.0 vs. 3054.1 vs. 2823.9 vs. 2987.0 vs. 2819.1 Mean length circumference (cm): 47.7 vs. 50.5 vs. 47.5 vs. 49.5 vs. 48.1 (NS) Premature: 27% (18/67) vs. 13% (1/8) vs. 36% (10/28) vs. 10% (2/20) vs. 19% (10/52) Low birth weight: 21% (14/67) vs. 13% (1/8) vs. 11% (3/28) vs. 5% (1/20) vs. 25% (13/52) Mean Apgar at 5 min: 8.7 vs. 8.6 vs. 8.5 vs. 8.3 vs. 8.6 Mean total length of stay for infant (days): 9.6 vs. 7.9 vs. 8.9 vs. 6.0 vs. 12.8 Treated for NAS: 25% (17/67) vs. 29% (2/8) vs. 36% (10/28) vs. 15% (3/20) vs. 27% (14/52)	Good

Table 20. Methadone rotation and adverse events

Parsons, 2010[197]	Pro-spective cohort	Consecutive first time methadone users; previous opioid was stopped at the day of methadone initiation	n=189 (initiations n=89, rotations n=100) Mean age 60 years 47% male 73% White 9% Hispanic 8% Black 10% other	Methadone: 5mg bid Opioid rotation: morphine equivalent daily dose Methadone: according to the previous opioid dose: 5:1 when previous morphine equivalent daily dose was 90 mg/d, 8:1 when it was between 91 and 300 mg/d, and 12:1 when it was 301mg/d	Withdrawals due to side effects, initiation vs rotation: 3%(3/89) versus 3% (3/100)	Fair

Table 21. Methadone dose and adverse events

Author, year Sample Size	Prospective Design	Adjustment for confounders	Method of analyzing methadone dose	Findings
Anchersen, 2009[57] n=200	Yes	No	Continuous variable	Methadone dose and QTc prolongation: correlation coefficient 0.367 (95% CI 0.22 to 0.51)
Athanasos, 2008[68] n=54	Yes	No	<60 mg/day vs. >60 mg/day	No correlation between methadone dose and QTc prolongation.
Bakstad, 2009[133] n=26 (prescribed methadone)	Yes	No	Continuous variable	No association between methadone dose and duration of neonatal abstinence syndrome.
Berghella, 2003[193] n=100	No	No	<80 vs. >=80 mg/day	No difference between higher and lower methadone dose in incidence, severity, or duration of neonatal abstinence syndrome.
Blake, 1973[210] n=41	Yes	No	Continuous variable	Increasing duration of treatment showed consistent trend toward lower anxiety and depression scores.
Brown, 1998[112] n=32	No	No	<50 vs. >=50 mg/day	No association between higher or lower methadone dose and birth weight, incidence of neonatal withdrawal.
Brown, 2005[100] n=92	No	No	Continuous variable	Dose showed no significant differences between groups in hormone levels.
Buster, 2002[174] 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 to 5.8)
Chang, 2012[62] n=283	No	Yes	Continuous variable	Methadone dose and QTc prolongation: correlation coefficient 0.210 (p=0.0014) in males and 0.164 (p=0.2363) in females
Connaughton, 1977[105] n=278	No	No	Continuous variable	No association between daily methadone dose and severity of withdrawal.
Cousins, 2011[176] n=3,162	No	Yes	<60 vs. ≥60 mg/day	Drug-related mortality: adjusted HR 0.98 (CI 0.44 to 2.18)
Cruciani, 2005[70] n=110	Yes	No	Continuous variable	Effect size 0.03, p=0.89 for methadone dose.
Cushman, 1973[101] n=19	Yes	No	Mean dose not reported	No change in mean testosterone levels during MMT; normal LH levels before, during MMT.
Dryden, 2009[134] n=450	No	Yes	1-29, 30-59, 60-89, and >=90 mg/day	Highest dose associated with increased risk of receiving treatment for neonatal abstinence syndrome compared to lowest dose: OR 4.8 (95% CI 2.2 to 11).
Ehret, 2006[59] n=247	No	Yes	Continuous variable	Correlation between daily methadone dose and QTc prolongation - rs=0.20; p<0.01.
Fanoe, 2007[69] 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 to 1.4).

Table 21. Methadone dose and adverse events

Author, year Sample Size	Prospective Design	Adjustment for confounders	Method of analyzing methadone dose	Findings
Green, 1979[212] n=105	No	Yes	Continuous variable	No association between methadone dose and birth weight.
Harper, 1977[117] n=22	Yes	No	Continuous variable	Higher total maternal methadone use during last 12 weeks of pregnancy associated with more severe neonatal withdrawal symptoms (p<0.02).
Huh, 2010[60] n=90	No	No	Continuous variable	No association between methadone dose and QTc interval (average dose 30 mg/day)
Justo, 2006[78] n=40	No	No	Continuous variable	High-dose methadone commonly associated with TdP (98% of patients).
Kandall, 1976[109] n=365	No	No	Continuous variable	Higher methadone dose associated with higher birth weight (p<0.005).
Kandall, 1977[104] n=233	No	No	Continuous variable	No association between methadone dose and severity of neonatal withdrawal symptoms.
Katz 2013[73] n=531	No	Yes	Continuous variable	Higher methadone dose associated with greater magnitude of increase in the QTc interval from baseline (p=0.009)
Krantz, 2002[19] & 2003[190] n=17	No	Yes	Continuous variable	Higher methadone dose associated with increased risk of TdP (r= 0.51; p=0.03).
Krebs 2011[145] n=108,492	No	Yes	Continuous variable	Mortality risk lower for methadone compared to morphine; dose-adjusted HR 0.58 (95% CI 0.52 to 0.64). Most deaths occurred during the first 30 days of use in both groups.
Langrod, 1981[206] n=102	Yes	No	Continuous variable	Methadone treatment associated with minor complaints: sweating, constipation, sleepiness, sexual problems, and aches in bones and joints.
Lim, 2009[194] n=68	No	No	Continuous variable	Each 1 mg increase in last methadone dose before delivery associated with an additional 0.18 (95% CI 0.11 to 0.26) days of treatment for neonatal abstinence syndrome.
Lombardo, 1976[209] n=57.	Yes	Unclear	50 vs. 80 mg/day variable	No significant differences between groups on intelligence tests.
Longwell, 1979[205] n=51	Yes	No	Before and during maintenance comparisons	Most complaints present prior to methadone maintenance, when analyzed individually, a statistically significant number of patients [NR] reported more severe complaints after 9 months; some related to withdrawal.
Malpas, 1995[196] n=70 (40 exposed to methadone)	No	No	Continuous variable	Higher mean maternal methadone dose associated with longer duration of hospital stay (p<0.001), infants treated for withdrawal (p<0.001), and duration of treatment (p<0.001).

Table 21. Methadone dose and adverse events

Author, year Sample Size	Prospective Design	Adjustment for confounders	Method of analyzing methadone dose	Findings
Martell, 2005[53] n=160	Yes	Yes	Continuous variable	Higher serum methadone level significantly associated with QTc prolongation at 6 and 12 months.
Mayet, 2011[75] n=83	Yes	Yes	Continuous variable	Methadone dose predicted longer QTc duration (β 0.318; p=0.003)
McCowan, 2009[173] n=2,378	No	Yes	Continuous variable	Increased duration of treatment associated with decreased risk of all-cause mortality: HR 0.95 (95% CI 0.94 to 0.96)
Newman, 1974[214] n=313	No	No	<40, 40-60, 70-90, 100, or >100 mg/day	No differences in length of gestation, birth weight, or incidence of neonatal withdrawal symptoms.
Rosen, 1975[114] n=31	Unclear	No	Continuous variable	No clear association between methadone dose and severity of neonatal withdrawal syndrome.
Rosen, 1985[105] n=57 (methadone exposed)	Yes	No	Continuous variable	Higher dose associated with increased risk of obstetrical complications (p<0.01), increased severity of narcotic abstinence syndrome (p<0.05), and higher birth weight (p<0.05).
Roy, 2011[89] n=180	No	Yes	Continuous variable	No association between methadone dose and degree of QTc prolongation (average dose ~80 mg/day)
Sharkey, 2010[178] n=95	Yes	Yes	Continuous variable	Longer duration associated with more sleep disordered breathing and obstructive sleep apneia.
Shaw, 1994[120] n=32 (methadone exposed)	Yes	No	>20 vs. <=20 mg/day	No difference between higher and lower dose in risk of neonatal abstinence syndrome.
Stallvik, 2013[95] n=45	No	Yes	Continuous variable	No association between methadone dose and degree of QTc prolongation (average dose 88-96 mg/day
Strain, 1991[194] n=58	Yes	No	At admission and each week up to 4 weeks mean of 25 mg	Decreased depression for all timepoints compared with admission scores on BDI (p<0.01).
Strauss, 1976[202] n=70	No	No	>20 vs. <=20 mg/day	Higher dose associated with higher incidence of withdrawal symptoms (p<0.025), greater use of pharmacological interventions for withdrawal (p<0.05), longer hospitalization (p<0.05). No difference in birth weight, gestational age, birth length, and Apgar scores.
Soyka, 2010[195] n=77	No	Yes	30 days of use; 6 months of use	Better cognitive functioning with longer use (p<0.03 for all measures).
van Ameijden, 1999[42] 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.

Table 21. Methadone dose and adverse events

Author, year Sample Size	Prospective Design	Adjustment for confounders	Method of analyzing methadone dose	Findings
Wouldes, 2010[109] n=74 (32 methadone exposed)	Yes	Yes	None, <58, or >59 mg/day	Higher dose associated younger gestational age, longer hospitalization, lower birth weight, higher birth length, greater birth head circumference in adjusted models (p=0.001 for all).
Webster, 2008[145] n=140	No	Yes	Daily dose of 266 mg	Higher dose associated with more severe sleep apnea (p=0.002 for apnea-hypopapnea; p=0.008 for central apnea).
Zador, 2000[191] n=238	No	Yes	Daily dose of 266 mg	Higher dose associated with more severe sleep apnea (p=0.002 for apnea-hypopapnea; p=0.008 for central apnea).

Abbreviations: TdP = Torsades de pointes

Table 22. Pregnancy outcomes in those prescribed methadone for pain compared with addiction

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Sharpe, 2004[216]	Cross-sectional	Not reported	n=43 (methadone for pain n=19, methadone for addiction n=24) 70% smokers Other maternal demographic data not reported	Methadone: median dose 40 mg among chronic pain patients; 60 mg among addiction patients	Pain group vs. addiction group Median gestational age (weeks): 36 vs. 39; p=0.0002 Emergency cesarean: 16% (3/19) vs. 17% (4/24) Median Apgar at 1min: 9 vs. 9 NAS diagnosis: 68% (13/19) vs. 100% (24/24) Treatment for NAS: 11% (2/19) vs. 58% (14/24); p=0.0016	Fair

Table 23. Adverse events with methadone use with the addition of concomitant medication

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Cobb, 1998[219]	RCT	Age >18 years; stable methadone dose for a minimum of 30 days; CD4+cell counts>250/μL within 3 months; negative urine toxicology screens (other than methadone) within 14 days	n=33 Mean age 40 years 64% male 52% Hispanic 48% Black	Oral methadone mean dose 57 mg + fluconazole 200 mg Placebo	Methadone + fluconazole vs. methadone + placebo 24-hour serum methadone level: 254.4 ng/ml (SE 40.6) vs. 327.0 ng/ml (SE 56.6) Overdose symptoms (lightheadedness, drowsiness, and diaphoresis): 8% (1/13) vs. 17% (2/12) week 1; 23% (3/13) vs. 0% (0/12) week 2	Poor
Cornish, 2002[220]	RCT	Men age 21-55 years; good general health; DSM-IV diagnosis of opiate dependence; enrolled in a methadone program in which they were stabilized on a consistent dose of 50-70 mg of daily methadone for minimum of 10 consecutive days	n=16 Mean age 44 years; 100% male 80% Black	Oral methadone 50-70 mg + dextromethorphan 120 mg/day titrated to 480 mg/day Placebo	Methadone + dextromethorphan vs. methadone + placebo Constipation: 40% (4/10) vs.40% (2/5) Diarrhea: 20% (2/10) vs. 20% (1/5) Gastric upset/nervous stomach: 10% (1/10) vs. 40% (2/5) Nausea: 10% (1/10) vs. 20% (1/5) Vomiting: 20% (2/10) vs. 20% (1/5) Drowsiness: 50% (5/10) vs. 20% (1/5) Anxiety: 10% (1/10) vs. 0% (0/5) Hyperactive: 10% (1/10) vs. 0% (0/5) Dizziness: 20% (2/10) vs. 0% (0/5) Confusion: 30% (3/10) vs. 0% (0/5) Insomnia: 10% (1/10) vs. 0% (0/5) Difficulty breathing: 10% (1/10) vs. 0% (0/5)	Fair
Cubero, 2010[221]	RCT	Age >18 years; oncologic pain; stable morphine dose for at least 1 week	n=50 Mean age 59 years 53% male Race not reported Median morphine dose 60 mg	Oral methadone mean dose not reported; dose varied according to pre-trail morphine dose + acetaminophen Placebo	Methadone + acetaminophen vs. methadone + placebo Somnolence, proportion of patients with worsening from baseline: 42%(10/24) vs. 10% (3/25); p=0.04 No differences in incidence of constipation, nausea, or vomiting	Fair

Table 23. Adverse events with methadone use with the addition of concomitant medication

Author, year	Study design	Inclusion criteria	Population characteristics	Interventions	Results	Quality
Titievsky, 1982[217]	RCT	Methadone clinic patients with Hamilton Rating Scale for Depression score at least 18 (of 24)	n=76 Mean age 30 years 46% male Race not reported	Oral methadone maximum dose 100 mg + doxepin 50 mg/day titrated to 200 mg/day Placebo	Methadone + doxepin vs. methadone + placebo (Results reported for 48 completers only) Drowsiness: 43% (9/21) vs. 19% (5/27) Sluggishness: 29% (6/21) vs. 19% (5/27) Hypotensive symptoms: 5% (1/21) vs. 0% (0/27) Lack of coordination: 10% (2/21) vs. 4% (1/27) Constipation: 0% (0/21) vs. 4% (1/27)	Fair
Woody, 1975[218]	RCT	Men age 20-50 years meeting FDA requirements for methadone treatment; medically healthy; free of addiction to drugs other than narcotics; symptomatic depression; initiating methadone treatment	n=35 Mean age 29 years 100% male Race not reported	Oral methadone + doxepin 100-150 mg/day Placebo	Methadone + doxepin vs. methadone + placebo Withdrawals due to AEs: 12% (2/17) vs. 4% (1/28) No other adverse events reported	Poor

Table 24. Take-home methadone maintenance policies and retention rates

Author, year	Study design	Inclusion criteria	Population characteristics	Take-home policies	Results	Quality
Peles, 2010[224]	Retro-spective cohort	Patients admitted to a MMT clinic between June 25, 1993 and June 24, 2008	n=657 (methadone, ever had take-home privileges n=435, never had take-home privileges n=222) Mean age 38 years 74% male Race not reported	MMT patients may be allowed to take-home doses after 3 months compliance on MMT, then each additional dose is available after 1 month of compliance on MMT, to gain a 6th dose MMT patients must be compliant the whole time and involved in a vocational activity, with 13 doses being the max allowed to take home and can be achieved in 2 years. If medical or other reason for why patient can't make it to MMT, they may be allowed to take-home doses before being admitted for 3 months.	Methadone maintenance ever allowed vs. never allowed Time from methadone maintenance treatment to death: mean 13 vs. 12 years, p=0.04 Among ever allowed, 3 to 6 months after starting treatment - privileges ≥3 months vs. <3 months, mean survival time 13 to 14 years versus 10 years	Good

Appendix A. List of panel members

Panel Co-chairs

American Pain Society Co-chair
Ricardo Cruciani MD – Pain medicine
Pain Medicine and Palliative Care

College on Problems of Drug Dependence Co-chair
David Fiellin MD – Primary care/Addiction
Yale School of Medicine

Panel Members

Eric Strain MD - Psych/Addiction
Johns Hopkins Bay View Medical Center

Sharon Walsh PhD - Pharmacology
Department of Behavioral Science; Center on Drug and Alcohol Research

Russ Portenoy MD - Palliative care/Neurology
Department of Pain Medicine and Palliative Care

Seddon Savage MD, MS - Anesthesia/Pain medicine/Addiction
Dartmouth Medical School

John Knight MD - Adolescent psych/Addiction
Children's Hospital Boston

Lonnie Zeltzer MD – Pediatric Pain Program
Mattel Children's Hospital at UCLA

Charles (Chuck) Inturrisi PhD - Pharmacology
Weill Cornell Medical College

Steven M Marcus MD
New Jersey Medical School of University of Medicine & Dentistry of NJ

Mark C Haigney MD - Director of Cardiology
Uniformed Services University of the Health Sciences

Davendra Mehta MD - Professor; Medicine/Cardiology
Heart Rhythm Society

Margaret (Peggy) Compton RN, PhD - Associate Professor
University of California, Los Angeles; School of Nursing

Appendix A. List of panel members

Shirley Otis-Green MSW, ACSW - Senior Research Specialist
Division of Nursing Research and Education

John T. Farrar MD, PhD - Senior Scholar
University of Pennsylvania

Marjorie C. Meyer MD - Associate Professor, OB/GYN
University of Vermont

Appendix B. Scope and key questions

Scope

Population

- Adults & children being prescribed methadone
    - Methadone maintenance
    - Methadone for chronic pain
    - Methadone during pregnancy
    - Methadone in adolescents & children/infants
    - Methadone in elderly
    - Cancer pain/palliative care
    - Patients with acute pain already on methadone
    - Methadone in patients with comorbid medical conditions that may increase risk, including cardiovascular, respiratory or other conditions
    - Methadone in patients on concomitant meds
    - Patients at higher risk for misuse (including incarcerated persons)

Interventions

- Oral and intravenous methadone
    - (R) – methadone
    - (R,S) – methadone

Comparators

- Methadone vs. placebo
- Methadone vs. other opioid agonists/partial agonists
- Methadone + another drug(s) vs. methadone
- Methadone vs. other analgesics
- Methadone vs. naltrexone

Outcomes (Adverse Events)

- Overdose
- Mortality (including sudden death)
- Discontinuation due to adverse events
- Syncope
- QT prolongation
- Torsades/arrhythmias
- Endocrinologic/bone density/immunologic
- Pregnancy outcomes
- Neonatal withdrawal
- Constipation/GI
- Cognitive functioning/other psychiatric disorders
- Respiratory depression/sleep apnea
- Abuse/addiction/hyperalgesia

Appendix B. Scope and key questions

Study design

- RCTs (if available, most likely lacking for the outcomes we are interested in)
- Observational studies
- Limit to English language studies
    - Keep track of what is excluded due to language, so we can retrieve quickly if needed
- Systematic reviews

Searches

- MEDLINE
- PsychINFO
- Cochrane
- Methadone National Meetings

Key Questions

1. In populations prescribed methadone, what is the risk of adverse events compared to non-use of methadone?
2. What are the comparative risks of adverse events for methadone compared to other opioids or drugs?
3. In populations prescribed methadone, what factors predict increased risk of adverse events?
4. In populations prescribed methadone, what are the effects of different dosing strategies on 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 prolongation, what are the benefits of correcting conditions associated with QTc prolongation?
8. In populations prescribed methadone with evidence of QTc prolongation, what are the benefits and harms of continued use of methadone versus switching to another opioid agonist or discontinuation of methadone?
9. In populations prescribed methadone at higher risk for adverse events, what are the benefits of methods for reducing risk?
10. In populations prescribed methadone, what is the effectiveness of methods for reducing risk of diversion or non-prescribed use?
11. How does risk of adverse events associated with methadone vary according to dose or duration of therapy?

12. How are risks of methadone affected by the indication for treatment?
13. How are risks of methadone affected by the addition of concomitant medications?
14. How do differences in adherence and access to care affect risk of adverse events associated with methadone?
15. In populations prescribed methadone, what is the accuracy of urine drug testing or prescription drug monitoring for predicting adverse events?
16. In populations prescribed methadone, what are the benefits and harms of urine drug testing or prescription drug monitoring?
17. In populations prescribed methadone, what are the benefits and harms of different methods for structuring and managing care?

Appendix C. Search strategies

Methadone – Search Strategies
Database: Ovid MEDLINE(R) and Ovid OLDMEDLINE(R) <1948 to July 2012>
1 Methadone/
2 (ae or po or to or de or co).fs.
3 (safety or harm$ or adverse or side effect$).mp.
4 1 and (2 or 3)
5 limit 4 to humans
6 limit 5 to English language
7 limit 5 to abstracts
8 6 or 7
9 (case reports or editorial or letter or comment).pt.
10 8 not 9

Database: PsycINFO <1806 to July 2012>
1 exp Methadone Maintenance/ or exp Methadone/ or methadone.mp.
2 (safety or harm$ or adverse or side effect$).mp.
3 1 and 2

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <through July 2012>
1 Methadone/
2 (ae or po or to or de or co).fs.
3 (safety or harm$ or adverse or side effect$).mp.
4 1 and (2 or 3)
5 limit 4 to humans
6 limit 5 to English language
7 limit 5 to abstracts
8 6 or 7
9 (case reports or editorial or letter or comment).pt.
10 8 not 9

Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to July 2012>
Search Strategy:
1 methadone.mp.
2 (safe$ or adverse or harm$).mp.
3 1 and 2
4 limit 3 to full systematic reviews

Appendix D. Quality assessment criteria

Criteria for rating systematic reviews[1]

Criteria	Operationalization of Criteria	Scoring
1. Was an *a priori* design provided?	The research question should be established before the conduct of the review.	Yes/No/ Can't answer/ Not applicable
2. Was there duplicate study selection and data extraction?	There should be at least two independent data extractors and a consensus procedure for disagreements should be in place.	
3. Was a comprehensive literature search performed?	At least two electronic sources should be searched. The report must include years and databases used (e.g. Central, EMBASE, and MEDLINE). Key words and/or MESH terms must be stated and where feasible the search strategy should be provided. All searches should be supplemented by consulting current contents, reviews, textbooks, specialized registers, or experts in the particular field of study, and by reviewing the references in the studies found.	
4. Was the status of publication (i.e. grey literature) used as an inclusion criterion?	The authors should state that they searched for reports regardless of their publication type. The authors should state whether or not they excluded any reports (from the systematic review), based on their publication status, language etc.	
5. Was a list of studies (included and excluded) provided?	A list of included and excluded studies should be provided.	
6. Were the characteristics of the included studies provided?	In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed e.g. age, race, sex, relevant socioeconomic data, disease status, duration, severity, or other diseases should be reported.	
7. Was the scientific quality of the included studies assessed and documented?	*A priori* methods of assessment should be provided (e.g., for effectiveness studies if the author(s) chose to include only randomized, double-blind, placebo controlled studies, or allocation concealment as inclusion criteria); for other types of studies alternative items will be relevant.	
8. Was the scientific quality of the included studies used appropriately in formulating conclusions?	The results of the methodological rigor and scientific quality should be considered in the analysis and the conclusions of the review, and explicitly stated in formulating recommendations.	

Appendix D. Quality assessment criteria

Criteria	Operationalization of Criteria	Scoring
9. Were the methods used to combine the findings of studies appropriate?	For the pooled results, a test should be done to ensure the studies were combinable, to assess their homogeneity (i.e. Chi squared test for homogeneity, I2). If heterogeneity exists a random effects model should be used and/or the clinical appropriateness of combining should be taken into consideration (i.e. is it sensible to combine?).	
10. Was the likelihood of publication bias assessed?	An assessment of publication bias should include a combination of graphical aids (e.g., funnel plot, other available tests) and/or statistical tests (e.g., Egger regression test).	
11. Was the conflict of interest stated?	Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.	

Appendix D. Quality assessment criteria

Criteria for rating randomized controlled trials[2]

Criteria	Operationalization of Criteria	Scoring
1. Was the method of randomization adequate?	A random (unpredictable) assignment sequence. An example of adequate methods is a computer generated random number table and use of sealed opaque envelopes. Methods of allocation using DOB, date of admission, hospital numbers, or alternation should not be regarded as appropriate.	Yes/No/ Don't know
2. Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.	
3. Were the groups similar at baseline regarding the most important prognostic factors? *"Yes", if similar:* • *Age & gender* • *Description of type of pain* • *Intensity, duration or severity of pain*	In order to receive a "yes", groups have to be similar in baseline regarding demographic factors, duration or severity of complaints, percentage of patients with neurologic symptoms, and value of main outcome measure(s).	
4. Was the patient blinded to the intervention?	The reviewer determines if enough information about the blinding is given in order to score a "yes": Use the author's statement on blinding, unless there is a differing statement/reason not to (no need for explicit information on blinding).	
5. Was the care provider blinded to the intervention?	The reviewer determines if enough information about the blinding is given in order to score a "yes": Use the author's statement on blinding, unless there is a differing statement/reason not to (no need for explicit information on blinding).	

Appendix D. Quality assessment criteria

Criteria	Operationalization of Criteria	Scoring
6. Was the outcome assessor blinded to the intervention?	The reviewer determines if enough information about the blinding is given in order to score a "yes": Use the author's statement on blinding, unless there is a differing statement/reason not to (no need for explicit information on blinding).	Yes/No/ Don't know
7. Were co-interventions avoided or similar?	Co-interventions should either be avoided in the trial design or similar between the index and control groups.	
8. Was the compliance acceptable in all groups?	The reviewer determines if the compliance to the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s).	
9. Was the attrition rate described and acceptable?	Attrition should be reported by group and overall attrition of <15% is acceptable.	
10. Timing of outcome assessments in all groups similar?	The reviewer determines if the outcome assessments were conducted at the same time of the disease, course of treatment or other similar timing in all groups.	
11. Did the article include an intention-to-treat analysis?	All patients that were randomized were included in the analysis. Specify if imputation methods (e.g., last-observation carried forward) were used. OR Exclusion of 5% of patients or less is acceptable, given that the reasons for exclusion are not related to outcome (e.g., did not take study medication) and that the exclusions would not be expected to have an important impact on the effect size)	

Appendix D. Quality assessment criteria

Criteria for rating observational studies[3, 4]

Criteria	Scoring
1. Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random sample (inception cohort)?	Yes/ No/Don't know
2. Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	
3. Did the study use accurate methods for ascertaining exposures, potential confounders, and outcomes?	
4. Were outcome assessors and/or data analysts blinded to treatment?	
5. Did the article report attrition?	
6. Did the study perform appropriate statistical analyses on potential confounders?	
7. Is there important differential loss to follow-up or overall high loss to follow-up?	
8. Were outcomes pre-specified and defined, and ascertained using accurate methods?	

References

1. Shea BJ, Hamel C, Wells GA, et al. AMSTAR is a reliable and valid measurement tool to assess the methodological quality of systematic reviews. *J Clin Epidemiol.* 2009;62(10):1013-1020.

2. 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.* 2003;28(12):1290-1299.

3. 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.* 1998;52(6):377-384.

4. Harris RP, Helfand M, Woolf SH, et al. Current Methods of the U.S. Preventive Services Task Force: A Review of the Process. *Am J Prev Med.* 2001;20(3 Suppl):21-35.

Appendix E. List of acronyms and abbreviations

	Definition
ADHD	Attention deficit hyperactivity disorder
AE	Adverse effects
AF	Atrial fibrilation
AHI	Apnea hypopnea index
AHR	Adjusted hazard ratio
AHRQ	Agency for Healthcare Research and Quality
ALT	Alanine transaminase
AMSTAR	Assessment of Multiple SystemAtic Reviews
AOR	Adjusted Odds Ratio
APS	American Pain Society
ARR	Adjusted Relative Risk
AST	Aspartate aminotransferase
BDI	Beck Depression Inventory
BID	Twice a day
BMI	Body Mass Index
BMT	Buprenorphine maintenance treatment
BN	Buprenorphine/Naloxone
BPM	Beats per minute
BVRT	Benton's Visual Retention Test
BWR	Blood Wassermann Reaction
BZD	Benzodiazepine
CAD	Coronary artery disease
CAI	Central apnea index
CFT	Complex Figure Test
CHF	Congestive heart failure
CI	Confidence Interval
CKD	Chronic kidney disease
cm	Centimeter
CO	Controls with optimal deliveries
COPD	Chronic obstructive pulmonary disease
COWAT	Controlled Oral Word Association Test
CPDD	College on Problems of Drug Dependence
CSA	Central sleep apnea
CVD	Cardiovascular disease
CYP450	Cytochrome P450
DAWN	Drug abuse warning network
DF	Drug free
DLCO	Diffusion capacity of the lung for carbon monoxide
DM	Dextromethorphan hydrobromide
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders- Third Edition-Revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders- Fourth Edition
DSST	Digital symbol substitution task, subset of WAIS
ECG	Electrocardiography
ED	Emergency Department
EDDP	2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine
EEG	Electroencephalography
ER	Emergency Room
FDA	U.S. Food and Drug Administration
FHR	Fetal heart rate

Appendix E. List of acronyms and abbreviations

g	Gram (s)
GCI	General Cognitive Index
GED	General Education Development
GRADE	Grading of Recommendations Assessment, Development and Evaluation
Grp	Group
HBV	Hepatitis B Virus
HCl	Hydrogen chloride
HCV	Hepatitis C Virus
HCVR	Hyercapnic ventilary response
HIV	Human Immuno-Deficiency Virus
HO	Methadone plus heroin
HON	Methadone plus opiates and nonopiates
HR	Hazard Ratio
HS	High School
HVR	Hypoxic ventilary response
Hx	History
ICD-9	International Statistical Classification of Diseases and Related Health Problems
IUGR	Intrauterine growth restriction
IV	Intravenous
kg	Kilogram(s)
KQ	Key Question
lbs	Pounds
LH	Leutinizing Hormone
LO	Methadone only
LVH	Left ventricular hypertrophy
MCPT	Modified Continuous Performance Test
M/F	Male/Female
mg	Milligram
mg/L	Milligrams per Liter
MI	Myocardial infarction
min	Minute (s)
MMSE	Mini-mental state examination
MMT	Methadone maintenance treatment
MNW	Non-working methadone
MPD	Memory for Personal Data
ms	Millisecond (s)
MW	Working methadone
n	Sample size
N/A	Not applicable
NAS	Neonatal abstinence syndrome
NC	Controls with nonoptimal deliveries
NCHS	National center for health statistics
ND	Narcotic dependence
ng/ml	Nanogram per milliliter
NICU	Neonatal intensive care unit
NMDA	N-methyl-D-aspartate
nmol/L	Nano mols per liter
NNNS	Neonatal Network Neurobehavioral Scale
NR	Not reported
NS	Not significant

Appendix E. List of acronyms and abbreviations

NSAIDs	Non-steroidal anti-inflammatory drugs
NY	New York
NYC	New York City
OAI	Obstructive Apnea Index
OCME	Office of chief medical examiner
OOA	Other opioid analgesics
OMT	Opioid maintenance treatment
OR	Odds Ratio
OSA	Obstructive Sleep Apnea
OSAHI	Obstructive sleep apnea/hypopnea index
OST	Opioid substitution treatment
OTP	Opioid treatment program
PASAT	Paced Auditory Serial Addition Test
PCP	Phencyclidine
PE	Pulmonary Embolism
PICO	Populations, Interventions, Comparators, and Outcomes
PRN	As needed
PSG	Polysomnography
PVD	Peripheral artery disease
q12h	Once every 12 hours
q4h	Once every 4 hours
qd	Once a day
QRS	Deflections in the tracing of an electrocardiogram, comprising the Q, R and S waves
QTc	Heart rate corrected QT interval
RBBB	Right bundle branch block
RCT	Randomized controlled trial
RR	Relative risk
RWT	Regensburger Word Fluency Test
RVH	Right ventricular hypertrophy
SAMHSA	Substance abuse and mental health services administration
SE	Standard error
SD	Standard deviation
SDB	Sleep-disordered breathing
SIDS	Sudden Infant Death Syndrome
SS	Statistically significant
STAI	State Trait Anxiety Index
TAP	Test for attention performance
TCA	Tricyclic antidepressant
TdP	Torsades de pointes
TMT-A	Trail-Making Test A
TMT-B	Trail-Making Test B
TSH	Thyroid stimulating hormone
Tx	Treatment
UDT	Urine drug testing
µIU/ml	Micro international unit per milliliter
µl	Micro liter
USA	United States of America
VA	Veteran’s Affairs
VLMT	Verbal Learning Memory Test
vs	Versus

Appendix E. List of acronyms and abbreviations

Vt	Tidal volume (breathing)
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Test
wks	Weeks
WMS-III	Wechsler Memory Scale, third version

Appendix F. Quality rating of systematic reviews

Author, year, title	Study design predetermined?	Dual review of studies and data abstraction?	Comprehensive literature search?	Publication status used as inclusion criteria?	List of included and excluded studies provided?	Characteristics of included studies provided?	Included studies quality assessed?
Cleary, 2010[211]	Yes	Yes	Yes	Yes	Included studies: Yes Excluded studies: No	Yes	Yes
Mattick, 2009[2]	Yes	Yes	Yes	Yes	Yes for both	Yes	Yes

Appendix F. Quality rating of systematic reviews

Author, year, title	Quality of included studies considered in formulating conclusions?	Appropriate methods used to combine studies?	Publication bias assessed?	Conflict of interest stated?	Number of criteria met?	Quality
Cleary, 2010[211]	Yes	Yes	Yes	Yes	10	Good
Mattick, 2009[2]	Yes	Yes	Yes	Yes	11	Good

Appendix G. Quality ratings of randomized controlled trials

Author, year, title	Randomization	Concealed treatment allocation	Baseline group similarity	Patient blinded	Care provider blinded	Outcome assessor blinded
Binder, 2008[110]	Unclear	Unclear	Yes	Unclear	Unclear	Unclear
Bruera, 2004[137]	Yes	Yes	Yes	Yes	Yes	Yes
Cobb, 1998[219]	Unclear	Unclear	Yes	Unclear	Unclear	Unclear
Cornish, 2002[220]	Unclear	Unclear	Yes	Yes	Yes	Unclear
Cubero, 2010[221]	Yes	Yes	Yes	Unclear	Unclear	Unclear
Eder 2005[162]	Yes	Yes	Yes	Yes	Yes	Yes
Fischer, 1999[172]	Unclear	Unclear	Yes	No	No	No
Fischer, 2006[132]	Unclear	Unclear	Yes	Yes	Yes	Unclear
Johnson, 1992[157]	Unclear	Unclear	Yes	Yes	Yes	Unclear
Johnson, 2000[141]	Yes	Unclear	Yes	Unclear	Unclear	Unclear
Jones, 2005[170]	Yes	Unclear	Yes	Yes	Yes	Unclear
Jones, 2010[169]	Yes	Unclear	Yes	Yes	Yes	Yes
Kinlock, 2009[47] other publications: Kinlock, 2007[45]	Unclear	Unclear	Yes	No	No	No
Ling, 1996[158]	Yes	Unclear	Yes	Yes	Yes	Yes
Lofwall, 2005[156]	Unclear	Unclear	Yes	Yes	Yes	Yes
Lombardo, 1976[209]	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Appendix G. Quality ratings of randomized controlled trials

Author, year, title	Co- interventions avoided, similar, or measured as an outcome	Compliance acceptable in all groups	Drop-out rate described and acceptable (<15%)	Timing of outcome assessment in all groups similar	Intention to treat analysis (>95% analyzed in groups to which they were allocated)	Quality
Binder, 2008[110]	Unclear	Unclear	No	Yes	No	Poor
Bruera, 2004[137]	Yes	Unclear	No	Yes	No (for later outcomes)	Fair
Cobb, 1998[219]	Unclear	Yes	No	Yes	No	Poor
Cornish, 2002[220]	Unclear	Yes	Yes	Yes	Yes	Fair
Cubero, 2010[221]	Unclear	Unclear	No	Yes	Yes	Fair
Eder 2005[162]	Unclear	Unclear	Yes	Yes	No	Fair
Fischer, 1999[172]	Yes	Unclear	Yes	Yes	Yes	Fair
Fischer, 2006[132]	Unclear	Unclear	No	Yes	No	Fair
Johnson, 1992[157]	Unclear	Unclear	No	Yes	Unclear	Poor
Johnson, 2000[141]	Unclear	Unclear	No	Yes	Unclear	Fair
Jones, 2005[170]	Unclear	Unclear	No	Yes	No	Fair
Jones, 2010[169]	Yes	Yes	No (25% dropped)	Yes	No	Fair
Kinlock, 2009[47] other publications: Kinlock, 2007[45]	Unclear	Unclear	No	Yes	Yes	Fair
Ling, 1996[158]	Yes	Unclear	No	Yes	Unclear	Fair
Lofwall, 2005[156]	Unclear	Yes	No (high)	Yes	Yes	Fair
Lombardo, 1976[209]	Unclear	Unclear	Unclear	Yes	Unclear	Poor

Appendix G. Quality ratings of randomized controlled trials

Author, year, title	Randomization	Concealed treatment allocation	Baseline group similarity	Patient blinded	Care provider blinded	Outcome assessor blinded
Mattick, 2003[142]	Yes	Yes	Yes	Yes	Yes	Yes
Matts, 1964[161]	Unclear	Unclear	Unclear	Yes	Yes	Unclear
Mercadante, 2008[139]	Yes	Unclear	Yes	Unclear	Unclear	Unclear
Mercadante, 1998[138]	Unclear	Unclear	Yes	Unclear	Unclear	Unclear
Pirastu, 2006[164]	Unclear	Unclear	Yes	Unclear	Unclear	Unclear
Schmittner, 2009[64]	Yes	Not applicable	Yes	Unclear	Yes	No
Schottenfeld, 1997[155]	Yes	Unclear	Yes	Yes	Yes	Unclear
Soyka, 2008[163]	Unclear	Unclear	Unclear	No	No	No
Titievsky, 1982[217]	Unclear	Unclear	Yes	Unclear	Yes	Yes
Ventafridda, 1986[140]	Unclear	Unclear	Unclear (age)	Unclear	Unclear	Unclear
Wedam et al, 2007[61] other publications: Johnson et al, 2000[141]	Yes	Unclear	Yes	Yes	Yes	Unclear
Woody, 1975[218]	Unclear	Unclear	Yes	Unclear	Unclear	Unclear

Appendix G. Quality ratings of randomized controlled trials

Author, year, title	Co- interventions avoided, similar, or measured as an outcome	Compliance acceptable in all groups	Drop-out rate described and acceptable (<15%)	Timing of outcome assessment in all groups similar	Intention to treat analysis (>95% analyzed in groups to which they were allocated)	Quality
Mattick, 2003[142]	Unclear	Unclear	No	Yes	Yes	Fair
Matts, 1964[161]	Unclear	Unclear	No	Unclear	Unclear	Poor
Mercadante, 2008[139]	Yes	Unclear	No	Yes	No	Fair
Mercadante, 1998[138]	Yes	Unclear	Unclear	Yes	Unclear	Fair
Pirastu, 2006[164]	Unclear	Yes	No	Yes	Unclear	Poor
Schmittner, 2009[64]	No	Yes	Fair			
Schottenfeld, 1997[155]	Yes	Unclear	No	Yes	Yes	Fair
Soyka, 2008[163]	Unclear	Unclear	No	Yes	No	Poor
Titievsky, 1982[217]	Unclear	Unclear	No	Yes	No	Fair
Ventafridda, 1986[140]	Unclear	Unclear	Yes	Yes	No (18% excluded from analysis)	Poor
Wedam et al, 2007[61] other publications: Johnson et al, 2000[141]	Unclear	Unclear	No	Yes	No	Good
Woody, 1975[218]	Unclear	Unclear	No	Yes	No	Poor

Appendix H. Quality ratings of observational studies

Author, year, title	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random (or matched) sample?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to treatment or exposures?
Anchersen, 2009[57]	Yes	No	Unclear	Yes
Anyaegbunam, 1997[111]	Unclear	Yes	Yes	No
Appel, 1976[88]	No	No	No	NR
Appel, 1982[89]	No	No	No	NR
Athanasos, 2008[68]	Unclear	No	Unclear	Yes
Bakstad, 2009[133]	Yes	Yes	Yes	No
Berghella, 2003[193]	Yes	Yes	Yes	No
Blake, 1973[210]	Unclear	Unclear	Yes	Unclear
Brown, 1998[112]	Unclear	No (see Table 1)	Yes	No
Brown, 2005[100]	Yes	No	Yes	Unclear
Burns, 2010[126]	Yes	Unclear	Yes	Unclear
Buster, 2002[174]	Yes	Not applicable	Yes	Unclear
Choo, 2004[195]	Unclear	Yes	Yes	No
Chugh, 2008[48]	Yes	Yes	Unclear	Unclear
Connaughton, 1977[105]	Unclear	Unclear	Yes	No
Cornish, 2010[49]	Yes	Unclear	Yes	Unclear

Appendix H. Quality ratings of observational studies

Author, year, title	Did the article report attrition? OR Did the article report the number of subjects who met inclusion criteria and were evaluated?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to follow-up or overall high loss to follow-up? OR High numbers of cases or controls who met inclusion criteria who were not analyzed?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality
Anchersen, 2009[57]	No	Yes	Unclear	Yes	Fair
Anyaegbunam, 1997[111]	No	No	Unclear	Yes	Poor
Appel, 1976[88]	No	No	NR	No	Poor
Appel, 1982[89]	No	No	NR	Yes	Poor
Athanasos, 2008[68]	No	No	Unclear	Yes	Poor
Bakstad, 2009[133]	Yes	No	No	Yes	Fair
Berghella, 2003[193]	Yes	No	Yes	Yes	Fair
Blake, 1973[210]	No	No	Unclear	Yes	Poor
Brown, 1998[112]	No	No	Unclear	Yes	Poor
Brown, 2005[100]	Yes	No	Yes	Yes	Fair
Burns, 2010[126]	No	Yes	Unclear	Yes	Fair
Buster, 2002[174]	Unclear	Yes	Unclear	Yes	Fair
Choo, 2004[195]	Yes	Yes	No	Yes	Fair
Chugh, 2008[48]	Yes	No	Yes	Yes	Fair
Connaughton, 1977[105]	No	No	Unclear	No	Poor
Cornish, 2010[49]	Unclear	Yes	Unclear	Yes	Fair

Appendix H. Quality ratings of observational studies

Author, year, title	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random (or matched) sample?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to treatment or exposures?
Cousins, 2011[176]	Yes	Not applicable	Yes	Unclear
Cruciani, 2005[70]	Yes	Not applicable	Yes	Unclear
Cushman, 1973[101]	Unclear	Yes	Yes	Unclear
Darke, 2000[90]	No	No	No	NR
Davis, 1973[106]	Unclear	No	Yes	No
Dinges, 1980[115]	Unclear	Unclear	Yes	No
Doverty, 2001[99]	Yes	Yes	Unclear	Unclear
Dryden, 2009[134]	Yes	Not applicable	Yes	No
Ehret, 2006[59]	Yes	Yes	Yes	Unclear
English, 1988[102]	No	NR	No	NR
Fajemirokun-Odudeyi, 2006[108]	Yes	Yes	Unclear	Unclear
Fanoe et al, 2007[69]	Yes	Not applicable	Yes	Yes
Fareed, 2010[71] other publications: Fareed 2013[118]	Unclear	Not applicable	Yes	Unclear
Fonesca et al, 2009[72]	Unclear	Not applicable	Yes	Unclear
Gearing, 1974[50]	No	No	No	NR

Appendix H. Quality ratings of observational studies

Author, year, title	Did the article report attrition? OR Did the article report the number of subjects who met inclusion criteria and were evaluated?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to follow-up or overall high loss to follow-up? OR High numbers of cases or controls who met inclusion criteria who were not analyzed?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality
Cousins, 2011[176]	Not applicable	Yes	Not applicable	Yes	Fair
Cruciani, 2005[70]	Yes	Yes	No	Yes	Fair
Cushman, 1973[101]	No	No	Unclear	Yes	Fair
Darke, 2000[90]	No	Yes	NR	Yes	Poor
Davis, 1973[106]	No	No	Unclear	Unclear	Poor
Dinges, 1980[115]	No	No	Unclear	Yes	Poor
Doverty, 2001[99]	No	No	No	Yes	Fair
Dryden, 2009[134]	Yes	Yes	No	Yes	Good
Ehret, 2006[59]	Yes	Yes	Not reported	Yes	Fair
English, 1988[102]	No	No	Not reported	Yes	Poor
Fajemirokun-Odudeyi, 2006[108]	Yes	Yes	No	Unclear	Poor
Fanoe et al, 2007[69]	Yes	Yes	Yes	Yes	Fair
Fareed, 2010[71] other publications: Fareed 2013[118]	No	Yes	Unclear	Yes	Poor
Fonesca et al, 2009[72]	No	Yes	Unclear	Yes	Fair
Gearing, 1974[50]	Yes	No	No	Yes	Poor

Appendix H. Quality ratings of observational studies

Author, year, title	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random (or matched) sample?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to treatment or exposures?
Giacomuzzi, 2003[159]	Yes	Yes	Yes	No
Gordon, 1970[98]	No	Unclear	Unclear	No
Green, 1979[212]	Yes	Not applicable	Yes	No
Grevert, 1977[165]	Unclear	Yes	Unclear	No
Gritz, 1975[87]	Unclear	Yes	Unclear	No
Gruber, 2006[94]	Unclear	Not applicable	Yes	No
Hallinan, 2008[167] other publication Hallinan 2007[168]	Yes	Yes	Yes	Unclear
Hanon, 2010[153]	Yes	Not applicable	Unclear	Unclear
Harper, 1977[117]	Yes	Yes	Yes	No
Hartung, 2007[144]	Yes	No	Yes	Unclear
Jones, 2008[198]	Yes	No	Yes	No
Kakko, 2008[127]	Yes	Yes	Yes	No
Kandall, 1977[104] other publications Kandall, 1976[109]; Kandall, 1975[213]	Yes	Unclear	Yes	No
Kandall, 1993[118]	Yes	Unclear	Yes	No

Appendix H. Quality ratings of observational studies

Author, year, title	Did the article report attrition? OR Did the article report the number of subjects who met inclusion criteria and were evaluated?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to follow-up or overall high loss to follow-up? OR High numbers of cases or controls who met inclusion criteria who were not analyzed?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality
Giacomuzzi, 2003[159]	Yes	No	No	No	Fair
Gordon, 1970[98]	No	No	Unclear	Yes	Poor
Green, 1979[212]	No	No	Unclear	Yes	Poor
Grevert, 1977[165]	Yes	No	No	Yes	Poor
Gritz, 1975[87]	No	No	Unclear	Yes	Poor
Gruber, 2006[94]	No	Yes	Unclear	Yes	Fair
Hallinan, 2008[167] other publication Hallinan 2007[168]	Yes	No	No	Yes	Fair
Hanon, 2010[153]	Yes	No	No	Yes	Fair
Harper, 1977[117]	Yes	No	Yes	Yes	Fair
Hartung, 2007[144]	Unclear	Yes	Unclear	Yes	Fair
Jones, 2008[198]	Yes	Yes	No	Yes	Good
Kakko, 2008[127]	No	No	Unclear	Yes	Fair
Kandall, 1977[104] other publications Kandall, 1976[109]; Kandall, 1975[213]	No	No	Unclear	Yes	Poor
Kandall, 1993[118]	No	No	Unclear	Yes	Poor

Appendix H. Quality ratings of observational studies

Author, year, title	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random (or matched) sample?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to treatment or exposures?
Kornick, 2003[154]	Yes	Yes	Yes	Yes
Krantz, 2005[54]	Yes	Not applicable	Yes	Unclear
Krantz, 2008[63] see also Martell, 2005[53]	Yes	Not applicable	Yes	Unclear
Krebs, 2011[145]	Yes	No	Yes	Unclear
LaCroix, 2011[171]	Yes	Yes	Yes	Unclear
Langrod, 1981[206]	Unclear	Unclear	Yes	Unclear
Lejeune, 2006[135]	Yes	Yes	Yes	Unclear
Lenn, 1976[85]	No	NR	No	Yes
Lifschitz, 1985[103]	Unclear	No	Yes	No
Lim, 2009[194]	Yes	Yes	Yes	No
Lipski et al, 1973[56]	Unclear	Unclear	Unclear	Unclear
Longwell, 1979[205]	Unclear	Not applicable	Unclear	Unclear
Malpas, 1995[196]	Yes	Unclear	Yes	No
Maremmani et al, 2005[74]	Unclear	Not applicable	Unclear	Not applicable
Martell et al, 2005[53]	Yes	Not applicable	Yes	Yes
McCowan 2009[173]	yes	Not applicable	Yes	Unclear

Appendix H. Quality ratings of observational studies

Author, year, title	Did the article report attrition? OR Did the article report the number of subjects who met inclusion criteria and were evaluated?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to follow-up or overall high loss to follow-up? OR High numbers of cases or controls who met inclusion criteria who were not analyzed?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality
Kornick, 2003[154]	Yes	Yes	No	Yes	Good
Krantz, 2005[54]	Yes	Yes	Yes	Yes	Fair
Krantz, 2008[63] see also Martell, 2005[53]	No	No	Unclear	Yes	Fair
Krebs, 2011[145]	Unclear	Yes	Unclear	Yes	Fair
LaCroix, 2011[171]	Yes	Yes	No	Yes	Good
Langrod, 1981[206]	No	No	Unclear	Unclear	Poor
Lejeune, 2006[135]	No	Yes	Unclear	Yes	Fair
Lenn, 1976[85]	No	No	Unclear	No	Poor
Lifschitz, 1985[103]	Yes	No	No	Yes	Fair
Lim, 2009[194]	Yes	No	No	Yes	Fair
Lipski et al, 1973[56]	No	No	Unclear	No	Poor
Longwell, 1979[205]	No	No	Unclear	Yes	Poor
Malpas, 1995[196]	No	No	Unclear	Yes	Poor
Maremmani et al, 2005[74]	No	No	Unclear	Yes	Poor
Martell et al, 2005[53]	Yes	Yes	Yes	Yes	Fair
McCowan 2009[173]	No	Yes	Unclear	Yes	Fair

Appendix H. Quality ratings of observational studies

Author, year, title	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random (or matched) sample?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to treatment or exposures?
Mintzer, 2002[95]	Unclear	Yes	Yes	No
Mintzer, 2005[86]	No	Yes	Yes	No
Moskowitz, 1985[96]	No	Unclear	Unclear	No
Newman, 1975[128]	Yes	Unclear	Unclear	No
Parikh, 2011[77]	Yes	Unclear	Unclear	Yes
Parsons, 2010[197]	Yes	Yes	Yes	Unclear
Peles et al, 2007[55]	Unclear	Not applicable	Yes	Yes
Peles, 2010[224]	Yes	No	Yes	Unclear
Prosser, 2006[93]	No	No	Unclear	No
Quick, 2009[119]	Unclear	No	Yes	No
Rajegowda, 1972[129]	Unclear	Unclear	Yes	No
Ramirez-Cacho, 2006[120]	Yes	Yes	Yes	No
Rapeli, 2007[92]	No	No	No	NR
Rapeli, 2009[166]	No	No	No	NR
Reddy, 2004[66]	Unclear	Not applicable	Unclear	Unclear
Reddy, 2010[67]	Yes	Not applicable	Yes	Unclear

Appendix H. Quality ratings of observational studies

Author, year, title	Did the article report attrition? OR Did the article report the number of subjects who met inclusion criteria and were evaluated?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to follow-up or overall high loss to follow-up? OR High numbers of cases or controls who met inclusion criteria who were not analyzed?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality
Mintzer, 2002[95]	No	Yes	No	Yes	Fair
Mintzer, 2005[86]	No	No	Unclear	Yes	Fair
Moskowitz, 1985[96]	No	No	Unclear	Yes	Poor
Newman, 1975[128]	No	No	Unclear	No	Poor
Parikh, 2011[77]	Yes	Yes	No	Yes	Fair
Parsons, 2010[197]	Yes	No	No	Yes	Fair
Peles et al, 2007[55]	No	Yes	Unclear	Yes	Fair
Peles, 2010[224]	No	No	Unclear	Yes	Good
Prosser, 2006[93]	No	Yes	Unclear	Yes	Poor
Quick, 2009[119]	No	No	Unclear	Yes	Poor
Rajegowda, 1972[129]	No	No	Unclear	Yes	Poor
Ramirez-Cacho, 2006[120]	Yes	No	No	Yes	Fair
Rapeli, 2007[92]	No	No	NR	No	Poor
Rapeli, 2009[166]	Yes	No	Yes	No	Poor
Reddy, 2004[66]	No	No	Unclear	No	Poor
Reddy, 2010[67]	Yes	No	Yes	Yes	Poor

Appendix H. Quality ratings of observational studies

Author, year, title	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random (or matched) sample?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to treatment or exposures?
Rosen, 1975[130]	Yes	Not applicable	Yes	No
Rosen, 1985[121]	Unclear	No	Yes	No
Rotheram-Fuller, 2004[192]	No	Yes	Yes	No
Sharkey, 2010[191]	Yes	Not applicable	Yes	Unclear
Sharpe, 2004[216]	Yes	Unclear	Yes	Unclear
Shaw, 1994[136]	Yes	Yes	Yes	No
Soyka, 2010[208]	Unclear	Yes	Yes	No
Specka, 2000[91]	No	NR	No	NR
Stimmel, 1976[107]	Yes	No	Yes	No
Strain, 1991[207]	Yes	Unclear	Yes	No
Strauss, 1976[215]	Unclear	Not applicable	Yes	Yes
Teichtahl, 2005[83]	No	No	No	NR
van Ameijden, 1999[51]	Unclear	Not applicable	Yes	Unclear
Verdejo, 2005[97]	Unclear	Yes	Yes	No
Wagner-Servais, 2003[58]	Yes	Not applicable	Yes	No
Wang, 2005[81]	NR	No	No	NR

Appendix H. Quality ratings of observational studies

Author, year, title	Did the article report attrition? OR Did the article report the number of subjects who met inclusion criteria and were evaluated?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to follow-up or overall high loss to follow-up? OR High numbers of cases or controls who met inclusion criteria who were not analyzed?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality
Rosen, 1975[130]	No	No	Unclear	No	Poor
Rosen, 1985[121]	No	No	Unclear	Yes	Poor
Rotheram-Fuller, 2004[192]	Yes	Yes	No	Yes	Fair
Sharkey, 2010[191]	Yes	Yes	No	Yes	Fair
Sharpe, 2004[216]	No	No	Unclear	Yes	Fair
Shaw, 1994[136]	No	No	Unclear	Yes	Poor
Soyka, 2010[208]	Yes	Yes	No	Yes	Fair
Specka, 2000[91]	No	Yes	No	Not clear	Poor
Stimmel, 1976[107]	No	No	Unclear	No	Poor
Strain, 1991[207]	Yes	No	No	Yes	Fair
Strauss, 1976[215]	No	No	Unclear	No	Poor
Teichtahl, 2005[83]	No	Yes	NR	Yes	Fair
van Ameijden, 1999[51]	No	Yes	Unclear	Yes	Fair
Verdejo, 2005[97]	No	Yes	Unclear	Yes	Fair
Wagner-Servais, 2003[58]	Not applicable	No	Not applicable	Yes	Fair
Wang, 2005[81]	Yes	No	No	No	Poor

Appendix H. Quality ratings of observational studies

Author, year, title	Did the study attempt to enroll all (or a random sample of) patients meeting inclusion criteria, or a random (or matched) sample?	Were the groups comparable at baseline on key prognostic factors (e.g., by restriction or matching)?	Did the study use accurate methods for ascertaining exposures and potential confounders?	Were outcome assessors and/or data analysts blinded to treatment or exposures?
Wang, 2008[82]	NR	No	No	NR
Webster, 2008[160]	No	NR	No	NR
Wouldes, 2004[124]	Unclear	No	Yes	No
Wouldes, 2010[125]	Yes	Unclear	Yes	No
Zelson, 1973[131]	No	Unclear	No	No

Appendix H. Quality ratings of observational studies

Author, year, title	Did the article report attrition? OR Did the article report the number of subjects who met inclusion criteria and were evaluated?	Did the study perform appropriate statistical analyses on potential confounders?	Is there important differential loss to follow-up or overall high loss to follow-up? OR High numbers of cases or controls who met inclusion criteria who were not analyzed?	Were outcomes pre-specified and defined, and ascertained using accurate methods?	Quality
Wang, 2008[82]	No	No	No	Not clear	Poor
Webster, 2008[160]	Yes	No	No	Yes	Poor
Wouldes, 2004[124]	No	No	Unclear	No	Poor
Wouldes, 2010[125]	No	Yes	Unclear	Yes	Fair
Zelson, 1973[131]	No	No	No	Yes	Poor

Appendix I. Data abstraction of systematic reviews

Author, year	Purpose	Databases searched, date of last search	Number of studies	Types of studies included/limitations of primary studies	Methods for rating methodological quality of primary studies
Cleary, 2010[211]	To examine the impact of maternal methadone dose on the incidence of NAS in neonates of opioid-dependent pregnant women.	MEDLINE (1966-August 2009), Cochrane (2009, Issue 1), EMBASE (1974-January 2009) and PsychINFO (1967-Janary 2009)	67 studies 29 included in meta-analysis	2 randomized trial, 37 prospective and 28 retrospective cohorts - Limitations: most studies did not adjust for potential confounders, diagnosis of NAS could have been biased by the knowledge of the maternal methadone dose and drug use, some studies did not define NAS clearly, and only 3 reported blinded assessment of NAS	Modified AHRQ checklist: study populations, exposures, and outcomes clearly defined; confounding was assessed; outcomes measured appropriately; and conclusions supported by results
Mattick, 2009[2]	Evaluate the effects of methadone maintenance treatment compared with non-opioid therapy for opioid dependence	CCRCT; EMBASE; PubMed; CINAHL; Current Contents; PsychLit; CORK; Alcohol and Drug Council of Australia, Australia Drug Foundation, Center for Education and Infromation on Drugs and Alcohol, Australian Bibliographic Network and Library of Congress databases; NIDA monographs; College on Problems of Drug Dependence proceedings; reference lists through December 2008	11 studies (4 reported mortality outcomes)	RCTs	Bias assessment based on method of randomization (blinding was usually not possible among included studies)

Appendix I. Data abstraction of systematic reviews

Author, year	Methods for synthesizing results of primary studies	Number of patients (treatment and control)	Interventions	Results	Quality rating
Cleary, 2010[211]	Data pooled using random effects model and reported as RR for dichotomous outcome of diagnosed/ medically treated NAS	Total=5139 Breakdown by treatment and control not reported	Methadone Comparisons not reported - Mean dose of studies that showed a relationship (19 studies): 39.4 mg, SD 25.2 - Mean dose of studies that did not show a relationship (18 studies): 64.6 mg, SD 30.1, p=0.06	- Dose of <=20 mg vs. >20 mg (10 studies, n=558): RR 0.52 (95% CI 0.33 to 0.81), 48% risk difference (0.56 vs. 0.27) - Dose of <=40 mg vs. >40 mg (9 studies, n=773): RR 0.69 (95% CI 0.51 to 0.94), 31% risk difference (0.73 vs. 0.43) - No other differences between dosages	Good
Mattick, 2009[2]	Results pooled; meta-analysis conducted when possible	Among studies reporting mortality - methadone n=287 controls n=289	Among studies reporting mortality - Oral methadone, doses 60 and 97 mg (2 studies), variable (1 study) or not reported (1 study)	Mortality, methadone use vs non-use (4 studies): RR 0.48 (CI 0.10 to 2.39; p=0.37)	Good

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Anchersen, 2009[57]	To evaluate prevalence of QTc prolongation and to investigate the incidence of death attributable to methadone-induced QTc prolongation.	Cross-sectional	Outpatient opioid maintenance treatment (OMT) distribution centers Norway	OMT patients willing to participate (all subjects were recruited)	976 approached 200 enrolled (173 methadone; 27 buprenorphine)	1/200
Anyaegbunam, 1997[111]	To investigate parameters of fetal well-being in the prenatal period as well as conventional neonatal outcomes in pregnant women on methadone.	Case-control	Municipal hospital United States	Not reported	48 enrolled 24 cases (methadone) 24 controls (no methadone)	Not reported
Appel, 1976[88] and Appel, 1982[89]	To assess attention in patients who had been receiving blocking doses of methadone (80-120 mg) daily for about a year.	Cross-sectional	Subjects from hospitals and drug treatment programs United States	Methadone patients with a minimum addiction history of 2 years Exclusion criteria was individuals receiving prescribed psychotropic drug who were likely to have a neurological problem based on self reports of head or brain injury or of frequent overdoses	96 enrolled (24 in each group) Four groups of 24 subjects	Subjects with inappropriate positives on urinalysis not included in results

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Anchersen, 2009[57]	Total cohort Mean age 41 years 31% female Methadone cohort Mean age 42 years 31% female Buprenorphine cohort Mean age 37 years 33% female	- Oral methadone, mean dose 111 mg (SD 35) - Sublingual buprenorphine 19 mg (SD 5)	Methadone population: QTc interval >500ms: 5% (8/173) Buprenorphine population: QTc interval >500ms: 0% (0/27)	Norwegian Center for Addiction Research	Fair
Anyaegbunam, 1997[111]	Mean maternal age (years) Cases: 30.5 Controls: 30.0 % nulliparity Cases: 12.5 Controls: 12.5	- Methadone, mean dose 60 mg (range 20-70 mg)	Cases vs. controls - Mean birthweight (g): 2985 vs. 3010 - Meconium: 12.5% vs. 16.7% - Apgar <7 at 1min: 16.7% vs. 12.5% - Apgar <7 at 5min: 8.3% vs. 4.2%	Not reported	Poor
Appel, 1976[88] and Appel, 1982[89]	Men, aged 25-40 years	- Methadone, range 70-120 mg (mean not reported) - Non-use	- No significant differences between working methadone patients and drug free controls, but means of each of those groups were significantly higher than that of the non-working methadone patients ($p<0.05$) - No indications that attentional function of methadone patients adversely affected by high doses of methadone in maintenance schedule	Not reported	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Athanasos, 2008[68]	To evaluate the effects of methadone and buprenorphine on QTc duration and prevalence of U-waves.	Cross-sectional	Setting not described Australia	Methadone or buprenorphine dependent; a healthy control group was also included Exclusion criteria was pregnant or lactating, consumption of medication that delayed cardiac depolarization or affected methadone and buprenorphine metabolism, infection with HIV, ALT or AST values >3 times normal, history of structural heart disease, hypertension, supraventricular rhythms, AF, signs of intoxication (any substance) based on the judgment of 2 clinicians	54 enrolled (healthy control group data omitted)	Single ECG reading (no follow-up)
Bakstad, 2009[133]	To describe the characteristics of a national cohort of women in opioid maintenance treatment (OMT) programs who gave birth during a 2-year period to describe birth outcomes for infants exposed to methadone and buprenorphine, to investigate the association between maternal OMT dose in pregnancy and the prevalence and duration of NAS treatment.	Pro-spective cohort	OMT program Norway	Pregnant women enrolled in OMT programs in Norway with delivery between 2005-2007	41 enrolled 38 analyzed	2 dropped due to miscarriage 1 dropped for personal reasons

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Athanasos, 2008[68]	Mean age 35 years 37% female Race not reported	- Methadone, mean dose 69 mg (SD 29) - Buprenorphine, mean dose 11 mg (SD 5)	- Mean QTc duration, methadone vs. buprenorphine: 407 ms vs. 407 ms; p=0.27 - Prolonged (>430 in men) QTc interval: methadone 6% (2/35) vs. buprenorphine 0% (0/19); all subjects with prolonged QTc interval were men - Presence of U-waves: methadone 31% (11/35) vs. buprenorphine 0% (0/19)	Not reported	Poor
Bakstad, 2009[133]	Mean maternal age 32 years Time in treatment 3 years	- Methadone, mean dose at delivery: 90 mg (range: 7 to 260 mg) - Buprenorphine, mean dose at delivery: 13 mg (range: 3 to 24 mg)	Methadone vs. buprenorphine - Mean gestational age (weeks): 39.3 vs. 39.2 - Mean birth weight (g): 3150 vs. 3130 - Mean birth length (cm): 47.8 vs. 48.5 - Mean head circumference (cm): 33.9 vs. 34.3 - % male: 65.4% vs. 25% - Preterm birth (<37 weeks): 3.8% vs. 8.3% - Cesarean section: 30.8% vs. 33.3% - Treatment for NAS: 57.7% vs. 66.7% - NAS duration (days): 42.8 vs. 37	Not reported	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Ballesteros, 2003[177]	To examine deaths due to methadone in North Carolina between 1997 and 2001 and ascertain the manner by which methadone had been obtained.	Case series	Medical examiner data United States	Accidental death with methadone as primary cause	198 cases (deaths due to methadone)	N/A
Barrett, 1996[178]	Determine if the number of deaths due to methadone was different from such deaths in previous years, determine the role of methadone in the cause of death, and determine whether the deaths were associated with enrollment in a MMTP.	Case series	Chart review United States	Inclusion: Medical examiner cases where drug screen was performed and there was evidence of methadone	91 cases total, 27 cases in 1991	N/A

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Ballesteros, 2003[177]	Mean age 39 years 36% female 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): - 73/97 (75%) prescribed by a physician - 24/97 (25%) obtained illicitly In opiate treatment program in North Carolina at time of death (available for 198 cases): - 8/198 (4%) identified as in treatment - 190/198 (96%) not identified as in treatment	Not reported	Not Rated
Barrett, 1996[178]	Median age 35 years Female 33% White 85%	- Methadone, mean dose not reported	In 1991, methadone was a primary cause of death in 3 decedents (11%) and a contributing cause in 9 decedents (33%) - 18 (20%) of decedents were enrolled in MMT at time of death - 13 (14%) had a history of MMT, but were not current - Trauma was the leading cause of death (43%, n=14) in decedents who were enrolled in MMT >7 days - Polydrug toxicity was the predominant cause of death in MMT decedents on MMT <7 days (75%, n=3) - Cause of death was poly-drug in 37% - Methadone toxicity alone 11% - One other drug was found in 85% of methadone-detected cases (diazepam was the most commonly detected medication, 42% of cases)	Not reported	Not Rated

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Bell, 2009[150]	To compare overdose mortality associated with methadone and buprenorphine treatment for opioid dependence.	Case series	Chart review Australia	Inclusion: ICD-10 codes (T40.0-40.4, X42; opioid overdose or multiple drug toxicity) as cause of death in medical examiner cases with concurrent methadone and buprenorphine were present Exclusion: cases where source of drug was known to be other than for opioid treatment	63 methadone, 10 buprenorphine	3 methadone cases
Berghella, 2003[193]	To examine the relationship of maternal methadone dosage and the severity of neonatal abstinence in a large, heroin-addicted, methadone-maintained pregnant population in which methadone dosage was based on therapeutically effective methadone maintenance, with doses that ranged from 20-200mg/day.	Prevalence	Family Center Methadone Program of Thomas Jefferson University	Maternal and neonatal records of heroin-addicted pregnancies from 9/1996-12/1999	100 enrolled	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Bell, 2009[150]	Mean age 39 years 76% male Race not reported	- Methadone (mean dose not reported) - Buprenorphine (mean dose not reported)	Methadone vs. buprenorphine - Death: 60/67 (90%) vs. 7/67 (10%) - Overdose death: 43/60 (72%) vs. 2/7 (29%); p<0.05	NSW Mental Health and Drug and Alcohol Research Grants Program	Not Rated
Berghella, 2003[193]	Mean maternal age (years) - Mean M<80: 29.4 - Mean M>=80: 28.4 - Last M<80:29.1 - Last M>=80: 28.8 Mean parity - Mean M<80: 2.0 - Mean M>=80: 1.9 - Last M<80: 1.8 - Last M>=80: 2.0 Smoking - Mean M<80: 86% - Mean M>=80: 76% - Last M<80: 87% - Last M>=80: 77%	- Methadone, mean dose not reported (results stratified to < 80 mg and >= 80 mg)	Mean methadone use <80 mg/day vs. >=80 mg/day - Mean birth weight (g): 2769 vs. 2663 - Mean highest NAS score: 11.1 vs. 11.5 - NAS treatment: 68% vs. 66% - Length of NAS treatment (days): 13.3 vs. 13.6 Last M<80 vs. Last M>=80 - Mean birth weight (g): 2811 vs. 2655 - Mean highest NAS score: 11.5 vs. 11.2 - NAS treatment: 74% vs. 62% - Length of NAS treatment (days): 14.2 vs. 12.9	Not reported	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Binder, 2008[110]	To evaluate the effect of substitution therapy in heroin addicted pregnant women on the course of pregnancy, perinatal outcomes, and course of neonatal abstinence syndrome.	RCT	Perinatal care unit Czech Republic	Participation in substitution program by 12th week of pregnancy, up to 30 year, dependence on IV applied opiates for 3-5 years, HIV negative, primigravidity or second gravidity with uneventful course of the preceding pregnancy, absence of any other chronic conditions	117 enrolled	None
Blake, 1973[210]	To measure levels of anxiety, depression and hostility along with the steady-state plasma concentration of methadone in former heroin addicts who had been receiving methadone on a maintenance dosage schedule.	Cohort	Not reported United States	All enrolled in Man Alive Research methadone maintenance program	41 enrolled	Not reported
Brown, 1998[112]	To retrospectively evaluate pregnancy outcome in women enrolled in a methadone maintenance program.	Cross-sectional	University hospital Country not reported	Pregnant women followed up at methadone clinic	96 enrolled 32 methadone 32 cocaine 32 controls	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Binder, 2008[110]	Mean age 27 years Mean duration of addiction 4 years Mean parity Heroin: 1.3 Buprenorphine: 1.2 Methadone: 1.3 Mean number of perinatal care unit visits Heroin: 5.8 Buprenorphine: 6.4 Methadone: 7.2	- Methadone, buprenorphine mean doses not reported - No methadone treatment (heroin use)	Methadone vs. buprenorphine - Mean duration of pregnancy (days): 270 vs. 261 (p=NS) - Premature labors (>34 weeks): 26.8% vs. 21.8% (p=NS) - Mean birth weight (g): 3050 vs. 2900 - IUGR: 9.3% vs. 10.5% - Cesarean rate: 6.2% vs. 7.9% (NS) - Apgar scores at 1, 5 and 10 minutes: No differences between groups - Finnegan neonatal abstinence syndrome score: 18 vs. 9.2 (p<0.001) - Delayed onset of withdrawal symptoms (days): 0 vs. 1, p<0.000001	Grant support	Poor
Blake, 1973[210]	Mean age not reported 85% White 15% Black 30 males 11 females 70% Medicaid eligible	Methadone HCl 80 or 90 mg/day Subjects divided into four groups based on duration of time in treatment: - < 2 months, n=10 - 2 to 6 months, n=11 - 6 to 12 months, n=11 - >12 months, n=9	<2 months vs. 2 to 6 months vs. 6 to 12 months vs. >12 months - Anxiety: 8.0 vs. 8.3 vs. 7.3 vs. 7.6 - Depression: 17.3 vs. 15.2 vs. 14.4 vs. 14.2 - Hostility: 8.6 vs. 9.0 vs. 8.0 vs. 9.4 - No statistically significant differences between groups, but there was a consistent trend toward lower anxiety and depression scores with increasing duration of treatment	Grant from Eli Lilly Company, Indianapolis, IN	Poor
Brown, 1998[112]	Mean maternal age Methadone: 31 years Controls: 23 years Mean parity Methadone: 1.8 Controls: 1.4 Black Methadone 28% Controls: 57%	- Methadone, mean dose not reported - Controls (no methadone)	Methadone vs. control - Mean birthweight (g): 2748 vs. 3032 - Mean head circumference (cm): 32.4 vs. 33.5 (p<0.05) - Mean gestational age (weeks): 37.8 vs. 38.0	Not reported	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Brown, 2005[100]	To discern the prevalence and potential causative factors for sexual dysfunction in a sample of methadone-maintained men.	Cross-sectional	MMT clinic in United States	Not reported	92 enrolled	5 withdrew

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Brown, 2005[100]	New vs. continuous patients Mean age: 35 vs. 43 years Caucasian: 81% vs. 80% African-Am: 19% vs. 18% Hispanic: 0% vs. 1%	Methadone (mean dose): - New patients: 38 mg - Continuous patients: 100 mg	New vs. continuous (normal range) - Mean TSH (uIU/ml): 1.3* vs. 2.0* (0.5 to 5.1); p=0.046 -TSH>5.11 uIU/mL: 0% vs. 7.9% vs. 6.5% -Mean testosterone (ng/mL): 5.8 vs. 4.6 (1.3 to 7.6); NS - Testosterone <1.3 ng/mL: 6.3% vs. 9.2%; NS -Mean prolactin (ng/mL): 8.8 vs. 9.8 (0 to 15.0); NS - Prolactin > 15.0 ng/mL: 18.8% vs. 13.2%; NS	Not reported	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Bruera, 2004[137]	To compare the effectiveness and side effects of methadone and morphine as first-line treatment with opioids for cancer pain.	RCT	International palliative care groups Argentina, Yugoslavia, Brazil, Columbia, Chile, Australia, and Spain	Inclusion: Patients with advanced cancer and poor control of pain requiring initiation of strong opioids, normal renal function, life expectancy of at least 4 weeks, and normal cognition Exclusion: Patients already receiving strong opioids, radiation therapy for pain control, or antineoplastic therapy expected to produce an analgesic response	152 approached 103 randomized (49 methadone, 54 morphine)	11 withdrew by day 8 37 withdrew by day 29 - Number of opioid-related dropouts was greater for methadone (11/49, 22%) than morphine (3/54,6%; P=0.02).
Bryant, 2004[179]	To assess the changing contribution of methadone to overdose death over time; compare the relative contribution of methadone and heroin to overdose deaths; and compare characteristics of methadone and heroin decedents.	Case series	Chart review United States	Inclusion: accidental overdose deaths from methadone or heroin Exclusion: not identified Does not specify if methadone is prescribed	1024 methadone cases, 4,627 heroin cases	N/A

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Bruera, 2004[137]	Methadone vs morphine Median Age 59 vs. 60 years 67% vs 61% female Primary Cancer Diagnosis: GI 16% vs. 24%, Breast 18% vs. 18%, -Gym/GU: 24% vs. 31%, Thoracic 10% vs. 13%, Other 30% vs. 14% Similar baseline scores of pain, sedation, nausea, confusion, and constipation	- Oral methadone 7.5 mg and methadone 5mg for breakthrough pain - Morphine: slow-release morphine 15 mg and immediate-release morphine 5 mg for breakthrough pain - Dose adjusted for uncontrolled breakthrough pain or excessive sedation	Methadone vs. morphine - Proportion of patients with 20% or more composite toxicity at 4 weeks: 0.67 (95% CI 0.53 to 0.82) vs. 0.67 (95% CI 0.53 to 0.80), p=0.94 - Proportion of patients with a 20% or more reduction in pain at 4 weeks: 0.49 (95% CI 0.34 to 0.64) vs. 0.56 (95% CI 0.41 to 0.70), p=0.50 - Death: 0/49 (0%) vs. 1/54 (2%)	Brown Foundation, Houston, TX Tobacco Settlement Foundation Swiss Cancer Research	Fair
Bryant, 2004[179]	Mean age: not reported Age 15-24 5%; age 24-34: 29%; age 35-44: 43% age 45-54: 19%; age 55-64: 4% 21% female 34% White 36% Black 30% Hispanic 81% methadone detected	- Methadone - Heroin	Methadone-induced overdose deaths, risk factors: - Men vs. women AOR 0.6 (CI 0.52 to 0.70) - Age 15-24 vs.: age 25-34 years, AOR 1.69 (CI 1.08 to 2.64); age 35-44 years, AOR 3.03 (CI 1.97 to 4.67); age 45-54 years AOR 2.79 (CI 1.78 to 4.35); age 55-64 years, AOR 2.34 (95% CI 1.37 to 4.01) - Cocaine detected vs. no cocaine detected in toxicology AOR 0.56 (CI 0.49 to 0.64) - Heroin vs. no heroin detected in toxicology AOR 0.46 (CI 0.40 to 0.53) - Alcohol vs. no alcohol present in toxicology AOR 0.78 (CI 0.68 to 0.91) - Deaths in 1990 vs.: 1997 AOR 0.58 (CI 0.42 to 0.82); 1998 AOR 0.69 (CI 0.50 to 0.96)	NIDA	Not Rated

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Burns, 2010[126]	To determine the infant death rates of infants born to women on a methadone program and to identify any modifiable risk factors.	Cross-sectional	Database study Australia	Women in New South Wales health databases with live births, women on a methadone program with infants who died or did not die and comparison group of women not on methadone program with infants who died and who did not die	865 in methadone program 674,445 comparison not in methadone program	None
Buster, 2002[174]	To describe the incidence of overdose mortality in relation to time after entering (or re-entering) or leaving methadone maintenance treatment	Retro-spective cohort study	Methadone clinic The Netherlands	Current and former methadone patients (within 1 year of leaving treatment) in Amsterdam, The Netherlands between January 1, 1986 and December 1998	5,200 patients; 68 overdose deaths	N/A
Chan, 2006[180]	To investigate the potential relationship between TCA use and benzodiazepine use in patients who died as a result of accident methadone overdose.	Case series	Chart review United States	Inclusion: decedents with methadone found in their toxicological analyses at death, hospitalized patients Exclusion: lack of complete autopsy or incomplete medical examiner charts	500 total cases, 212 accidental overdose, 251 deaths from other causes	37

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Burns, 2010[126]	Mean maternal age not reported; 93% ages 20 to 39 years Race not reported	- Methadone, mean dose not reported - Controls (no methadone)	Methadone vs. control - Infant deaths: 2.42% (21/865) vs. 0.4% (2698/674445) - Infant mortality rate: 24.3/1,000 live births vs. 4.0/1,000 live births; RR: 6.2 (95% CI: 4.0 to 9.6) - Neonatal death rate: 12.71/1,000 live births vs. 2.8/1,000 live births; RR: 4.5 - Late infant death rate: 11.6/1,000 live births vs. 1.2/1,000 live births; RR: 9.7 - SIDS: 38% (n=8) of deaths vs. 10% (n=278) of deaths	Not reported	Fair
Buster, 2002[174]	Mean age not reported 71% age 30-39 years 77% male Race not reported	Methadone, mean dose not reported	68 overdose deaths (1.3%) Risk of mortality - Men vs. women: ARR 3.3 (95% CI 1.5 to 7.2), and being born in Native of the Netherlands vs. other countries: ARR 5.0 (95% CI 2.3 to11).	Amsterdam Municipal Health Service	Fair
Chan, 2006[180]	Accidental overdose vs. other causes Mean age 44 vs. 48 73% vs. 78% male 41% vs. 23% White Unclear who was prescribed methadone for analgesia vs. for methadone maintenance	- Methadone, mean dose not reported	Overdose due to methadone vs. death from other cause: - Concomitant benzodiazepines OR 1.66 (CI 1.12 to 2.45) - Concomitant tricyclic antidepressant and benzodiazepine OR 4.34 (CI 1.97 to 9.56) Risk Factors associated with a methadone overdose vs. death from another cause: - White race OR 4.27 (CI 2.57 to 7.12) - Amitriptyline use OR 2.12 (CI 1.17 to 3.85) - Cocaine use OR 3.16 (CI 1.35 to 7.40) - Morphine use OR 2.13 (CI 1.05 to 4.33) - Opiate use OR 2.84 (CI 1.38 to 5.85) - Citalopram use OR 0.31 (CI 0.10 to 0.92)	Not reported	Not Rated

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Chasnoff, 1982[114]	To compare the intrauterine growth and neonatal behavior of drug-addicted, and normal control subjects.	Cross-sectional	Hospital-based perinatal addiction project United States	Women enrolled in the Perinatal Addiction Project during the first or early second trimester of pregnancy and completed a course of intensive prenatal care	85 enrolled Other comparison not included in our review (polydrug use, N=19)	Not reported
Chasnoff, 1984[114]	To review all infants delivered to women enrolled in a methadone program since 1976 and compare the intrauterine growth and neonatal neurobehavior of these infants.	Cross-sectional	Hospital-based perinatal addiction project United States	Women enrolled in the Perinatal Addiction Project during the first or early second trimester of pregnancy and completed a course of intensive prenatal care	122 enrolled 51 Methadone 27 Drug-free Other comparisons not included in our review (sedative/stimulant, N=22, Pentazocine and tripelennamine, N=13, or PCP, N=9)	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Chasnoff, 1982[114]	Mean maternal age Methadone 24 years Drug-free 22 years White Methadone 62% Drug-free 26% Black Methadone 31% Drug-free 44% Hispanic Methadone 5% Drug-free 26% Other ethnicity Methadone: 0 Drug-free 4%	- Methadone: mean dose: 15 mg (range 5 to 40 mg) - No methadone (drug-free)	Methadone vs. drug-free - Mean birthweight (g): 2815 vs. 3492 (p<0.05) - Mean length (cm): 47.9 vs. 51.1 (p<0.05) - Mean head circumference (cm): 32.5 vs. 34.6 (p<0.05	Not reported	Poor
Chasnoff, 1984[114]	Mean maternal age Methadone 24 years Drug-free 22 years White Methadone 62% Drug-free 26% Black Methadone 31% Drug-free 44% Hispanic Methadone 5% Drug-free 26% Other ethnicity Methadone: 0 Drug-free 4%	- Methadone: mean dose : 15 mg (range 5 to 40 mg) - No methadone (drug-free)	Methadone vs. drug-free - Mean birthweight (g): 2840 vs. 3479 (p<0.01) - Mean length (cm): 48.2 vs. 51.1 (p<0.01) - Mean head circumference (cm): 32.2 vs. 34.7 (p<0.01)	Not reported	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Choo, 2004[195]	To examine neonatal withdrawal in infants born to mothers maintained on methadone for their opiate addiction and who also smoked cigarettes during their pregnancy.	Pro-spective cohort	Johns Hopkins Center for Addiction and Pregnancy United States	Women diagnosed with current opiate dependence and traded with methadone pharmacotherapy, less than 28 weeks pregnant	29 enrolled - 16 light smokers (<= 10 cigarettes/ day, mean is 8.4) - 13 heavy smokers (>= 20 cigarettes/day, mean is 21)	
Chugh, 2008[48]	To evaluate the association between sudden death and methadone use.	Case-control	Autopsy reports United States	Sudden cardiac death between 2002 and 2006 in the Portland, OR metro area Exclusion criteria was expected death (e.g. terminal cancer), noncardiac causes of sudden death were identified (e.g. trauma, drug overdose, PE)	140 enrolled 128 analyzed (22 cases; 106 controls)	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Choo, 2004[195]	Mean age 30 years African American 88%	- Methadone, mean dose 77.0 mg/day	Light smokers vs. heavy smokers - Mean gestational age (weeks): 36.8 vs. 38.3 (NS) - Mean birth weight (g): 2471.9 vs. 2784.6 (NS) - Mean head circumference (cm): 31.5 vs. 32.3 (NS) - Mean Apgar at 5 min: 8.7 vs. 8.8 (NS) - NAS peak score: 5.6 vs. 9.8 (p=0.014) - Time to NAS peak score (hours): 37.8 vs. 113.8 (p=0.016) - Adjusted analysis for gestational age and opiate-positive neonatal toxicology, time to NAS peak score still significant: p=0.025 - Mean duration of NAS (days): 5.1 vs. 9.5 (p=0.054) Subsample of term infants Light smokers vs. heavy smokers - NAS peak score: 6.8 vs. 11.0 (p=0.039) - Time to NAS peak score (hours): 42.9 vs. 116.9 (p=0.042) - Mean duration of NAS (days): 5.9 vs. 10.6 (NS)	National Institute on Drug Abuse	Fair
Chugh, 2008[48]	Total cohort Mean age 41 years (SD 13) 69% male Methadone cases Mean age 37 years (SD 10) 68% male Indications for methadone use: 55% (12/22) pain control 14% (3/22) opioid withdrawal 18% (4/22) reason for use unknown	- Methadone (route unknown; determined by blood toxicology screen) mean level 0.48 mg/L	Methadone vs. no methadone - Sudden cardiac death (absence of underlying cardiac disease): 17/22 (77%) vs. 42/106 (40%); p=0.003	National Heart, Lung and Blood Institute	

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Cobb, 1998[219]	To determine the effect of fluconazole on methadone disposition and any resulting clinical effects, using a drug-drug interaction trial.	RCT	University hospital United States	Age >18 years; stable methadone dose for a minimum of 30 days; CD4+ cell counts>250/µL within 3 months; negative urine toxicology screens (other than methadone) within 14 days	33 enrolled - 13 Fluconazole - 12 Placebo	1 withdrew

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Cobb, 1998[219]	Mean age 41 years 48% male 52% Hispanic 48% Black	- Oral methadone (mean dose 57 mg) + fluconazole 200 mg or placebo	Methadone + fluconazole vs. methadone + placebo - 24-hour serum methadone level: 254.4 ng/ml (SE 40.6) vs. 327.0 ng/ml (SE 56.6) - Overdose symptoms (lightheadedness, drowsiness, and diaphoresis): 7.7% vs. 16.6% at week 1, 23.1% vs. 0 at week 2	Grant from the Terry Beirn Community Programs for Clinical Research on AIDS, National Institute of Allergy and Infectious Diseases, National Institutes of Health	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Connaughton, 1977[105]	To describe a program of treatment that can be followed and discuss the data that have been generated so far and compare to those of previously published studies.	Pro-spective cohort	Hospital United States	Drug-dependent women giving birth between 1969 to 1974	428 enrolled	Not reported
Cornish, 2002[220]	To set the stage for efficacy studies of DM plus methadone by exploring adverse effects resulting from the addition of DM to a stable dose of methadone in opiate-dependent inpatients	RCT	VA inpatient substance abuse treatment and research unit United States	Men age 21-55 years; good general health; DSM-IV diagnosis of opiate dependence; enrolled in a methadone program in which they were stabilized on a consistent dose of 50-70 mg of daily methadone for minimum of 10 consecutive days	38 screened 16 enrolled	1 withdrew 49 analyzed

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Connaughton, 1977[105]	Not reported	- Methadone treatment, mean dose not reported and prenatal care - Heroin: no treatment addicts - Nonclinic control: nonaddicted patients with no prenatal care - Clinic control: nonaddicted patients with prenatal care	Methadone vs. nonclinic control vs. clinic control - Low birthweight: 18.8% vs. 20.0% vs. 16.0% - Prolonged rupture of membranes (>20 hours): 6.6% vs. 6.6% vs. 2.6% - Breech presentation: 2.2% vs. 4.0% vs. 1.3% - Abruptio placentae: 0.7% vs. 4.0% vs. 0 - Pre-eclampsia: 5.9% vs. 8.0% vs. 9.3% - Postpartum hemorrhage: 1.5% vs. 0 vs. 0 - Cesarean delivery: 5.2% vs. 1.3% vs. 6.3% - Incidence of neonatal morbidity: 69.9% vs. 25.3% vs. 32.0% - Incidence of intrauterine growth retardation: 7.5% vs. 2.7% vs. 9.0% - Mean apgar at 1min: 7.6 vs. 7.9 vs. 8.2 - Mean apgar at 5min: 8.9 vs. 9.2 vs. 9.4	Research Grant DA-00325 from the National Institute on Drug Abuse Research Contract No. 1674 from the Governor's Council on Drug and Alcohol Abuse, Commonwealth of Pennsylvania	Poor
Cornish, 2002[220]	Mean age 44 years 100% male 80% Black	- Oral methadone 50 to 70 mg + dextromethorphan 120 mg/day titrated to 480 mg/day or placebo	Methadone + dextromethorphan vs. methadone + placebo - Number of AEs: 174 vs. 21 Specific AEs: - Constipation: 40% vs.40% - Diarrhea: 20% vs. 20% - Gastric upset/nervous stomach: 10% vs. 40% - Nausea: 10% vs. 20% - Vomiting: 20% vs. 20% - Drowsiness: 50% vs. 20% - Anxiety: 10% vs. 0% - Hyperactive: 10% vs. 0% - Dizziness: 20% vs. 0% - Confusion: 30% vs. 0% - Insomnia: 10% vs. 0% - Difficulty breathing: 10% vs. 0%	NIDA Center Grant #P60-DA-05186	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Cornish, 2010[49]	To investigate the effect of opiate substitution treatment at the beginning and end of treatment and according to duration of treatment.	Retro-spective cohort study	GRPD database United Kingdom	Diagnosis of substance misuse, at least one prescription of methadone or buprenorphine	6,252 (5577 with data)	430/6,252
Cousins, 2011[176]	To identify periods of elevated risk of drug-related mortality during methadone maintenance treatment (MMT) in primary care	Retro-spective cohort study	Outpatient MMT Scotland	Residents of Tayside, Scotland receiving prescribed methadone between January 1993 and February 2004	3,162 enrolled	None
Cruciani, 2005[70]	To evaluate prevalence of QTc prolongation and identify factors associated with prolongation.	Cross-sectional	Inpatient medical, psychiatric and hospice clinics and one outpatient pain practice Untied States	Adults receiving >=20 mg/day for more than 2 weeks Exclusion criteria was congenital long QT syndrome, implanted pacemaker, AF or wide QRS complex on prior ECGs	110 enrolled	6/110 excluded from analysis

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Cornish, 2010[49]	Mean age not reported; 85% 20 to 39 years of age 69% male	Methadone Methadone plus another opioid Buprenoprhine without methadone Mean doses not reported	Mortality, off treatment vs. on treatment: 1.32 vs. 0.69 per 100 person-years, adjusted rate ratio 2.3 (95% CI 1.7 to 3.1)	National Institute of Health Research (NIHR) for the Centre for Research on Drugs and Health Behaviour.	Fair
Cousins, 2011[176]	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 psychiatirc admission: adjusted HR 7.0 (95% CI 3.5 to 14) Prescription for benzodiazepines vs no prescription: adjusted HR (1.4, 95% CI 1.2 to 1.7)	Health Research Board (HRB) of Ireland	Fair
Cruciani, 2005[70]	Mean age 45 years (SD 9) 61% male 82% White 14% Black 5% other 7% history of CHF, CAD or 24% probable or definite high-risk for QTc prolongation 14% possible or probably risk for TdP 29% use of drugs interacting with methadone	- Oral methadone, mean dose 110 mg/day	Methadone use - Median QTc duration: 428 ms - Proportion of patients with QTc prolongation: 33/104 (32%) Univariate analysis - Methadone dose: Effect size 0.03; p=0.89 - Duration of methadone treatment: Effect size 0.02; p=0.94	Baron Edward de Rothschild Chemical Dependency Institute Fund	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Cubero, 2010[221]	To evaluate if patients in use of morphine due to oncologic pain could benefit from its substitution for methadone before even presenting side effects or analgesic control failures.	RCT	Brazil	Age >18 years; oncologic pain; stable morphine dose for at least 1 week	50 enrolled - 25 methadone - 25 methadone + acetaminophen	28 dropped (16 doxepine; 12 placebo) for withdrawn consent, failure to attend, failure to follow protocol and incarceration

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Cubero, 2010[221]	Mean age 59 years 53% male Race not reported	-Oral methadone (mean dose not reported; dose varied according to pre-trail morphine dose) + acetaminophen (dose not reported) or placebo	Methadone + acetaminophen vs. methadone + placebo - Somnolence, proportion of patients with worsening from baseline: 42% vs. 10%, p=0.04 - No differences in incidence of constipation, nausea, or vomiting	Not reported	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Curran, 200[184]	To overcome limitations of previous studies [illicit drug use outside of clinics due to patients being out-patients] in investigating the side effects of methadone on cognitive function, craving and mood in chronic opiate users.	Crossover RCT	In-patient detox unit	Inclusion criteria was opiate dependence of more than 6 mos., aged 18 to 55 years, no current major psychiatric diagnosis other than substance abuse, no current major physical illness, basic literary skills. Exclusion criteria was pregnancy, organic cognitive dysfunction or any past history of severe head injury.	24 agreed to enrolled 20 completed both testing sessions	4/24
Cushman, 1973[101]	To ascertain what effects, if any, methadone maintenance may have on testosterone.	Before-after	St. Luke's Hospital Center, NY	Not reported	19 enrolled	3 withdrew

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Curran, 200[184]	Mean age 33 years 67% male 10 mean years opiate use	- Methadone - Split dose (50% in am and 50% in pm) - Single dose (100% in am and placebo in pm) - Placebo	Single dose vs. split dose vs. placebo (post treatment results): no differences between groups Cognitive outcomes - Prose recall; immediate: 8.8 vs. 8.1 vs. 9.6 - Prose recall; delayed: 5.9 vs. 7.4 vs. 7.6 - Cancellation; single (seconds): 1.4 vs. 1.8 vs. 2.2 - Cancellation; double (seconds): 4.3 vs. 6.6 vs. 4.9 - DSST: 52.0 vs. 49.0 vs. 51.0 - Tapping (number): 187.3 vs. 174.4 vs. 180.5 - Simple reaction time (ms): 307.6 vs. 308.0 vs. 336.0 Craving outcomes - Desire to use: 14.9 vs. 20.6 vs. 15.7 - Intention to use: 15.0 vs. 17.1 vs. 15.4 - Anticipation of positive outcome: 23.3 vs. 25.3 vs. 23.7 - Relief from withdrawal: 32.0 vs. 37.4 vs. 35.0 - Lack of control: 32.5 vs. 28.5 vs. 26.6 - Total craving: 117.6 vs. 128.9 vs. 116.4 - Opiate withdrawal scores: 15.7 vs. 23.3 vs. 22.7 Mood factors - Alertness: 36.5 vs. 43.8 vs. 47.0 - Contentedness: 43.6 vs. 43.9 vs. 42.4 - Calmness-anxiety: 41.0 vs. 42.2 vs. 37.7	Not reported	Fair
Cushman, 1973[101]	Mean age 34 years 100% male 36% Black	- Methadone, mean dose not reported	- No change in mean testosterone levels observed during MMT - Normal LH levels before and during MMT	Not reported	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Darke, 2000[90]	To compare the cognitive performance of MMPs and a matched sample of non-heroin using control subjects; and to ascertain risk factors for poorer cognitive performance.	Cross-sectional	Australia	To be eligible for the study, control subjects had to have used heroin less than three times in their life. Subjects must have been enrolled in current methadone maintenance program >=3 months or be non-heroin users living in SW Sydney. Controls matched with methadone group for age, gender, and education, and subjects in control group had to have not used heroin more than three times in their life.	60 enrolled (30 methadone maintenance; 30 controls)	None
Davis, 1973[106]	To compare the characteristics of infants born to mothers who were receiving differing levels of methadone dosage and to compare them with those of infants born to heroin-addicted women.	Pro-spective cohort	Not reported	Mothers being maintained on methadone and gave birth during a 17 month period (9/1971 to 2/1973)	49 enrolled 31 Low dose (Methadone ≤50 mg) 18 High dose (Methadone ≥60 mg)	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Darke, 2000[90]	Mean age 36years 60 % male Race not reported	-Methadone, mean dose: 77 mg - Non-use	Meth vs. control (mean raw scores) - Digital symbol: 53.5 vs. 70.4 - Symbol search: 24.7 vs. 31.4 - Digit span: 14.4 vs. 17.3 - WCST (CLR): -0.28 vs. 0.28 - COWAT: 31.6 vs. 36.4 - CFT-copy: 29.1 vs. 31.1	Not reported	Poor
Davis, 1973[106]	Mean maternal age Low dose 22 years years High dose 24 years years Prenatal care Low dose: 68% High dose: 56%	- Low-dose methadone <=50 mg, mean dose not reported. - High-dose methadone >=60 mg, mean dose not reported - No methadone treatment (heroin addicts not receiving methadone)	Low-dose methadone vs. high-dose methadone vs. no methadone - Mean gestational age (weeks): 38.61 vs. 39.61 vs. 39.81 - Mean birth weight (pounds): 5.90 vs. 6.45 vs. 6.52 - Mean apgar at 1min: 8.12 vs. 7.08 vs. 7.45 - Mean apgar at 5min: 9.07 vs. 8.59 vs. 8.60 - % infants with mod-severe withdrawal symptoms: 45.2 vs. 61.1 vs. 28.6 (p=0.05)	Not reported	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Dinges, 1980[115]	To clarify the nature of sleep states and perinatal outcomes during narcotic withdrawal in neonates by taking into account the actual fetal drug exposure.	Cross-sectional	Hospital	Pregnant women participating in an urban methadone treatment program and pregnant women not drug-dependent	58 enrolled 28 Methadone -Methadone only: 8; Methadone + heroin: 7; Methadone + opiates and nonopiates: 13 30 Controls -Controls with optimal deliveries: 15; Controls with nonoptimal deliveries: 15	Not reported
Doberczak, 1987[116]	To determine whether drug-related antepartum variables might affect intrauterine growth patterns, as reflected in weight and head circumference at birth.	Cross-sectional	Beth Israel Medical Center United States	- Cases were drug-dependent mothers enrolled in methadone treatment programs in NY - Controls were mothers at the same clinic seen immediately after cases	300 enrolled 150 cases 150 controls	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Dinges, 1980[115]	Not reported	- Methadone, mean dose: 18 mg - No methadone treatment	Optimal controls vs. nonoptimal controls vs. methadone only vs. methadone + heroin vs. methadone + opiates and nonopiates - Male infants: 40% vs. 26.6% vs. 12.5% vs. 71.4% vs. 46.1% - Maternal methadone dose (mg/day): N/A vs. N/A vs. 12.1 vs. 14.3 vs. 21.7 - Mean birthweight (g): 3358 vs. 3309 vs. 2956 vs. 2927 vs. 2783 (p<0.05) - Mean gestational age (weeks): 40.1 vs. 39.1 vs. 39.1 vs. 38.9 vs. 38.2 (p<0.06) - Mean apgar at 1min: 8.7 vs. 8.1 vs. 6.6 vs. 7.7 vs. 8.2 (p<0.04) - Mean apgar at 5min: 9.3 vs. 8.6 vs. 7.4 vs. 8.7 vs. 8.9 (p<0.01)	Not reported	Poor
Doberczak, 1987[116]	Mean maternal age Cases 27 years Controls 25 years White Cases:31% Controls 34% Black Cases 28% Control 19% Hispanic Cases 41% Controls 47%	- Methadone dosage in the 3rd trimester averaged 41.2 mg/day (range: 2.5 to 100 mg/day)	Cases vs. controls - Cesarean delivery: 16% vs. 16% - Mean birthweight (g): 2800 vs. 3248 (p<0.001) - Mean birthweight percentile: 25 vs. 50 to 75 (p<0.001) - Mean gestational age (weeks): 38.9 vs. 39.3 (NS) - Preterm birth: (10% vs. 7% (NS) - Intrauterine growth retardation: 20% vs. 4% (p<0.001) - Male infants: 46% vs. 55% (NS) - Mean head circumference (cm): 32.6 vs. 33.8 (p<0.001) - Head circumference percentile: 25 vs. 50-75 (p<0.001)	Not reported	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Dryden, 2009[134]	To investigate factors associated with the development of neonatal abstinence syndrome and to assess the implications for healthcare resources of infants born to drug-misusing women.	Prevalence	Community-based obstetric clinic United Kingdom	Singleton infants born to drug abusing women prescribed substitute methadone	450 infants 444 live births 437 with complete data	None
Eder 2005[162]	To test the hypothesis that slow-release morphine is at least as effective as methadone in preventing withdrawal, reducing craving and use of heroin with a similar duration of action.	Crossover RCT	Drug Addiction Clinic Austria	Between ages 19-60 years; had to have diagnosis of opioid dependence according to Diagnostic and Statistical Manual of Mental Disorders version IV Exclusion criteria serious psychiatric or somatic illnesses, excluding hepatitis or already receiving maintenance therapy	153 screened 64 entered 55 completed	1 for protocol violation
Ehret, 2006[59]	To evaluate the frequency of QT interval prolongation in methadone maintenance patients hospitalized in a tertiary care setting and to identify associated risk factors.	Cross-sectional	Tertiary care hospital, internal medicine and orthopedic surgery units Switzerland	Active or former injections drugs users hospitalized between January 1999 and December 2003 Exclusion criteria was voluntary methadone intoxication; severe structural heart disease; heart or lung transplantation; cardiorespiratory arrest; MI during hospitalization	527 eligible 247 enrolled	Not reported

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Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Dryden, 2009[134]	Median age 28 years (range 15 to 41) Race not reported Median parity 1 (range 0-7)	- Methadone, mean dose not reported; - 22% 1 to 29 mg - 38% 30 to 59 mg - 30% 60 to 89 mg - 10% >=90	Factors predictive of treatment for neonatal abstinence syndrome - Methadone dose (>90 mg vs. 1-29 mg): 43 vs. 98; OR: 5.09 (95% CI: 2.32 to 11.18); p<0.001 - Breastfeeding >72 hours: 99; OR: 0.52 (95% CI: 0.33 to 0.83); p=0.006	None	Good
Eder 2005[162]	Mean age 29 years 88% male Race not reported	- Methadone, mean dose, 85 mg - Slow-release morphine, mean dose 680 mg	Methadone vs. morphine - No significant differences among groups for psychiatric outcomes but methadone associated with worse scores (higher): - BDI: 15 vs. 7 - STAI: 46 vs. 39	Educational grant from Mundipharma GesmbH, Vienns	Fair
Ehret, 2006[59]	Mean age 37 years (range 18 to 60) 66% male Race not reported HIV 28% HBV 28% HCV 29%	- Methadone group (median): 100 mg/day (range: 4 to 300 mg) - Control group: no methadone use	Methadone use vs. no use (control group) - Median QTc: 0.44 $s^{1/2}$ vs. 0.43 $s^{1/2}$ - QTc >= 50 $s^{1/2}$: 27/167 (16%) vs. 0/80 (0%) - QTc >= 46 $s^{1/2}$: 50/167 (30%) vs. 8/80 (10%) - TdP: 6/167 (4%); incidence not reported in control group - Correlation between daily methadone dose and QTc prolongation r_s=0.20; p<0.01	ASPIC Fund, Geneva University Hospital; Clinic I of Internal Medicine, Geneva University Hospital	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
English, 1988[102]	To examine in more detail the effects of chronic methadone therapy on thyroid function.	Cross-sectional	Not reported	Patients in MMT for heroin withdrawal, undergoing screening for 1 to 12 weeks	145 enrolled	Not reported
Ernst, 2002[181]	To describe methadone-related deaths and determine differences between deaths in methadone maintenance treatment in public and private sectors.	Case series	Chart review Australia	Inclusion: methadone-related deaths with methadone in toxicological analysis between 1993-1999 Exclusion: not reported	84 total deaths, 40 deaths in patients prescribed methadone	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
English, 1988[102]	Mean age not reported, range 17 to 42 years 54% male Race not reported	- Methadone, mean dose not reported (range 15 to 45 mg)	145 MMT patients vs. 50 blood bank donors (euthyroid controls) - T4 nmol/L: 139.8 vs. 97.4 (p<0.001) - Ts nmol/L: 2.7 vs. 2.15 (p<0.001) - T3U %: 89 vs. 103.4 (p<0.001) - FTI: 120.5 vs. 98.5 (p<0.001) - TSH, mill-int units/L: 1.6 vs. 1.7 - FT4 pmol/L: 15.2 vs. 14.6 - FT3 pmol/L: 5.4 vs. 5.2 - TBG, ug/L: 30.4 vs. 21.5 (p<0.001) - Significant increases (p< 0.001) in mean concentrations of T3, T4, FTI, and TBG in the serum and a significant decrease in T3U of MMT patients vs. controls. Most striking finding according to authors was increased concentration of TBG in serum of 54% or 69 of 127 patients.	Not reported	Poor
Ernst, 2002[181]	Mean age 31 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 initial dose 28 mg; mean final dose 69 mg	- 64% died from accidental causes - 74% of accidental cause of death was combination of drug effects - 28% died during methadone induction (<1 week) - 72% died after the first week of MMT	Not reported	Not Rated

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Fajemirokun-Odudeyi, 2006[108]	To assess the pregnancy outcome in women who have used opiates and who were cared for by a multidisciplinary team who use a methadone substitution program as treatment.	Retro-spective cohort	Maternity hospital United Kingdom	Women who used heroin or methadone and who gave birth to babies with possible withdrawal symptoms	52 methadone 47 heroin 9 unknown	None
Fanoe et al, 2007[69]	To compare the effect of methadone and buprenorphine on QT interval and to evaluate arrhythmia symptoms in heroin addicts.	Retro-spective cohort	Multicenter, outpatient drug addiction service centers Denmark	Age >18 years treated with methadone or buprenorphine on a daily basis	870 enrolled 450 analyzed	No loss to follow-up
Fareed, 2010[188] Other publications: Fareed 2013[188]	To improve the electrocardiogram screening process and early detection of patients at high risk for cardiac arrhythmias	Retro-spective cohort	VA methadone maintenance clinic United States	Methadone maintenance, treated at clinic for at least 6 months	n=55	No loss to follow-up
Fischer, 1999[72]	To investigate whether the neonatal abstinence syndrome is different in children born to women maintained on slow-release morphine, compared with those maintained on methadone.	RCT	University Hospital of Psychiatry Austria	Opioid-dependent pregnant females, presented at the drug addiction outpatient clinic, and willing to follow the maintenance program	48 enrolled - 24 Methadone - 24 Morphine	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Fajemirokun-Odudeyi, 2006[108]	Mean age 25 years Race not reported	- Methadone (mean): 32 mg - No methadone (pregnant women abusing IV drugs, not enrolled in methadone substitution program)	Methadone vs. no methadone - Mean gestational age (weeks): 38.2 vs. 38.4 - Mean birth weight (g): 2784 vs. 2803 - Premature delivery (<37 weeks): 16 (30%) vs. 11 (23%) - Neonatal death: 1 (1.9%) vs. 1 (2.1%) - Apgar <7 at 1min: 0 vs. 5 (11%); p=0.01 - Apgar <7 at 5min: 0 vs. 2 (4%) - Maximum NAS score: 4.7 vs. 5.8; p=0.004	Not reported	Poor
Fanoe et al, 2007[69]	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 Self-report syncope: methadone 21% (87/407) vs. buprenorphine 9% (4/43); RR 2.3, 95% CI 0.87 to 5.8 OR, per 50 mg increase of methadone: 1.2 (95% CI 1.1 to 1.4) QTc interval >440 ms: 127/407 (31%) vs. 0/34 (0%) OR, per 1 ms longer QTc duration: 1.11 (95% CI 1.04 to 1.20)	Danish Ministry of the Interior and Health	Fair
Fareed, 2010[188] Other publications: Fareed 2013[188]	Mean age 56 years 93% male 64% non-white	Oral methadone: mean dose 90 mg	Baseline (already on methadone) vs. follow-up ECG Mean QTc interval: 417 vs. 442 ms QTc >450 ms on most recent ECG: 27% (14/52) QTc >500 ms on most recent ECG: 5.8% (3/52)	Not reported	Poor
Fischer, 1999[72]	Mean age 27 years Race not reported	- Methadone: mean dose at delivery was 53.48mg (range was 13 to 20mg) - Morphine: mean dose at delivery was 300.43mg (range 60 to 660mg)	Methadone vs. Morphine: no differences between groups - Vaginal delivery: 75% vs. 75% - Male newborn: 66.7% vs. 62.5% - Mean birth weight (g): 3036.46 vs. 2912.92	Grant from Mayor of Vienna (Fonds zur Forderung der wisenschaftliche r Forschung, No 1334)	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Fischer, 2006[132]	To provide a preliminary indication of the relative safety and efficacy of buprenorphine and methadone in opioid-dependent women.	RCT	Medical university Austria	Opioid-dependent pregnant women, over 18 years, and willing to follow protocol and avoid use of illegal drugs	18 enrolled 14 analyzed 6 in Methadone 8 in Buprenorphine	4 dropped 14 analyzed
Fonseca, 2009[72]	To evaluate prevalence of and risk factors associated with prolonged QTc interval with methadone use.	Cross-sectional	Outpatient methadone maintenance clinic Spain	MMT with stable dose for at least 2 months Exclusion criteria was language barriers, cognitive impairment preventing understanding of study details or unable to provide informed consent	109 enrolled	None reported
Gagajewski, 2003[12]	To conduct a retrospective review of methadone-associated deaths over 10 years to determine the role of methadone in these deaths.	Case series	Chart review United States	Inclusion: intentional and unintentional deaths associated with methadone as found in toxicological analysis during autopsy between 1992-2002, Exclusion: not indicated	96 cases	N/A

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Fischer, 2006[132]	Mean age: (years) - Methadone: 25.6 - Buprenorphine: 26.2 Mean duration of heroin consumption (years) - Methadone: 5.1 - Buprenorphine: 4.9	- Methadone, mean dose not reported (range 40 to 100 mg) - Buprenorphine, mean dose not reported (range 8 to 24 mg)	Methadone vs. buprenorphine - Neonatal abstinence symptoms: 50% vs. 62.5% - Treatment for neonatal abstinence syndrome: 45% vs. 20% (p=0.23) - Mean cumulative dose for treatment for neonatal abstinence syndrome: 2.71 mg vs. 2.00 mg - No difference between groups in birth weights (data not shown)	Schering Plough	Fair
Fonseca, 2009[72]	Mean age 38 years 68% male 92% White Mean resting HR 71 bpm	- Oral methadone (mean): 64 mg	- Proportion of patients with QTc duration >440 ms (in men) or >450 ms (in women): 10/109 (9.2%; 7 men, 3 women) - Older age was the only variable with significantly increased risk of prolonged QTc interval in multivariate analysis (OR 1.15; CI 1.03 to 1.27)	Fondo de Investigaciones Sanitarias; Agencia de Gestio d'Ajuts Universitaris de Recerca	Fair
Gagajewski, 2003[12]	Mean age 45 years 77% male 91% White	- Methadone, mean dose not reported	- Three patients died during the first week of methadone induction - Benzodiazepines were frequently found in the MMT group (67%) - For those who were prescribed methadone for pain, 46.6% died from overdose vs. 53.4% from natural causes	Not reported	Not Rated

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Gearing, 1974[50]	To demonstrate that patients who volunteer for methadone maintenance and remain under treatment show a marked decrease in antisocial behavior as measured by arrests, and, that when proper training facilities can be made available and properly utilized they are employable, and the majority can and do become self-supporting.	Pro-spective cohort	United States	MMT patients who volunteered for treatment after 2 years of addiction	17,550 over 7 years	24% (13,397)
Giacomuzzi, 2003[159]	To compare the effects of methadone vs. buprenorphine.	Pro-spective cohort	Outpatient clinic Austria	Confirmed diagnosis of opioid dependence Exclusion criteria was drug trafficking; aggressive behavior	67 enrolled	24-weeks 14/67 (21%) did not complete treatment
Gordon, 1970[98]	To report reaction times of outpatients under methadone treatment to non-drug users and to subjects recently withdrawn from narcotics use.	Pro-spective cohort	University medical center United States	Male outpatients on average daily does 100 mg methadone; male non-drug using controls; male detoxified heroin-dependent for minimum 14 days; males detoxified at least 4 days; Female outpatients on average daily dose 100 mg methadone; and female non-drug using controls	95 enrolled 27 Methadone 29 Non-drug 20 Detox 14-days 19 Detox 4-days	None

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Gearing, 1974[50]	21% women Mean age 30 years 79% male 34% White 41% Black 24% Hispanic 1% other	- Oral methadone, mean dose not reported (range 80 to 120 mg)	Observed vs. expected death rates (deaths per 1,000 population): death rate among patients in treatment resembles death rate for same age group in general NY population - While in treatment: 7.6 vs. 6.6 - After discharge from treatment: 28.2 vs. 7.6 - Known adults: 82.5 vs. 7.8 - Young adults: 5.6 vs. not reported	Not reported	Poor
Giacomuzzi, 2003[159]	Mean age 28 years 73% male Race not reported	- Methadone, mean dose 25 mg (range 5-160) - Sublingual buprenorphine, mean dose 10 mg (range 2-32 mg)	Methadone vs. buprenorphine: no significant differences at baseline vs. follow-up or between groups - Proportion of patients reporting constipation at baseline: 11/23 (48%) vs. 10/30 (33%) - At follow-up: 2/23 (22%) vs. 6/30 (20%)	Not reported	Fair
Gordon, 1970[98]	Mean age 30 years 81% male Race not reported	- Methadone, 100 mg average dose	Methadone vs. non-use - Simple reaction time (mean, msec): 226 vs. 294 ($p<0.01$) for males, 288 vs. 348 ($p<0.01$) for females - Multiple-discrimination-single-response task (mean, msec): 250 vs. 313 ($p<0.05$) for males, 305 vs. 336 ($p<0.01$) for females	Not reported	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Green, 1979[212]	To help meet an ongoing need for feedback of information about treatment for problems of maternal addiction in order that the special programs and any others that in fact meet such problems can strengthen their ability to handle them.	Case-control	Pregnant Addicts and Addicted Mothers Program at NY Medical College United States	Not reported	105 cases Unclear number of comparison controls	Not reported
Grevert, 1977[165]	To determine if a significant change in memory functioning occurred during methadone or levo-methadyl acetate maintenance	Pro-spective cohort	United States	Methadone subjects in methadone maintenance program, levomethadyl acetate subjects from the Addiction Research Foundation Clinic, and matched controls receiving unemployment from the California Employment Development Department, no other criteria reported	124 enrolled 42 Methadone 42 Levomethadyle acetate 40 Control	37 did not complete final test session

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Green, 1979[212]	Not reported	- Methadone, max of 60 mg/day	Methadone vs. controls - Abnormal fetal heart rate: 12% vs. 12% - Premature rupture of membranes: 52% vs. 55% - Premature delivery: 17% vs. 18% - Hypertension during labor: 3% vs. 3% - Gestational age <37 weeks: 17% vs. 18% - Birth weight <=2500 g: 33% vs. 35% - Withdrawal symptoms present: 73% vs. 64% - Male infant: 61% vs. 64% - Presence of congenital abnormality: 2% vs. 2% - Meconium staining: 9% vs. 9% - Apgar >=7 at 1min: 90% vs. 95% - Apgar >=7 at 5min: 94% vs. 99% - Infant death: 3% vs. 3%	National Institute on Drug Grant No. 7 H81 DA 09141	Poor
Grevert, 1977[165]	Median age 27 years Methadone 77% male Levomethadyl acetate 91% male Control 66% male Methadone 50% White, 27% Black Levomethadyl acetate 71% White, 19% Black Control 62% White Black, 31% Black	- Methadone, mean dose: 52 mg/day (range: 20 to 80) - Levomethadyl acetate, mean dose: 54 mg at 2nd session and 60 mg at final session (range: 15 to 100)	Methadone vs. levomethadyl acetate vs. control - Reported decrease in memory function: 30% vs. 39% vs. 42% (NS) - Mean memory score at final test (estimated from graph, 0 to 25 score): 19 vs. 19 vs. 18 (NS) - Mean number of guesses on memory test (estimated from graph, 0 to 50 score): 43 vs. 39 vs. 35 (NS) - Mean number score on memory test at final test (estimated from graph, 0 to 50): 59 vs. 59 vs. 64 (NS)	Grant DA-1199 from the National Institute of Drug Abuse	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Gritz, 1975[87]	To investigate the effects of methadone on a number of physiological and psychological variables including cognitive functioning	Cross-sectional	VA Hospital United States	Ex- heroin addicts from the methadone maintenance outpatient program and the total abstinence colony at the Brentwood VA Hospital, Los Angeles	25 enrolled 10 Methadone 10 Abstinent 5 Controls	Not reported
Gruber, 2006[94]	To examine several areas of cognitive functioning in a group of opiate-dependent subjects at the beginning of a methadone maintenance program and after two months of treatment	Cross-sectional	Habit Management Institute United States	Subjects enrolled in a methadone maintenance program, ages 18 to 45 years, met DSM–IV criteria for opiate dependence, and were beginning methadone maintenance treatment, subjects were excluded if they were pregnant, had an organic mental disorder, seizure disorder, or central nervous system disease (e.g., multiple sclerosis or cerebral vascular incident), or if they had a history of head trauma or loss of consciousness	17 enrolled	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Gritz, 1975[87]	Median age Methadone 31 years -Abstient 25 years Controls 22 years 100% male	- Methadone, median dose: 65 mg/day (quartile range: 35 to 85 mg) - Methadone, median duration: 5 months - Abstient, median duration: 2 months	Methadone vs. abstinent vs. controls - Mean heart rate (bpm): 66.0 vs. 76.6 vs. 66.2 (p<0.05 for abstient vs. others) - Mean respiration rate (breaths/minute): 13.6 vs. 17.4 vs. 16.4 (p<0.01 for methadone vs. abstient) - Mean BP: 127.4/79.6 vs. 132.6/82.5 vs. 117.4/70.8 (NS) - Peak EEG left alpha (Hz): 8.3 vs. 8.8 vs. 9.6 (p<0.02 for methadone vs. control) - Peak EEG right alpha (Hz): 8.4 vs. 8.5 vs. 9.5 (p<0.03 for methadone vs. control) - Mean Wechler pairs total score (0 to 20 score): 18.4 (SD: 1.6) vs. 15.6 (SD: 2.8) vs. NR (p=0.01) - Mean hidden word test (scale NR): 19.3 (SD: 3.9) vs. 14.7 (SD: 4.8) vs. NR (p=0.03) - Mean story recall (scale NR): 13.2 (SD: 0.8) vs. 10.0 (SD: 2.5) vs. NR (p=0.003) - Mean verbal learning (0 to 8 score): 5.6 (SD: 1.3) vs. 4.2 (1.1) vs. NR (p=002)	National Institutes of Health Special Research Resources grant RR-3	Poor
Gruber, 2006[94]	Mean age 41 years (range: 25.8 to 60.1) 65% male Race not reported	- Methadone, mean dose: 68.0 mg/kg	Baseline vs. 2 month follow-up - Mean Rey Auditory Verbal Learning (words recalled): 40.9 vs. 47.4 (p=0.004) - Mean WAIS-R: 42.9 vs. 49.2 (p=0.03) - Mean Rey-Osterrieth Complex Figure Test (delay condition): 11.0 vs. 14.03 (p=0.03) All other neuropsyhological tests not significant, including: controlled oral word association test, trail making test, stroop test	Not reported	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Harper, 1977[117]	To understand the relationship between the quantity of methadone ingested by the pregnant mother and the quantity of methadone in maternal and neonatal body fluids and subsequent neonatal withdrawal.	Cross-sectional	Hospital Addictive Disease Center United States	>=18 years old, <=29 weeks pregnant, planning to continue the pregnancy to term, free of pre-existing medical diseases and/or obstetric complications during pregnancy, willing to have blood drawn periodically and urine screened periodically	64 screened 41 enrolled 22 Methadone 19 Controls	None
Hall, 2008[175]	To evaluate the risk characteristics of persons dying of unintentional pharmaceutical overdose in West Virginia, the types of drugs involved, and the role of drug abuse in the deaths.	Case series	Chart review United States	Unintentional drug overdoses in West Virginia in 2006, determined by ICD-10 codes X40-X44	295 enrolled	60 excluded
Hallinan 2007[168] and Hallinan 2008[167]	To determine prevalence and investigate etiology of sexual dysfunction in men on methadone or buprenorphine maintenance treatment	Pro-spective cohort	Opioid treatment center Australia	Men treated with MMT or BMT in December 2003; excluded those receiving antiviral treatment for viral hepatitis or HIV, or androgen replacement treatment; or newly in treatment (<8 weeks).	103 enrolled (84 methadone, 19 buprenorphine)	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Harper, 1977[117]	Not reported	- Methadone, mean dose not reported	Methadone vs. controls - Elective repeat cesarean delivery: 4.5% vs. 36.8% (p<0.02) - Male infants: 59% vs. 52.6% (NS) - Mean birthweight (g): 2946 vs. 3423 (p<0.05) - Below 50th birthweight percentile: 77.3% vs. 31.6% (p<0.05) -I infants with withdrawal symptoms: 95.5% vs. 10.5% - Severity of withdrawal positively correlated with total dose of methadone during last 12 weeks of pregnancy (p<0.02) and maternal daily dose at time of delivery (p<0.01)	Not reported	Fair
Hall, 2008[175]	Mean age 39 years 67% male Race not reported	Methadone: mean dose not reported	40% (112/295) methadone associated overdose; 32% (94/295) prescribed methadone	CDC	Not Rated
Hallinan 2007[168] and Hallinan 2008[167]	Mean age 37 years 100% male Race not reported	Methadone: Mean dose 106 mg (SD 70) Buprenorphine: Mean dose 10 mg (SD 7.5)	Methadone vs buprenorphine Erectile dysfunction: 53% (45/84) vs. 21% (4/19); p=0.048 Worse scores on the International Index of Erectile Dysfunction, and lower serum total testosterone in the methadone group	Not reported	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Hanon, 2010[153]	To determine optimal management methadone induced QT prolongation (QTP) and Torsades de Pointes (TdP) in patients treated for opioid dependence.	Case series	Hospital-based MMT program United States	All methadone maintenance patients with QT prolongation and ventricular arrhythmias admitted between July 2007 and April 2009	12 cases	N/A
Hartung, 2007[144]	To compare rates of adverse events among patients newly prescribed a long acting opioid (fentanyl, methadone, ER oxycodone, ER morphine). Outcome was time until first adverse event (ED visit or hospitalization for opioid-related event, all-caused ED visit or hospitalization, death, or diagnoses for opioid related adverse events.	Retro-spective cohort study	United States	≥1 prescription of ≥28 days supply filled between January 1, 2000, and December 31, 2004, and at least 180 days of continuous Medicaid fee for service program eligibility prior to their first (index) fill.	5,684 enrolled	N/A

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Hanon, 2010[153]	Mean age 54 years 75% male Race not reported	Methadone: mean dose 135 mg (range 35 to 250 mg)	Patients (n=3) who transitioned to buprenorphine had resolution of QT prolongation on no further incidence of arrhythmia at follow-up (mean 8 months, range 1-11 months.) Patients who reduced methadone doses (n=5) had reduced QT duration and no further incidence of arrhythmia.	No outside funding	Not Rated
Hartung, 2007[144]	Significant differences across treatment groups - fentanyl vs. methadone vs. oxycodone vs. morphine: Mean age: 71 vs. 51 vs. 57 vs. 59 years Male: 26% vs. 37% vs. 36% vs. 35%	- Methadone - Transdermal fentanyl - Extended release oxycodone - Extended release morphine (mean doses not reported)	Opioid poisoning (overdose): - Methadone vs. morphine (reference group) HR 3.22 (95% CI 0.60 to 17.25) - Fentanyl vs. morphine HR 0.46 (95% CI 0.04 to 5.12) CIs for other outcomes, including mortality, hospitalizations, and overdose symptoms overlapped for methadone, oxycodone and fentanyl vs. morphine	Not reported	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Johnson, 1992[157]	To determine efficacy of buprenorphine vs. morphine.	Controlled trial	Outpatient clinic United States	Age 21-50 years; self-report addiction at least 4 months in duration; > episodes heroin use/day; heroin cost >$50/day; self-rated score of > 4 on withdrawal scale (0 [no withdrawal] to 9 [worst withdrawal ever]); positive opioid urine screening Exclusion criteria was acute or chronic medical condition; pregnancy; psychiatric condition that could compromise ability to participate in study	162 enrolled buprenorphine n=53 low-dose methadone n=55 high-dose methadone n=54	94% of low-dose, 80% of high-dose and 70% of buprenorphine patients did not complete study
Johnson, 2000[141] Other publications: Wedam, 2007[61]	Compare the effects of levomethadyl acetate, buprenorphine, and methadone.	RCT	Outpatient clinic United States	Age 21-55 years; opioid dependent; evidence of recent opioid use Exclusion criteria was serious medical or psychiatric illness requiring long-term treatment; pregnancy	220 enrolled -buprenorphine n=55 -low-dose methadone n=55 -high-dose methadone n=55 -(levomethadyl n=55)	14 had no severity assessment; 14 dropped out prior to final assessment and were excluded
Jones, 2005[170]	To compare the neonatal abstinence syndrome (NAS) in neonates of methadone and buprenorphine maintained pregnant opioid-dependent women	RCT	Inpatient substance abuse unit	21-40 years of age, with estimated gestational age of 6-30 weeks, DSM-IV diagnosis of current opioid dependence, requesting maintenance pharmacology, recent self-reported opioid use, opiate-positive urine specimen at intake	30 enrolled	10 non-completers

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Johnson, 1992[157]	Mean age: 33 years 30% female 58% White 40% Black 2% other	- Oral methadone, 20 mg; 60 mg - Buprenorphine, 8 mg	- Adverse effects (including loss of appetite, difficulty urinating, anxiety, sedation, constipation) varied among groups throughout the study period but no consistent differences between groups were observed	National Institute on Drug Abuse	Poor
Johnson, 2000[141] Other publications: Wedam, 2007[61]	Mean age 36 years 68% male 62% non-white	- Low-dose oral methadone, mean dose 20 mg - High-dose oral methadone, mean dose 90 mg (range 60-100) - Buprenorphine, mean dose 27 mg (range 16-32 mg)	Low-dose methadone vs. high-dose methadone vs. buprenorphine - Withdrawals due to AEs: 0/55 (0%) vs. 1/55 (2%) vs. 1/55 (2%)	National Institute on Drug Abuse	Fair
Jones, 2005[170]	Mean maternal age 30 years 67% Black 28% White 5% other	Methadone: mean dose not reported (range 20-100 mg) Buprenorphine: mean dose not reported (range 4-24 mg)	Methadone vs buprenorphine Treatment for neonatal abstinence syndrome: 45% (5/11) vs. 22% (2/9); p=0.23 NICU admission: 18% (2/11) vs. 10% (1/9); p=0.453 Total length of stay for neonate (days): 8.1 vs. 6.8 (p=0.021) Mean birth weight (g): 3001.8 vs. 3530.4, (p=0.091) Preterm birth: 9% (1/11) vs. 0%; p=NR Cesarean section: 9% (1/11) vs.11% (1/9); p=NR	National Institute on Drug Abuse; General Clinical Research Centers Program of the National Center of Research Resources, National Institutes of Health.	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Jones, 2008[198]	To compare methadone maintenance with a methadone tapering program during pregnancy on maternal and neonatal outcomes.	Retro-spective cohort	Johns Hopkins Center for Addiction and Pregnancy United States	Methadone maintained during pregnancy or receiving a prescription for either 3 or 7 days of methadone-assisted withdrawal, with no other concurrently medication-assisted tapers from alcohol or benzodiazepines, and have available maternal medical chart and complete delivery outcome information	123 enrolled in methadone taper program 75 3-day taper 48 7-day taper 52 enrolled in methadone maintenance program	None, retrospective review

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Jones, 2008[198]	Mean age 26 years 14% White 86% Black or other race	- Methadone 3-day taper withdrawal (20 mg, 10 mg, and 10 mg given days 1 to 3, respectively) - Methadone 7-day taper withdrawal (40 mg, 30 mg, 25 mg, 20 mg, 15 mg, 10 mg, and 5 mg given days 1 to 7, respectively) - Methadone maintenance (30 mg, 40 mg, 50 mg, and 60 mg given days 1 to 4, respectively, then additional increases in 5 mg or 10 mg doses were provided based upon clinical indications) Mothers could be in a taper program +/- a methadone maintenance program	3-day taper vs. 3-day taper + maintenance vs. 7-day taper vs. 7-day taper + maintenance vs. maintenance only - Maternal urine toxicology positive for illicit drugs at delivery: 53% vs. 33.3% vs. 57.1% vs. 15% vs. 23.1% (p<0.001) - Mean head circumference (cm): 32.9 vs. 33.2 vs. 31.2 vs. 32.8 vs. 31.8 (p=0.6) - NICU admission: 30% vs. 13% vs. 36% vs. 0 vs. 46% (p=0.003) - Mean birth weight (g): 2834.0 vs. 3054.1 vs. 2823.9 vs. 2987.0 vs. 2819.1 (NS) - Mean length circumference (cm): 47.7 vs. 50.5 vs. 47.5 vs. 49.5 vs. 48.1 (NS) - Premature: 26.9% vs. 12.5% vs. 35.7% vs. 10% vs. 19.2% (NS) - Low birth weight: 21% vs. 13% vs. 11% vs. 5% vs. 25% (NS) - Mean Apgar at 5 min: 8.7 vs. 8.6 vs. 8.5 vs. 8.3 vs. 8.6 (NS) - Mean total length of stay for infant (days): 9.6 vs. 7.9 vs. 8.9 vs. 6.0 vs. 12.8 (NS) - Treated for NAS: 25% vs. 29% vs. 36% vs. 15% vs. 27% (NS)	Grant R01 DA-14979 from the National Institute on Drug Abuse	Good

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Jones, 2010[169]	To compare buprenorphine with methadone for the treatment of opioid dependent pregnant patients.	RCT	6 US sites, 1 site in Austria, and 1 site in Canada	Opioid-dependent women aged 18-41 years with a singleton pregnancy between 6-30 weeks of gestation, with no medical or other conditions contraindicating participation, not subject to pending legal action, no disorders related to use of benzodiazepines or alcohol	1,074 screened 175 randomized - 86 buprenorphine - 89 methadone	28 in buprenorphine and 16 in methadone dropped
Jones, 2010[169] continued	see above	see above	see above	see above	see above	see above

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Jones, 2010[169]	Methadone vs. buprenorphine (those that completed the study) Mean maternal age 28 vs. 25years (p=0.014) White: 85% vs. 91% Black: 14% vs. 3% Other race: 1% vs. 5%	- Methadone, mean dose not reported, starting dose not reported, dose adjustments of 50 to 10 mg as needed, range 20 to 140 mg - Buprenorphine, mean dose not reported, starting dose not reported, dose adjustments of 2 mg as needed, range 2 to 32 mg	Methadone vs. buprenorphine - Treated for NAS: 41/73 (57%) vs. 27/58 (47%); OR 0.7 (02 to 1.8, NS) - NAS peak score (0 to 42 scale): 12.8 vs. 11.0 (p=0.04) - Morphine for NAS (mean, mg): 10.4 vs. 1.1 (p<0.0091) - Infant's hospital stay (mean, days): 17.5 vs. 10.0 (p<0.0091) - Head circumference (mean, cm): 33.0 vs. 33.8 (p=0.03) - Duration of NAS treatment (mean, days): 9.9 vs. 4.1 (p<0.003125) - Birth weight (mean, g): 2878.5 vs. 3093.7 (p=0.005) - Birth length (mean, cm): 47.8 vs. 49.8 (p=0.005) - Gestational age (mean, weeks): 37.9 vs. 39.1 (p=0.007) - Preterm birth (<37 weeks): 14/73 (19%) vs. 4/58 (7%), NS	NIDA grant R01 DA015778, R01 DA015764, R01 DA018417, R01 DA015738, R01 DA015741, R01 DA018410, M01 RR109, R01 DA017513, M01 RR00095, R01 DA15832	Fair
Jones, 2010[169] continued	see above	see above	continued - - Apgar score (mean): 8.0 vs. 8.1 at 1 minute (NS) and 9.0 vs. 9.0 at 5 minutes (NS) - Cesarean delivery: 27/73 (37%) vs. 17/58 (29%); OR 0.6 (0.2 to 2.0, NS) - Maternal weight gain (mean, kg): 8.6 vs. 8.3 (NS) - Abnormal fetal presentation during delivery: 10/73 (14%) vs. 3/58 (5%), NS - Serious abnormal fetal health: 3% vs. 0 (NS) - Non-serious abnormal fetal health: 7% vs. 5% (NS) - Obstetrical symptoms: 7% vs. 2% (NS) - Cardiovascular symptoms: 33% vs. 16% (p=0.01) - Non-serious AEs: 93% vs. 77% (p=0.003)	see above	see above

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Justo, 2006[78]	To define the prevalence of risk factors for methadone-associated TdP during episodes of TdP.	Case series	Not reported	Not reported	40 enrolled	None, retrospective
Kakko, 2008[127]	To compare the effects of fetal buprenorphine and methadone exposure during maintenance treatment of pregnant heroin dependent subjects.	Pro-spective cohort	Sweden	Pregnant opiate-dependent women enrolled in either the methadone maintenance treatment (MMT) program from 1982-2006 or the buprenorphine maintenance treatment (BMT) program from 2001-2006	65 enrolled	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Justo, 2006[78]	Mean age 40 years (range: 20 to 60 years) Gender, race not reported	- Methadone mean dose: 231 mg/day (range: 60 to 1000 mg/day)	- High-dose methadone was the most common risk factor for TdP: accounting for 39/40 (97.5%)) - Second common risk factor being concomitant use of agents that increase serum methadone levels inhibiting liver metabolism or those that trigger TdP: accounting for 22/40 (55%)	Not reported	Not rated
Kakko, 2008[127]	Mean maternal age 31 years Race not reported	Methadone: mean dose 71 mg (range 20-120 mg) Buprenorphine: mean dose 15.4 mg (range 2-32mg)	Methadone vs buprenorphine Apgar score <4 at 1min: 3 vs. 0 (p=NS) Apgar score <4 at 5min: 0 vs. 0 Preterm infants (30-32 weeks): 0% (0/36) vs. 2.1% (1/47); p=NS Preterm infants (35-37 weeks): 9% (3/36) vs. 6.% (1/47) Cesarean section: 36% (13/36) vs. 21% (10/47); p=0.14 Mean gestational age (weeks): 38.6 vs. 39.5 (p=0.06) Mean birth weight (g): 2941 vs. 3250 (p=0.008) Mean birth height (cm): 47.6 vs. 48.4 (p=0.12) Mean head circumference (cm): 33.8 vs. 34.0 (NS) Birth weight <2500g: 25% vs. 6.4% (p=0.03) Birth weight <-2SD: 30.6% vs. 12.8% (p=NS) Neonatal abstinence syndrome: 78% (28/36) vs. 40% (19/47); p=0.0008 Treated for neonatal abstinence syndrome: 53% (19/36) vs. 15% (7/47); p=0.0004 Length of hospital stay: 20 vs. 9.4 days (p=0.0009)	Stockholm County	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Kandall, 1976[109]	To determine birthweight patterns of infants born to populations of women with varying drug histories.	Cross-sectional	Bronx Municipal Hospital Center United States	Mothers with histories of past or present narcotic United Statesge and controls	365 enrolled 106 Methadone 40 Specific Methadone program during entire pregnancy 59 Methadone + Heroin 33 Ex-addicts 66 Control Others 61 Heroin	Not reported
Kandall, 1977[104]	To study the comparative impact of different patterns of drug use on perinatal events.	Retro-spective cohort	Bronx Municipal Hospital Center United States	Infants born to mothers with past illicit drug histories	316 enrolled reported 89 Methadone 61 Methadone + Heroin 34 Ex-addicts 66 Controls Not included in review here 66 Heroin only	Not reported
Kandall, 1993[118]	To assess relationship between maternal drug use during pregnancy and SIDS in offspring.	Retro-spective cohort	United States	All live-born infants between 1/1979 to 2/1989	1,209,534 cases (3,416 Methadone, 1,193,079 controls)	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Kandall, 1976[109]	Not reported	- Mean dose not reported for any group	Methadone vs. methadone + heroin vs. methadone specific program vs. ex-addicts vs. controls - Mean birthweight (g): 2961 vs. 2535 vs. 3032 vs. 2615 vs. 3176 (p<0.01 for methadone vs. control) - Mean gestational age (weeks): 39.4 vs. 38.3 vs. 39.6 vs. 38.6 vs. 40.0 (p<0.05 for methadone vs. control) Within Methadone group Mean birthweight (g) - White: 3147; black: 2510; Puerto Rican: 2638 (p<0.001 white vs. others)	Not reported	Poor
Kandall, 1977[104]	Mean maternal age Methadone 23 years Methadone + heroin 23 years Ex-addict 20 years Control 22 years Methadone 20% White, 48% Black Methadone + heroin 7% White, 71% Black Ex-addict 6% White, 65% Black Control 14% White, 39% Black	- Drug dependent women (methadone or methadone + heroin) vs. ex-addicts vs. no treatment (heroin only)	Methadone vs. methadone + heroin vs. ex-addicts vs. controls - Mean birth weight (g): 2936 vs. 2535 vs. 2615 vs. 3170 (p<0.001 for methadone + heroin and ex-addicts vs. controls; p<0.01 for methadone vs. controls) - Mean gestational age (weeks): 39.2 vs. 38.3 vs. 38.6 vs. 40.0 (p<0.001 for methadone + heroin vs. controls; p<0.01 for methadone and ex-addicts vs. controls) - Preterm infants (<37 weeks): 18% vs. 26.2% vs. 27.3% vs. 7.6% (NS) - Early infant deaths: 3.4% vs. 4.8% vs. not reported vs. not reported - Infants with withdrawal symptoms: 83% vs. 81% vs. not reported vs. not reported - Infants treatment for withdrawal: 77% vs. 68% vs. not reported vs. not reported (p<0.001)	Not reported	Poor
Kandall, 1993[118]	Not reported	- Methadone, mean dose not reported	Methadone vs. no drugs - SIDS deaths: 0.96% vs. 0.139% (p<0.01)	Not reported	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Kornick, 2003[154]	To determine if methadone administration causes QTc prolongation.	Cross sectional	Specialty pain service (patients with cancer pain) United States	Patients receiving IV methadone or morphine at Memorial Sloan Kettering Cancer Center between July 1999 and March 2001	82 enrolled	Not reported
Krantz, 2002[19] and Krantz, 2003[190]	To evaluate a series of methadone-treated patients experiencing torsades de pointes.	Case series	MMTUnited States and Out-patient pain clinic Canada	Inclusion: use of methadone, QTc > 500msec in the setting of polymorphic ventricular tachycardia Exclusion: congenital long QT syndrome, inadequate documentation of arrhythmia	9 MMT cases, 8 chronic pain clinic cases	3 withdrew

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Kornick, 2003[154]	Not reported	IV methadone, mean dose 17.8 mg/hr (range 0.1 to 97.1; SE 20.6) IV morphine, mean dose 9.8 mg (range 0.7 to 35; SE 7.9)	Methadone vs. no methadone Mean difference QTc interval, 41.7 ms (SE 7.8 ms); p<0.0001 Morphine vs. no morphine Mean difference QTc interval: 9.0 ms (SE 6.1 ms); p=0.15	National Cancer Institute; General Clinical Research Center; NIH	Good
Krantz, 2002[19] and Krantz, 2003[190]	Mean age 49 years 41% male Race not reported	- Mean daily dose of methadone was 397 to 283 mg	- Mean QTc interval was 615+77msec - Mean heart rate 64+15 beats/min - 41% Hypokalemia - 53% receiving potential QT prolonging drugs - 18% had structural heart disease - 82% had one potential risk factor for arrhythmia - 35% patients had their methadone dose increased within 1 month prior to QT prolongation - 41% patients had been receiving methadone therapy for 3 or fewer months	Not reported	Not rated

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Krantz, 2005[54]	To evaluate the effects of methadone on QT-interval dispersion.	Pro-spective cohort	Outpatient methadone maintenance treatment facility United States	Age >18 years with opioid addiction duration of at least 1 year and at least 1 previous attempt at detoxification Exclusion criteria was self-reported methadone use within 2 weeks of study entry; transfer from another methadone program	233 enrolled 149 analyzed	6 months 31/149 lacked followup data
Krebs, 2011[145]	To use national VA data to evaluate all-cause mortality among patients who received methadone compared with those who received long-acting morphine for chronic non-end-of-life pain.	Retro-spective cohort	VA hospital United States	New prescription for >=28 days' supply of oral methadone or long-acting morphine from a VA outpatient pharmacy between January 1, 2000 and December 31, 2007; >=30-day window free of long-acting opioid prescriptions before the index prescription date to avoid contamination	98,068 enrolled	10424 not analyzed at end (3347 died, 94721 censored, but no reason given)

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Krantz, 2005[54]	Mean age 43 years (SD 8) 37% female 44% Hep C 18% HIV 12% history of CVD Use of other medications: - antidepressants: 10% - calcium channel blockers: 3% - phenytoin: 3% - diuretics: 4% - beta blockers: 3% Baseline ECG findings: - bradycardia 14% - prolonged QTc 16% - LVH or RVH: 12% - U waves: 1% - nonspecific ST-T wave changes: 4% - prior MI: 1%	- Oral methadone, 30 mg qd starting dose titrated according to self-reported heroin use, opioid withdrawal symptoms and urine toxicology - Mean dose, 6 months: 80 mg qd (SD 32, range 20 to 120 mg)	Methadone use, baseline vs. 6 months (n=118) - Mean HR: 65 bpm vs. 69 bpm, mean change 4 bpm; p=0.0005 - Mean QRS duration: 92.8 ms vs. 92.6 ms, mean difference -0.2; p=0.76 - Mean QTc interval: 415.3 ms vs. 429.4 ms, mean difference 14.1 ms; p<0.0001 - Proportion of patients with increased QTc (>430 ms for men; >450 ms for women): 14% (17/118) vs. 31% (37/118); p=0.2 - Mean QT dispersion: 32.9 ms vs. 42.4 ms, mean change 9.5 ms; p<0.0001 - No incidence of TdP, arrhythmia or sudden death	VA Connecticut Healthcare Cooperative Studies Program Career Development Award; Robert Wood Johnson Generalist Physician Faculty Scholar Award; NIH	Fair
Krebs, 2011[145]	Mean age Methadone 56 years Morphine 59 years Methadone 93% male Morphine 95% male Methdaone 52% non-white Morphine 49% non-white	Oral methadone or oral morphine (mean doses not reported)	Methadone vs. morphine, all-cause mortality Propensity-adjusted mortality HR 0.56 (95% CI 0.51 to 0.62) Quintile 1 HR 0.36 (95% CI 0.26 to 0.49) Quintile 2 HR 0.46 (95% CI 0.37 to 0.56) Quintile 3 HR 0.50 (95% CI 0.41 to 0.61) Quintile 4 HR 0.66 (95% CI 0.54 to 0.81) Quintile 5 HR 0.92 (95% CI 0.74 to 1.61)	VA Substance Use Disorder QUERI	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
LaCroix, 2011[171]	To investigate the effects of exposure to buprenorphine compared with methadone during pregnancy,	Pro-spective cohort	Methadone maintenance therapy centers, general practitioner networks involved in addiction, maternity hospitals, and centers for drug information France	Pregnant women enrolled in OMT programs in France between January 1, 1998 and December 31, 2006	135 enrolled	No loss to follow-up
Langrod, 1981[206]	To examine physical complaints commonly attributed to methadone.	Cross-sectional	Hospital MMT program United States	Long-term and new patients to MMT program	102 enrolled	No loss to follow-up
Lenn, 1976[85]	To explore the neurologic status of patients chronically maintained on methadone by assessing the presence of clinically demonstrable neurologic dysfunction among long-term methadone-maintained and abstinence subjects.	Cross-sectional	Illinois Drug Abuse Program United States	Not reported	50 enrolled	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
LaCroix, 2011[171]	Mean age 31 years Race not reported Duration of opioid dependence not reported	Methadone: mean dose 38-42 mg/day Buprenorphine: mean dose 5.1-6.3 mg/day	Methadone vs buprenorphine Live births 89% (40/45) vs 94% (85/90); p=0.42 Stillbirth 4% (2/45) vs 1% (1/90); p=0.5 Premature birth 10% (4/40) vs 19% (16/85); p=0.5 Malformations present at birth 3% (1/40) vs 5% (4/85); p=0.9 Neonatal abstinence syndrome 63% (25/45) vs 41% (35/90); p=0.03 Neonatal abstinence syndrome requiring treatment with hydrochloride 80% vs 57%; p=0.03	French Programme Hospitalier de Recherche Clinique.	Good
Langrod, 1981[206]	52 long term MMT patients 49 new patients	- Methadone median dose: 100 mg (range: 65 to 130 mg)	Physical complaints minor with NS in these areas: sweating, constipation, sleepiness, sexual problems, and aches in bones and joints.	Not reported	Poor
Lenn, 1976[85]	Mean age 34 years 52% male Race not reported	- Methadone, 0 to 50 mg - Non-use	Methadone use vs. non-use - History of headache: 8/25 (32%) vs. 4/25 (16%) - History of tremor: 8/25 (32%) vs. 2/25 (8%) - History of vertigo: 1/25 (4%) vs. 0/25 (0%) - Tremor on exam: 3/25 (12%) vs. 0/25 (0%) - Abnormal exam: 0/25 (0%) vs. 2/25 (8%) - Abnormal EEG: 2/25 (8%) vs. 3/25 (12%)	Public Health Service Grant No. PHS H81 DA 01094	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
LeJeune, 2006[135]	To compare the perinatal morbidity and NAS of infants born to women taking methadone or high-dose buprenorphine during their pregnancies.	Pro-spective cohort	Perinatal centers of public hospitals France	Live births to mothers receiving drug substitution that had started before or during this pregnancy within the framework of a maintenance protocol, continued until delivery	259 women (260 infants) enrolled	Not reported
Lifschitz, 1985[103]	To determine whether narcotic dependency during pregnancy is associated with impaired head growth when possible confounding variables are controlled, and whether intellectual potential is related to head size in children of narcotic-dependent women.	Pro-spective cohort	Public hospital United States	Mothers enrolled in a methadone treatment program for at least 2 consecutive months during pregnancy	67 enrolled 26 Methadone 41 Drug-free	Not reported
Lim, 2009[194]	To investigate further the relationship between maternal methadone dosage and the occurrence and duration of NAS.	Cross-sectional	University medical center United States	Pregnant women receiving methadone therapy	66 enrolled - 23 Low dose - 25 Moderate dose - 17 High dose	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
LeJeune, 2006[135]	Mean age 29 years Race not reported Mean length of opiate dependence 8 years	Methadone: mean dose at delivery 57 mg (range: 10 to 180 mg) Buprenorphine: mean dose at delivery 5.4 mg (range: 0.4 to 24 mg)	Methadone vs buprenorphine Mean birth weight (g) 2790 vs. 2843 (p=NS) Mean gestational age (weeks) 38.4 vs. 38.8 (p=NS) IUGR 38% (38/101) vs. 31% (49/159); p=NS Premature birth (<37 weeks) 16% (16/101) vs. 10% (16/159); p=NS Mean Apgar at 5 min 9.9 vs. 9.8; p=NS Breastfed 23% (23/101) vs. 21% (33/159); p=NS Lipsitz score >9 for NAS (scale 0 to 20) 30% (30/101) vs. 32% (51/159); p=NS	Observatoire Francais des Drogues et des Toxicomanies	Fair
Lifschitz, 1985[103]	White Methadone: 58% Drug-free: 42% Hispanic Methadone: 31% Drug-free: 34% Black Methadone: 11% Drug-free: 24%	- Methadone, mean dose not reported	Methadone vs. Drug-free -Mean gestational age (weeks): 38.8 vs. 39.2 -Small for gestational age: 12% vs. 2% -Mean birth weight (g): 2910 vs. 3289 (p<0.01) -Mean birth length (cm): 47.8 vs. 49.7 (p<0.01) -Mean head circumference (cm): 33.2 vs. 34.5 (p<0.01) - % male: 54 vs. 554 - 88% of methadone group required treatment for NAS	National Institute of Drug Abuse, grant DA-00915; the Foundations of the American Legion, Maternity and Infant Care Project R 2620; and the USDA/ARS Children's Nutrition Research	Fair
Lim, 2009[194]	Mean maternal age: 26 years 97% White 3% Black	Methadone, mean dose: 97 mg (range: 15 to 240) - Low dose: methadone <70 mg - Moderate dose: methadone 71 to 139 mg - High dose: methadone >140 mg	Low dose (<= 70 mg) vs. moderate dose (71 to 139 mg) vs. high dose (>=140 mg) - Cesarean section: 48% vs. 35% vs. 35% - Treatment for NAS: 65% vs. 73% vs. 100% (p=0.01 for low dose vs. moderate dose and p=0.005 for low dose vs. high dose) - Length of stay (days): 19.1 vs. 25.6 vs. 27.8 - Breastfed: 17% vs. 23% vs. 41%	Not reported	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Ling, 1996[158]	Compare the effects of buprenorphine and methadone.	RCT	Outpatient clinic United States	Age 18-65 years; competent to give informed consent; in good general health; met DSM-III-R criteria for diagnosis of opioid dependence and methadone maintenance treatment	225 enrolled	Approximately 20-30% of population still in study at 52 weeks
Lipski, 19735[65]	To define the effect of heroin and other drugs of abuse on ECG.	Cross-sectional	Outpatient methadone maintenance treatment program United States	Asymptomatic (not described) MMT patients	75 enrolled (41 methadone patients)	Not reported
Lombardo, 1976[209]	To investigate the effects of moderate (80 mg) vs. low (50 mg) oral dosages of methadone on cognitive functioning,	RCT	Methadone maintenance program United States	Males with 10th grade education or GED	57 enrolled - 30 in 50 mg group - 27 in 80 mg group	19/57 analyzed

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Ling, 1996[158]	Mean age 41 years 80% male 14% White 20% Black 65% Hispanic <1% other	Oral methadone: 30 mg/day or 80 mg/day Buprenorphine: 8 mg/day	No significant differences among non-specific AEs described as equally represented in all groups	National Institute on Drug Abuse	Fair
Lipski, 19735[65]	Mean age 33 years 75% male	- Heroin - Methadone - No intervention	Methadone vs. no intervention - QTc prolongation (not defined) 14/41 (34%) vs. 0/32 (0%)	Not reported	Poor
Lombardo, 1976[209]	Age range 20-55 years	- Stabilized at least 1 month on 50 mg/day methadone HCl, dosage not varied - Stabilized at least 1 month at 80 mg/day, following initial testing, dose lowered 5 mg /day to 50 mg, and when stabilized at 50 mg for 1 month, WAIS scores taken	- In group subtest means for the two administrations of the WAIS in scaled scores, no significant differences were found in drug effect or interaction of drug and scale. - In summary, statistics results failed to reveal consistent differences between 2 methadone groups in cognitive abilities or any tests.	Supported in part by drug abuse research center grant DA-293 from National Institute on Drug Abuse, US Public Health Service	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Longwell, 1979[205]	To gather and report side effects of methadone patients on 38 complaints via a survey.	Cohort	VA Hospital Substance Abuse Program, United States	Patients in MMT at least 9 months	51 enrolled	None

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Longwell, 1979[205]	Median age 26 years 70% male Chicano 49% Caucasian 30% Black 8% Indian 10% Other 3%	- Methadone, mean not reported	- Most complaints present prior to MMT, however, when analyzed individually, a statistically significant number (not reported) of patients reported more severe complaints after 9 months on methadone: some complaints related to withdrawal, and main finding was a need for more research. - Severity of symptoms after 9 months of MMT compared with before: - Severity worse - Drowsiness in daytime: 15 - Nausea: 5 - Vomiting: 2 - Constipation: 13 - Nervousness: 5 - Hallucinations: 1 - Anxiety: 4 - Feeling depressed: 7	Not reported	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Malpas, 1995[196]	To compare methadone dosage at delivery and the severity of neonatal symptoms as assessed by the Neonatal Abstinence Score.	Cross-sectional	New Zealand	Mothers and babies coded for drug abuse or neonatal withdrawal, respectively, from 1/1987 to 12/1991 compared with population seen at Christchurch Health and Development Study (longitudinal birth cohort)	70 Methadone during pregnancy At time of delivery - 30 No dose - 15 Low dose (methadone 1-10 mg/day) - 19 Mod dose (methadone 11 to 20 mg/day) - 6 High dose (methadone >=21 mg/day) - 1265 Controls	None implied, retrospective
Maremmani, 2005[74]	To assess the incidence of abnormal QTc intervals in patients on long-term methadone maintenance.	Case series	Italy Outpatient methadone maintenance clinic	Methadone treatment for at least 6 months, steady methadone dose for at least 4 months, active clinic participation	83 enrolled	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Malpas, 1995[196]	Not reported	-Methadone, mean dose not reported - No methadone	Methadone, low-dose (1 to 10 mg) vs. moderate dose (11 to 20 mg) vs. high-dose (>=21 mg) vs. no methadone - Mean max symptom score: 10.4 vs. 10.7 vs. 12.7 vs. 3.4 (p<0.001 for No dose vs. others) - Mean length of stay (days): 0.6 vs. 16.5 vs. 26.0 vs. 7.9 (p<0.001) - Infants receiving neonatal abstinence syndrome: 20.0% vs. 52.6% vs. 66.7% vs. 3.3 (p<0.001) - Mean duration of treatment (days): 2.4 vs. 7.3 vs. 12.3 vs. 0.9 (p<0.001) - Breastfeeding: no relationship found, data not reported All methadone vs. no methadone - Mean gestational age (weeks): 39 vs. 39.6 (NS) - Mean birth weight (g): 2987 vs. 3356 (p<0.001) - Mean head circumference (cm): 33.6 vs. 34.6 (p<0.001) - Mean birth length (cm): 50.3 vs. 51.0 (NS)	Not reported	Poor
Maremmani, 2005[74]	Mean age 34 years (SD 6) 76% male Race not reported	- Oral methadone, mean dose 87 mg (range 10 to 600; median 70)	- Proportion of patients with pathological QTc duration (>470 ms in men, >480 ms in women): 2% (2/83; both male) - Methadone dose, gender not associated with prolongation	Not reported	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Mattick, 2001[42]	To assess the efficacy of buprenorphine compared with methadone maintenance therapy for opioid dependence in a large sample using flexible dosing and the marketed buprenorphine tablet.	RCT	Methadone clinics Australia	Opioid dependent; age 18 or older; live in commuting distance of clinic; competent to give consent; signed consent	405 enrolled - 205 methadone maintenance treatment - 200 buprenorphine treatment	Loss to follow-up: 189/405 (47 %) did not complete trial
Martell, 2005[53] and Krantz, 2008[63]	To assess the effect of methadone on QTc interval.	Pro-spective cohort (before/after)	Substance abuse clinic United States	Age >18 years with opioid addiction duration of at least 1 year and at least 1 previous attempt at detoxification Exclusion criteria was self-reported methadone use within 2 weeks of study entry; transfer from another methadone program	233 enrolled (baseline values provided for 160 patients)	12 months 11/160 (7%) and 6 month follow-up; 52/160 (33%) at 12 month follow-up

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Mattick, 2001[42]	Mean age 30 years Methadone 69% male Buprenorphine 70% male English-speaking background Methadone: 79% Buprenorphine: 79%	- Flexible dose regime: weeks 1-6, patients dosed daily; from weeks 7-13, buprenorphine group received double the week 6 does on alternate days	- No significant differences between groups for constipation, nauseas, or vomiting	Not reported	Fair
Martell, 2005[53] and Krantz, 2008[63]	Mean age 43 years (SD 8) 67% male 52% Hep C 23% HIV Use of other medications: -antiretrovirals 11% -antidepressants: 11% -calcium antagonists: 5% -phenytoin: 3% -diuretics: 3% -Beta blockers: 3% Baseline ECG findings: -bradycardia 29% -prolonged QTc interval (>450ms in men or >470ms in women): 3% -ST changes: 13% -LVH or RVH: 11% -U waves: 2% -RBBB: 1% -prior MI: 1%	-Oral methadone, 30 mg qd starting dose titrated according to self-reported heroin use, opioid withdrawal symptoms and urine toxicology -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 - Methadone use, baseline (n=160) vs. 12 months (n=108) - Variables predictive of QTc prolongation in multivariate analysis: methadone (p=0.08, not significant)	Public Health Research Grants, Univ. of California at Irvine	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Matts, 1964[161]	Assess the effect of methadone, pethidine and dextromoramide on severe pain.	RCT	Inpatient clinic United States	Patients in severe pain; other criteria not reported Exclusion criteria was not reported	60 enrolled methadone n=20 pethidine n=20 dextromoramide n=20	No withdrawals
Mayet, 2011[75]	To assess the percentage of patients prescribed methadone maintenance treatment on a stable dose fulfilling the MHRA criteria for ECG monitoring	Case series	Outpatient addictions clinic UK	Opioid dependence, receiving stable dose of methadone for ≥4 weeks	155 enrolled (83 with follow-up data)	47% did not receive and ECG

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Matts, 1964[161]	No demographic data reported	- Methadone 5 mg (range 5 to 10 mg) - Pethidine 50 mg (range 50 to 100) - Dextromoramide 5 mg (range 5 to 10 mg)	Methadone vs. pethidine vs. dextromoramide - Incidence of respiratory depression: 2/30 (7%) vs. 2/30 (7%) vs. 0/30 (0%)	Birmingham Regional Hospital Board	Poor
Mayet, 2011[75]	Mean age 40 years 29% female 12% non-white	Oral methadone: mean dose 75 mg	Mean QTc interval: 429 ms Proportion with QTc interval ≥450ms (men) or ≥470ms (women): 18% (15/83) Proportion with QTc interval >500 ms: 0% (0/83)	Maudsley NHS Foundation Trust.	Not rated

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
McCowan, 2009[173]	To assess predictors of mortality in a population of people prescribed methadone for methadone maintenance therapy in primary care.	Retro-spective Cohort study	Out-patient MMT Scotland	Inclusion: registered with a Tayside, Scotland general practitioner; prescribed and dispensed methadone between January 1993-February 2004 Exclusion: not reported	2,378 enrolled	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
McCowan, 2009[173]	Mean age not reported; range 16 to 60 years 55% of population age 20 to 29 67% male	- Oral methadone; mean dose not reported, 85% mean dose <60 mg	Incidence: - All-cause mortality 181/2378 (8%) - Death due to drug dependence 60/2378 (3%) Risk factors (adjusted HR): - Charlson Comorbidity Index 1-2: 1.08 (95% CI 1.02 to 1.14) - Charlson Comorbidity Index > 3: 1.20 (95% CI 1.15 to 1.26) - Overusing methadone: 1.67 (95% CI 1.05 to 2.67) Protective factors: - Duration of methadone treatment (years): 0.95 (95% CI 0.94 to 0.96) - Time since last prescription filled (4-6 months): 0.91 (95% CI 0.84 to 0.99) - Time since last prescription filled (>6 months): 0.70 (95% CI 0.66 to 0.73) - Having urine tested: 0.33 (95% CI 0.22 to 0.49) - Duration of treatment years: 0.93 (95% CI 0.92 to 0.95) - >6 months since prescription: 0.02 (95% CI 0.00 to 0.05), - History of psychiatric admission: 2.41 (95% CI 1.25 to 4.64) - Use of benzodiazepines : 4.35 (95% CI 1.32 to 14.30) - Antipsychotic use: 0.27 (95% CI 0.08 to 0.89) - Antidepressant use: 0.51 (95% CI 0.30 to 0.98)	Chief Scientists Office, NHS Scotland and Eastern project grant 116-05	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Mercadante, 1998[138]	To compare the analgesic efficacy, adverse effects, and opioid consumption of morphine and methadone in patients with advanced cancer followed up at home.	RCT	Italy	Required strong opioids for pain management	40 enrolled - 20 Morphine - 20 Methadone	None
Mercadante, 2008[139]	To compare the analgesic efficacy, adverse effects, the need of increasing opioid doses, and quality of life, in advanced cancer patients who commence morphine, fentanyl and methadone.	RCT	Italy	Pain requiring strong opioids; had received opioids for mild to moderate pain	108 enrolled - 36 Morphine - 36 Fentanyl - 36 Methadone	38 withdrew

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Mercadante, 1998[138]	Mean age 63 years 48% male M/F ratio Primary Cancer (Morphine vs. Methadone) - Lung: 4 vs. 6 - Breast: 3 vs. 3 - Colon: 2 vs. 1 - Esophagus: 0 vs. 1 - Liver: 2 vs. 1 - Larynx: 0 vs. 1 - Leiomioma: 0 vs. 1 - Melanoma: 1 vs. 0 - Ovarian: 1 vs. 2 - Pancreas: 2 vs. 1 - Rectum: 3 vs. 1 - Stomach: 1 vs. 1 - Uterus: 1 vs. 1	- Morphine: sustained-release 10, 30, 60, and 100mg or morphine q8-12h according to need - Methadone: oral liquid preparation of 0.1% methadone administered 2 to 3 times a day according to need	- No differences between groups for scores on nausea, vomiting, sweating, drowsiness, dry mouth, constipation, or confusion	Not reported	Fair
Mercadante, 2008[139]	Mean age: (years) - Morphine: 59 - Fentanyl: 57 - Methadone: 61 M/F ratio - Morphine: 10/12 - Fentanyl: 14/11 - Methadone: 12/11	- Morphine: sustained-release morphine using initial doses of 60 mg/day - Fentanyl: transdermal fentanyl 0.6 mg/day -Methadone: oral methadone 15 mg/day divided in 3 doses	- No differences between groups for scores on nausea, vomiting, drowsiness, constipation, or confusion Within group differences seen for morphine and methadone: Morphine - Nausea-vomiting: 0.2 at baseline vs. 0.6 at week 4 (p value not reported) - Constipation: 0.3 at baseline vs. 0.8 at week 4 (p value not reported) Methadone - Drowsiness: 0.3 at baseline vs. 0.9 at week 4 (p value not reported) - Confusion: 0.0 at baseline vs. 0.4 at week 4 (p value not reported)	Not reported	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Mintzer, 2002[92]	To evaluate performance of MMP on a broad range of psychomotor and cognitive measures relative to controls without drug abuse histories.	Cohort	University Hospital Methadone maintenance programs United States	Enrolled in outpatient methadone maintenance programs free of significant medical problems or Axis I psychiatric disorders; healthy matched controls	39 enrolled 18 MMP subjects 21 controls	Not reported
Mintzer, 2005[86]	To attempt to differentiate the effects of a history of long-term abuse from the effects of methadone maintenance in a previous study (Mintzer 2002) by comparing performance of currently abstinent former opioid abusers retrospectively to 2 groups previously reported.	Cross-sectional	University Hospital Methadone maintenance programs United States	Opioid-dependent methadone maintenance patients; matched controls Compared with currently abstinent former opioid abusers	59 enrolled (18 methadone, 21 matched controls, 20 former users)	Not reported
Moskowitz, 1985[96]	To examine the effects of methadone maintenance treatment on performance of tracking tasks.	Pro-spective cohort	United States	Former heroin addicts enrolled in methadone maintenance programs for at least 6 month and considered stabilized in treatment; healthy controls	24 enrolled Study 1 30 enrolled Study 2	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Mintzer, 2002[92]	Mean age 38 years 44% male	- Methadone, mean dose not reported, - No methadone (healthy controls)	Methadone vs. control - DSST (mean number correct): 20.17 vs. 28.86 (p=0.004) - DSST (mean number attempted): 21.17 vs. 30.57 (p=0.002) - Trail-making A (mean seconds): 77.61 vs. 56.17 (p=0.007) - Trail-making B (mean seconds): 136.09 vs. 94.73 (p=0.014)	Not reported	Fair
Mintzer, 2005[86]	Methadone vs. controls vs. former users Mean age 38 vs. 35 vs. 40 years Black 72% vs. 67% vs. 95%	- Methadone, mean dose not reported	Methadone vs. non-use vs. former abuser - DSST (mean correct): 20.17 vs. 28.86 vs. 24.05 (p<0.005 methadone vs. non-use) - Trail-making A (mean total time, seconds): 77.61 vs. 56.17 vs. 106.52 (p<0.05 methadone vs. others) - Trail-making B (mean total time, seconds): 136.09 vs. 94.73 vs. 131.88 (p<0.05 non-use vs. others) - Two-back task (mean sensitivity): 1.70 vs. 2.20 vs. 2.08 (p<0.05 methadone vs. non-use)	National Institute on Drug Abuse Research Grant DA-05273	Fair
Moskowitz, 1985[96]	Study 1 - n=24 (methadone n=12, non users n=12) - All male Study 2 - n=30 (methadone n=15, former users n=15) - All male	- Methadone, mean dose not reported - No methadone (controls)	- There were no differences between groups in either study on any of the cognitive test	National Institute on Drug Abuse, grant # 5-RO1 DA00978; Health Sciences Computing Facility, UCLA, funded by NIH Special Resources Grant RR-3	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Neale, 2000[182]	Qualitative interviews to elucidate the role of methadone and methadone treatment in non-fatal illicit drug overdose.	Case series	Hospital and ED visits Scotland	Inclusion: non-fatal overdose treated in the hospital or ED and current methadone prescription, use of methadone prior to overdose, or desire for methadone at the time of the interview Exclusion: refUnited Statesl to participate	33 cases	None
Newman, 1975[128]	To present data regarding all 313 babies born live to women enrolled in the New York City methadone maintenance treatment program from November 1970 through June 1973.	Prevalence	United States	Enrolled in New York City methadone maintenance treatment program	313 enrolled 44 Methadone <40 mg 122 Methadone 40-60 mg 72 Methadone 70-90 mg 47 Methadone 100 mg 28 Methadone >100 mg	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Neale, 2000[182]	Mean age 26 years(range 18-36) 64% male 97% White 21 (64%) had current methadone prescription, mean dosage 65mg (range 30-110mg) 6 used methadone prior to overdose had desire for methadone at time of interview	- Methadone, mean dose for 64% of population 65 mg (range 30-110)	- Reported dose of methadone taken prior to overdose was 35-1000mg (median 110mg) - Accidental overdose n=4 - Abuse of someone else's methadone prescription by purchasing it n=3 - Preferring illegal drugs to prescribed methadone n=8	Scottish Office Depart-ment of Health	Not Rated
Newman, 1975[128]	Mean maternal age 25 years (range: 18-42) Primiparas: 38% Prenatal care: 80% Puerto Rican - M<40 mg: 20.5% - M40-60 mg: 31.1% - M70-90 mg: 19.4% - M100 mg: 21.3% - M>100 mg: 21.4% Black - M<40 mg: 52.3% - M40-60 mg: 51.6% - M70-90 mg: 56.9%% - M100 mg: 48.9% - M>100 mg: 17.8% White - M<40 mg: 27.3% - M40-60 mg: 17.2% - M70-90 mg: 23.6% - M100 mg: 29.8% - M>100 mg: 60.7%	- Methadone, mean dose not reported (range <40 to >100 mg; 39% 40-60 mg)	M<40mg vs. M40-60mg vs. M70-90mg vs. M100mg vs. M>100mg - Mean birth weight (g): 2806 vs. 2783 vs. 2649 vs. 2555 vs. 2967 - Infants with withdrawal symptoms: 71% vs. 77% vs. 81% vs. 81% vs. 85% 7 infants died, distribution by dose Not reported	Not reported	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Parikh, 2011[77]	Compare QTc interval in infants born to mothers on methadone maintenance therapy to healthy infants.	Case-control	Inpatient England	Cases: Term infants born to methadone maintained mothers not requiring resuscitation Controls: Healthy infants born to mothers with no medication use during pregnancy or underlying medical conditions	52 enrolled	Cases: 7 days Controls: 2 days Cases compared to normative ECG data beyond day 2 as healthy controls discharged from hospital after 2 days
Parsons, 2010[197]	To determine the efficacy and safety of methadone initiation (in strong opioid-naïve patients) rotation from another strong opioid in treating cancer-related pain in an out-patient palliative care clinic at a comprehensive cancer center.	Pro-spective cohort	Palliative Care Outpatient Clinic United States	Consecutive first time methadone users; previous opioid was stopped at the day of methadone initiation	189 enrolled (89 in each group)	7 had no follow-up visits Data available for 70% of rotation and 68% of initiation patients at time of 2nd followup visit.

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Parikh, 2011[77]	No demographic data reported	- Maternal methadone, 30 to 85 mg/day	Cases vs. controls - Proportion of infants with QTc duration >460 ms 2 days following birth: 4/26 (15%) vs. 0/26 (0%) - QTc prolongation resolved by day 7 - No differences mean HR between groups	Not reported	Fair
Parsons, 2010[197]	Mean age (years) - Initiation: 60 - Rotation: 58 Women - Initiation: 45 - Rotation: 55 African American - Initiation: 11 (12%) - Rotation: 4 (4%) Hispanic - Initiation: 7 (8.5%) - Rotation: 10 (10%) Caucasian - Initiation: 62 (70%) - Rotation: 77 (77%) Other - Initiation: 9 (10%) - Rotation: 9 (9%)	- Patients initiated on methadone at 5 mg twice/day - Opioid rotation: morphine equivalent daily dose - Methadone according to the previous opioid dose: 5:1 when previous morphine equivalent daily dose was 90 mg/day, 8:1 when it was between 91 and 300 mg/day, and 12:1 when it was 301 mg/day	Follow-up visit 1: - 92% of initiation to methadone completed (43% of those that discontinued did so due to appearance/persistence of side effects) - 85% of rotation to methadone completed (80% of those that discontinued did so due to appearance/persistence of side effects) Follow-up visit 2: - 84% of rotation and 96% of initiation patients continued to receive methadone (p=0.03)	National Cancer Institute R01 grants CA 122292-01 and CA124481-01 and National Institute of Nursing Research grant NR010162-01A1	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Paulozzi, 2009[11]	To describe all people dying from unintentional overdoses of methadone or other opioid analgesics in West Virginia in 2006.	Case series	Chart review United States	Death certificate documented unintentional drug poisoning	250 cases	N/A
Pearson, 2005[79]	To review and analyze QT prolongation and TdP reported to the FDA to determine the patient characteristics, dosages of methadone, and outcomes of methadone-treated patients.	Case series	FDA database United States	All methadone-associated adverse events reported to the FDA from 1969 to October 2002	59 enrolled	N/A
Peles, 2007[55]	To determine and evaluate QTc interval in MMT patients.	Cross-sectional	Outpatient methadone maintenance clinic volunteers Isreal	Methadone maintenance for at least 100 days	153 enrolled 138 analyzed	Unclear

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Paulozzi, 2009[11]	Mean age 34 years methadone group (n=87); Mean age: for other opioid analgesic group not reported; methadone group tended to be younger (38% were 18-24 years vs. 10% in the other opioid group; p=0.001) Race not reported	- Methadone; mean dose not reported - Other opioid analgesic (most commonly hydrocodone or oxycodone)	Characteristics of unintentional deaths, methadone vs. other opioid analgesic - Use any non-medical route AOR 0.34 (95% CI 0.16 to 0.70) - Injecting medication AOR 0.21 (95% CI 0.06 to 0.73) - Benzodiazepines AOR 0.71 (95% CI 0.40 to 1.25)	None	Not Rated
Pearson, 2005[79]	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 one risk factor for QTc prolongation or torsades de pointes other than methadone use	US Agency for Healthcare Research and Quality	Not Rated
Peles, 2007[55]	Mean age 41 years 71% male Duration of MMT: 4.4 years Comorbidities: - HIV positive 8% - Hep B positive 7% - Hep C positive 76%	- Oral methadone, mean dose 171 mg	QTc interval: - 450 to 460 ms: 12/138 (9%) - 461 to 500 ms: 7/138 (5%) - >500 ms: 3/138 (2%) - Mortality, mean follow-up 1.2 years: 2/138 (2%)	National Institutes of Health - National Institute on Drug Abuse Research Center grants Ko5-DA00049 and P60-DA05130	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Peles, 2010[224]	To compare patients who were granted take-home privileges with those who were not, to evaluate whether the interval to the first take-home privilege was associated with retention in MMT and with survival, and to evaluate whether the clinic's adherence to guidelines with respect to times of take-home doses has any effect on patient's outcomes.	Retro-spective cohort	Outpatient methadone maintenance clinic volunteers Isreal	Patients admitted to a MMT clinic between June 25, 1993 and June 24, 2008	657 enrolled 435 methadone, ever had take-home privileges 222 never had take-home privileges	None
Pirastu, 2006[164]	To evaluate decision-making using the GT in individuals maintained on methadone compared to individuals maintained on buprenorphine as well as non drug-dependent controls.	RCT	Italy	Opiate-dependent patients attending local drug addiction clinic for at least 12 months, with no central nervous system pathology or axis 1 disorder, no head trauma or dementia, no medication known to affect cognitive functioning, no past or present alcohol or other illicit substance dependencies	69 enrolled 30 methadone-maintained outpatients 18 buprenorphine-maintained outpatients 21 non-opiate dependent controls	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Peles, 2010[224]	Mean age 38 years 74% male Race not reported	MMT patients may be allowed to take-home doses after 3 months compliance on MMT, then each additional dose is available after 1 month of compliance on MMT, to gain a 6th dose MMT patients must be compliant the whole time and involved in a vocational activity, with 13 doses being the max allowed to take home and can be achieved in 2 years. If medical or other reason for why patient can't make it to MMT, they may be allowed to take-home doses before being admitted for 3 months.	Methadone maintenance ever allowed vs. never allowed - Time from MMT to death (mean, years): 13 versus 12, p=0.04 - Among ever allowed, 3 to 6 months after starting treatment - privileges >=3 months vs. < 3 months, mean survival time 13 to 14 years versus 10 years	Adelson Family Foundation	Good
Pirastu, 2006[164]	Mean age (years) Methadone 35 years Buprenorphine 33 years Controls 34 years Male: Methadone 97% Buprenorphine: 94% Controls: 67%	- Methadone, mean dose not reported - Buprenorphine, mean dose not reported - No methadone (healthy controls)	Methadone vs. buprenorphine vs. controls - Gambling task net scores (mean): 2.93 vs. 19.67 vs. 15.33 (p<0.05 methadone vs. buprenorphine) - Wisconsin card sorting task perseverative errors (mean): 28.7 vs. 22.8 vs. 12.6 (p<0.05 methadone vs. controls) - WAIS (mean): 85 vs. 89.3 vs. 104 (p<0.05 controls vs. others) - BVRT correct (mean): 5.67 vs. 6.06 vs. 7.90 (p<0.05 controls vs. others) - BVRT errors (mean): 6.5 vs. 5.22 vs. 2.57 (NS)	Not reported	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Pirnay, 2004[152]	To assess the cause of death in fatalities in which buprenorphine, methadone, or both were analytically detected.	Case series	Toxicology lab of the Paris police department France	Inclusion: deceased individuals with positive toxicology for buprenorphine or methadone in the blood or urine Exclusion: deceased individuals with no toxicological analyses	69 cases 35 methadone 34 buprenorphine	N/A
Prosser, 2006[93]	To test the hypothesis that former heroin users who have detoxified from methadone maintenance therapy and are drug-free have less pronounced cognitive impairment than patients continuing long-term MMT.	Cross-sectional	Short stay and abstinence programs United States	Healthy patients 21 to 55 years, either opiate-dependent currently receiving MMT or opiate-dependent who have received MMT and currently abstinent or controls without a history of opiate-dependence	29 former heroin addicts receiving methadone maintenance treatment 27 former heroin addicts withdrawn from all opiates 29 healthy controls with no history of drug dependence	Not reported

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Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Pirnay, 2004[152]	Median age 33 years, range 20 to 48 72% male	- Methadone, - Buprenorphine mean doses not reported	- Buprenorphine was directly implicated in 4 (12%) of deaths and strongly plausible in 8 deaths - Methadone was directly implicated in 3 (9%) of deaths and strongly plausible in 11 deaths	Mission Interministerielle de Lutte contre les Drogues et Toxicomanies (MILDT) and Schering-Plough Company	Not Rated
Prosser, 2006[93]	MMT vs. former users vs. controls Mean age 38 vs. 43 vs. 34 years Male: 79% vs. 74% vs. 72% Black: 21% vs. 41% vs. 35% White: 38% vs. 26% vs. 41% Hispanic: 41% vs. 26% vs. 10% Asian: 0 vs. 0 vs. 3.4% Native American/Pacific Island: 0 vs. 0 vs. 3% Other race: 0 vs. 8% vs. 7%	- Methadone, mean dose not reported, max dose (mg/day) 73.79 MMT and 60.00 former users	MMT vs. former users vs. controls - WAIS (mean): 8.05 vs. 8.6 vs. 12.16 (p<0.001 controls vs. others) - BVRT correct (mean): 6.7 vs. 4.65 vs. 7.63 (p=0.001 former users vs. others) - BVRT errors (mean): 5.4 vs. 7.82 vs. 2.36 (p<0.001 controls vs. others) - BVRT right errors (mean): 2.55 vs. 3.96 vs. 1.05 (p<0.001 former users vs. controls) - BVRT left errors (mean): 2.4 vs. 3.22 vs. 1.21 (p=0.011 former users vs. controls)	Supported in part by RO1 DA 12273, the NIDA Intramural Research Program and the Counterdrug Technology Center, Office of National Drug Control Policy.	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Quick, 2009[119]	To compare acoustic cry characteristics of infants born to mother maintained on methadone during pregnancy with those of infants not exposed to methadone during pregnancy.	Case-control	Women's hospital New Zealand	Sub-sample of case-control study Exclusions: fetal alcohol syndrome, congenital abnormalities, HIV, gestational age <32 weeks or birth weight <1500 g	20 enrolled 10 Methadone exposed 10 Non-methadone exposed	Not reported
Rajegowda, 1972[129]	To compare withdrawal symptoms in a group of newborn infants of mothers on methadone maintenance therapy with infants whose mothers were untreated heroin addicts.	Cross-sectional	Hospital United States	Not reported	30 heroin 15 methadone	Not reported
Ramirez-Cacho, 2006[120]	To determine the effect of MMT on intrapartum FHR pattern.	Retro-spective cohort	University Hospital	Pregnant women enrolled from January 2001 to December 2003 in a specialized prenatal methadone maintenance program and a control group of patients followed in general obstetrics clinic	107 enrolled (56 methadone; 52 control)	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Quick, 2009[119]	Not reported	- Methadone, mean dose varied by trimester; range 53 mg (1st trimester) - 62 mg (3rd trimester)	Methadone exposed vs. non-methadone exposed - Mean gestational age (weeks): 39.08 vs. 39.09 - Mean birth weight (g): 3238 vs. 3438 - Mean length (cm): 51.60 vs. 52.20 - Mean head circumference (cm): 34.80 vs. 34.65 - Mean length of stay (days): 17.40 vs. 2.90 (p=0.005) - Mean highest Finnegan score: 13.20 vs. 0.20 (p<0.0001) - Mean NNNS stress abstienence score: 0.17 vs. 0.10 (p=0.04) - % NAS: 80 vs. 0 (p<0.0001)	New Zealand Lottery Grants Board Postgraduate scholarship from the University of Canterbury	Poor
Rajegowda, 1972[129]	Maternal characteristics not reported	- Methadone, mean dose not reported (newborns of mothers receiving methadone) - No methadone (newborns of mothers addicted to heroin receiving no methadone)	Methadone vs. no methadone - Newborns with NAS: 86.6% vs. 39.5%, p<0.005	US Public Health Service General Research Support Grant No. RR-05486-08 and by NIH Research Fellowship NS 02534	Poor
Ramirez-Cacho, 2006[120]	Mean maternal age 28 years 27% White 67% Hispanic 6% other	- Methadone, median dose 70 mg/day (range: 20-130 mg)	Methadone vs. controls - Apgar at 1 min: 8 vs. 9 - Apgar at 5 min: 9 vs. 9	Not reported	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Rapeli, 2007[92]	To evaluate attention, working memory, and verbal memory of methadone or buprenorphine/naloxone-treated patients starting OST, and to compare these to controls.	Cross-sectional	Addiction clinics, adult education centers Finland	Inclusion: age 18 to 50; for OST patients, opioid dependence according to DSM-IV and start of OST in last 6 weeks Exclusion: participants with current uncontrolled polysubstance abuse, acute alcohol abuse, or acute axis I psychiatric morbidity according to DSM-IV other than substance abuse disorders, also excluded patients w/ severe brain injury, chronic neurological disease, history of other-than substance abuse psychosis, epileptic seizures, HIV infection, pregnancy, or primary cognitive deficit.	50 enrolled 16 methadone 17 buprenorphine/ naloxone-treated patients 17 controls	None
Rapeli, 2009[166]	To determine whether working memory function in OST patients treated with BZDs would be impaired relative to normal comparison participants in first testing (T1) and would show improvement; and to determine whether memory consolidation would be impaired in OST patients; and to determine whether among OST patients subjective and objective memory function would correlate negatively.	Pro-spective cohort	Addiction clinics, adult education centers Finland	Participants with opioid dependence were volunteers admitted for standard OST in addiction clinics; and had an opioid dependence diagnosis, benzodiazepine dependence or abuse diagnosis, start of OST in last 2 months, and treatment of opioid dependence with either methadone, buprenorphine, or buprenorphine/naloxone. All participants required to read, understand patient info sheet and sign consent form.	43 enrolled 13 methadone patients 15 buprenorphine/naloxone or buprenorphine patients 15 control patients	- 8 volunteer patients excluded due to substance abuse before test - 14 eligible patients and 4 controls dropped between T1 and T2

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Rapeli, 2007[92]	Methadone vs. buprenorphine vs. control Mean age 31 vs. 28 vs. 31 years 68% male Race not reported	- Methadone, mean dose 53 mg - Buprenorphine, mean dose 16 mg - Naloxone, mean dose 4 mg - Non-use	Methadone vs. control - Tonic alertness: 256 vs. 244 - Phasic alertness: 245.6 vs. 230.3 - TAP Go/No-go reaction time: 528.3 vs. 465.5 - TAP Go/No-go errors: 0.6 vs. 0.5 - Wechsler Memory Scale (WMS), logical memory recall:12.5 vs. 16.3 - WMS, logical memory, delayed recall: 11.1 vs. 14.5	Finnish National Public Health Institute (KTL) and Psychiatry Dept. of Helsinki University central Hospital	Poor
Rapeli, 2009[166]	Mean age 29 years 56% male Race not reported Benzodiazepine use: - 100% in opioid users - 0% in healthy controls	- Methadone, mean dose 126 mg - Buprenorphine, mean dose 23 mg - No methadone (healthy controls)	Methadone vs. buprenorphine vs. controls - No significant difference among groups in tests of memory over time	Finnish National Public Health Institute (KTL), Yrjo Jahnsson Foundation, the Rauha and Jalmari Ahokas Foundation, and Emil Aaltnonen Foundation, and Psychiatry Dept of Helsinki University Central Hosp	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Reddy, 2004[66]	To review the incidence of QTc prolongation in patients taking methadone for cancer pain.	Retro-spective (before/ after)	Outpatient cancer treatment center United States	Outpatients treated with methadone for cancer pain, based on prescription data, with ECG data	520 eligible 56 enrolled	None reported
Reddy, 2010[67]	To determine the effect of initiation of methadone on QTc interval in patients with cancer pain seen at the palliative care setting.	Pro-spective before-after	In- or outpatient cancer center United States	Cancer diagnosis, no prior history of methadone use, started on methadone for pain management	100 enrolled	34/100
Rosen, 1975[130]	To investigate the placental transfer of methadone from the mother to her newborn, the relationship of neonatal plasma methadone concentration to withdrawal symptomatology, and the relationship between maternal methadone dose and severity of neonatal withdrawal.	Prevalence	United States	Mothers entering the labor-delivery suite who was on methadone maintenance	31 enrolled	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Reddy, 2004[66]	No demographic data reported	- Oral methadone, median dose 30 mg (range 2 to 480 mg)	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)	Not reported	Poor
Reddy, 2010[67]	Median age 56 years 54% female 30% non-white	Oral methadone: median dose 23 mg, range 3-90 mg	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	NIH	Poor
Rosen, 1975[130]	Not reported	- Methadone, mean dose 38.1 mg/day	Maternal methadone dose was not correlated with withdrawal symptoms Maternal methadone dosage - Severe symptoms: 10 to 100mg/day - Moderate symptoms: 10 to 65mg/day - Absent or mild symptoms: 20 to 60mg/day	Not reported	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Rosen, 1985[121]	To report on the long-term effects of methadone maintenance during pregnancy on the child's somatic and neurobehavioral development.	Pro-spective cohort	Methadone clinics United States	Pregnant women on methadone maintenance from the High Risk Perinatal Clinic and various methadone clinics	88 enrolled 57 Methadone 31 Comparisons	Not reported
Rotheram-Fuller, 2004[192]	To test the hypothesis that performance on the gambling task would differ significantly as a function of two forms of substance abuse, opiate dependence and tobacco smoking.	Pro-spective cohort	United States	Stable methadone maintenance >=6 months, healthy controls	9 methadone smokers 9 methadone non-smokers 9 control smokers 10 control non-smokers	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Rosen, 1985[121]	Mean maternal age Methadone: 27 years Comparison: 22 years (p<0.05) White Methadone: 7% Comparison: 4% Black Methadone: 78% Comparison: 79% Hispanic Methadone: 15% Comparison: 18% Smoke >1 pack/day Methadone: 90% Comparison: 29%	- Methadone, mean dose 42 mg	Methadone vs. comparison - Male infants: 54.2% vs. 54.8%* - Mean birth weight (g): 3129 vs. 3037.1* - Preterm (28-36 weeks): 15.4% vs. 11.0%* *Matched on these things - Mean apgar score 1min: 7.4 vs. 8.1 (NS) - Mean agpar score 5min: 8.5 vs. 9.0 (NS) - Infants with severe withdrawal: 23.3% vs. 0 - Infants with moderate withdrawal: 51.8% vs. 0 - Infants with none/mild withdrawal: 24.9% vs. 0 - Infants hospitalized: 27.8% vs. 11.1% - Small for gestational age: 13% vs. 3% - Infants with withdrawal syndrome: 75.1% vs. 0	National Institute of Drug Abuse, grant DA01663	Poor
Rotheram-Fuller, 2004[192]	Mean age 40 years White: 22% vs. 11% vs. 89% vs. 40% Black: 67% vs. 33% vs. 0 vs. 30% Latino: 11% vs. 56% vs. 11% vs. 30%	- Methadone mean dose (mg): 68.0 smokers and 55.3 non-smokers - No methadone (smokers and non-smokers controls)	Methadone smokers vs. methadone non-smokers vs. control smokers vs. control non-smokers - Gambling task net score (mean): -30.7 vs. -8.0 vs. 5.8 vs. -1.2 (p<0.05 for methadone smokers vs. others)	NIDA Grants 1 R01 DA 09992; 1 P50 DA 12755; and 1 Y01 DA 50038	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Schmittner, 2009[64]	To determine ECG effects of lofexidine + morphine vs. morphine alone.	RCT	Outpatient clinic United States	Age 18-45 years; physically opioid dependent according to DSM-IV criteria; self-report at least 30 day use; willing to undergo urine toxicology screening Exclusion criteria was axis I psychiatric disorder; cognitive impairment; pregnancy; relative hypotension (consistent <110/70 mmHg); relative bradycardia (consistent <50 bpm); chronic hypertension; MI; stroke; CAD; creatinine >1.7 mg/dl; use of antihypertensives, antiepileptics, psychoactives, hypoglecemics, anticholinergics or antiparkinsonian agents	14 enrolled All patients received run-in methadone	14/26 (54%) enrolled analyzed 12 withdrew or were disqualified from participation
Schottenfeld, 1997[155]	To compare the effects of buprenorphine and methadone.	RCT	Outpatient clinic United States	DSM-III-R criteria for opioid and cocaine dependence eligible for methadone maintenance Excluded for alcohol or sedative dependence; psychosis or suicide risk; inability to read or understand rating forms and symptoms checklists; pregnancy	132 enrolled - buprenorphine 4 mg n=33 - buprenorphine 12 mg n=33 - methadone 20 mg n=34 - methadone 65 mg n=32	Retention at 24 weeks ranged from 35% to 64% across treatments

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Schmittner, 2009[64]	Mean age 35 years (SD 5) 47% male 57% Black (other races not reported) 50% bradycardia at baseline	- 3 week oral methadone 30 to 80 mg run-in followed by 1 week oral methadone 30 to 80 mg + lofexidine 0.4 mg/day or placebo (results for placebo phase not reported)	Methadone vs. baseline (no methadone use) - No statistically significant differences in PR, QRS or QTc intervals reported in text; data not shown Methadone alone vs. methadone + lofexidine - Heart rate: mean difference -8.0 (SD 7.3) bpm; p=0.0006 - Mean maximal heart rate decrease: 9.6 (SD 5.8) bpm; p<0.0001 - Mean PR interval increase: 11.1 (SD 19.8) ms; p=0.026 - Mean QRS interval maximal increase: 3.7 (SD 4.3); p=0.002 - Mean QTc interval increase: 21.9 (SD 40.8) ms; p=0.018	Intramural Research Program, National Institute on Drug Abuse, National Institutes of Health	Fair
Schottenfeld, 1997[155]	Mean age 33 years 69% male 78% white (other races not reported)	- Oral methadone, 20 mg or 65 mg - Buprenorphine, 4 mg or 12 mg	- No withdrawals due to AEs in any treatment group	National Institute on Drug Abuse	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Seymour, 2003[183]	To describe methadone-related deaths in Scotland.	Case series	Chart review Scotland	Inclusion: methadone found on toxicological analyses at death and found to contribute to cause of death Exclusion: deaths where the concentration of methadone was too low to be related to death	270 cases	83 deaths
Shah, 2005[14]	To determine death rates from methadone over time, to characterize methadone-related death, to determine likelihood for methadone overdose in all overdose deaths, analyze bivariate comparisons within methadone-related deaths.	Case series	Chart review United States	Inclusion: unintentional drug methadone-related overdose between 1998 and 2002 based on cause of death determination and finding methadone in the toxicological analyses at death, residents of New Mexico, Exclusion: methadone and alcohol co-intoxication deaths	143 methadone related deaths	N/A

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Seymour, 2003[183]	Mean age 27 years (range 15-58) 79% male 97% History of substance abuse 68% were active IV drug users 43% in MMT 37% prescribed methadone 55% obtained illicit methadone	- Methadone, mean dose not reported	- 85% of deaths were polydrug related - 65% decedents died with concomitant diazepam - 31% decedents died with concomitant temazepam - 34% decedents died with concomitant heroin - 55% of deaths occurred over the weekend - 46% of weekend deaths were in MMT - No association between timing of death and MMT (p=0.13) - 11% died within 2 weeks of prison release	Medical Research Council Fellowship	Not Rated
Shah, 2005[14]	Median age 40 years 75% male 55% White (other races not reported) History of illicit drug use 67% Chronic pain 40% Source of methadone available for 55% - Methadone maintenance therapy 22% - Chronic pain methadone prescription: 19% - Unknown reason for physician prescription 7% - Diverted methadone 8%	-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 reported	Not Rated

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Sharkey, 2010[191]	To characterize the extent of OSA and CSA in MMT patients; to examine factors associated with SDB in this population; and to investigate whether SDB is related to severity subjective reports of sleep disturbance in patients enrolled in MMT for opioid addiction.	Case-control	MMT clinics United States	Pittsburgh Sleep Quality Index score >5; plans to continue MMT for >= 6 months;. Exclusion was currently experiencing psychotic symptoms or being treated for bipolar disorder; schizophrenia, schizoaffective disorder, schizophreniform disorder; had sued trazodone in previous 30 days; were pregnant; had known chronic medical illness; and known obstructive sleep apnea.	368 screened 101 enrolled 95 completed at least one PSG	6 withdrew
Sharpe, 2004[216]	To compare outcomes of infants exposed in utero to methadone administered for the treatment of maternal pain compared with treatment for opiate addiction.	Cross-sectional	National Women's Hospital in New Zealand	Not reported	19 methadone for pain 24 methadone for addiction	None
Shaw, 1994[136]	To determine the incidence, timing and frequency of persistence of symptoms in infants born to maternal methadone users.	Pro-spective cohort	Maternity hospital England	Women receiving methadone replacement at the local drug dependency unit	64 enrolled 32 Addicts 32 Controls	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Sharkey, 2010[191]	Mean age 38 years (range: 21 to 52 years) 41% male 80% White 11% Hispanic 7% African American 1% other ethnicity Mean BMI: 28.4 kg/m2 MMT duration: 22.3 months (range: 3 months to 10.5 years)	-Methadone mean dose: 108.3 mg (range: 25 to 310 mg)	- Longer duration associated with more sleep disordered breathing and obstructive sleep apnea	NIH RO1 DA 020479	Fair
Sharpe, 2004[216]	70% smokers Other maternal demographic data not reported	Methadone, median dose - 40 mg among chronic pain patients - 60 mg among addiction patients	Pain group vs. addiction group - Median gestational age (weeks): 36 vs. 39; p=0.0002 - Emergency cesarean: 3/19 (16%) vs. 4/24 (17%) - Median Apgar at 1min: 9 vs. 9 - NAS diagnosis: 13/19 (68%) vs. 24/24 (100%) - Treatment for NAS: 2/19 (11%) vs. 14/24 (58%); p=0.0016	Not reported	Fair
Shaw, 1994[136]	Not reported	Methadone, median dose 35 mg (range 5 to 80)	Methadone vs. controls - Male infants: 38% vs. 44% - Median gestational age (weeks): 40 vs. 40 - Preterm birth (<36 weeks): 5.55% vs. 3.1% - Median birth weight (kg): 2.83 vs. 3.52 (p<0.001) - Breastfed: 3.1% vs. 34.4%	Not reported	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Soyka, 2006[151]	To further examine the safety profile of different substitution treatments with respect to fatal overdose.	Case series	Chart review Germany	Inclusion: Non-natural deaths that were autopsied in 2002-2003 Exclusion: not mentioned	126 in 2002 146 in 2003	N/A
Soyka, 2008[163]	To evaluate and compare cognitive performance in opioid-dependent patients during treatment with BUP or MMP and in healthy normal controls.	RCT	Methadone outpatient clinic Germany	No confirmed subjective memory complaints or history of organic brain syndrom or seizures; no measurable cognitive and memory impairment; IQ of 85 or greater; neither neurological nor psychiatric diagnosis or history apart from the opioid dependence in the patient group	59 enrolled	13 dropped 46 analyzed
Soyka, 2010[208]	To evaluate and compare cognitive performance in patients receiving short- and long-term substitution treatment with methadone.	Cross-sectional	Methadone outpatient clinic Germany	Opioid-dependent, IQ >=85 with no history of brain damage or seizures, no neurological diagnosis, no memory complaints, no ADHD	35 short-term 42 long-term	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Soyka, 2006[151]	Mean age 30 to 31 years 72% male Race not reported	- Methadone - Heroin - Buprenorphine mean doses not reported	- Methadone was found in 96 cases (35%) vs. buprenorphine in 1 case (0.4%) - 53 (55%) of deaths were in MMT - 35 (62%) methadone-related deaths had marks of recent IV drug use - 16 deaths due to methadone on MMT occurred during the first days of adaptation or after discontinuation of methadone	Federal Ministry of Education and Research	Not Rated
Soyka, 2008[163]	Not reported	Methadone given orally, doses and timing NR Buprenorphine given sublingual, doses and timing NR Non-use of opioids	Buprenorphine vs methadone vs healthy controls TMT-A: 29.8 vs. 30.2 vs. 24.3 TMT-B: 85.4 vs. 81.0 vs. 59.4 RWT-lexical generation: 30.2 vs. 29.3 vs. 37.4 RWT-lexical shifting: 18.6 vs. 19.7 vs. 22.0 VLMT-verbal lerning: 46.0 vs. 47.2 vs. 58.5 d2-Test-quality: 158.5 vs. 171.9 vs. 170.0	Justin Rockola Foundatino	Fair
Soyka, 2010[208]	Mean age Short-term 33 years Long-term 37 years Male Short-term 54% Long-term 67% Race not reported	- Short-term methadone use was at least 30 days of use - Long-term methadone use was at least 6 months of use - Methadone last dose (mg): 62.8 vs. 69.3	Short-term vs. long-term - Rey figure test copy (mean): 20.6 vs. 32.3 (p=0.03) - Regensburger word fluency test single category (mean): 25.9 vs. 30.9 (p=0.01) - Regensburger word fluency test double category (mean): 16.5 vs. 19.9 (p=0.00)	Federal Ministry of Education and Research (01 EB 0440-0441, 01 EB 0142) Unrestricted educational grant from Sanofi Aventis	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Specka, 2000[97]	To further determine direction and size of effects (on six cognitive-psychomotor performance tests completed by methadone maintained patients and healthy controls) with a more numerous sample.	Cross-sectional	University clinic Germany	Inclusion: patients had to have been treated with methadone for at least 4 months; methadone dose had to be stable for at least 6 weeks; free of diagnosed polytoxicomania, psychosis or psychosis-like disorders or any somatic diseases or disablements which might have impaired performance; had to pass urine screening day of the investigation	108 enrolled 54 methadone patients 54 controls	Not reported
Stimmel, 1976[107]	To compare the course of gestation in patients enrolled in a comprehensive methadone maintenance treatment program and women taking narcotics under essentially uncontrolled conditions and women not exposed to narcotic agents during antepartum period.	Retro-spective cohort	United States	Women who gave birth while enrolled in the methadone maintenance program from March 1968 to May 1974 at The Mount Sinai Hospital and a comparison group selected from the population of women whose infants were delivered in the obstetrical service from January through October 1972 without a recorded history of drug abuse	115 enrolled 28 Methadone 30 Comparison Not included in results here 57 Street drug users	Not reported
Strain, 1991[207]	To determine whether depressive symptoms increase or decrease early in treatment and to track the time course of change after treatment entry.	Pro-spective cohort	Methadone detoxification program United States	Patients admitted to a methadone detoxification program during a 6-month period and in treatment for at least 4 weeks	58 enrolled	17 dropped out before 4 weeks

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Specka, 2000[97]	Mean age 29 years 65% male Race not reported	- Methadone, mean dose 93 mg (range 10-240 mg) - Non-use	Methadone use vs. non-use - Labyrinth of lines, number of responses: 26.4 vs. 29.3 - Simple Choice Reaction decision errors: 2.1 vs.1.6 - Mean decision time, ms: 369 vs. 386 - Mean reaction time, ms: 509 vs. 546 - Attention, number of responses: 456.6 vs.503.2	Not reported	Poor
Stimmel, 1976[107]	Mean maternal age Methadone 24 years Comparison 26 years Black Methadone 29% Comparison: 33% Hispanic Methadone 68% Comparison 57% White Methadone 4% Comparison 10%	- Methadone, mean dose not reported - Comparison (drug-free controls) - No treatment (heroin or methadone users)	Methadone vs. comparison - Mean gestational age (weeks): 39.2 vs. 39.6 - Fetal distress: 16.1% vs. 23.3% - Birthweight <2,500 g: 22.6% vs. 3.3% (p<0.01) - Mean birth weight (g): 2933 vs. 3309 - Mean apgar at 1min: 8.5 vs. 8.3 - Mean apgar at 5min: 9.7 vs. 9.8 - Meconium: 16.1% vs. 20% - Infant respiratory distress: 9.6% vs. 0 - Narcotic withdrawal: 58.1% vs. 0	Not reported	Poor
Strain, 1991[207]	Mean age 34 years 67% male 59% Black	Methadone (mean, mg): 25 (range 10 to 40)	BDI scores (mean, 0 to 25) - Admission vs. week 1 vs. week 2 vs. week 3 vs. week 4 (estimated from graph): 20 vs. 15 vs. 12.5 vs. 13 vs. 14 (p<0.01 for admission vs. others) - Men vs. women - Admission: 18.21 vs. 22.32 (NS) - Week 4: 12.06 vs. 16.61 (NS) - White vs. black - Admission: 21.75 vs. 18.00 (p<0.003) - Week 4: 18.52 vs. 10.04 (p<0.003)	Research Grant DA 05792 and Training Grant T32 DA 07209 from the National Institute on Drug Abuse	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Strauss, 1974[122]	To examine the incidence of low birth weight in low-dose methadone-comprehensive prenatal care program.	Cross-sectional	Hutzel Hospital United States	Not reported	144 enrolled 72 Methadone maintained 36 Clinical control 36 High-risk control	Not reported

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Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Strauss, 1974[122]	Mean maternal age 23 years Race not reported	- Methadone, low-dose ≤ 60 mg/day; high-dose methadone 80-150 mg/day - Non-addicts	Methadone vs. Clinic control vs. High-risk control Incidence (%) obstetric complications - Pre-eclampsia: 0 vs. 0 vs. 5.6 ($p<0.05$) - Eclampsia: 1.4 vs. 0 vs. 0 - Placental infarcts: 1.4 vs. 5.6 vs. 2.8 - Blood loss in trimester 1 or 2: 1.4 vs. 0 vs. 8.3 - Blood loss in trimester 3: 4.2 vs. 2.8 vs. 5.6 - False labor: 1.4 vs. 0 vs. 0 - Premature rupture of membranes: 11.1 vs. 5.6 vs. 8.3 - Premature separation of membranes: 5.6 vs. 2.8 vs. 0 - Placenta previa: 1.4 vs. 2.8 vs. 2.8 - Threatened abortion: 0 vs. 0 vs. 2.8 - Breech: 2.8 vs. 2.7 vs. 0 - Cord complications: 8.3 vs. 11.1 vs. 11.1 - Premature labor: 5.6 vs. 2.7 vs. 5.6 - Induced labor: 22.2 vs. 33.3 vs. 47.2 ($p<0.05$) - Meconium: 23.6 vs. 19.4 vs. 11.1 ($p<0.05$) - Mean birth weight (g): 2897.6 vs. 3002.8 vs. 3016.6 - Mean gestational age (weeks): 38.9 vs. 39.3 vs. 39.1 - Mean apgar at 1min: 7.5 vs. 7.8 vs. 7.6 - Mean apgar at 5min: 8.7 vs. 8.6 vs. 8.9 - Length of stay (days): 11.4 vs. 4.9 vs. 5.1 ($p<0.001$)	Spencer Foundation and National Institute of Mental Health Grant No 1 R03 DA00696-01	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Strauss, 1976[215]	To analyze the differences in withdrawal characteristics of infants whose mothers were able to meet the program goal of <=20mg/day in comparison with the progeny of mothers receiving higher doses.	Retro-spective cohort	Hutzel Hospital United States	Infants born to methadone-treated opiate addicts enrolled in the Hutzel Hospital Methadone-Prenatal Care Program at Wayne State University	72 enrolled - 33 Low dose - 37 High dose	Not reported
Sunjic, 1997[184]	To describe methadone-related deaths in Wales.	Case series	Australia	Inclusion: medical examiner methadone-related deaths Exclusion: not reported	25 cases	Not reported

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Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Strauss, 1976[215]	Not reported	Methadone - Low dose : <20 mg/day - High dose: >20 mg/day	High dose vs. low dose - Median duration of irritability: 8 vs. 3 (p<0.01) - Required treatment for withdrawal symptoms: 35.1% vs. 18.2% (p<0.05) - Mean birth weight (g): 2894 vs. 2901 (NS) - Mean gestational age (weeks): 39 vs. 39 (NS) - Mean length (cm): 48 vs. 48 (NS) - Mean apgar at 1min: 7.4 vs. 7.6 (NS) - Mean apgar at 5min: 8.6 vs. 8.6 - Lost birth weight: 7.7% vs. 5.5% (p<0.01) - Length of stay (days): 13.1 vs. 10.0 (p<0.05) - Higher incidence of 13 of 17 withdrawal symptoms in higher dose group vs. low dose group (p<0.025)	NIDA Grant No. 00696 NIDA Grant No. 01310	Poor
Sunjic, 1997[184]	Mean age 30 years (range 17-53) 76% male 56% known heroin users 40% drank alcohol heavily 12% used amphetamines 24% prescribed methadone for chronic pain 28% MMT	- Methadone, mean dose not reported	- 92% died from polydrug toxicity - 44% died with alcohol - 53% died with benzodiazepines - 50% of these were taking methadone for pain - 14% of these were in MMT - 40% injected methadone prior to death	Not reported	Not Rated

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Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Teichtahl, 2005[83]	To determine whether HVR and HCVR findings are abnormal in clinically stable MMT patients compared to normal, non-opioid-using subjects; and to determine whether physiologic and toxicologic factors explain these abnormalities. (part of a project assessing sleep architecture and sleep-disordered breathing in stable MMT patients).	Cross-sectional	Australia	Exclusion: significant cardiorespiratory, neurologic, liver, and psychotic disorders, and pregnancy.	70 enrolled 50 MMT 20 Controls	None
Titievsky, 19822[17]	To investigate the incidence of anxiety and depression in our addict population and then perform a double-blind comparison of placebo and doxepin in patients with these symptoms.	RCT	Beth Israel Medical Center United States	Methadone clinic patients with Hamilton Rating Scale for Depression score at least 18 (of 24)	76 screened 48 analyzed	Doxepin patient retention =10 (59%) Placebo patients=6 (33%) (Only data from patients with at least 4 weeks of study treatment used in stat analysis)
van Ameijden, 1999[51]	To review the effectiveness of low-dose methadone in reducing overdose mortality.	Pro-spective cohort	Outpatient clinic The Netherlands	Methadone maintenance patients Exclusion criteria was nationality other than Dutch	498 enrolled	Not reported

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Teichtahl, 2005[83]	Mean age 35 years 50% male Race not reported	- Stable methadone dose for >= 2 months in methadone group	MMT vs. Control - HCVR (estimated from graph): 1.25 vs. 1.5 - HVR (estimated from graph): 2.2 vs. 1.2	Not reported	Fair
Titievsky, 19822[17]	Mean age 30 years 46% male Race not reported	- Oral methadone maximum dose 100 mg + doxepin 50 mg/day titrated to 200 mg/day or placebo	Methadone + doxepin vs. methadone + placebo (Results reported for 48 completers only) - Drowsiness: 9/21 (43%) vs. 5/27 (19%) - Sluggishness: 6/21 (29%) vs. 5/27 (19%) - Hypotensive symptoms: 1/21 (5%) vs. 0 - Lack of coordination: 2/21 (10%) vs. 1/27 (4%) -Constipation: 0 vs. 1/27 (4%)	Not reported	Fair
van Ameijden, 1999[51]	Mean age 33 years 67% male Race not reported 29% HIV positive	- Oral methadone, mean dose 49 mg (77% of enrolled population)	Methadone maintenance vs. no methadone maintenance: - All-cause mortality RR 0.83 (CI, p-value not reported) - Death due to overdose RR 0.35 (CI not reported; p=0.045)	The Netherlands Foundation for Preventive Medicine	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
van Baar, 1989[123]	To study long-term development of infants of drug dependent mothers and to find out if they need special intervention or support.	Pro-spective cohort	The Netherlands	Drug-dependent women giving birth between 6/1983 to 7/1985 and comparison group of same area	72 enrolled 35 Methadone 37 Control	Not reported
Ventafridda, 1986[140]	To compare morphine to methadone from the standpoint of analgesic efficacy, side effects, hours of sleep, hours standing, performance status, and the request for increased doses of morphine and methadone by oral administration in outpatients.	RCT	Italy	Not reported	66 enrolled	6 withdrawn 2 due to side effects

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
van Baar, 1989[123]	Mean maternal age 28 years Race not reported	- Methadone, mean dose range not reported (5 to 80 mg/day) - No methadone	Methadone vs. control - Mean gestational age (weeks): 38.0 vs. 39.7 - Mean birth weight (g): 2880.8 vs. 3428.8 - Birthweight <2.3% growth curve: 11.4% vs. 0 - Apgar score <7 at 1min: 11.4% vs. 5.4% - Apgar score <7 at 5min: 2.9% vs. 0 - Male infants: 48.6% vs. 45.9%	Praeventiefonds, No 28-856	Poor
Ventafridda, 1986[140]	Mean age not reported 57% male Race not reported	- Morphine: 1st day 4 mg q4h titrated up to a max of 24 mg q4h - Methadone: 1st day 8 to 28 mg q6h for 3 days then q8h	Methadone vs. morphine, proportion of days with side effects - Drowsiness: 47% vs. 54% (NS) - Restlessness: 19% vs. 20% (NS) - Nausea: 21% vs. 26% (NS) - Vomiting: 15% vs. 18% (NS) - Tremors: 10% vs. 13% (NS) - Dry mouth: 43% vs. 57% (p<0.001) - Headache: 18% vs. 9% (p<0.001) - Incidence of death: 18.5% vs. 7.4% (p value not reported)	Grant from National Research Council, Rome, Gran N. 85.02049.44	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Verdejo, 2005[97]	To discriminate the differential effects of current methadone prescription on cognitive-executive functioning from the effects of former opioid abuse, and to assess the potential consequences of these deficits over the course of drug abuse treatment for both groups	Pro-spective cohort	Spain	Abstinent heroin abusers with a minimum abstinence period of 15 days for any substance, or methadone maintenance patients involved in a formal methadone maintenance treatment, being stabilized in their current methadone dose for at least 15 days and a minimum abstinence period of 48 hours from any drug except methadone, those who had previously been diagnosed with any other disorder from Axis 1 or 2 of the DSM-IV were excluded	41 enrolled 23 Abstinent 18 Methadone	Not reported
Wagner-Servais, 2003[58]	To assess the drug related deaths occurring in Germany at one institution between 1994 and 1998.	Retro-spective cohort	Institute of Forensic Medicine, University of Aachen Germany	All deaths occurring at the institution between 1994 and 1998 that were related to methadone	102 reviewed 19 methadone related	NA

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Verdejo, 2005[97]	Mean age MMP 35 years Abstinent 32 years Gender, race not reported	- Methadone dose, mean: 83.82 mg - Mean time in MMP (months): 38.66	Methadone vs. abstinent - Mean WCST (percentage perseverative errors): 15.00 vs. 18.98 (NS) - Mean WCST (percentage conceptual level responses): 54.52 vs. 46.81 (NS) - Mean letter number sequencing (raw score): 6.93 vs. 8.30 (NS) - Mean animal recognition task (scale NR): 19.46 vs. 19.43 (NS) - Mean fruit recognition task (scale NR): 12.40 vs. 13.00 (NS) - Mean FAS word recognition task (scale NR): 29.20 vs. 31.95 (NS) - Mean digit test, group 1 (time of performance): 22.64 vs. 19.30 (p=0.009) - Mean digit test, group 2 (time of performance): 22.64 vs. 20.91 (NS) - Mean digit test, group 3 (time of performance): 36.50 vs. 31.65 (p=0.044) - Mean digit test, group 4 (time of performance): 51.21 vs. 44.00 (NS) - Mean oral trails test, group 1 (time of performance): 56.53 vs. 40.91 (p=0.003) - Mean oral traits test, group 2 (time of performance): 92.90 vs. 62.39 (p=0.003) - Mean oral traits, interference (time part 2-time part 1): 36.07 vs. 21.48 (p=0.044)	Research Grants BSO2003-07169 from the Spanish "Ministerio de Ciencia y Technologia" and INT/2012/2002 from the Spanish "Ministerio del Interior"	Fair
Wagner-Servais, 2003[58]	Mean age 29 years 68% male Race not reported	- Methadone in blood at time of death: 200-1000 µg/l	12/19 (63.2%) prescribed methadone - 8/12 (66.6%) prescribed methadone died within 3 days of initial dose - 6/12 (50%) prescribed 30-40 mg as initial dose	Not reported	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Wang, 2005[81]	To further assess the prevalence of CSA (central sleep apnea) in clinically stable MMT patients and to investigate possible pathogenic mechanisms associated with this.	Cross-sectional	Australia	In MMT program for >= 2 months and receiving a stable methadone dose Exclusion was significant cardiorespiratory, neurologic, liver disease, psychotic disorders, and pregnancy	70 enrolled	N/A after 50 MMTs enrolled and started participation (and 20 controls)
Wang, 2008[82]	To investigate the subjective daytime sleepiness and daytime function of patients on stable MMT and to compare data with those from matched control subjects.	Cross-sectional	Australia	Patients on MMT had to be on methadone for 2 ms or longer and be on stable dose Exclusion was severe cardiac, respiratory, neurologic, or liver disease, or with diagnosed psychotic disorders or pregnant.	70 enrolled (50 MMT patients and 20 controls)	None
Ward, 2001[185]	To determine the number of opiate-related deaths in Dublin City and County during 1999, to establish the number of methadone-related deaths and determine the proportion of deaths associated with prescribed methadone.	Case series	Ireland	Inclusion: opioid-related deaths examined by the medical examiner Exclusion: addresses outside Dublin	84 opiate-related deaths, 45 methadone-related deaths, 15 decedents on prescribed methadone	N/A

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Wang, 2005[81]	Mean age 35 years Gender, race not reported	- Stable methadone dose for >= 2 months in methadone group	Methadone vs. control - Apnea/Hypopnea Index events per hour: 13 vs. 8 (p<0.05) - Central Apnea Index events per hour: 1.7 vs. 0.15 (p<0.001) - Obstructive Apnea Index: NS differences	Not reported	Poor
Wang, 2008[82]	Mean age not reported 50% male Race not reported	- Stable methadone dose for >= 2 months in methadone group	Methadone use vs. non-use - Obstructive Sleep Apnea-Hypopnea Index:10.8 hours vs. 9.4 hours; p=0.59 - Central Apnea Index: 6.7 hours vs. 0.25 hours; p<0.001 - Mini Mental State Exam: 28.66 vs. 29.35, p=0.09 - BDI: 14.64 vs. 2.05; p<0.001	Noted that this is not an industry-supported study, but supported by an Australian Postgraduate Award, Western Hosp Education, Equipment and Research Fund, and Western Hospital Liver Research Fund	Poor
Ward, 2001[185]	Mean age 30 years (range 17-48) 93% male Race not reported Two or more drugs on toxicological analysis (n=73, 86.9%)	- Methadone, mean dose not reported	- 18% on prescribed methadone at time of death - The proportion of methadone-associated deaths in people on prescribed methadone declined from 38% before the introduction of new regulations to 29% after the introduction of regulations (p>0.5) - Mean time on Central Methadone Treatment List prior to death for those who died while receiving prescribed methadone prescribed = 44 weeks (range 1-248 weeks)	Not reported	Not Rated

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Webster, 2008[160]	To assess the potential prevalence of central obstructive sleep apnea in opioid-treated pain patients.	Cohort	Private clinic specializing in chronic pain treatment United States	Inclusion: Chronic pain, on around-the-clock opioid therapy, had undergone polysomnography between February 2004 to July 2005.	392 screened 140 enrolled All patients prescribed round-the-clock opioids: 4% on methadone; 67% opioids other than methadone; and 29% on methadone and other opioids.	None
Wedam et al, 2007[61] other publications: Johnson et al, 2000[141]	Compare the effects of levomethadyl acetate, buprenorphine and methadone on QT interval.	RCT	Outpatient clinic United States	Age 21-55 years; DSM-IV opioid-dependent; evidence of recent opioid use on toxicologic screen Exclusion criteria was pregnancy; serious medical or psychiatric illness requiring long-term medication	154 enrolled 53 methadone 54 buprenorphine 47 levomethadyl	Data from 45 patients not completing treatment included in ECG analysis

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Webster, 2008[160]	Mean age 51 years (22 to 84) 33% male Race not reported	- Median daily dosage of all opioids was 266 mg of morphine equivalents (range 15 to 5,985 mg).	Methadone vs. NSAIDs - Effect of medications on apnea-hypopnea (correlation coefficient): 0.139 (SE 0.051); p=0.007 vs. 0.042 (SE 0.075); p=0.571 - Effect of medications on central apnea indices (correlation coefficient): 0.164 (SE 0.056); p=0.004 vs. 0.044 (SE 0.083); p=0.598 Methadone vs. non-methadone opioids - Dose response relations for apnea-hypopnea (correlation coefficient): 0.138 (SE 0.044); p=0.002 vs. 0.113 (SE 0.076); p=0.140 - Dose response relations for central apnea index (correlation coefficient): 0.130 (SE 0.049); p=0.008 vs. 0.073 (SE 0.083); p=0.385	NR	Poor
Wedam et al, 2007[61] other publications: Johnson et al, 2000[141]	Mean age 36 years 62% male 60% non-white (not described) Mean heart rate 64 bpm	- Methadone 60-100 mg - Buprenorphine 16-32 mg - Levomethadyl 75-155 mg	Methadone vs. buprenorphine - QTc >470 (men)/490 (women)ms: 12/53 (23%) vs. 0/54 (0%) - Bazett equation OR 14.1 (95% CI 1.9 to 109.5; p=0.01) - Fridericia equation OR 8.5 (95% CI 1.0 to 72.1; p=0.05)	National Institute on Drug Abuse	Good

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Weimer, 2011[9]	To describe medical examiner cases in rural Virginia in 2004 with methadone identified by toxicology and compare cases by source of methadone.	Case series	Medical examiner records United States	All deaths where methadone was found on the toxicology at death	203 cases	N/A
Williamson, 1997[186]	To compare overdose deaths in people prescribed methadone to people who obtain it illicitly and to compare methadone deaths from MMT to chronic pain.	Case series	Chart review Australia	Inclusion: decedents with methadone in toxicological analyses at death and cause of death drug overdose Exclusion: not reported	47 cases	Not reported
Woody, 1975[218]	To test whether patients in a methadone treatment program with ratable depressive symptomatology should show more improvement when treated with doxepin than with placebo.	RCT	VA drug treatment center United States	Men age 20-50 years meeting FDA requirements for methadone treatment; medically healthy; free of addiction to drugs other than narcotics; symptomatic depression; initiating methadone treatment	35 enrolled	Not reported

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Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Weimer, 2011[9]	Mean age 36 years 64% male 95% White 44% rural 54% history of substance abuse 61% died of polysubstance overdose	- Methadone, mean dose not reported	Methadone source: - 67% (41) obtained illicitly - 28% (17) prescribed by a physician for analgesia - 5% (3) obtained from an OTP Prescribed methadone vs. illicit source: - Older age OR 1.16 (95% CI 1.06 to 1.26) - Antidepressant use OR 8.78 (95% CI 2.3 to 33.2) Illicit methadone vs. prescription or MMT source: - Younger age OR 0.92 (95% CI 0.86 to 0.97) - Less likely to have antidepressants OR 0.17 (95% CI 0.05 to 0.61)	None	Not Rated
Williamson, 1997[186]	Mean age 30 years 64% male 36% prescribed methadone tablets for pain 19% MMT	- Methadone, mean dose not reported	- RR 7.29 (95% CI 2.15 to 31.48) to die from methadone tablets for pain vs. methadone syrup for MMT	Not reported	Not Rated
Woody, 1975[218]	Mean age 29 years 100% male Race not reported	- Oral methadone + doxepin 100 to 150 mg/day or placebo	Methadone + doxepin vs. methadone + placebo - Withdrawals due to AEs: 2/17 (12%) vs. 1/28 (4%) - No other adverse events reported	Not reported	Poor

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Wouldes, 2004[124]	To evaluate the effect of daily maternal methadone maintenance treatment on the quality and quantity of fetal movement.	Pro-spective cohort	National Women's Hospital New Zealand	Agreeable to undergoing 2 further ultrasounds during the 3rd trimester of pregnancy, gestational age confirmed by ultrasound scan prior to 20 weeks gestation, no evidence of preterm labor within 48 hours of scheduled ultrasounds	34 enrolled 17 Methadone 17 Controls	Not reported
Wouldes, 2010[125]	To examine relations between maternal methadone dose during pregnancy and a range of infant clinical outcomes.	Cross-sectional	National Women's Hospital New Zealand	Women seen at the women's hospital or in the same region	74 enrolled 42 Controls (not on methadone)	Not reported

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Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Woulides, 2004[124]	Mean age 30 years Race not reported	- Methadone, mean dose 52 mg - No methadone	Methadone vs. controls - Mean gestational age (weeks): 39.22 vs. 40.66 (p=0.003) - Mean birth weight (g): 3033.24 vs. 3656.76 (p=0.0005) - Mean birth length (cm): 49.14 vs. 52.24 (p=0.0005) - Mean head circumference (cm): 33.99 vs. 35.79 (p=0.001)	Not reported	Poor
Woulides, 2010[125]	Not reported	Methadone, mean dose 64 mg - Low dose: methadone <=58mg/day - High dose: methadone >=59mg/day No methadone	Controls vs. low dose vs. high dose - Mean adjusted gestation age (weeks): 40.41 vs. 39.36 vs. 36.21 (p=0.001) - Mean adjusted infant stay (days): 5.92 vs. 10.32 vs. 21.74 (p=0.001) - Mean adjusted birth weight (g): 3419.42 vs. 3137.50 vs. 2870.27 (p=0.001) - Mean adjusted birth length (cm): 50.75 vs. 49.23 vs. 48.49 (p=0.001) - Mean adjusted head circumference (cm): 35.52 vs. 33.84 vs. 32.86 (p=0.001) - % male: 66.7 vs. 50.0 vs. 37.6 (p=0.111) - % preterm (<37 complete weeks): 2.40 vs. 18.8 vs. 56.30 (p=0.001) - % with respiratory distress: 4.80 vs. 0 vs. 18.80 (p=0.079) - % SIDs: 0 vs. 0 vs. 18.8 (p=0.003) - % treated for NAS: 0 vs. 18.8 vs. 50.0 (p=0.264)	University of Auckland and the Wallath Trust Foundation	Fair

Appendix J. Data abstraction of randomized controlled trials and observational studies

Author, year Title	Purpose	Study design	Setting Country (if reported)	Inclusion/exclusion criteria	# Enrolled	Withdrawn or loss to f/u
Zador, 2002[187]	To attempt to put deaths during induction into a different context by determining the number of deaths in this phase of MMT as a proportion of all inductions into treatment in 1996 in New South Wales.	Case series	Australia	Deaths with methadone in blood at autopsy	87 (methadone detected deaths)	N/A
Zelson, 1973[131]	To compare neonatal withdrawal symptoms of infants born to methadone and heroin user mothers.	Cross-sectional	Not reported	Not reported	45 heroin 46 methadone - 9 methadone only - 16 heroin + methadone - 21 irregular use of heroin and methadone	Not reported

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Author, year Title	Population characteristics	Interventions	Results	Funding	Quality
Zador, 2002[187]	Methadone tablet deaths Mean age 38 years 53% male Methadone syrup deaths Mean age 32 years 76% male Race not reported	- Methadone, tablet or syrup, mean dose not reported	Methadone tablet deaths (n=16) - 29% suicide death - 47% died of drug-related causes - 24% died of medically-related causes - 75% history of chronic pain Methadone syrup deaths (n=63) - 78% died drug-related causes - 11% died of trauma - 2% died of medically-related causes - 5% died of a combination of causes - 54% were enrolled in methadone maintenance Mortality rate in methadone maintenance: - 34 deaths in MMT - 7 deaths during induction (first 7 days) - 86% of induction deaths were drug-related - Overall mortality rate during induction 8.6 deaths/10,000 inductions (95% CI 2.2 to 15.0)	New South Wales Health Department absorbed costs of accessing coronial files.	Not Rated
Zelson, 1973[131]	Mean maternal age 22 years Race not reported	- Methadone, mean dose not reported (range 10-160 mg) - No methadone treatment (heroin use)	Methadone vs. no treatment - Mean birth weight (g): 2625 vs. 2464 - Signs of withdrawal: 76% vs. 91% - Treated for withdrawal: 47.6% vs. 17.6%	Research grant (MC-R-360049-02.0) from Maternal and Child Health and Crippled Children's Services (US Department of Health,	Poor