

Medication-Assisted Treatment With Methadone: Assessing the Evidence

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Objective: Detoxification followed by abstinence has shown little success in reducing illicit opioid use. Methadone maintenance treatment (MMT) helps individuals with an opioid use disorder abstain from or decrease use of illegal or nonmedical opiates. This review examined evidence for MMT's effectiveness. **Methods:** Authors reviewed meta-analyses, systematic reviews, and individual studies of MMT from 1995 through 2012. Databases searched were PubMed, PsycINFO, Applied Social Sciences Index and Abstracts, Sociological Abstracts, Social Services Abstracts, and Published International Literature on Traumatic Stress. The authors rated the level of evidence (high, moderate, and low) based on benchmarks for the number of studies and quality of their methodology. They also described the evidence of service effectiveness and examined maternal and fetal results of MMT for pregnant women. **Results:** The review included seven randomized controlled trials and two quasi-experimental studies of MMT, indicating a high level of evidence for the positive impact of MMT on treatment retention and illicit opioid use, particularly at doses greater than 60 mg. Evidence suggests positive impacts on drug-related HIV risk behaviors, mortality, and criminality. Meta-analyses were difficult to perform or yielded nonsignificant results. Studies found little association between MMT and sex-related HIV risk behaviors. MMT in pregnancy was associated with improved maternal and fetal outcomes, and rates of neonatal abstinence syndrome were similar for mothers receiving different doses. Reports of adverse events were also found. **Conclusions:** MMT is associated with improved outcomes for individuals and pregnant women with opioid use disorders. MMT should be a covered service available to all individuals. (*Psychiatric Services* 65: 146–157, 2014; doi: 10.1176/appi.ps.201300235)

Opioid dependence is a serious public health concern. In the United States, approximately 800,000 individuals are heroin dependent (1), and 1.7 million report a substance use disorder involving prescription opioids (2). Opioid dependence is associated with premature mortality, criminality, violence, suicide, HIV and hepatitis C infection, and poor quality of life (3,4). Detoxification followed by abstinence-oriented treatments has shown little success in curtailing illicit opioid use over time (5,6). Methadone, an opioid agonist, and buprenorphine, a partial agonist, may be used in maintenance treatment to improve treatment outcomes. This review focused on methadone maintenance treatment (MMT); a companion review in this series examines buprenorphine (7).

The Substance Abuse and Mental Health Services Administration (SAMHSA) describes medication-assisted treatment as a direct service that provides a person who has a substance use disorder or a mental disorder with pharmacotherapy in conjunction with behavioral therapies as treatment for associated symptoms or disabilities. Treatment is individualized. Medication-assisted treatment with methadone refers to the use of methadone to treat individuals addicted to opioids. A definition of MMT and features of medication-assisted treatment are presented in Table 1.

This article reports the results of a literature review that was undertaken as part of the Assessing the

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Evidence Base Series (see box on next page). The literature review was undertaken to describe MMT and its primary and secondary treatment goals, rate the levels of evidence (methodological quality) of existing studies for this treatment, and describe the effectiveness of this service. The results provide state mental health directors and their staff, purchasers of health services, state policy officials, community health care administrators, consumers, and family members with an accessible summary of the evidence for MMT and its implications for the treatment of opioid use disorders. To address the concerns of the target audiences, this review examined the evidence for MMT in various populations (including pregnant women), appropriate dosing guidelines, and serious adverse events related to methadone use.

Description of MMT

MMT has been available since 1964. In the United States, MMT is offered through specialized methadone treatment programs that provide psychosocial support as well as close patient monitoring. Typically, methadone doses are dispensed daily at the methadone treatment facility to minimize risks of diversion. However, individuals may become eligible for take-home doses on the basis of appropriate clinic attendance, absence of behavioral problems at the clinic or recent drug abuse, lack of known criminal activity, and evidence of a stable home with the ability to store methadone safely.

Because individuals remain dependent on methadone, MMT is not considered an abstinence treatment. The duration of methadone treatment is indefinite (8). The goals of methadone treatment are to reduce or eliminate illicit opioid use and, as a result, to decrease its associated negative outcomes (Table 1). For pregnant women, the goals of MMT include improved maternal and fetal outcomes.

MMT aims to allow individuals with opioid use disorders to minimize many of the negative health and societal outcomes associated with opioid use. Despite the long history of methadone use, studies have suggested that a majority of individuals

Table 1

Description of medication-assisted treatment with methadone

Feature	Description
Service definition	Medication-assisted treatment is a direct service that provides a person with a substance use or mental disorder with pharmacotherapy in conjunction with behavioral therapies as treatment for associated symptoms or disabilities. The nature of the services provided is determined by the person's current status or needs. Methadone maintenance treatment is a medication-assisted treatment that uses methadone to assist individuals with an opiate use disorder to abstain from or decrease the use of illegal opiates (for example, intravenous heroin) or the use of opiates in a nonprescribed manner (for example, abuse of prescription pain medications).
Service goals	Retention in treatment; decrease in illegal opioid use; decrease in mortality; decrease in nonopioid drug use; decrease in criminal activity; decrease in risk behaviors related to HIV and hepatitis C
Populations	Adults with opioid use disorders; pregnant women with opioid use disorders
Settings of service delivery	Methadone treatment centers

treated at methadone clinics receive inadequate doses and that many clinics place an arbitrary limit on the duration of treatment (9,10). This assessment of the available research will help inform behavioral health policy leaders about the effects of MMT on the lives of those with opioid use disorders and about its value as a treatment option and a covered health benefit.

Methods

Search strategy

We conducted a literature search of major databases: PubMed (U.S. National Library of Medicine and National Institutes of Health), PsycINFO (American Psychological Association), Applied Social Sciences Index and Abstracts, Sociological Abstracts, Social Services Abstracts, and Published International Literature on Traumatic Stress. We identified meta-analyses, research reviews, clinical guidelines, and individual studies about MMT that were published from 1995 through 2012. We used combinations of the following search terms: methadone, opioid maintenance treatment, opioid treatment, addiction pharmacotherapy, medication-assisted maintenance treatment, MMT, and pregnancy.

Additional literature was found by examining the bibliographies of major

reviews and meta-analyses, major clinical texts, and professional clinical society reviews. We relied on systematic reviews and meta-analyses to summarize relevant findings from earlier years. To provide additional information from recent years that may not have been included in review articles, we supplemented these review articles with articles presenting results from individual randomized controlled trials (RCTs) and quasi-experimental observational studies. We considered studies that were focused on MMT for adults with opioid use disorders, including pregnant women. Specific topics, such as adverse events and medication interactions, were also examined.

Inclusion and exclusion criteria

The abstracts of the identified articles were examined to determine compliance with inclusion and exclusion criteria. Articles on which opinions concurred were accepted. The following inclusion criteria were used: RCTs, quasi-experimental studies, systematic review articles, meta-analyses, and clinical guidelines; English-language studies conducted in the United States, including international studies that used U.S.-based sites and international reviews encompassing U.S.-based studies; and studies that

About the AEB Series

The Assessing the Evidence Base (AEB) Series presents literature reviews for 14 commonly used, recovery-focused mental health and substance use services. Authors evaluated research articles and reviews specific to each service that were published from 1995 through 2012 or 2013. Each AEB Series article presents ratings of the strength of the evidence for the service, descriptions of service effectiveness, and recommendations for future implementation and research. The target audience includes state mental health and substance use program directors and their senior staff, Medicaid staff, other purchasers of health care services (for example, managed care organizations and commercial insurance), leaders in community health organizations, providers, consumers and family members, and others interested in the empirical evidence base for these services. The research was sponsored by the Substance Abuse and Mental Health Services Administration to help inform decisions about which services should be covered in public and commercially funded plans. Details about the research methodology and bases for the conclusions are included in the introduction to the AEB Series (11).

focused on MMT for individuals with opioid use disorders or the use of MMT during pregnancy. Excluded were case studies, single-subject designs, and cross-sectional studies; studies that focused on methadone use for pain management or for detoxification from opioids; and reviews and meta-analyses that contained only articles that did not meet the inclusion criteria.

Strength of the evidence

The methodology used to rate the strength of the evidence is described in detail in the introduction to this series (11). The research designs of the studies identified during the literature search were examined. Three levels of evidence (high, moderate, and low) were used to indicate the overall research quality of the collection of studies. Ratings were based on predefined benchmarks that considered the number of studies and their methodological quality. If ratings were dissimilar, a consensus opinion was reached.

High ratings indicate confidence in the reported outcomes and are based on three or more RCTs with adequate designs or two RCTs plus two quasi-experimental studies with adequate designs. Moderate ratings indicate that there is some adequate research to judge the service, although it is possible that future research could influence reported results. Moderate

ratings are based on the following three options: two or more quasi-experimental studies with adequate design; one quasi-experimental study plus one RCT with adequate design; or at least two RCTs with some methodological weaknesses or at least three quasi-experimental studies with some methodological weaknesses. Low ratings indicate that research for this service is not adequate to draw evidence-based conclusions. Low ratings indicate that studies have nonexperimental designs, there are no RCTs, or there is no more than one adequately designed quasi-experimental study.

We accounted for other design factors that could increase or decrease the evidence rating, such as how the service, populations, and interventions were defined; use of statistical methods to account for baseline differences between experimental and comparison groups; identification of moderating or confounding variables with appropriate statistical controls; examination of attrition and follow-up; use of psychometrically sound measures; and indications of potential research bias.

Effectiveness of the service

We described the effectiveness of MMT—that is, how well the outcomes of the studies met the goals of MMT. We compiled the findings for separate outcome measures and study populations, summarized the results,

and noted differences across investigations. We considered the quality of the research design in our conclusions about the strength of the evidence and the effectiveness of MMT.

Results and discussion

Level of evidence

The literature search found seven RCTs (12–18) and two retrospective, quasi-experimental studies (19,20). Summaries of these individual studies are provided in Table 2. We also included 15 reviews or meta-analyses that examined multiple studies (21–35). Summaries of these reviews are included in Table 3.

Because of the large number of trials included as individual studies or as part of review articles, the overall evidence rating for MMT is high. Several meta-analyses, reviews, and RCTs representing more than three independent RCTs have reported on the primary outcomes of MMT, which are retention in treatment and reduction of illicit opioid use (12–16,21–24). In addition, meta-analyses, reviews, RCTs, and quasi-experimental studies representing more than three RCTs or two RCTs and two quasi-experimental studies have addressed secondary outcomes such as other illicit drug use, HIV risk behaviors, criminal behaviors, heroin craving, and mortality (15–17,21,23–27).

Effectiveness of MMT

Research supports MMT's positive impact on treatment retention and suppression of heroin use, particularly at higher methadone doses. Findings regarding secondary outcomes are mixed, although there is general support that MMT has a positive impact on criminal activity associated with heroin use, as well as on mortality and risk behaviors for HIV and hepatitis C infection.

MMT versus placebo or no pharmaceutical maintenance treatment. Most of the literature on the effectiveness of MMT versus placebo or no medication-assisted treatment was published between the 1960s and 1990s. In general, these and later studies found that when MMT is provided at adequate dose levels, it is more effective than no medication treatment

Table 2Individual studies of methadone maintenance treatment (MMT) included in the review^a

Study	Design and objectives	Population and conditions	Outcomes measured	Summary of findings
Strain et al., 1999 (13)	Double-blind, 40-week RCT to compare moderate versus high doses of methadone in treatment of adults with opioid dependence	Patients randomly assigned to daily oral methadone hydrochloride; patients receiving a dose ranging from 40–50 mg (N=97) compared with those receiving a dose ranging from 80–100 mg (N=95); all received substance abuse counseling	Primary: opioid-positive urinalysis and treatment retention	No differences in treatment retention through week 40 (mean retention in high-dose group, 159 days; in moderate-dose group, 157 days). The high-dose group had significantly greater reduction in opioid-positive urinalysis compared with the medium-dose group: 53.0% (CI=46.9%–59.2%) versus 61.9% (CI=55.9%–68.0%) (p=.047).
Sees et al., 2000 (12)	RCT to compare outcomes of patients with opioid dependence treated with MMT or with psychosocially enriched, 180-day methadone-assisted detoxification	Patients randomly assigned to MMT (N=91), including 2 hours of psychosocial therapy per week during first 6 months; patients randomly assigned to detoxification (N=88), including 3 hours of psychosocial therapy per week, 14 educational sessions, and 1 hour of cocaine group therapy (if needed) for 6 months	Primary: treatment retention, heroin and cocaine abstinence (by self-report and monthly urinalysis), HIV risk behaviors, and functioning in 5 problem areas (employment, family, psychiatric, legal, and alcohol use)	MMT resulted in greater treatment retention (median retention, 438.5 days versus 174.0 days for comparison group) and lower heroin use. MMT group had a lower rate of drug-related HIV risk behaviors at 12 months (mean±SD=.05±.13 versus .13±.19).
McCarthy et al., 2005 (19)	Retrospective cohort study to compare the effects of high-dose versus low-dose methadone during pregnancy on maternal and fetal outcomes	Mothers who received methadone (N=81) and their offspring; half of mothers assigned to a high-dose group (≥100 mg) and half to a low-dose group (<100 mg)	Primary: rate of medication treatment for neonatal abstinence symptoms, days of infant hospitalization	High doses of methadone were not associated with increased risks of NAS symptoms. High doses had a positive effect on maternal drug abuse: in high-dose group, 11% of infant toxicology screens were positive for illicit drugs, compared with 27% in low-dose group (p=.05).
Schwartz et al., 2006 (14)	RCT to compare outcomes of adults assigned to interim methadone treatment or to a wait-list control group	Participants (N=319) meeting criteria for heroin dependence and for receipt of MMT assigned to interim methadone treatment (N=199) or wait-list control group (N=120)	Primary: rate of standard MMT enrollment, self-reported heroin use, opioid-positive urinalysis, illegal income received, and money spent on drugs	Participants who received interim methadone treatment entered standard MMT at a significantly higher rate than those on the wait list (75.9% versus 20.8%, p<.001). At 4 months, the interim methadone treatment group reported significantly fewer days of heroin use (p<.001), had reduced heroin-positive urine screens (p<.001), reported spending less on drugs (p<.001), and received less illegal income (p<.02).
Jones et al., 2010 (44)	Double-blind RCT to compare neonatal and maternal outcomes of opioid-dependent women treated with methadone or with buprenorphine during pregnancy	Pregnant women (N=175) with opioid dependence; methadone group (N=89; 16 dropped out) and buprenorphine group (N=86; 28 dropped out); 131 neonates of mothers who were followed to the end of pregnancy (58 exposed to buprenorphine, 73 exposed to methadone)	Primary: percentage of neonates treated for NAS, NAS peak score, duration of hospital stay, morphine required to treat NAS, and neonatal head circumference; secondary: treatment retention and reduction in opiate use	Buprenorphine group required less morphine for NAS than methadone group (mean dose=1.1 mg versus 10.4 mg, p<.009), had a shorter hospital stay (10.0 days versus 17.5 days, p<.009), and had a shorter duration of treatment for NAS (4.1 days versus 9.9 days, p<.003); 33% of buprenorphine group discontinued treatment before delivery, compared with 16% of methadone group.
Wilson et al., 2010 (17)	RCT to examine use of interim methadone treatment on HIV risk behavior among adults with heroin dependence	Heroin-dependent adults (N=319) randomly assigned to interim methadone treatment without counseling (N=199) or to wait-list control group (N=120) without automatic admission after 120 days	Primary: AIDS Risk Assessment questionnaire (assesses HIV infection and HIV sex risk behaviors) at baseline and follow-up	For injection risk scale score, injected drugs, and sex risk score, treatment condition (p<.008, p<.03, and p<.04, respectively) and time effects (p<.001, p<.001, p<.02) were significant for injection risk, with interim methadone group performing better than wait-list control group.

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Table 2

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Study	Design and objectives	Population and conditions	Outcomes measured	Summary of findings
Pizarro et al., 2011 (20)	Retrospective cohort study to assess the incidence of clinically significant NAS	Pregnant methadone users (N=174) stratified into three dose groups: low (0–50 mg per day, N=59), medium (51–100 mg per day, N=63), and high (>100 mg per day, N=52)	Primary: rate and severity of NAS, birth weight, preterm birth rate, and neonatal morbidities and mortality	Regardless of methadone dose, rates of NAS were similar among low-dose, medium-dose, and high-dose groups (40.7%, 52.4%, and 40.8%, respectively; $p>.05$). No significant outcomes were found.
Schwartz et al., 2011 (15)	RCT to evaluate the impact of counseling on the first 4 months of MMT among 3 comparison groups	Participants (N=244) newly admitted to methadone treatment programs from wait lists and randomly assigned to emergency counseling only for 120 days followed by standard treatment (N=108), standard psychosocial services (N=107), or counseling by case managers with small caseloads (N=29)	Primary: treatment retention and Addiction Severity Index, which includes alcohol and drug use; medical, psychological, and legal issues; family and social relationships; and employment status	Counseling had no significant impact on treatment retention or rate of positive urine tests for methadone group. All groups showed reduction in self-reported days of criminal activity, money spent on drugs, and illegal income compared with baseline (all $p<.001$).
Schwartz et al., 2012 (16)	RCT to evaluate the impact of counseling on MMT among 3 comparison groups at 12 months (follow-up of the Schwartz et al. [15] sample)	Participants (N=230) from previous RCT; 3 conditions: emergency counseling (N=99), standard counseling (N=104), or counseling by case managers with small caseloads (N=27)	Primary: treatment retention and Addiction Severity Index, which includes alcohol and drug use; medical, psychological, and legal issues; family and social relationships; and employment status	No significant differences were found in treatment retention between the supervised methadone (60.6%), standard methadone (54.8), and restored methadone (37.0%) treatment groups. Positive urine screens declined significantly from baseline for all groups ($p<.001$ for heroin and $p<.003$ for cocaine metabolites). No significant group \times time interactions were found for these measures.

^a Studies are listed in chronological order. Abbreviations: CI, 95% confidence interval; NAS, neonatal abstinence syndrome; RCT, randomized controlled trial

in retaining patients in treatment and reducing illicit opioid use (21,22,28,29).

Recently, Mattick and colleagues (21) conducted a review for the Cochrane Collaboration of 11 RCTs (two of which were double-blinded) that assessed the effectiveness of MMT compared with treatments with no opioid replacement therapy (that is, detoxification protocols, drug-free rehabilitation protocols, placebo medications, or wait-list control groups). The combined total of participants across 11 studies was 1,969. On the basis of meta-analyses, the authors concluded that methadone was significantly more effective than non-pharmacological treatment in retaining patients in treatment and in suppressing heroin use as measured by urine drug testing. No significant difference was found between the two treatment conditions (MMT and no opioid replacement therapy) in their impact on criminal activity or mortality, although

individual studies showed a greater reduction in both outcomes among patients receiving MMT. Three of the 11 studies reviewed by Mattick and colleagues measured criminal activity, and four measured mortality.

Sees and colleagues (12) compared outcomes of individuals with opioid dependence who were receiving MMT (N=91) or who were in a 180-day psychosocially enriched detoxification program (N=88). One goal of this study was to examine alternatives to indefinite MMT use by looking at a six-month detoxification rather than the faster detoxification programs (usually one month) studied in the past. For six months the detoxification group received psychosocial services that included three hours of psychosocial therapy per week, 14 educational sessions, and one hour of group therapy focused on cocaine use; the group also received six months of aftercare. The group receiving MMT

had longer retention in treatment compared with the detoxification group (median of 438.5 versus 174 days). The MMT group also showed lower rates of heroin use and lower rates of drug-related HIV risk behaviors compared with the detoxification group. There were no differences between the two groups in sex-related HIV risk behaviors or in employment, family functioning, or alcohol use outcomes.

Two systematic reviews and meta-analyses have examined the impact of MMT on HIV high-risk behaviors. Both reviews noted the limited number of RCTs that contributed to their results. One review (N=12 studies) found that MMT was associated with a 54% reduction in the risk of HIV infection (25). The second review (N=36 studies) was unable to combine results from the studies; the authors concluded that across studies MMT reduced drug-related risk factors such as sharing of injection

Table 3Review articles about methadone maintenance treatment (MMT) included in the review^a

Study	Focus of review	Studies included	Outcomes measured	Summary of findings
Hall et al., 1998 (22)	Effectiveness of MMT on heroin use and crime	6 RCTs assessing MMT, and 8 additional generalized observational studies	Primary: reduction in heroin use and illicit opioid use, criminal activity	Although variation in outcomes between different programs was noted, the effectiveness of MMT in controlling heroin and illicit opioid use and crime was generally supported through the RCTs and observational studies.
Fletcher and Battjes, 1999 (29)	Epidemiological Drug Abuse Treatment Outcome Studies (DATOS) conducted at multiple U.S. sites	12-month follow-up sample based on 2,966 interviews from 76 U.S. programs	Primary: treatment retention and various other treatment outcomes	DATOS study results for drug treatment outcomes were consistent with prior evaluation findings, indicating that the major treatment modalities (including outpatient methadone treatment) are effective in reducing illicit drug use, reducing the incidence of drug-related criminal behavior, and supporting improvement of health, mental health, and social functioning.
Faggiano et al., 2003 (23)	Efficacy and safety of various dose ranges of MMT for opioid dependence	21 studies, including 11 RCTs (2,279 total participants) and 10 controlled prospective studies (3,715 total participants)	Primary: retention rate, opioid use (self-reported), opioid abstinence (urine screen), cocaine abstinence (urine screen), and overdose mortality	RCTs showed that high doses of MMT were associated with better treatment retention (high versus low doses at longer follow-ups, RR=1.62, CI=.95–2.77), opioid abstinence (high versus low, RR=1.59, CI=1.16–2.18; high versus middle, RR=1.51, CI=.63–3.61), and cocaine abstinence (high versus low, RR=1.81, CI=1.15–2.85). At 6-year follow-up, controlled prospective studies showed lower overdose mortality at higher doses (high versus low doses, RR=.29, CI=.02–5.34; high versus middle, RR=.38, CI=.02–9.34; and middle versus low, RR=.57, CI=.06–5.06).
Center for Substance Abuse Treatment, 2004 (32)	National assessment of deaths associated with methadone use; recommendations for reducing mortality from methadone	National assessment of methadone-associated mortality in May 2003	Primary: methadone-associated mortality	Evidence suggests that an increase in methadone-attributable deaths in 1999–2004 was largely related to increased use for pain analgesia. SAMHSA highlights the importance of public understanding that related mortality is essentially eliminated when methadone is prescribed, dispensed, and used appropriately.
Connock et al., 2007 (28)	Clinical and cost effectiveness of BMT and MMT for the management of opioid-dependent individuals	31 systematic reviews and 27 RCTs	Primary: retention in treatment and illicit use of opioids	At all doses used in the studies (MMT, 20–97 mg per day; BMT ≤5–18 mg per day), treatment retention was better than in the placebo or no therapy groups (MMT, RR=3.91, CI=1.17–13.2; BMT, RR=1.74, CI=1.06–2.87). Higher doses of MMT and BMT were almost always more effective than lower doses for treatment retention and illicit use reduction. Across comparable doses, MMT was more effective than BMT for treatment retention, except at low doses. At low doses, the two medications appeared comparable (≤35 mg of MMT versus 6–16 mg of BMT, RR=1.01, CI=.66–1.54). No significant difference across studies was found in illicit opiate use between flexible-dose MMT and BMT.

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Study	Focus of review	Studies included	Outcomes measured	Summary of findings
Mattick et al., 2009 (21)	Effectiveness of MMT compared with treatments not involving opioid replacement therapy	11 RCTs (1,969 total participants)	Primary: patient retention in treatment and heroin use suppression as measured by urine drug testing; secondary: criminal activity and mortality	MMT was significantly more effective than nonreplacement approaches in treatment retention and suppression of heroin use (measured by self-report and lab analysis) (6 RCTs, RR=.66, CI=.56-.78). No significant differences were found for criminal activity (3 RCTs, RR=.39, CI=.12-1.25) or mortality (4 RCTs, RR=.48, CI=.10-2.39).
Cleary et al., 2010 (31)	Relationship between maternal methadone dose in pregnancy and diagnosis or medical treatment of NAS	67 studies in the systematic review; 29 studies in the meta-analysis	Primary: key conclusions, including incidence, severity, and duration of NAS outcomes in relation to maternal methadone dose	Meta-analysis did not demonstrate a consistent, significant difference in NAS incidence among neonates of women on low versus high methadone doses at delivery. Nineteen studies found a relationship between methadone dose and incidence, severity, or duration of NAS; 18 did not find a relationship; 30 did not report on the relationship.
Fareed et al., 2010 (24)	Update for clinicians about methadone dosing, with dose recommendations	24 studies, including 12 RCTs, 10 observational studies, and 2 meta-analyses	Primary: effect of methadone dose on retention in treatment, illicit opioid use, and mortality	Treatment retention: 9 studies reported that the daily dose range of 60–100 mg showed significant improvement for treatment retention compared with lower doses. Six studies did not find a significant difference in retention for this dose range. Illicit opioid use: 10 studies recommended a daily dose range of 60–100 mg; 2 studies suggested that doses over 100 mg are more effective for decreasing heroin use. Mortality rate: 2 long-term observational studies reported doses greater than 100 mg daily to be safe and effective in long-term MMT (the authors stated that more research is needed).
Modesto-Lowe et al., 2010 (35)	Risk factors for methadone mortality in opioid-dependent and pain populations; guidelines for initiating methadone treatment in these populations to minimize risk of death	Literature review (N of studies not reported) of pharmacological properties and relationship to risk factors for adverse events	Primary: pharmacological profile of methadone and relationship to risk factors for methadone mortality	Risk factors of respiratory depression include advanced age, medically compromised status, liver or pulmonary pathology, sleep apnea, polysubstance abuse, opioid-naïve or low opioid tolerance, high doses of methadone, and rapid titration of methadone. Risk factors for Torsades de Pointe include female sex, electrolyte imbalance, liver or cardiac pathology, unexplained syncope or seizures, other drug and medication use that prolongs QT interval or inhibits CYP 3A4, prolonged QT interval, and high doses of methadone.
Amato et al., 2011 (30)	Effectiveness of any psychosocial and any agonist maintenance treatment compared with standard agonist treatment for opiate dependence	35 RCTs considering 13 different psychosocial interventions (4,319 total participants)	Primary: treatment retention, opiate use during treatment, compliance with sessions during treatment, and other psychological health measures	Compared with standard maintenance treatment, psychosocial and any maintenance treatment showed no benefit for treatment retention (27 studies, 3,124 participants, RR=1.03, CI=.98-1.07), opiate abstinence during treatment (8 studies, 1,002 participants, RR=1.12, CI=.92-1.37), or compliance (3 studies, mean difference=.43, CI=-.05 to .92), among other findings. Comparisons of the various

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Table 3

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Study	Focus of review	Studies included	Outcomes measured	Summary of findings
Fareed et al., 2011 (27)	Effect of MMT on opiate craving	Total of 16 studies: RCTs, observational studies, meta-analyses, and reviews	Primary: effect of MMT on subjective opiate craving and on objective measures of opiate craving	psychosocial approaches showed no significant differences in any outcomes. Seven studies reported that methadone could reduce heroin craving, 4 reported that MMT patients are still at risk for craving, 1 study reported that methadone could increase heroin craving, and 4 studies reported that methadone had a neutral effect on heroin craving.
Gowing et al., 2011 (26)	Effect of oral substitution treatment for opioid-dependent drug injectors on behaviors associated with high risk of HIV transmission; incidence of HIV infections	38 studies (nearly 12,400 total participants). Two studies were RCTs; 11 were controlled trials, but the intervention was not relevant to the review, and therefore, these trials were used as a baseline versus postintervention comparison; 21 were observational prospective studies; 4 were cross-sectional.	Primary: HIV transmission risk behaviors, including drug use; secondary: rates of HIV infection	Substitution treatment for opioid-dependent, injecting drug users with methadone or buprenorphine was consistently associated with significant reductions in illicit opioid use, injecting drug use, and sharing of needles. It was associated with a reduction in the use of multiple sex partners or the exchange of sex for money or drugs, but it was not associated with increased condom use. The risk behavior reduction appeared to relate to reductions in cases of HIV infection, although data were not pooled because of variability and bias among studies.
Martin et al., 2011 (34)	Adverse cardiac events associated with methadone	Expert panel examined the peer-reviewed literature, regulatory actions, professional guidance, and opioid treatment program outcomes	Primary: cardiac events associated with methadone, cardiac QT interval impact	Results established the connection between methadone and prolongation of QT interval and suggested a dose-dependent effect for methadone. Authors recommended that every opioid treatment program should have a universal cardiac risk management plan (to the extent possible) for patients with identified risk factors for adverse cardiac events.
Webster et al., 2011 (33)	Causes and risk factors for opioid-related poisoning deaths and recommendations to reduce death rates	91 documents were assessed by a panel of experts	Primary: frequency, demographic characteristics, and risk factors for opioid-related deaths attributable to overdose in the past decade	Risk factors for methadone-related deaths were unanticipated medical or mental health comorbidities, payer policies that encourage or mandate methadone as first-line therapy, the presence of additional central nervous system–depressant drugs, and sleep-disordered breathing. Cardiac irregularities in the presence of methadone remain an uncommon cause of death.
MacArthur et al., 2012 (25)	HIV risk: quantify the effect of opiate substitution treatment in relation to HIV transmission among individuals who inject drugs	Pooled data from 9 observational studies, including 819 incident HIV infections over 23,608 person-years of follow-up	Primary: impact of opiate substitution treatment as related to HIV incidence; secondary: effect of variables such as mode and duration of treatment, geographical region, study setting, and participant characteristics	Substitution treatment was associated with an average 54% reduction in the risk of HIV infection among individuals who inject drugs (rate ratio=.46, CI=.32-.67; p<.001). Heterogeneity was found between studies that could not be explained by region, site of recruitment, or incentives.

^a Studies are listed in chronological order. Abbreviations: BMT, buprenorphine maintenance treatment; CI, 95% confidence interval; NAS, neonatal abstinence syndrome; RCT, randomized controlled trial; RR, relative risk or risk ratio

equipment (26). The second review reported that there were too few studies to be conclusive but stated that MMT was associated with lower rates of multiple sex partners and the exchange of sex for drugs or money and had no effect on the use of condoms.

Interim methadone treatment is a program that allows provision of methadone under daily supervision for up to 120 days while the individual is awaiting placement in a standard methadone program. It does not include counseling other than emergency counseling. One RCT examined HIV risk behaviors for 319 opioid-addicted adults who were randomly assigned to interim methadone treatment or a wait list (17). Rates of drug injection and sex while high on drugs were significantly lower for individuals randomly assigned to the interim methadone program.

Another review examined the effect of MMT on heroin craving and included 16 studies (27). It found mixed results; seven studies showed that MMT reduced heroin craving, four studies showed that patients were still at risk of heroin craving, one study showed that methadone could increase heroin craving, and four studies showed a neutral effect. In general, the studies that showed positive results used higher methadone doses, and those with negative or neutral results used lower doses or were in the setting of methadone detoxification.

Levels of methadone doses. The literature has consistently shown that the effectiveness of MMT increases when methadone is used at doses above 60 mg. Two systematic reviews suggested that higher doses of methadone were associated with improved outcomes. First, Faggiano and colleagues (23) performed a systematic review for the Cochrane Collaboration that evaluated the efficacy and safety of different doses of methadone for opioid dependence. This review included 21 studies (11 RCTs and ten controlled, prospective, quasi-experimental studies). The authors examined outcomes for four different dose ranges: low (1–39 mg), medium (40–59 mg), high (60–109 mg), and very high (≥ 110 mg). Results showed that high doses were associated with

better treatment retention and cocaine abstinence, less heroin use during treatment, and fewer withdrawal symptoms. Few studies included doses above 110 mg; therefore, the data were less reliable for these doses. Only one underpowered study examined mortality and criminal activity, but a trend that did not reach statistical significance suggested that individuals receiving higher doses had lower mortality rates. A second review showed similar results; doses above 60 mg were associated with better treatment retention and fewer urine drug tests that were positive for opioids (24).

Strain and colleagues (13) conducted a 40-week, double-blinded RCT comparing moderate (40–50 mg, N=97) and high (80–100 mg, N=95) doses of methadone in the treatment of adults with opioid dependence. There were two main outcome measures: opioid-positive urinalysis and treatment retention. The study found no difference in treatment retention through week 40. The high-dose group had significantly greater reduction in opioid-positive urinalysis (53%) compared with the medium-dose group (62%).

Service delivery and psychosocial treatments. Many methadone treatment centers have wait lists, which indicate a lack of access to desired treatment. Given the high social cost of opioid addiction, a research group investigated the use of interim methadone treatment as a way to improve access and decrease waiting lists. Schwartz and colleagues (14) conducted an RCT to compare outcomes for adults assigned to interim methadone treatment (N=199) or a wait-list control group (N=120). The study found that participants in the interim methadone treatment cohort entered standard MMT at a significantly higher rate (75%) than those assigned to the wait list (20.8%). In addition, at four months, interim methadone treatment participants reported significantly lower rates of heroin use than wait listed participants, had fewer positive drug tests for heroin, reported spending significantly less money on drugs, and received less illegal income.

Schwartz and colleagues (15,16) compared individuals who were admitted to interim methadone (N=99),

standard methadone (N=104), and restored methadone (N=27) treatment. Restored methadone treatment refers to treatment by counselors with reduced caseloads, which allows them to provide more intensive treatment. The studies found no difference between groups in treatment retention at four months and better treatment retention for the interim and standard methadone treatment groups at 12 months. No between-group differences in opiate use or other drug use were found at the four- and 12-month follow-up assessments. At 12 months, no difference was noted between groups in arrests, criminal activity, or money spent on drugs. Self-reported illegal income was significantly higher in the standard methadone treatment group.

A Cochrane Collaboration systematic review by Amato and associates in 2011 (30) examined 35 studies that evaluated whether outcomes improved after the addition of a specific, structured psychosocial intervention to standard agonist maintenance treatment (either methadone or buprenorphine) that already included psychosocial treatment. The studies included 13 different psychosocial interventions that were added to standard treatment. Taken as a whole, additional psychosocial treatment did not statistically improve retention in treatment, use of opiates during treatment, session attendance during treatment, or other measures of psychological health. When the review was limited to studies with contingency management approaches, there still was no statistically significant effect of additional psychosocial services on treatment retention or decreased opioid use. Contingency management describes behavioral modification programs that provide rewards, such as retail gift cards, for desired behaviors, such as negative urinalyses. Because standard treatment included psychosocial treatment, Amato and colleagues could draw conclusions only regarding the addition of a structured psychotherapy and not regarding the efficacy of psychosocial treatment.

Pregnant women subgroup. Early studies established the efficacy of using MMT to reduce pregnancy-related maternal and fetal morbidity among

opioid-addicted pregnant women (36,37). MMT during pregnancy was associated with decreased illicit opioid use, increased rates of prenatal retention in treatment, decreased pregnancy complications, and generally improved fetal outcomes (18,38). However, MMT has been found to put newborn infants at risk for neonatal abstinence syndrome (NAS)—a condition characterized by dysfunction of the autonomic nervous system, gastrointestinal tract, and respiratory system and by irritability of the central nervous system. NAS often requires detoxification treatment in the hospital with a morphine taper (19,37,39–41). Reported rates of withdrawal symptoms among neonates born to opioid-addicted mothers who continued to use opiates within a week of giving birth range from 55% to 94% (42), and rates of NAS that develop among neonates as a result of treating the mother with MMT during pregnancy fall into this range (31). Recent studies on the long-term impact of NAS on development are scant. Older studies indicated no differences in cognitive performance among four-year-old children of mothers receiving MMT and children of mothers with similar demographic characteristics in a control group. However, scores of children in both groups were lower than population norms (43).

To guide clinicians regarding the necessity of tapering MMT before delivery, researchers have examined the relationship between methadone dose during pregnancy and the incidence and severity of NAS among newborn infants. Because of increased methadone metabolism during pregnancy, pregnant women often require higher doses. Cleary and colleagues (31) performed a systematic review and meta-analysis and found that methadone dose had no consistent effect on rates of NAS and other neonatal outcomes. Two of the 67 studies included in that review were RCTs, and the remaining studies had quasi-experimental observational designs. Additional retrospective cohort studies showed similar results; no difference in NAS rate or severity was found on the basis of methadone dose during pregnancy (19,20).

The Maternal Opioid Treatment: Human Experimental Research

Evidence for the effectiveness of methadone maintenance treatment: high

Evidence clearly shows that MMT has a positive impact on:

- Retention in treatment
- Illicit opioid use

Evidence is less clear but suggestive that MMT has a positive impact on:

- Mortality
- Illicit drug use (nonopioid)
- Drug-related HIV risk behaviors
- Criminal activity

Evidence suggests that MMT has little impact on:

- Sex-related HIV risk behaviors

(MOTHER) study was a large, multi-center, double-blind RCT published in 2010 (44). The authors compared neonatal and maternal outcomes between pregnant women treated during their pregnancies with methadone (dose range 20–140 mg) or buprenorphine (dose range 2–32 mg). Eighty-nine women were randomly assigned to receive methadone, and 86 were randomly assigned to receive buprenorphine. Thirty-three percent of women in the buprenorphine group discontinued treatment before delivery, compared with 16% in the methadone group. No significant differences were found in the percentage of newborns treated for NAS. However, infants born to women treated with methadone required higher doses of morphine to treat NAS, required more days of treatment for NAS, and had longer hospital stays. There were no differences in maternal use of illicit drugs at delivery or other fetal or maternal outcomes. These results suggest that less severe NAS among infants born to mothers treated with buprenorphine may be confounded by poorer treatment retention rates for these mothers, especially for mothers with a longer history of heroin use.

Adverse events. Between 1999 and 2004, deaths attributed to methadone increased by 390%. Evidence suggests that this change was largely related to the increased use of methadone for pain analgesia rather than MMT (32,33). Nonetheless, the sharp rise of methadone-related deaths highlights safety issues—in particular, the risks of respiratory depression and cardiac QT interval

prolongation. The QT interval is a measure of time between the start of the Q wave and the end of the T wave in the heart's electrical cycle that is measured by an electrocardiogram. Prolongation of the QT interval can lead to serious heart arrhythmias such as Torsades de Pointes (TdP) and sudden death. As a result of this rise in mortality, the U.S. Food and Drug Administration issued a physician safety alert in 2006 highlighting fatalities and cardiac arrhythmias associated with methadone (34).

Respiratory depression is most often a consequence of methadone accumulation and use of concurrent illicit drugs or medications that also suppress the central nervous system. Reviews suggest that initiation into methadone treatment is a particularly vulnerable time in both methadone maintenance and pain therapy populations, particularly if the dose is increased rapidly (33,35). The most common drugs associated with respiratory suppression are benzodiazepines and alcohol. Deaths from respiratory depression may also be caused by inappropriate dosing by methadone recipients and by diversion of methadone, which occurs when individuals who have a prescription for methadone sell or give their methadone to others rather than using it themselves.

In 2007–2009, a panel established by SAMHSA summarized evidence of methadone's impact on the cardiac QT interval and derived guidelines for methadone treatment programs (34). The review established a connection between methadone and prolongation of the QT interval and suggested

a dose-dependent effect for methadone. Prolongation of the QT interval greater than 500 ms confers significant risk with respect to arrhythmias such as TdP (34). Use of additional medications that might increase the QT interval increases an individual's risk of cardiac arrhythmias. Despite these findings, cardiac irregularities in the presence of methadone remain an uncommon cause of death (33).

Conclusions

Overall, there is a high level of evidence for the effectiveness of MMT in improving treatment retention and decreasing illicit opioid use (see box on previous page). Research findings regarding the impact of MMT on many secondary outcomes, such as mortality, drug-related HIV risk behaviors, and criminal activity, are less conclusive but suggest positive trends. Finally, research has not conclusively shown positive impacts on sex-related HIV risk behaviors, non-opioid illicit drug or alcohol use, or other social consequences. Methadone maintenance doses above 60 mg confer greater efficacy in retention and suppression of illicit opioid use; however, there is limited evidence that doses above 100 mg provide additional benefits. No evidence has emerged to delineate the duration of MMT beyond an indefinite period. Although MMT generally is believed to reduce mortality risk among individuals with opioid dependence, methadone is also associated with significant adverse events, such as respiratory depression and cardiac arrhythmias, in the presence of rapid titrations or other risk factors. There is no clear evidence that structured psychotherapy provided in addition to the psychosocial support normally offered at methadone treatment centers conveys additional benefit.

MMT improves pregnancy-related outcomes by reducing illicit drug use and increasing treatment retention. However, newborn infants of mothers treated with methadone during pregnancy may be born with NAS irrespective of the methadone dose used by the mothers.

Potential areas for future research include increased focus on the impact

of MMT on secondary outcomes, development of a better understanding of the efficacy and safety tradeoffs of very high methadone doses (>100 mg), confirmation of the results of interim methadone treatment as a potential avenue to improve outcomes of MMT, and use of MMT in specific subpopulations, such as racial and ethnic minority groups and individuals who use prescription drugs compared with those who use intravenous heroin.

Given the poor success rates of abstinence-based treatments for opioid use disorders, MMT is an important treatment option for opioid dependence. Providers, consumers, and family members should be educated about the benefits of MMT in helping individuals manage opioid use disorders and about appropriate ways to avoid the significant adverse events that can occur with methadone. Providers and consumers need to be educated regarding appropriate doses to improve efficacy and appropriate initiation to minimize adverse events.

Because of MMT's relative efficacy, efforts should be made to increase access to MMT for all individuals who struggle with opioid use disorders. Directors of state mental health and substance abuse agencies and community health organizations should look for methods to increase access to MMT, and purchasers of health care services should cover appropriately monitored MMT.

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