Medication-Assisted Treatment With Buprenorphine: Assessing the Evidence

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Objective: **Buprenorphine maintenance treatment (BMT) and methadone maintenance treatment (MMT) are pharmacological treatment programs for individuals with opioid use disorders. MMT is discussed in a companion article. This article describes BMT and reviews available research on its efficacy.** ***Methods:*** **Authors reviewed meta-analyses, systematic reviews, and individual studies of BMT from 1995 through 2012. Databases surveyed were PubMed, PsycINFO, Applied Social Sciences Index and Abstracts, Sociological Abstracts, Social Services Abstracts, and Published International Literature on Traumatic Stress. They chose from three levels 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.** ***Results:*** **Sixteen adequately designed randomized controlled trials of BMT indicated a high level of evidence for its positive impact on treatment retention and illicit opioid use. Seven reviews or meta-analyses were also included. When the medication was dosed adequately, BMT and MMT showed similar reduction in illicit opioid use, but BMT was associated with less risk of adverse events. Results suggested better treatment retention with MMT. BMT was associated with improved maternal and fetal outcomes in pregnancy, compared with no medication-assisted treatment. Rates of neonatal abstinence syndrome were similar for mothers treated with BMT and MMT during pregnancy, but symptoms were less severe for infants whose mothers were treated with BMT.** ***Conclusions:*** **BMT is associated with improved outcomes compared with placebo for individuals and pregnant women with opioid use disorders. BMT should be considered for inclusion as a covered benefit. (*Psychiatric Services* 65:158–170, 2014; doi: 10.1176/appi.ps.201300256)**

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More than two million individuals in the United States are addicted to opioids (1). Two common options for pharmacological maintenance treatment of opioid dependence are the opioid agonists methadone and buprenorphine. Over 300,000 individuals receive methadone through outpatient treatment programs (2). Over half of these programs and thousands of physicians now offer buprenorphine. Such pharmacological treatment is typically provided in combination with psychosocial or other support services.

This article reports the results of a literature review that was undertaken as part of the Assessing the Evidence Base Series (see box on next page). Methadone maintenance treatment (MMT) is reviewed in a companion article in this series (3). As discussed in that review, research has shown that MMT improves treatment outcomes for individuals with opioid dependence (4–7). However, MMT is associated with serious adverse events, such as respiratory depression and cardiac arrhythmias (8–10). Because of concern about these adverse events and medication diversion, MMT is restricted to dedicated opioid treatment programs that provide daily medication dosing and offer psychosocial treatment services. In this article, we review buprenorphine maintenance treatment (BMT) as an alternative to MMT for the long-term management of opioid use disorders.

For purposes of this initiative, the Substance Abuse and Mental Health Services Administration describes

medication-assisted treatment as a direct service that provides a person who has a substance use or mental disorder with pharmacotherapy in conjunction with behavioral therapies as treatment for associated symptoms or disabilities. BMT is a medication-assisted treatment that uses buprenorphine or buprenorphine-naloxone to treat individuals with an opioid use disorder. A definition of medication-assisted treatment with buprenorphine for opioid use disorders is presented in Table 1.

The objectives of this review were to describe BMT and its primary and secondary treatment goals, rate the level of evidence (methodological quality) of existing studies for this treatment, describe the degree of effectiveness of this service on the basis of the research literature, and compare the relative advantages and disadvantages of BMT and MMT.

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 (14).

Description of BMT

Buprenorphine has been available as an injectable medication at low doses to treat pain since the 1980s. In 2000, Congress passed the Drug Abuse Treatment Act (DATA), which allowed physicians to prescribe approved medications for long-term opioid treatment in settings other than opioid treatment clinics, such as in office-based facilities (11). In 2002, the U.S. Food and Drug Administration (FDA) approved high-dose sublingual formulations of buprenorphine and buprenorphine-naloxone for the treatment of opioid use disorders (11,12). Naloxone induces withdrawal symptoms if taken intravenously but not if taken orally. The manufacturer developed the combination buprenorphine-naloxone medication to decrease the potential for abuse and diversion. Buprenorphine and buprenorphine-naloxone became the first medications to be approved under DATA and the first medications available through DATA for office-based treatment of opioid dependence in the United States. Prescribing must be done within the guidelines of DATA, which requires that physicians receive specific training and certification before prescribing buprenorphine and that the number of patients they treat at one time be limited to 100 (originally 30 patients and amended in 2006) (13). In this review, we use buprenorphine in reference to both buprenorphine and buprenorphine-naloxone sublingual tablets. Although buprenorphine can be used to manage withdrawal symptoms during acute detoxification from opioids, BMT refers to the maintenance use of buprenorphine to decrease illicit opioid use.

Because individuals remain dependent on buprenorphine, BMT is not considered an abstinence treatment. The goals of BMT are to reduce or eliminate illicit opioid use and, as a result, to decrease its associated negative outcomes (Table 1). This assessment of the research will help inform behavioral health policy leaders about the merits of BMT as distinct from and in comparison to MMT. A summary of its value as a covered health benefit will also be of use to third-party payers, providers, and people making personal decisions about which medication to use.

Methods

Search strategy

We conducted a literature search of major databases: PubMed (U.S. National Library of Medicine and

Table 1

Description of medication-assisted treatment with buprenorphine

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. Buprenorphine maintenance therapy is a medication-assisted treatment that uses buprenorphine or buprenorphine-naloxone to help individuals with an opioid use disorder abstain from or decrease the use of illegal opioids (for example, intravenous heroin) or the use of opioids 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	Office-based facilities; opioid treatment centers

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 BMT that were published from 1995 through 2012. We found additional literature 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. These review articles were supplemented with individual randomized controlled trails (RCTs) and quasi-experimental observational studies to provide additional information from recent years.

The terms used to search the literature were buprenorphine, buprenorphine/naloxone, opioid maintenance therapy, opioid treatment, addiction pharmacotherapy, medication-assisted maintenance treatment, buprenorphine maintenance therapy, and pregnancy. This review did not compare BMT to naltrexone, another medication used in opioid maintenance treatment, because the literature review uncovered no studies directly comparing the two medications.

Inclusion and exclusion criteria

The abstracts of identified articles were examined to determine compliance with the review inclusion and exclusion criteria. The following types of articles were included: 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 focused on BMT for individuals with opioid use disorders or the use of BMT during pregnancy.

Excluded were case studies, cross-sectional studies, and those with single-subject designs. Also excluded were studies that focused on buprenorphine use for pain management or for detoxification from opioids. Finally, reviews and meta-analyses that examined only studies that did not meet the inclusion criteria were excluded.

Strength of the evidence

The methodology used to rate the strength of the evidence is described in detail in the introduction to this series (14). The research designs of the identified studies 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 (occurring for 13% of the studies rated), a consensus opinion was reached.

In general, 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 the service—that is, how well the outcomes of the studies met the service goals. 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 ffectiveness of the service.

Results and discussion

Level of evidence

The literature search revealed 16 RCTs (15–30), a randomized cross-over study (31), a study using a self-administered survey (32), and a retrospective descriptive study (33). Summaries of these studies are provided in Table 2. RCTs used either buprenorphine alone or buprenorphine-naloxone, as noted in the table. The search also found seven reviews or meta-analyses (10,34–39), and summaries of these are provided in Table 3.

Because of the large number of trials, the overall evidence for BMT was rated as high. Thus the level of research evidence is similar for BMT and MMT (3). In addition, multiple meta-analyses, reviews, and more than three independent RCTs have compared BMT with MMT on the primary outcomes stated above, and these results are also based on a high level of evidence in RCTs (19,20) or reviews (34,36). Secondary outcomes, such as use of other illicit drugs, criminal behaviors, and other measures of addiction severity or psychosocial functioning varied among studies; as a result, the evidence for these secondary outcomes is not as strong.

Effectiveness of BMT

Buprenorphine versus placebo. Studies since 1995 have found buprenorphine to be a safe and effective treatment for opioid dependence. Compared with placebo, buprenorphine significantly improved treatment retention at low (2–6 mg), medium (7–15 mg), and high (≥16 mg) doses (15–17,34). In one meta-analysis, buprenorphine showed an improvement in treatment retention over placebo at low doses (relative risk [RR]=1.50, $p<.05$), medium doses (RR=1.74, $p<.05$), and high doses (RR=1.74, $p<.05$) (34). Higher dose ranges (16–32 mg) have been associated with better retention in treatment, compared with the

Table 2

Individual studies of buprenorphine maintenance treatment (BMT) included in the review[a]

Study	Design and objectives	Population and conditions	Outcomes measured	Summary of findings
Johnson et al., 1995 (18)	RCT to assess early clinical effectiveness of buprenorphine versus placebo in an opioid-dependent population	Patients randomly assigned to placebo (N=60) or to 2 mg (N=60) or 8 mg (N=30) daily of sublingual buprenorphine. On days 6–13, patients could request a dose change, knowing that the new dose would be randomly chosen from the 2 other alternatives.	Primary: percentage of patients in each group requesting a dose change. Secondary: positive urine opioid screens and patient satisfaction with treatment	Significant main effect of buprenorphine versus placebo. Patients taking buprenorphine requested fewer dose changes (27% for 2 mg and 32% for 8 mg versus 65% for placebo, $p<.01$). They also had fewer positive urine drug screens ($p<.05$) and rated dose adequacy higher ($p<.01$). Effects were significant for buprenorphine versus placebo but not for various doses.
Ling et al., 1996 (19)	RCT to evaluate safety and efficacy of long-term, fixed-dose BMT versus low- and high-dose MMT	225 treatment-seeking patients with opioid dependence randomly assigned to receive 8 mg per day of buprenorphine, 30 mg per day of methadone (low dose), or 80 mg of MMT (high dose), all over a 1-year period	Primary: urine toxicology, retention, craving, and withdrawal symptoms; safety data	At 26 and 52 weeks, the high-dose MMT group had better retention (31% versus 20% at 52 weeks, $p=.009$) and less opioid use ($p=.002$) than the low-dose MMT or fixed-dose BMT groups. Results were comparable in the latter two groups. No serious adverse health effects were noted for 8 mg of buprenorphine.
Ling et al., 1998 (16)	RCT to evaluate safety and efficacy of an 8 mg per day sublingual dose of buprenorphine versus a 1 mg per day dose over a 16-week treatment period in a heroin-dependent population; secondary analysis of 2 other dose levels (4 mg and 16 mg)	736 total patients in 4 dose groups: 1 mg, N=185; 4 mg, N=182; 8 mg, N=188; and 16 mg, N=181. Total of 375 completed the full 16 treatment weeks.	Primary: retention in treatment, illicit opioid use as indicated by urine drug screens, opioid craving, and global ratings	For retention, 40% in 1-mg group completed treatment, 51% in 4-mg group, 52% in 8-mg group, and 61% in 16-mg group. The 1-mg group had poorer retention than the 8-mg ($p=.019$) or 16-mg ($p<.001$) groups. The 8-mg group had significantly fewer positive screens than the 1-mg group, less craving, and higher global ratings ($p<.05$).
O'Connor et al., 1998 (25)	RCT to evaluate the effect of thrice weekly BMT in a primary care setting versus a traditional treatment facility	46 patients assigned to primary care treatment (N=23) or traditional treatment setting (N=23) for 12 weeks	Primary: treatment retention and urine drug tests	A trend toward higher retention at 12 weeks was noted in the primary care setting (78% versus 52%, $p=.06$). Patients in that setting had significantly lower rates of illicit opioid use as measured by urine drug tests (63% versus 85%, $p<.01$) but no difference in rates of cocaine use.
Johnson et al., 2000 (20)	RCT to compare levomethadyl acetate (75–115 mg), buprenorphine (16–32 mg), and high-dose (60–100 mg) and low-dose (20 mg) methadone as treatments for opioid dependence	220 patients, with 55 in each group; 51% completed the 17-week trial.	Primary: treatment retention, opioid use (percentage of positive urine screens), degree of continuous abstinence from opioid use (at least 12 consecutive opioid-free urine screens), and patients' reports of use. Secondary: percentage of cocaine-positive urine screens, abstinence from cocaine use, breath alcohol readings, side effects, and sex-related differences	No difference was found between high-dose buprenorphine and high-dose methadone in days in treatment (mean of 96 and 105 days, respectively) or percentage of patients with 12 or more consecutive negative screens (26% versus 28%, respectively). High-dose buprenorphine was superior to low-dose methadone for both outcomes (mean days, 96 versus 70, $p<.001$; consecutive negative screens, 26% versus 8%, $p=.005$).

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Table 2

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Study	Design and objectives	Population and conditions	Outcomes measured	Summary of findings
Fudala et al., 2003 (17)	RCT to compare 4 weeks of office-based treatment with daily sublingual tablets of buprenorphine (16 mg) in combination with naloxone (4 mg), buprenorphine alone (16 mg), or placebo for patients addicted to opioids	323 patients receiving at least one dose of study medication; 109 randomly assigned to the combination medication, 105 to buprenorphine alone, and 109 to placebo	Primary: percentage of urine screens negative for opiates and self-reported craving for opiates by patients	During each of the 4 weeks, mean craving scores in the combined and buprenorphine groups were significantly lower than in the placebo group ($p<.001$ for both). Both groups with buprenorphine-based treatments had reduced opioid use. Opioid-negative screens: combined group, 17.8%; buprenorphine group, 20.7%; and placebo group, 5.8% ($p<.001$ for all)
Kakko et al., 2003 (15)	RCT to compare daily buprenorphine (fixed dose) versus a 6-day tapered regimen of buprenorphine followed by placebo; 12-month program combined with psychotherapy	40 patients randomly assigned to fixed-dose buprenorphine (N=20) or the tapered regimen (N=20)	Primary: 1-year retention in treatment and negative urine drug screens	One-year retention was 75% in the buprenorphine group and 0% in the placebo group ($p=.001$). Roughly 75% of the patients retained in treatment had negative urine screens for illicit opiates, stimulants, cannabinoids, and benzodiazepines.
Jones et al., 2005 (28)	RCT to compare NAS among neonates of MMT- and BMT-maintained pregnant, opioid-dependent women; provide preliminary safety and efficacy data	30 patients randomly assigned to MMT (N=15) or to BMT (N=15); 11 and 9, respectively, completed the study.	Primary: number of neonates treated for NAS, amount of medication used to treat NAS, length of neonatal hospitalization, and peak NAS score. Secondary: treatment retention and illicit opiate use	No significant difference in illicit opioid use between groups. Total of 20.0% and 45.5% of BMT-exposed and MMT-exposed neonates, respectively, were treated for NAS ($p=.23$). Other primary outcomes were also not significantly different, except that the BMT-exposed neonates had a shorter average hospital stay ($p=.021$).
Fischer et al., 2006 (29)	RCT to evaluate the efficacy and safety of MMT versus BMT for pregnant, opioid-dependent women	18 pregnant women randomly assigned to receive MMT (N=9) or BMT (N=9) during weeks 24–29 of pregnancy. After dropout, data were available from 14 cases (6 for methadone and 8 for buprenorphine.	Primary for mothers: treatment retention, urine drug screens, and nicotine use. Primary for neonates: routine birth data and severity and duration of NAS	For mothers, no significant difference in retention was found between groups. MMT group had significantly less use of additional opioids ($p=.029$). For neonates, earlier onset of NAS was noted in the MMT group; 43% of neonates n both groups combined did not require NAS treatment. Duration of NAS treatment was short in both groups (mean 5 days).
Kakko et al., 2007 (24)	RCT to compare adaptive, BMT stepped care versus optimal MMT	96 patients randomly assigned to flexible-dose MMT group (N=48) or BMT stepped-care group (N=48). In stepped treatment, buprenorphine could be increased to 32 mg. If participants required additional medication, they were switched (stepped) to high-dose methadone.	Primary: 6-month treatment retention, negative urine opioid screens, and problem severity	No differences between groups were found for retention (76% for both at 6 months) or the proportion of negative screens (80% for both groups). For the BMT stepped-care group, 17 completers did not switch to methadone and finished with a mean buprenorphine dose of 29.6 mg, and 20 completers switched to methadone and completed with a mean methadone dose of 111 mg. Methadone group ended with a mean dose of 110 mg.
Comer et al., 2010 (31)	Randomized cross-over study to assess intravenous abuse potential of buprenorphine-naloxone compared with buprenorphine among injection drug users receiving BMT	12 intravenous drug users living in a hospital for 8–9 weeks and receiving buprenorphine-naloxone under 3 BMT dose conditions: 2 mg, 8 mg, and 24 mg	Primary: reinforcing effects of intravenous buprenorphine-naloxone and buprenorphine among BMT-maintained intravenous drug users who were	Buprenorphine-naloxone intravenous abuse potential was lower than buprenorphine alone or heroin, particularly on higher maintenance doses. Intravenous buprenorphine-naloxone was self-administered less frequently than buprenorphine or heroin ($p<.001$). Selective ratings for

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Table 2

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Study	Design and objectives	Population and conditions	Outcomes measured	Summary of findings
			given a drug-versus-money choice exercise	"drug liking" and "desire to take the drug again" were lower for buprenorphine-naloxone than for buprenorphine alone or heroin (p=.001).
Jones et al., 2010 (27)	RCT to examine neurobehavioral effects for neonates exposed to MMT or BMT	175 pregnant women with opioid dependency assigned to MMT group (N=89) or BMT group (N=86)	Primary: reduction in opioid use, treatment retention, percentage of neonates treated for NAS, NAS peak score, length of hospital stay, morphine required to treat NAS	Treatment was discontinued by 18% of women in the MMT group and 33% in the BMT group; 58 mothers exposed to buprenorphine and 73 exposed to methadone were followed to the end of pregnancy. Neonates of the former group required less morphine (mean dose, 1.1 versus 10.4 mg, p<.009), had a shorter hospital stay (10.0 versus 17.5 days, p<.009), and had a shorter duration of NAS treatment (4.1 versus 9.9 days, p<.003).
Ling et al., 2010 (21)	RCT to determine efficacy of buprenorphine implants (6 month) versus placebo	163 patients received buprenorphine implants (N=108) or placebo implants (N=55) after induction with sublingual buprenorphine tablets	Primary: treatment retention and reduction in illicit opioid use as measured by urine drug screens. Secondary: drug craving and withdrawal symptoms	Significantly more patients with buprenorphine implants completed the study (65.7% versus 30.9%, p<.001). The buprenorphine group had more negative screens (40.4% versus 28.3%, p=.04), reduced withdrawal symptoms on the Clinical Opiate Withdrawal Scale (p<.001), and the Subjective Opiate Withdrawal Scale (p=.004), lower patient ratings for craving on the Visual Analog Scale–opioid craving (p<.001), fewer symptoms on the Clinical Global Impressions–Severity Scale (34.9% versus 19.1% with no symptoms, p<.001), and greater change on the Clinical Global Impressions–Improvement Scale (56.0% versus 23.4% reporting very much improvement at week 24, p<.001).
Lucas et al., 2010 (26)	RCT to compare clinic-based BMT with case management and referral and an opioid treatment program within an HIV clinic	93 HIV-positive, opioid-dependent patients not receiving opioid agonist therapy and not dependent on alcohol or benzodiazepines randomly assigned to receive BMT in an HIV clinic (N=46) or referred to an opioid treatment program, where they received either buprenorphine or methadone (N=47)	Primary: initiation and long-term treatment with opioid agonist therapy, urine screen results, visit attendance with primary HIV providers, use of antiretroviral therapy, and HIV treatment outcomes	A larger proportion of HIV clinic patients were on agonist therapy at 12 months (74% versus 41%; p<.001). Illicit opioid use was less in the clinic-based group (44% versus 65%; p=.015). HIV clinic patients had significantly fewer cocaine-positive screens and attended more HIV primary care visits. No difference was found in use of antiretroviral therapy or in improvements in HIV-monitoring tests.
Bazazi et al., 2011 (32)	Self-administered survey study to examine use, procurement, and motivations for use of diverted buprenorphine-naloxone	100 opioid users; 51 injecting users and 49 noninjecting users	Primary: illicit possession of buprenorphine-naloxone, use of diverted buprenorphine-naloxone, reasons for use, and use to "get high"	More noninjecting users reported ever using buprenorphine-naloxone to "get high" (69% versus 32%, p<.01). Most participants reporting past use of buprenorphine-naloxone stated that use was to treat withdrawal symptoms (74%) or to stop using other opioids (66%) or because they could not afford drug treatment (64%).

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Table 2

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Study	Design and objectives	Population and conditions	Outcomes measured	Summary of findings
Weiss et al., 2011 (22)	Multiphase RCT to evaluate efficacy of brief and extended buprenorphine-naloxone treatment with various counseling intensities	First phase (N=653): brief treatment with buprenorphine-naloxone with a 2-week stabilization, 2-week taper, and 8-week postmedication follow-up. Patients entered the second phase if they had opioid-positive urine samples during the first phase. Second phase (N=360): 12 weeks of buprenorphine-naloxone treatment, 4-week taper, and 8-week postmedication follow-up. In both phases, patients were randomly assigned to receive standard (15-minute medical visits) or enhanced medical management (standard medical management plus opioid dependence counseling during 45-minute visits).	Primary: minimal or no opioid use as measured by urine samples that confirmed self-reports	All urine samples were negative after the first phase for only 6.6% of patients. During extended treatment with buprenorphine-naloxone, 49.2% of patients had successful outcomes (opioid-negative urine samples); this rate fell to 8.6% at 8-week follow-up. Addition of counseling had no effect in either phase.
Coyle et al., 2012 (30)	RCT to determine impact on infant neurobehavior of in-utero exposure to buprenorphine or methadone	39 full-term infants exposed to methadone (N=21) or buprenorphine (N=18)	Primary: neonatal neurobehavioral effects, measured on the neonatal intensive care unit's Network Neurobehavioral Scale	Infants exposed to buprenorphine exhibited fewer signs of stress abstinence ($p<.001$) and were less excitable ($p<.001$), less overaroused ($p<.01$), less hypertonic ($p<.007$), and better self-regulated ($p<.04$).
Moore et al., 2012 (23)	RCT to investigate impact of directly observed therapy plus cognitive-behavioral therapy versus usual treatment among patients receiving BMT for 12 weeks in primary care	55 opioid-dependent patients assigned to physician management with weekly buprenorphine dispensing (N=28) or with directly observed, thrice-weekly buprenorphine and cognitive-behavioral therapy (N=27)	Primary: treatment retention and drug use as measured by self-reports or urine screens	No difference was found between groups in treatment retention or drug use.
Pritham et al., 2012 (33)	Retrospective descriptive study to examine opioid replacement treatment in pregnancy and effect on neonatal outcomes	152 opioid-dependent pregnant women receiving MMT (N=136) or BMT (N=16) during pregnancy and their neonates	Primary: length of hospital stay for NAS	Neonates with prenatal exposure to MMT spent more days in the hospital for NAS (21 versus 14 days) ($p=.05$).

[a] Studies are listed in chronological order. Abbreviations: MMT, methadone maintenance treatment; NAS, neonatal abstinence syndrome; RCT, randomized controlled trial

lower dose (69% versus 51%, p=.006) (35). At medium- and high-dose ranges, buprenorphine significantly reduced illicit opioid use compared with placebo or with buprenorphine at a very low dose, as measured by urine drug tests (15–18,34). For example, one RCT reported that for the group receiving 16 mg of buprenorphine,

38% of urine samples were negative for opioids, compared with 18% of samples for the group receiving 1 mg ($p<.001$) (16); another study found 21% opioid-negative urine samples with buprenorphine alone versus 6% with placebo ($p<.001$) (17). Studies have shown inconsistent results regarding reductions in nonopioid illicit drug use (for example, cocaine). However, most studies of buprenorphine have shown no statistically significant impact on reducing nonopioid illicit drug use compared with placebo (15,17,18,34). Although the addition of naloxone to buprenorphine has been shown to decrease abuse potential (31), naloxone has not been found to alter buprenorphine's efficacy (40).

Although buprenorphine implants were not FDA-approved in the United States at the time of this review, Ling and colleagues (21) examined the effect of six-month buprenorphine implants compared with placebo in a phase III trial. The study compared patients receiving buprenorphine implants (N=108) and those receiving placebo implants (N=55) after induction with sublingual buprenorphine tablets. Both groups had the option of receiving supplemental buprenorphine tablets for withdrawal symptoms or craving. Participants could also receive a supplemental dose upon request, if it was deemed suitable by the treating clinician. Results showed that a significantly higher percentage of those receiving buprenorphine implants completed the six-month study (65.7% versus 30.9%, $p<.001$). In addition, patients in the buprenorphine implant group had a significantly higher percentage of their urine samples negative for illicit opioids (40.4% versus 28.3%, $p=.04$). In regard to secondary outcomes, the buprenorphine implant group had significantly reduced withdrawal symptoms on the Clinical Opiate Withdrawal Scale ($p<.001$), and the Subjective Opiate Withdrawal Scale ($p=.004$), lower patient ratings of craving on the Visual Analog Scale–opioid craving ($p<.001$), fewer symptoms on the Clinical Global Impressions–Severity Scale (34.9% versus 19.1% with no symptoms, $p<.001$), and greater change on the Clinical Global Impressions–Improvement Scale (56.0% versus 23.4% reporting very much improvement at week 24, $p<.001$).

Illicit use of buprenorphine. Concerns regarding diversion or nonmedical use of buprenorphine have emerged, even with the buprenorphine-naloxone combination (31,32,41). Comer and colleagues (31) confirmed that buprenorphine-naloxone retains some potential for abuse intravenously, but the combination has less abuse potential as measured by self-administration than buprenorphine alone or heroin. Surveys of individuals with opioid use disorders suggest that up to half of clients who use opioid drugs and seek treatment have used illicit buprenorphine. The clients typically stated that they used opioids for management of withdrawal symptoms and in attempts to decrease other opioid use (32,41,42). Individuals addicted to prescription opioids were more likely than those addicted to intravenous heroin to use buprenorphine to "get high" (32).

Prescription opioid dependence. A recent study examined the use of buprenorphine to treat patients with prescription opioid dependence. Weiss and colleagues (22) conducted the Prescription Opioid Addiction Treatment Study multiphase clinical trial in community treatment settings, reporting outcomes compared with baseline. The first phase examined brief treatment with buprenorphine and provided a two-week buprenorphine stabilization, two-week taper, and eight-week postmedication follow-up. Patients entered the second phase if they had relapsed (opioid-positive urine sample) during the initial phase. The second phase consisted of a 12-week buprenorphine treatment, four-week taper, and eight-week postmedication follow-up. In both phases, patients were randomly assigned to receive standard medical management (15-minute medical visits) or enhanced management (standard medical management plus opioid dependence counseling in 45-minute visits). Results showed that all urine samples were negative for only 6.6% of patients after the first phase (note that all participants received buprenorphine). During extended treatment with buprenorphine, 49.2% of patients had successful outcomes (all urine samples were opioid negative), but this percentage fell to 8.6% at the eight-week follow-up after buprenorphine was discontinued. Opioid dependence counseling had no effect in either phase. The authors concluded that patients dependent on prescription opioids have good outcomes with improved abstinence while taking buprenorphine, but if they are tapered off of this drug, the likelihood of successful outcomes in terms of no opioid use is low.

Psychosocial interventions and support services

The addition of structured psychotherapy to standard treatment—which may include peer support services, 12-step programs, and other psychosocial treatment provided at the facility or office—has not been shown to improve outcomes for patients on opioid maintenance therapy. A meta-analysis examined the impact of adding a more structured psychotherapy to standard treatment that included three types of opioid agonist therapy: levomethadyl acetate (LAAM; now off the U.S. market) (one study), methadone (28 studies), or buprenorphine (six studies) (37). The authors found no improvements in treatment retention or abstinence from illicit opioids and no effect on other outcomes, compliance, or psychiatric symptoms. It is important to note that in this meta-analysis, standard treatment may have included peer support, psychosocial treatment and counseling sessions, and referrals for additional support, but the meta-analysis examined only the effects of structured treatment in addition to support services already provided. A more recent study investigated the impact of directly observed therapy plus cognitive-behavioral therapy compared with regular medical management of BMT (23). Results showed no improvement in retention or drug use. It has been noted that the literature on psychosocial treatments is heterogeneous, and there is a lack of sufficient, high-quality studies to assess which psychosocial interventions have the most success in various populations (43).

BMT versus MMT. Several studies and meta-analyses have examined the use of BMT compared with MMT. Dose levels have been shown to be

Table 3

Review articles about buprenorphine maintenance treatment (BMT) included in the review[a]

Study	Focus of review	Population and conditions	Outcomes measured	Summary of findings
Barnett et al., 2001 (36)	Compare the effectiveness of buprenorphine and of methadone	Patients receiving methadone at medium-high (50–80 mg) and low (20–35 mg) doses and buprenorphine at medium doses (6–12 mg) across 5 RCTs	Primary: retention in treatment and urine drug screens for opioids	Compared with patients on medium-high methadone doses, those on medium doses of buprenorphine had 1.26 times the relative risk (RR) of discontinuing treatment (p=.019), and the rate of positive drug screens was 8.3% higher (p=.002). Buprenorphine was more effective than low doses of methadone in treatment retention (RR of discontinuing treatment=.86; ns) and reduction of positive drug screens (8.4% fewer, p<.05).
Mattick et al., 2008 (34)	Compare the effects of BMT with placebo and MMT on treatment retention and suppression of illicit drug use	Evaluated 24 RCTs involving 4,497 patients	Primary: retention in treatment and illicit drug use suppression	Treatment retention was higher with BMT compared with placebo at low doses (RR=1.50, p<.05), medium doses (RR=1.74, p<.05), and high doses (RR=1.74, p<.05).
McCance-Katz et al., 2010 (38)	Examine literature on methadone and buprenorphine for drug interactions with concurrent medications	Populations varied; extensive literature review with 93 references	Primary: drug interactions with methadone or buprenorphine	Buprenorphine had fewer drug interactions than methadone, especially with HIV medications.
Amato et al., 2011 (37)	Evaluate the effectiveness of any psychosocial treatment plus any agonist maintenance treatment versus standard agonist treatment	4,319 patients in 35 studies	Primary: retention in treatment and opiate abstinence; secondary: treatment compliance, psychiatric symptoms, depression, and death	Adding any psychosocial support to standard maintenance treatments did not appear to give additional benefits.
Martin et al., 2011 (10)	Examine literature, regulatory actions, professional guidance, and opioid treatment program experiences regarding adverse cardiac events associated with methadone	Populations varied; extensive literature review with 108 references and input from panel and field experts	Primary: cardiac events associated with methadone; impact on cardiac QT interval	The pharmacology of buprenorphine affords it a better safety profile than methadone; buprenorphine (at standard doses) did not affect cardiac electrophysiology by lengthening the cardiac QT interval.
Fareed et al., 2012 (35)	Meta-analysis to provide information about proper dosing in BMT to improve treatment outcomes	Compared higher doses of buprenorphine (16–32 mg per day) to lower dose (<16 mg per day) across 21 RCTs involving 2,703 patients	Primary: treatment retention and reduction in opioid use	Higher doses of buprenorphine were associated with better treatment retention than the lower dose (69% versus 51%, p=.006).
Jones et al., 2012 (39)	Review literature on outcomes after maternal treatment with buprenorphine	Evaluated outcomes of 3 RCTs and 44 nonrandomized studies	Primary: fetal effects, neonatal effects, effects on breast milk, and longer-term developmental effects	Maternal treatment with buprenorphine had similar efficacy to methadone. Prenatal buprenorphine treatment resulted in less severe neonatal abstinence syndrome than methadone treatment. No adverse effects on infant development of in-utero buprenorphine exposure were found. Dose increases for methadone and buprenorphine may be needed during pregnancy.

[a] Studies are listed in chronological order. Abbreviations: MMT, methadone maintenance treatment; RCT, randomized controlled trial

important for efficacy of both drugs. In this discussion, we define methadone dose ranges as high (≥60 mg), medium (40–59 mg), and low (<40 mg). We define buprenorphine dose ranges as high (16–32 mg), medium (7–15 mg), and low (2–6 mg).

Barnett and colleagues (36) performed a meta-analysis of data from five RCTs conducted between 1992 and 1997. The authors compared the efficacy of methadone at medium-high doses (50–80 mg) and low doses (20–35 mg) and buprenorphine at medium doses (6–12 mg). Results

showed that patients on medium doses of buprenorphine had 1.26 times the relative risk of discontinuing treatment (p=.019), and the number of positive urine samples was 8.3% higher than the number for patients on medium-high doses of methadone (p=.002). However, compared with lower doses of methadone (20–30 mg per day), buprenorphine was more effective in treatment retention (RR for discontinuing treatment=.86, not significant) and in reduction of positive urine drug tests (8.4% fewer positive urine samples per patient, p<.05). Ling and colleagues (19) found similar results. High-dose methadone (80 mg) was superior to medium-dose buprenorphine (8 mg) and low-dose methadone (30 mg) for treatment retention and opioid use.

A more recent meta-analysis comparing BMT and MMT was based on 25 RCTs and 4,497 participants (34). The authors found results that were similar to the study by Barnett and colleagues (36). Specifically, this meta-analysis found mixed results for medium-dose buprenorphine versus medium- and low-dose methadone in retaining patients. Three studies suggested that MMT was superior, whereas seven found no difference between the groups, although results differed by dose. Medium-dose buprenorphine was less likely to suppress illicit opioid use than medium-dose methadone (standard mean difference [SMD]=.27, p<.05), but it was more likely to suppress illicit opioid use than low-dose methadone (SMD=–.23, p<.05). Treatment retention was worse for low-dose buprenorphine than for medium- and low-dose methadone (RR for both comparisons=.67, p<.05). Low-dose buprenorphine showed no difference in illicit opioid use compared with low-dose methadone, but low-dose buprenorphine was inferior to medium-dose methadone in terms of illicit opioid use (SMD=.88, p<.05). In the meta-analysis, flexible-dose buprenorphine and methadone had similar results for illicit opioid use, and methadone had a slight (but statistically significant) edge for retention in treatment—despite the fact that most studies found no difference. Of note, several of the studies used buprenorphine in low- or medium-dose ranges, and the flexible-dose ranges were not higher than 16 mg. No statistically significant differences were found between methadone and buprenorphine at any dose comparison for use of other illicit drugs (primarily cocaine) or criminal activity.

Johnson and colleagues (20) conducted a 17-week RCT (N=220) to compare the effects of LAAM (75–115 mg), high-dose buprenorphine (16–32 mg), high-dose methadone (60–100 mg), and low-dose methadone (20 mg). Although LAAM is no longer marketed in the United States, the comparison of high-dose buprenorphine, high-dose methadone, and low-dose methadone is still important. The results supported the value of high-dose buprenorphine; no difference was found between high-dose buprenorphine and high-dose methadone in the mean number of days in treatment (96 and 105 days, respectively) or in the percentage of participants with 12 or more consecutive urine samples that were negative for illicit opioids (26% and 28%). High-dose buprenorphine was superior to low-dose methadone in terms of the mean number of days in treatment (96 versus 70, respectively, p<.001) and percentage of participants with consecutive negative urine samples (26% versus 8%, p=.005).

Kakko and colleagues (24) tested the efficacy of a stepped-care strategy that used buprenorphine in increasing doses. The researchers compared a flexible-dose MMT group (n=48) and a stepped-care BMT group (N=48). In the stepped-treatment group that used a flexible-dose algorithm, buprenorphine could be increased up to 32 mg. If participants required additional medication, they were switched (stepped) to high-dose methadone. The study found no differences between the stepped-care BMT and MMT groups in treatment retention (76% for both at six months) or in the proportion of urine samples that were free of illicit opioids (80% for both groups). In the buprenorphine stepped-care group, 17 participants who completed treatment did not switch to methadone and finished with a mean buprenorphine dose of 29.6 mg, and 20 participants who completed treatment switched to methadone and finished with a mean methadone dose of 111.0 mg. Those in the methadone group ended with a mean dose of 110.0 mg.

The pharmacology of buprenorphine affords it a better safety profile than methadone, which is important considering that methadone is associated with one-third of opioid-related overdose deaths annually (44). Because it is a partial agonist at the mu opiate receptor, it has a ceiling effect that limits its potential to cause respiratory depression compared with methadone (45). However, this risk still exists, especially if buprenorphine is used in combination with other central nervous system depressants such as benzodiazepines or alcohol (8) or is used in higher doses. In addition, unlike methadone, buprenorphine at standard doses does not affect cardiac electrophysiology by lengthening the cardiac QT interval—a mechanism that can lead to serious cardiac arrhythmias (10). Buprenorphine also has fewer drug interactions than methadone, especially with HIV medications (38).

Taken together, the articles reviewed suggest that the efficacy of BMT is dose dependent, and dose is important to take into account when comparing medications. For comparisons at medium-dose ranges, evidence is mixed—some studies show similar effects of MMT and BMT and some studies suggest that MMT improves treatment retention or reduces illicit opioid use. Only one study reviewed compared high doses of buprenorphine and methadone, and it showed similar outcomes (20). Finally, the stepped-care approach—in which individuals begin with buprenorphine and switch to methadone if buprenorphine doses above 32 mg are required—suggests that MMT may be needed for patients who require high doses of opioid agonist treatment (24).

Treatment setting. We reviewed two studies examining the receipt of BMT in an office-based setting compared with treatment in a traditional drug treatment program. In an early RCT (1998), O'Connor and colleagues (25) compared patients randomly assigned to receive BMT in a primary care setting (N=23) or a traditional drug treatment program (N=23). During the 12-week study,

Evidence for the effectiveness of BMT: high

Evidence clearly shows that BMT has a positive impact compared with placebo on:
- Retention in treatment
- Illicit opioid use

Evidence is mixed for its impact on:
- Nonopioid illicit drug use

retention showed a trend toward being higher in the primary care setting, compared with the traditional setting (78% versus 52%, respectively, p=.06). Patients in the primary care setting had significantly lower rates of illicit opioid use on the basis of urine drug tests (63% versus 85%, p<.01), but they showed no difference in rates of cocaine use. Lucas and colleagues (26) compared outcomes of HIV-positive patients randomly assigned to receive BMT in an HIV clinic (N=46) or an opioid treatment program in which they received either buprenorphine or methadone (N=47). A significantly higher proportion of the patients in the HIV clinic were receiving agonist therapy at 12 months (74% versus 41%, p<.001). Illicit opioid use, as measured by urine drug tests, was less in the clinic-based group (44% versus 65% of patients; p=.015). In addition, the study showed that patients treated in the HIV clinic had significantly fewer cocaine-positive urine drug tests and attended more HIV primary care visits. The groups did not differ in use of antiretroviral therapy or in improvements in tests used to monitor HIV. The authors speculated that streamlined access to treatment in the clinic group was a major reason for the improved results.

None of the RCTs reviewed were implemented in incarcerated populations. A recent survey of criminal justice agencies indicated that medication-assisted treatment of incarcerated individuals is generally limited to pregnant women and detoxification (46).

Buprenorphine use in pregnancy. MMT has been used to treat opioid dependence during pregnancy to improve maternal and fetal outcomes (47,48). However, as discussed in the companion article (3), MMT puts newborn infants at risk for neonatal abstinence syndrome (NAS). NAS often requires detoxification treatment in the hospital with a morphine taper (49–53). As a result, clinicians and researchers have studied BMT as an alternative to MMT during pregnancy. RCTs were conducted with buprenorphine alone, to avoid prenatal exposure to naloxone.

Three RCTs and observational studies (27–29,39) have compared use of buprenorphine with use of methadone by pregnant women. Authors concluded that buprenorphine has similar efficacy to methadone in reducing illicit opioid use among pregnant women, and buprenorphine may lead to less severe NAS. With both MMT and BMT, dose increases may be necessary during pregnancy (39). Although the two smaller RCTs did not find a difference in treatment retention between BMT and MMT (28,29), the largest RCT—the Maternal Opioid Treatment: Human Experimental Research study (27)—found that a higher percentage of patients in the BMT group discontinued treatment before delivery (33% versus 18%, p=.02). Mothers were more likely to discontinue treatment in both groups if they had higher cumulative lifetime months and recent days of heroin use (27). Two RCTs showed no difference in illicit opioid use between the two medications (27,28), whereas one RCT suggested that methadone may be superior in reducing illicit opioid use (29). Infants born to mothers maintained with buprenorphine versus methadone had similar rates of NAS, but the manifestation of NAS was less severe. Infants whose mothers took buprenorphine required significantly lower doses of morphine to treat NAS and needed fewer hospital days (27,30,33).

Conclusions

Overall, a high level of evidence was found for the effectiveness of BMT in improving treatment retention and decreasing illicit opioid use (see box on this page). Research regarding the impact of BMT on nonopioid illicit drug use is less conclusive but suggests positive trends. The addition of any type of psychosocial regimen to BMT or MMT has not been shown to improve outcomes, but the heterogeneity of interventions across trials limits the ability to make strong conclusions. As with MMT, there is growing evidence that higher doses of buprenorphine (16–32 mg) are more efficacious than lower doses; however, because of the pharmacology of buprenorphine, doses above 32 mg do not provide additional efficacy. Research suggests that buprenorphine may be as effective for patients with prescription opioid dependence as it is for patients with heroin dependence. When the medications are dosed similarly, BMT appears to be as effective as MMT in reducing illicit opioid use. Results are mixed regarding treatment retention, but several studies suggest that MMT might confer some advantage. The advantage may be due, in part, to the supportive services or social reinforcement in outpatient MMT programs. However, buprenorphine has a better safety profile than methadone, and the ability to prescribe buprenorphine in office facilities as opposed to only in opioid treatment programs improves access to care and earlier initiation of treatment. A key advantage of buprenorphine is its availability. The number of clinicians approved to prescribe buprenorphine is growing, although many areas of the country do not have access to methadone programs (2).

Both BMT and MMT improve pregnancy-related outcomes by reducing illicit drug use during pregnancy. Infants of mothers treated with buprenorphine during pregnancy may be born with NAS, although NAS appears to be less severe in infants of mothers treated with buprenorphine than of those treated with methadone.

Potential areas for future research include increased focus on the impact of BMT on secondary outcomes, additional investigation of appropriate dosing to enhance treatment outcomes, confirmation of the results of the stepped-care protocol, improved

induction protocols to minimize initial problems with treatment retention (and thus potentially enhance adoption rates by providers), and examination of the differential effectiveness of BMT in specific subpopulations, such as patients dependent on prescription opioids versus heroin. Differential effects and access to BMT across racial and ethnic groups and geographic areas should also be studied.

Ongoing research needs do not diminish the strong evidence for this treatment approach. Given the poor success rates of abstinence-based treatments for opioid use disorders and the limited access to and more restrictive safety profile of MMT, BMT is an important treatment for opioid dependence. Policy makers have reason to promote access to BMT for patients in substance use treatment who may wish to choose BMT as a potentially safer alternative to MMT. Administrators of substance use treatment programs, community health centers, and managed care organizations and other purchasers of health care services, such as Medicare, Medicaid, and commercial insurance carriers, should give careful consideration to BMT as a covered benefit.

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