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Economic Evaluations of Opioid Use Disorder Interventions: A Systematic Review

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Abstract

Background—The economic costs associated with opioid misuse are immense. Effective interventions for opioid use disorders are available; however, given the scarce resources faced by substance-use treatment providers and payers of all kinds, evidence of effectiveness is not always sufficient to encourage the adoption of a given therapy, nor should it be. Economic evaluations can provide evidence that will help stakeholders efficiently allocate their resources.

Objective—The purpose of this study was to review the literature on economic evaluations of opioid use disorder interventions.

Methods—We performed a systematic review of the major electronic databases from inception until present (August 2015). A sensitive approach was used to ensure a comprehensive list of relevant articles. Given the quality of existing reviews, we narrowed our search to studies published since 2007. The Drummond checklist was used to evaluate and categorize economic-evaluation studies according to their quality.

Results—A total of 98 articles were identified as potentially relevant to the current study. Of these 98 articles, half (n=49) were included in this study. Six of the included articles were review in nature. The remaining 43 articles performed an economic evaluation of an intervention for opioid use disorders. In general, the evidence on methadone-maintenance therapy (MMT) supports previous findings that MMT is an economically advantageous opioid-use-disorder therapy. The economic literature comparing MMT to other opioid-use-disorder pharmacotherapies is limited, as is the literature on other forms of therapy.

Conclusions—With the possible exception of MMT, additional high-quality economic evaluations are needed in order to assess the relative value of existing opioid-use-disorder interventions.

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1. Introduction

Globally, opiates and opioids lead all other drugs in terms of disease burden and drug-related deaths with an estimated 33 million users.[1] Approximately half of the 33 million users suffer from an opioid use disorder; however, only about 10% of those are receiving therapy. [2] The misuse of opioids has been linked to a host of physiological and sociological consequences.[3-9] Concomitantly, the economic costs associated with opioid misuse are extremely high, over \$92 billion (2014 USD) annually in the U.S. alone.[6, 7] Birnbaum et al.[6] estimated the societal costs of prescription opioid misuse to be 46% workplace, 45% healthcare and 9% criminal justice related.

Effective interventions for opioid use disorders exist. The two primary types of therapy are psychosocial and pharmacological. Reports from the World Health Organization (WHO)[10] and the National Quality Forum[11] provide comprehensive overviews of the various types of therapies for opioid use disorders. Psychosocial therapies can be used by themselves or in combination with a pharmacotherapy and are designed to alter the patients motivation such that it is no longer one of substance use; examples include: cognitive behavioral therapies, relapse prevention, contingency management and motivational enhancement therapy. Pharmacotherapy options include opioid agonists, partial agonists and antagonists, as well as alpha-2-adrenergic agonists. Opioid agonist maintenance therapy, via the medications methadone (a full agonist) and buprenorphine (a partial agonist), is widely regarded as an, and possibly the most, effective form of therapy for opioid use disorders.[12-16] Methadone and buprenorphine can also be used to assist with short-term detoxification. Naloxone and Naltrexone are opioid antagonists, implying that they block the opioid receptors. These drugs have some advantages in that they are non-narcotic and non-addictive; however, because they block the opioid receptors they will initiate withdrawal symptoms if taken by an individual who is physically dependent on opioids. Naloxone, is typically combined with buprenorphine to reduce the likelihood of diversion, since it will counteract the effects of the opioids if the medication is administered parenterally. Naltrexone is available as a long-acting injectable, and is primarily used to prevent relapse in opioid-dependent patients who have already been detoxified for 7 to 14 days.[17, 18]

Given the scarce resources faced by substance-use treatment providers and payers of all kinds, evidence of effectiveness is not always sufficient to encourage the adoption of a given therapy, nor should it be. Economic evaluations can provide evidence that will help stakeholders efficiently allocate their resources. The purpose of this study is to review the literature on economic evaluations of opioid use disorder interventions.

2. Review Methods

We performed a systematic review of the major electronic databases from inception until present (August 2015). Searched databases included: PubMed/MEDLINE, Cochrane Library, Cost-Effectiveness Analysis Registry, Web of Science, JSTOR, ScienceDirect and Google Scholar, UK National Health Services (NHS) Economic Evaluation Library Database, EconLit, PsycINFO, SciELO Citation Index, Social Science Citation Index, and the Derwent Innovations Index. A sensitive approach was used to ensure a comprehensive

list of relevant articles. Searches included combinations of the following categories: (1) opioid or opiate, and dependence or disorder; (2) cost; (3) economic; and (4) benefit and effectiveness. The following is an example of a full electronic search strategy employed for PubMed/MEDLINE on articles published since 2007: (“cost-benefit analysis”[MeSH Terms] OR (“cost-benefit”[All Fields] AND “analysis”[All Fields]) OR “cost-benefit analysis”[All Fields] OR (“cost”[All Fields] AND “effectiveness”[All Fields]) OR “cost effectiveness” [All Fields]) AND (“analgesics, opioid”[Pharmacological Action] OR “analgesics, opioid” [MeSH Terms] OR (“analgesics”[All Fields] AND “opioid”[All Fields]) OR “opioid analgesics”[All Fields] OR “opioid”[All Fields]) AND (“disease”[MeSH Terms] OR “disease”[All Fields] OR “disorder”[All Fields])). A number of recent systematic reviews of economic evaluations for various opioid use disorder interventions were identified.[19-26] The most comprehensive review was performed by Doran[22] who included studies up to 2007. Given the quality of the Doran review, which is discussed below, we narrowed our search to focus on studies published since 2007.

The first author (Dr. Murphy) performed the initial database searches to identify pertinent articles. Studies were included based on consensus between both authors following rigorous discussion. Studies were excluded if they were not an economic evaluation of an opioid-use-disorder intervention. For example, studies were excluded if they were editorials; if their emphasis was the treatment of a disorder such as chronic pain, the use of another substance, etc.; or if they focused solely on identifying the costs associated with opioid misuse, as opposed to potential cost-offsets associated with various treatment alternatives, for example.

In order to build on the Doran[22] study, the Drummond checklist[27] was used to evaluate and categorize studies according to their quality. The Drummond checklist consists of 10 primary questions intended to evaluate the quality and comprehensiveness of an economic evaluation. The 10 questions focus on: 1) the research question; 2) the description of the competing alternatives; 3) the establishment of the intervention's effectiveness; 4) the inclusion of all relevant costs and consequences; 5) the measurement of costs and consequences; 6) the valuation of costs and consequences; 7) whether costs and consequences were adjusted for differential timing; 8) whether an incremental analysis of costs and consequences was performed; 9) whether uncertainty in costs and consequences was taken into consideration; and 10) the quality of the discussion of study results. Doran allocated a point to each question on the checklist and scored reviewed studies accordingly, categorizing them as follows: *poor quality (1-3 points)*; *average quality (4-7 points)*; and *good quality (8-10 points)*. We too used this ranking system, which was applied to all articles, with the exception of review studies.

3. Results

A total of 98 articles were identified as potentially relevant to the current study. Of these 98 articles, half (n=49) were included in this review (see Figure 1). Twenty of the articles were excluded because they did not focus on opioid use disorders (e.g., they focused on long-term opioid therapy or abuse-deterrent opioids), or they did not focus on the treatment of opioid use disorders as an outcome; 13 were excluded for not containing sufficient information on costs or other pertinent economic variables; 8 were excluded because they focused solely on

identifying the costs of opioid misuse or of providing a service; 5 were excluded for being editorial in nature; and 3 were excluded because they were poster abstracts published in conference proceedings.

3.1 Review articles

Six of the articles included in the study were review in nature. As mentioned above, Doran[22] performed a systematic review of studies published prior to 2007 that performed economic evaluations of opioid-use-disorder interventions. Doran concluded that, while the effectiveness of interventions for opioid use disorders (both pharmacological and behavioral) has been well established, information on the economic value of said interventions was limited. Based on the author's assessment via the Drummond checklist,[27] the studies reviewed were of decent quality, but fell short in a number of areas. According to Doran, there were too few well-designed cost-effectiveness analyses, particularly by important subgroups, such as primary-care and criminal-justice settings, adolescents, and pregnant women. Other shortcomings included: a) a lack of detailed evaluations on psychosocial interventions; b) limits on the range of costs and consequences (e.g., the inclusion of indirect costs such as productivity loss or cost offsets associated with reduced criminal activity); and c) the limited use of outcomes that capture a wider range of consequences associated with opioid use disorders (e.g., quality-adjusted life years, QALYs). Regarding the cost-effectiveness analyses reviewed by Doran, overall the evidence indicates that both buprenorphine/naloxone maintenance therapy (BMT) and methadone maintenance therapy (MMT) are cost-effective. Additionally, there was some evidence to indicate that adding psychosocial support to MMT improved outcomes. With regard to cost-benefit analyses of maintenance therapies, all studies reviewed by Doran demonstrated that the benefits outweighed the costs. In terms of the detoxification studies reviewed, Doran found buprenorphine in an outpatient setting to be one of the most cost-effective procedures and, again, found limited support that adding psychosocial support to pharmacotherapy improves outcomes.

Five other review studies were identified. Each contained at least one study that met the inclusion criteria for our review and, therefore, is discussed below. Hartung et al.[24], conducted a meta-analysis of extended-release naltrexone studies that evaluated economic and healthcare-utilization outcomes among individuals with opioid or alcohol use disorders. The only opioid study to meet the inclusion criteria for this paper was Baser et al.[28] Gastfriend[23] reviewed alcohol- and opioid-use-disorder pharmacotherapy studies to establish a pharmaceutical-industry perspective on the economics of these treatments. Four articles relevant to this study were included.[28-31] The Canadian Agency for Drugs and Technologies in Health[20] performed a review of the literature pertaining to the clinical- and cost-effectiveness of BMT relative to MMT for the treatment of opioid use disorders. Only one study meeting the criteria for this review was included.[32] Shearer et al.[26] conducted a systematic review of contingency management economic evaluations. Three of the studies identified by the authors targeted opioid use as one of the clinical outcomes, two of which met the inclusion criteria for this study.[33, 34] Finally, Shanahan and Mattick[35] reviewed economic evaluations pertaining to pharmacotherapies for opioid use disorders. Four studies met our inclusion criteria.[19, 21, 22, 36]

3.2 Cost and utilization

Thirty percent (n=13) of the economic-evaluation articles included in this paper focused primarily on comparing the levels of healthcare resource utilization and costs associated with different treatment modalities for opioid use disorders. Details on these papers and their Drummond-checklist [27] scores are presented in Tables 1 and 2, respectively.

3.2.1 Multiple medications—Baser et al.[28] performed a retrospective cohort analysis of beneficiaries of a large, multistate, US commercial healthcare insurer, who had an opioid use disorder. Beneficiaries who received one of the FDA-approved pharmacotherapies for opioid use disorders were compared to those who did not. On average, patients who received some type of pharmacotherapy utilized fewer healthcare resources and had lower total healthcare costs 6-months post treatment initiation than patients who did not receive pharmacotherapy (\$10,192 versus \$14,353 [2005-2009 USD]). Comparisons between opioid-use-disorder pharmacotherapies revealed no significant differences with regard to detoxification/rehabilitation admissions, but significantly fewer other-hospital admissions among extended-release-naltrexone (XR-NTX) patients. However, with regard to 6-month post-treatment costs MMT patients were significantly more expensive than patients in the other three groups (\$16,752 versus \$10,049 for BMT, \$8,903 for oral naltrexone and \$8,582 for XR-NTX).

Barnett[29] performed a retrospective cohort analysis of US Veterans Health Administration patients with an opioid use disorder. Patients with a new BMT treatment episode were compared to those with a new MMT treatment episode. BMT patients utilized fewer healthcare resources and had significantly lower predicted mean total healthcare costs, relative to MMT patients (\$11,597 versus \$14,921 [2005 USD]), for the 6 months following treatment initiation. Additionally, the Cox proportional-hazards regression indicated that new MMT episodes had a risk of ending that was approximately 1.6 times that of new BMT episodes.

3.2.2 MMT—McCarty et al.[37] conducted a retrospective cohort analysis of opioid-dependent members of a US commercial health plan. Beneficiaries receiving MMT were compared to those who did not receive MMT, but had at least 2 outpatient visits for addiction treatment, and those who did not receive MMT and had less than 2 outpatient addiction treatment visits. Beneficiaries who received MMT had the lowest costs (\$7,163 [2004 USD]), followed by members with 2 or more outpatient addiction treatment visits and no methadone (\$14,157), and members with 1 or 0 outpatient addiction treatment visits and no methadone (\$18,694). The relatively low cost of members receiving MMT was due to fewer emergency department (ED) and primary care visits, fewer inpatient stays, and less utilization of other non-addiction treatment services.

Gourevitch et al.[38] performed a retrospective cohort analysis of US Medicaid patients in an MMT program. Patients who received long-term (at least 6 months) drug treatment with “linked” on-site medical care, were compared to those who received long-term drug treatment only and those who did not receive MMT. “Linked” care was associated with more

outpatient visits, but fewer ED visits and hospitalizations, with no significant difference in total healthcare costs.

Krebs et al.[39] completed a retrospective cohort analysis of illicit drug users in Canada who had accessed MMT and were involved in one of the following studies: At-Risk Youth Study, AIDS Care Cohort to evaluate Exposure to Survival Services, or the Vancouver Injection Drug Users Study. The crime-related costs of individuals grouped into the following categories were compared: 1) MMT with high effectiveness, 2) MMT with low effectiveness, 3) opioid abstinent, or 4) relapsed. From a societal perspective, which included criminal-justice-system and victimization costs, relative to relapse, the highest rates of avoided criminal costs were associated with the abstinent group (\$6,563 [2013 CAD]), followed closely by the MMT-high-effectiveness group (\$6,298). MMT with low-effectiveness was not associated with significant crime-related cost savings.

3.2.3 BMT—Lynch et al.[40] conducted a retrospective cohort analysis of individuals with an opioid use disorder who belonged to one of 2 large integrated US commercial health systems. Eligible beneficiaries were categorized into one of the following groups: 1) BMT plus counseling, 2) counseling only, or 3) little-to-no addiction treatment. Beneficiaries with little-to-no treatment had significantly more primary-care, other-medical, and ED visits than those in the BMT-plus-counseling group. The BMT-plus-counseling group had more inpatient-detoxification, but fewer primary-care, other-medical, and mental-health visits than the counseling-only group. The BMT-plus-counseling group had significantly lower total healthcare costs than the little-to-no-addiction-treatment group (\$13,578 vs. \$31,035 [2008 USD]); however, total costs did not differ significantly from those of the counseling-only group (\$17,017).

Tkacz et al.[41] performed a retrospective cohort analysis of beneficiaries of a large US commercial healthcare insurer, who had an opioid use disorder and had been prescribed buprenorphine/naloxone. Beneficiaries who were adherent were compared to those who were not. Buprenorphine/naloxone-adherent patients incurred more pharmaceutical costs, but utilized fewer high-cost services, resulting in significantly lower total healthcare charges (\$28,458 vs. \$49,051 [2007-2012 USD]).

Martinez-Raga, González-Saiz, Pascual, Casado and Sabater Torres.[42] developed a budget impact model to estimate the healthcare costs of approving buprenorphine/naloxone as a method of treatment for opioid use disorders in Spain. In an updated model, Martínez-Raga, González-Saiz, Oñate, Oyagüez, Sabater and Casado [43] estimated the additional costs of buprenorphine/naloxone to be small relative to a methadone-only scenario, €10.58 [2010 EUR] per patient, or less, with higher pharmaceutical costs being offset by lower logistic/distribution, production, delivery, supervision and monitoring costs.

Clay et al.[44] conducted a retrospective cohort analysis of opioid-dependent beneficiaries of a commercial U.S. healthcare insurance company. Beneficiaries who had initiated treatment with buprenorphine/naloxone film were compared to those who had initiated treatment with the tablet version of the drug. Individuals treated with the film stayed with treatment longer, had significantly more outpatient visits, a lower likelihood of

hospitalization and significantly lower (-27%) total healthcare costs over the 12-month post-initiation study period.

Asche et al.[45] developed a Markov model to predict the relative costs of a cohort of patients with opioid use disorders being treated with either buprenorphine/naloxone film or tablet over 5 years. The authors found that although increased use of the film would result in increased outpatient-care costs, it would generate savings overall due to reduced utilization of ED and inpatient services.

Khemiri et al.[46] conducted a retrospective cohort analysis of US beneficiaries with an opioid use disorder who were enrolled in a commercial healthcare insurance plan or in Medicaid, and who had a new buprenorphine/naloxone prescription with at least 1 refill. Individuals receiving *low-dose* BMT were compared to those receiving *high-dose* BMT. *High-dose* BMT beneficiaries stayed in treatment longer and had a similar level of total direct healthcare costs as those receiving *low-dose* BMT, even though pharmacy costs were higher among the *high-dose* group.

Kaur et al.[47] performed a retrospective pre-post analysis of continuously enrolled beneficiaries in a US managed care organization, who had a new buprenorphine/naloxone prescription and at least 1 pharmacy claim for opioids in the previous 6 months. The researchers observed a significant decrease in the number of new opioid pharmacy claims. After accounting for the cost of the therapy (i.e., buprenorphine/naloxone) there was not a significant difference in drug cost.

3.3 Cost-effectiveness/cost-benefit of maintenance treatments

Tables 3 and 4 contain information on cost-benefit and cost-effectiveness studies that focused on methadone maintenance as the therapy of interest. Details on the remaining economic evaluation studies are displayed in Tables 5 and 6.

3.3.1 MMT pre-post—Vanagas et al.[48] performed a prospective cost-effectiveness analysis (CEA) of a 6-month MMT program in Lithuania using a pre-post study design. The study included patients with opioid use disorders who were first-time enrollees of the outpatient MMT program. Costs included those of the MMT program and those of the patient. The findings indicate significant increases in various components of quality-of-life, and an incremental-cost-effectiveness ratio (ICER) of €34,368 [2004 EUR] per QALY gained, which is below the commonly cited willingness-to-pay threshold of \$50,000 or €39,270 (2004 EUR) per QALY gained.[49]

3.3.2 MMT alone versus MMT with counseling—Schwartz et al.[50] conducted a cost-benefit analysis of a US randomized controlled trial (RCT) testing the effectiveness of MMT with drug-abuse counseling, relative to MMT without drug-abuse counseling. Study participants were newly-admitted heroin-dependent MMT patients. The analyses were conducted from the societal perspective. Although the cost per treatment episode was lower for MMT alone (\$2,052 vs. \$3,411 [2010 USD]), the authors found no significant difference in the benefit-cost ratio between groups.

3.3.3 MMT versus residential treatment—Basu et al.[51] performed a retrospective pre-post net-monetary-benefit analysis of patients in US residential and outpatient substance-abuse-treatment programs. Individuals were receiving either outpatient MMT, or residential short- or long-term inpatient therapy. For patients 25 years of age, and older, outpatient MMT produced a positive net monetary benefit for willingness-to-pay values above \$60,000 [2001 USD] per robbery averted. The thresholds for short-term and long-term residential therapy were roughly \$100,000 and \$180,000, respectively. For patients younger than 25, the threshold for all three modalities was approximately \$40,000.

3.3.4 MMT versus usual-care among HIV-positive drug users—Xing et al.[52] conducted a CEA of MMT, relative to no MMT, among intravenous drug users (IDUs) seeking treatment in MMT clinics in China, using a retrospective cohort design. Analyses were conducted from a provider perspective (i.e., the government and public health institutions) over a 30-month period. The average cost per HIV infection averted was \$3,704.7 [2007 USD].

Wammes et al.[53] conducted a CEA of MMT relative to current practice in a low-income setting in Indonesia over a 10-year time span. Data from the Asian Epidemic Model and the Resource Needs Model were used to model IDUs, female sex workers and men having sex with men. The analyses were performed using a societal perspective. The findings indicate that MMT would cost approximately \$7,000 [2010 USD] per HIV infection averted.

Alistar et al.[54] conducted a CEA using a 3-state dynamic compartmental model to assess the expansion of MMT, increased access to antiretroviral therapy (ART) or both over a 20-year time frame in the Ukraine. A dynamic compartmental model is a type of mathematical model in which the study population is divided into compartments and the transition from one compartment to the other is investigated. The 3 model compartments in this study were: IDUs receiving MMT, IDUs actively injecting opioids and non-IDUs. The expansion of MMT alone was found to be the most cost-effective at \$530 [~2007 USD] per QALY gained, relative to current practice.

Tran and Nguyen[55] performed a retrospective cohort analysis of HIV-positive drug users seeking treatment at hospitals and health centers in Vietnam, who responded to the HIV Services Users Survey. Individuals with HIV/AIDS who were being treated with MMT were compared to a propensity-matched group of non-MMT drug users with HIV/AIDS. The authors found MMT to be associated with significantly higher levels of health utility, lower levels of healthcare service utilization and fewer out-of-pocket healthcare costs. MMT patients paid approximately \$232 [2012 USD] less in out-of-pocket costs annually than non-MMT patients.

Tran, Ohinmaa, Duong, Do et al.[56] assessed the cost-effectiveness of MMT versus no MMT via a retrospective cohort analysis of HIV-positive patients seeking treatment for an opioid use disorder at a stand-alone MMT clinic in Vietnam. Analyses were conducted from the perspective of health services providers over 9 months. The cost per QALY gained was \$3,550.5 [2009 USD], which was just over 3 times Vietnam's GDP per-capita. The WHO's recommendations are that an intervention with an ICER less than the GDP per-capita be

considered *highly cost-effective*, those with an ICER between 1 and 3 times GDP per-capita be considered *cost-effective* and those with an ICER over 3 times GDP per-capita be considered *not cost-effective*.^[57]

Tran, Ohinmaa, Duong, Nguyen et al.^[58] used a decision analytic model to assess the cost-effectiveness of integrating MMT and ART, relative to ART and MMT at separate sites, and stand-alone ART, for HIV-positive drug users in Vietnam. The analyses in this study were also conducted from the health-provider's perspective. Relative to ART alone, the ICERs for providing ART and MMT in separate sites, and for integrating ART and MMT with direct administration were \$569.4 and \$1,227.8 [2009 USD] per QALY gained, respectively. According to the aforementioned WHO thresholds,^[57] the separate-site ART and MMT model was *highly cost-effective* and the direct administration model was *cost-effective*.

Tran, Ohinmaa, Duong, Nguyen et al.^[59] analyzed the cost-effectiveness and budgetary impact of MMT, relative to no MMT, using a decision analytic model. Study participants were HIV-positive IDUs seeking treatment for an opioid use disorder at a stand-alone MMT clinic in Vietnam. Again, the analyses were conducted from the health-provider's perspective. The estimated ICER for MMT relative to non-MMT was \$3,324 [2009 USD] per HIV case averted and \$964 per QALY gained. At 1.76 times the GDP per capita, this qualified MMT as *cost-effective*. At the threshold of 3 times GDP per capita, MMT would be considered *cost-effective* 80% of the time.

3.3.5 MMT versus deep-brain stimulation—Stephen et al.^[60] constructed a decision analytic model to assess the cost-effectiveness of deep-brain stimulation (DBS) relative to MMT from a US societal perspective. Study participants included individuals from 15 trials administering 6 months of MMT, and participants from 45 trials of deep-brain stimulation for movement disorders. The authors plotted the ICER (cost differential/QALY differential) against the probability of DBS success. MMT dominated DBS up to a success rate of 36.5%, at which point DBS became more effective. Using a willingness-to-pay threshold of \$200,000 [2011 USD] per QALY gained, DBS would likely not be considered cost-effective until a success rate of 50%. The upper limit for the range of threshold values by which U.S. society judges cost-effectiveness has recently been estimated to be between \$262,468-\$382,123 [2014 USD] per QALY gained.^[61] At the traditional threshold of \$50,000 per QALY gained, DBS would be cost-effective at success rates over 57%.

3.3.6 MMT or BMT versus rehabilitation or prison—Moore et al.^[62] evaluated the cost-effectiveness of pharmacotherapy maintenance (MMT or BMT) relative to residential rehabilitation and prison, using a retrospective cohort analysis of individuals seeking treatment for heroin dependence at a drug treatment agency in Australia. Data was obtained from the Australian Treatment Outcome Study, and analyses were conducted from a societal perspective. The authors predicted that if the post-program abstinence rates were sustained for 2 years, the average cost per abstinent year would be \$500 (2002 AUD) for pharmacotherapy maintenance, \$11,000 for residential rehabilitation and \$52,000 for prison.

3.3.7 MMT or BMT versus drug-free therapy—Clark, Baxter et al.^[63] performed a retrospective cohort analysis of Massachusetts Medicaid beneficiaries with an opioid use

disorder. Beneficiaries who were receiving either BMT or MMT were compared to those receiving behavioral health treatment without opioid agonist therapy. Patients receiving BMT or MMT were approximately 50% less likely to relapse, and had mean monthly total healthcare costs that were \$191 and \$184 [2004-2010 USD] lower, respectively, than those receiving behavioral health therapy without opioid agonist therapy.

Clark, Samnaliev et al.[30] conducted a retrospective cohort analysis of Massachusetts Medicaid beneficiaries with an opioid use disorder. Beneficiaries who received either BMT or MMT were compared to those who received drug-free treatment or no treatment. The predicted mean monthly total Medicaid cost for BMT beneficiaries was significantly lower than for beneficiaries receiving drug-free or no treatment when short-term-use episodes were included; the difference between BMT and MMT beneficiaries was not significant. Relapse rates were lowest among MMT beneficiaries followed by BMT and drug-free-treatment beneficiaries. The number of deaths among BMT beneficiaries was not significantly different than the number among MMT beneficiaries, but was significantly lower than the numbers for those in drug-free treatment and those receiving no treatment.

3.3.8 MMT versus injectable heroin—Nosyk et al.[64] assessed the cost-effectiveness of medically-prescribed injectable heroin (i.e., diacetylmorphine), relative to MMT, using a decision-analytic, semi-Markov cohort model of participants in the North American Opiate Medication Initiative trial. The authors considered 1-year, 5-year, 10-year and lifetime horizons, using a Canadian societal perspective that incorporated costs to the healthcare and criminal justice systems. Diacetylmorphine dominated MMT at each time horizon, with many of the savings coming in the form of reduced criminal activity. The probabilistic sensitivity analysis indicated that diacetylmorphine would be considered cost-effective at a willingness-to-pay threshold of \$100,000 [2009 CAD] per QALY gained with 95% confidence.

Byford et al.[65] evaluated the cost-effectiveness of an RCT testing the effectiveness of supervised injectable heroin relative to injectable and oral MMT. Study participants were chronic heroin users in the UK who were receiving oral MMT but continued to inject 'street' heroin on a regular basis. The analyses were conducted from the perspectives of society and the NHS. The authors found oral MMT to be dominated by both forms of injectable treatment from a societal perspective. Of the two forms of injectable treatment, injectable methadone appeared to be the more cost-effective option. Using NICE's cost-effectiveness threshold of £30,000 per QALY gained, injectable methadone had a slightly higher probability of being considered cost-effective relative to oral MMT, than injectable heroin (~75% versus ~70%). The authors note, however, that many of the savings attributed to the injectable treatments were associated with the criminal justice system and that the two treatments became cost-ineffective when considering an NHS perspective.

3.3.9 MMT versus BMT—Connock et al.[21] assessed the cost-effectiveness of BMT relative to MMT and no pharmacotherapy using a decision analytic model of individuals in England with an opioid use disorder. The analyses were conducted from an NHS/Personal-Social-Services (PSS) perspective. Both BMT and MMT were cost-effective relative to no

pharmacotherapy at £26,429 and £13,697 [2004 GBP] per QALY gained, respectively, while MMT dominated BMT.

Jones et al.[31] performed a CEA of an RCT testing the effectiveness of office-based BMT relative to clinic- and office-based MMT in the treatment of opioid use disorders. Study participants were individuals receiving outpatient MMT who had been stabilized for at least 1 year. The analyses were conducted from the perspectives of the provider and the patient. Clinic-based MMT was less expensive than office-based MMT or BMT for providers and patients. From a provider and patient perspective, respectively, the costs for each treatment modality were as follows: clinic-based MMT, \$147 and \$239; office-based MMT, \$220 and \$275; and office-based BMT, \$336 and \$378 [2006 USD]. With regard to abstinence rates, the three treatments were statistically similar. The authors concluded that the cost of buprenorphine/naloxone was a major determinant of its total cost, and therefore they would expect their results to change following the approval of a generic (generic approval of buprenorphine/naloxone occurred in 2013).

Maas et al.[66] evaluated the cost-effectiveness of BMT relative to MMT among individuals with an opioid use disorder in the UK, using a non-equivalent group research design. The analyses were conducted from the provider perspective. BMT was dominated by MMT with regard to the program's ability to retain patients for 6 months. However, with regard to the outcome of individuals who successfully detoxified, BMT generated a cost-effectiveness ratio of £903 [2010-2011 GBP] per individual who stopped using illicit opiates.

Geitona et al.[32] developed a budget impact model to evaluate the cost effectiveness of buprenorphine/naloxone relative to buprenorphine monotherapy and MMT, among individuals with an opioid use disorder who were participating in opioid addiction therapy in Greece. The analyses were performed from the perspective of the Greece National Health System. The mean annual cost was lowest for buprenorphine-naloxone (€2,875.6, versus €5,626.4 for MMT and €6,089.2 [2008 EUR] for buprenorphine monotherapy). Buprenorphine/naloxone dominated MMT, given the lower cost, increased percentage of participants completing therapy and lower number of avoided deaths.

3.3.10 Naltrexone versus MMT and BMT—Jackson et al.[67] developed a Markov model to estimate the cost-effectiveness of injectable XR-NTX relative to MMT and BMT for U.S. adult males receiving therapy for an opioid use disorder. From the perspective of state addiction treatment payers, the estimated cost-effectiveness ratio was \$72 [~2014 USD] per opioid-free day relative to the next most effective treatment, MMT.

3.3.11 BMT versus no treatment—Schackman et al.[68] developed a decision analytic model for a hypothetical cohort of clinically-stable individuals with an opioid use disorder who had completed 6 months of BMT in a primary care setting, in order to assess its long-term cost-effectiveness relative to no treatment. From a societal perspective, BMT had a cost-effectiveness ratio of \$35,000 [2010 USD] per QALY gained, at 24 months. The probabilistic sensitivity analysis indicated that the therapy had a 64% chance of being considered cost-effective at a willingness-to-pay threshold of \$100,000 per QALY gained.

3.3.12 BMT versus detoxification—Polsky et al.[69] analyzed the cost-effectiveness of BMT relative to detoxification in a 12-week clinical trial of US adolescents (15-21 years of age) with an opioid use disorder. The analyses were conducted from the perspectives of the payer, the provider and society. From the perspective of the payer, the therapy produced a cost-effectiveness ratio of \$1,376 [2006 USD] per QALY gained, with an 86% chance of being considered cost-effective at a willingness-to-pay threshold of \$100,000 per QALY gained. The outpatient-treatment-provider perspective resulted in a cost-effectiveness ratio of \$25,049 per QALY gained with a slightly lower (~85%) chance of being accepted as cost-effective using a willingness-to-pay value of \$100,000. Total net social costs were lower for BMT, but did not differ significantly.

3.3.13 BMT versus naltrexone—Ruger et al.[70] conducted a CEA of a randomized, double-blind, placebo-controlled clinical trial in Malaysia testing the effectiveness of BMT relative to naltrexone for the treatment of heroin dependence. Study participants were detoxified heroin-dependent patients from an outpatient research clinic and detoxification program. Primary outcomes tested were days in treatment, maximum consecutive days of heroin abstinence, days to first heroin use and days to heroin relapse. Secondary outcome measures were treatment retention, injection drug use, illicit opiate use, AIDS Risk Inventory total score, and drug- and sex-risk subscores. The authors concluded that buprenorphine was likely cost-effective relative to naltrexone from a societal standpoint, given that it was more effective for all primary outcomes and most secondary outcomes with cost-effectiveness ratios below \$50 [2004 USD] for the primary outcomes and \$350, generally, for secondary outcomes.

3.3.14 Naltrexone versus no-naltrexone—Adi et al.[19] performed a systematic review of the clinical- and cost-effectiveness naltrexone literature (up to September 2005) on its use as a therapy option for opioid use disorders. The authors were unable to identify any economic evaluations and therefore created a decision-analytic model to compare naltrexone as a supplementary treatment for opioid use disorder, relative to standard treatment, among detoxified individuals with a prior opioid use disorder in England. The analyses were conducted from an NHS/PSS perspective. The analysis revealed a point estimate of £42,500 [2004 GBP] per QALY gained. Due to the amount of variability in the costs and QALYs between groups, the probability of naltrexone being considered cost-effective never exceeded 55% at the NICE's cost-effectiveness threshold of £30,000 per QALY gained.

3.4 Cost-effectiveness/cost-benefit of programs and implementation strategies

3.4.1 Cost-effectiveness of contingency management (CM) add-on programs—Olmstead and Petry[33] examined the cost-effectiveness of CM with vouchers as an add-on to treatment as usual, relative to CM with prizes and standard treatment, in an RCT of cocaine- or heroin-dependent patients in community treatment centers in the US. From the clinic's perspective, the additional cost per week of abstinence was \$212 [2001-2002 USD] for voucher-based CM and \$166 for prize-based CM. The probabilistic sensitivity analysis indicated that at a willingness-to-pay value of roughly \$250 per additional week of abstinence, prize-based CM had an 88% chance of being considered cost-effective, while voucher-based CM only had an 8.6% chance.

Sindelar et al.[34] evaluated the cost-effectiveness of CM with prizes as an add-on to treatment as usual, relative to standard treatment, in an RCT of US patients in MMT treatment programs with a stimulant, alcohol or opioid use disorder. The analyses were performed from the perspective of the clinic. The authors found that CM plus treatment as usual resulted in a cost of \$141 [2001-2003 USD] per additional week of abstinence and \$70 per additional stimulant-negative urine sample.

3.4.2 Implementation—Barnett et al.[71] conducted a retrospective cohort analysis of patients seeking treatment for an opioid use disorder in a US Department of Veterans Affairs opioid substitution program. Individuals in opioid substitution programs that were highly concordant with clinical practice guidelines for MMT were compared to those in less concordant programs. Over the 12 months following their index treatment, individuals in highly concordant programs incurred \$3,776 [2002 USD] more in treatment costs and \$7,590 more in total healthcare costs, on average, than individuals in less concordant programs. However, clients in highly concordant programs experienced a number of significantly better outcomes than those in less concordant programs: group and individual therapy sessions (37 vs. 13.1 and 17.5 vs. 16.9, respectively); percentage of individuals who were abstinent from heroin in the 30 days prior to assessment at 6 months (69.1% vs. 54.9%) and 12 months (72.8% vs. 54.4%); and preference-weighted health-related quality-of-life at 6 months (0.675 vs. 0.609). With regard to time-abstinent, the estimated ICER for highly-concordant programs was \$102 per opiate-free day, relative to less-concordant programs.

Bell et al.[36] assessed the cost-effectiveness of observed versus unobserved dosing of BMT among Australian heroin users in a 3-month clinical trial. Costs primarily reflected those of the payer, but also included patient travel costs. The authors did not find any significant differences between participants in the observed and unobserved cohorts with respect to days of heroin use, quality of life or psychological state; however, they did find that the mean cost of treating the observed cohort exceeded that of the unobserved cohort by \$1,477 [2005 AUD].

3.4.3 Diversion and aftercare programs—Hayhurst et al.[25] developed a decision analytic model to assess the cost-effectiveness of diversion and aftercare programs, relative to no program, among adult class-A offenders in England who were using either opiates or crack. The analyses were performed from multiple UK-relevant perspectives. The high level of variance in costs and QALYs resulted in insignificant differences for each, and uncertainty regarding the cost-effectiveness of these programs.

4. Discussion

Almost a third of the economic-evaluation studies included in this paper focused on identifying potential direct healthcare cost offsets associated with treatment for opioid use disorders through a change in the types services utilized. According to our assessment via the Drummond checklist,[27] and as can be seen in Table 2, all but 2 of the articles in this category were *average*. Overall, findings from these articles indicate that in spite of the higher outpatient or prescription costs associated with the therapy, pharmacotherapy for opioid use disorders is associated with lower total healthcare costs due primarily to lower

utilization of high-cost services such as ED use and inpatient care. Other outcomes of interest included lower criminal-justice-related costs associated with methadone maintenance therapy (MMT),[39] lower costs associated with buprenorphine/naloxone film versus tablets,[44, 45] and improved retention for high-dose versus low-dose buprenorphine/naloxone patients, with no significant increase in total direct healthcare costs.[46]

The remaining economic-evaluation studies included in this paper assessed both the costs and benefits of pharmacotherapy for opioid use disorders. Of these 30 remaining studies, 40% (n=12) focused on MMT relative to residential therapy or an outpatient non-pharmacological alternative; 2 others assessed MMT or buprenorphine/naloxone maintenance therapy (BMT) relative to a non-pharmacological alternative. As shown in Table 4, 10 of these 14 articles were rated as *good* based on our evaluation via the Drummond checklist[27]; the remaining 4 articles were *average*. Six of the 14 studies used quality-adjusted life-years (QALYs) gained as an outcome measure,[48, 54, 56, 58-60] and all 6 incremental-cost-effectiveness ratio (ICER) point estimates indicate that MMT would be considered cost-effective according to the traditional U.S. threshold for defining value of \$50,000 per QALY gained, or the WHO's recommendations for assessing the ICER relative to the country's GDP/capita.[57] Two additional studies calculated ICERs using HIV infections averted as the measure of effectiveness,[52, 53] while a third estimated an ICER with abstinent years in the denominator.[62] While the results from these studies focusing on cost per clinical outcome appear promising for MMT, unfortunately there is not an established willingness-to-pay threshold by which cost-effectiveness can be judged, as there is with cost per QALY gained. Basu et al.[51] performed a net-monetary-benefit analysis using self-reported robbery as the unit of effectiveness, while Schwartz et al.[50] used benefit-cost ratios to assess relative value of MMT. The remaining studies evaluated costs and effects separately. The results from these studies were also favorable for MMT.

A number of studies compared MMT to other pharmacological therapies, including injectable heroin,[64, 65] BMT,[21, 31, 32, 66, 67] and naltrexone.[67] As can be seen in Table 6, all but one of these studies was rated as *good*. With regard to injectable heroin, Nosyk et al.[64] found that it dominated MMT, while Byford et al.[65] found that to be the case for oral methadone, but found injectable heroin to be slightly less cost-effective than injectable methadone. Of the papers comparing MMT and BMT, only one was based on an RCT,[31] and only one used QALYs as an outcome measure.[21] Moreover, the results of the studies comparing MMT and BMT were mixed, but generally favored MMT. Connock et al.[21] found both BMT and MMT to be cost-effective relative to no pharmacotherapy at £13,697 and £26,429 [2004 GBP] per QALY gained, respectively, but that MMT dominated BMT. Jones et al.[31] found abstinence rates to be statistically similar for BMT and MMT, but MMT to be less expensive. Maas et al.[66] found MMT to dominate BMT with regard to 6-month retention rates, but BMT to be more effective in terms of detox rates, generating an ICER of £903 [2010-2011 GBP] per individual who stopped using illicit opiates. Geitona et al.[32] found BMT to be significantly less expensive than MMT from the Greek National Health System's perspective, and more effective with regard to participants completing therapy and deaths avoided. Finally, Jackson et al.[67] found MMT to dominate BMT with regard to costs from a state-addiction-treatment-payer perspective and an outcome measure of opioid-free days.

BMT was also compared to no treatment,[68] detoxification[69], and naltrexone.[67, 70] As indicated in Table 6, the quality of these studies was *good*. In general the results from these studies favored BMT. Schackman et al.[68] and Polsky et al.[69] both estimated cost-per-QALY point estimates that fell within the aforementioned range of acceptable U.S. values for cost-effectiveness[61]; however, Schackman et al. only found the therapy to have a 64% chance of being considered cost-effective at a willingness-to-pay threshold of \$100,000, while Polsky et al.'s estimates revealed an 86% chance at the same threshold value. Jackson et al.[67] estimated an ICER of \$72 [~2014 USD] per opioid-free day relative to MMT, and Ruger et al.[70] estimated ICER values below \$50 for a host of primary outcomes, including abstinence; however, as mentioned above, we are unable to assess the general level of acceptance for cost-effectiveness for these estimates.

Regarding naltrexone, in addition to the studies mentioned above, Adi et al.[19] created a decision-analytic model comparing naltrexone to standard treatment from an NHS/PSS perspective. The estimated ICER of £42,500 [2004 GBP] per QALY gained is slightly higher than the NICE's cost-effectiveness threshold of £30,000 per QALY gained. Moreover, the probability of naltrexone being considered cost-effective at this threshold never exceeded 55%.

Two studies assessed the cost-effectiveness of contingency management (CM) as an add-on to treatment as usual for patients with a stimulant or opioid use disorder,[33] or a stimulant, alcohol or opioid use disorder.[34] Both studies used the longest duration of abstinence and number of negative urine specimens as effectiveness measures, finding ICERs below \$212 per week of abstinence and \$156 per negative urine specimen. Once again, we are unable to assess these values relative to an established range of acceptable values.

One treatment strategy that has received little attention in terms of cost-effectiveness is that of simply offering opioid-use-disorder therapy. That is, it may be that the availability of different modalities of treatment brings more people into treatment itself, which may be a cost-effective strategy. As mentioned in the Introduction, only about 10% of individuals with an opioid use disorder receive therapy[2]; however, the majority of the cost-effectiveness studies compare alternative therapies, as opposed to treatment versus no-treatment.

Regarding implementation strategies, Bell et al.'s[36] findings indicate that unobserved dosing of BMT is more advantageous than observed dosing, as it was found to be less expensive, with no significant differences in days of heroin use, quality of life or psychological state. And Barnett et al.[71] found MMT programs that were highly concordant with clinical practice guidelines were more expensive on average than less concordant programs, but were more effective with regard to therapy sessions completed, abstinence and preference-weighted health-related quality-of-life scores.

Finally, Hayhurst et al.[25] estimated the cost-effectiveness of drug-diversion and aftercare programs for criminal-justice-involved opiate- or crack-using individuals in the UK, via a decision analytic model. However, due to the level of variance around costs and QALYs, the authors concluded that there was not enough evidence to make a determination with regard to cost-effectiveness.

4.1 Limitations

There are some important limitations associated with the studies included in this review that not only limit the findings of particular studies, but also make it difficult to generate objective comparisons between studies. First, there is a wide range of study designs. Only 8 (19%) of the economic-evaluation studies included in this review were conducted for an RCT. Almost 42% (n=18) of the economic-evaluation studies reviewed were a retrospective cohort analysis and 33% (n=14) were model-based (e.g. decision analytic models). Quasi-experimental and model-based designs limit the ability of the researchers to make causal inferences,[72, 73] thereby limiting the validity of the economic outcomes as well. Second, there is a great deal of variability in the outcomes of interest. For example, many studies focused primarily on changes in healthcare utilization and the associated costs, with little-to-no attention on the effectiveness of the program in terms of whether the participants were made “better off”. Among those studies that did incorporate effectiveness measures, many were clinical in nature. One problem with clinical outcomes is that they fail to capture many of the consequences associated with opioid misuse, such as changes in quality of life. A second problem with these types of outcomes, as mentioned above, is that a generally accepted range of cost-effectiveness threshold values has not been established, as it has with QALYs.[49, 61] The Panel on Cost Effectiveness in Health and Medicine[74] has recommended the QALY as the primary effectiveness outcome measure for economic evaluation studies, as it allows for comparisons across diseases and interventions. Finally, of those studies that did incorporate QALYs, the inconsistency in perspectives adopted for the evaluation limits comparability.

5. Conclusion

In general, the methadone-maintenance-therapy (MMT) studies included in this review contribute to the strong existing evidence that MMT is an economically advantageous form of therapy for opioid use disorders. However, the literature comparing MMT to other opioid-use-disorder pharmacotherapies is still quite limited. Additional research is needed, as there is variation in research designs, perspectives and outcomes. The existing economic-evaluation literature pertaining to buprenorphine/naloxone maintenance therapy (BMT) and naltrexone is also rather limited at this point, particularly for naltrexone. The results appear promising for BMT, contingency management and the therapy-implementation strategies that were reviewed, but are mixed for naltrexone. However, with the possible exception of MMT, a great deal more work is required in these areas before solid inferences regarding their relative economic value can be made. Additionally, more cost-effectiveness analyses assessing treatment versus no-treatment are needed, given that only about 10% of individuals with an opioid use disorder receive therapy.[2]

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Key Points for Decision Makers

- The evidence on methadone-maintenance therapy supports previous findings that it is an economically advantageous opioid-use-disorder therapy.
- Additional high-quality economic evaluations are needed in order to assess the relative value of other opioid-use-disorder interventions.

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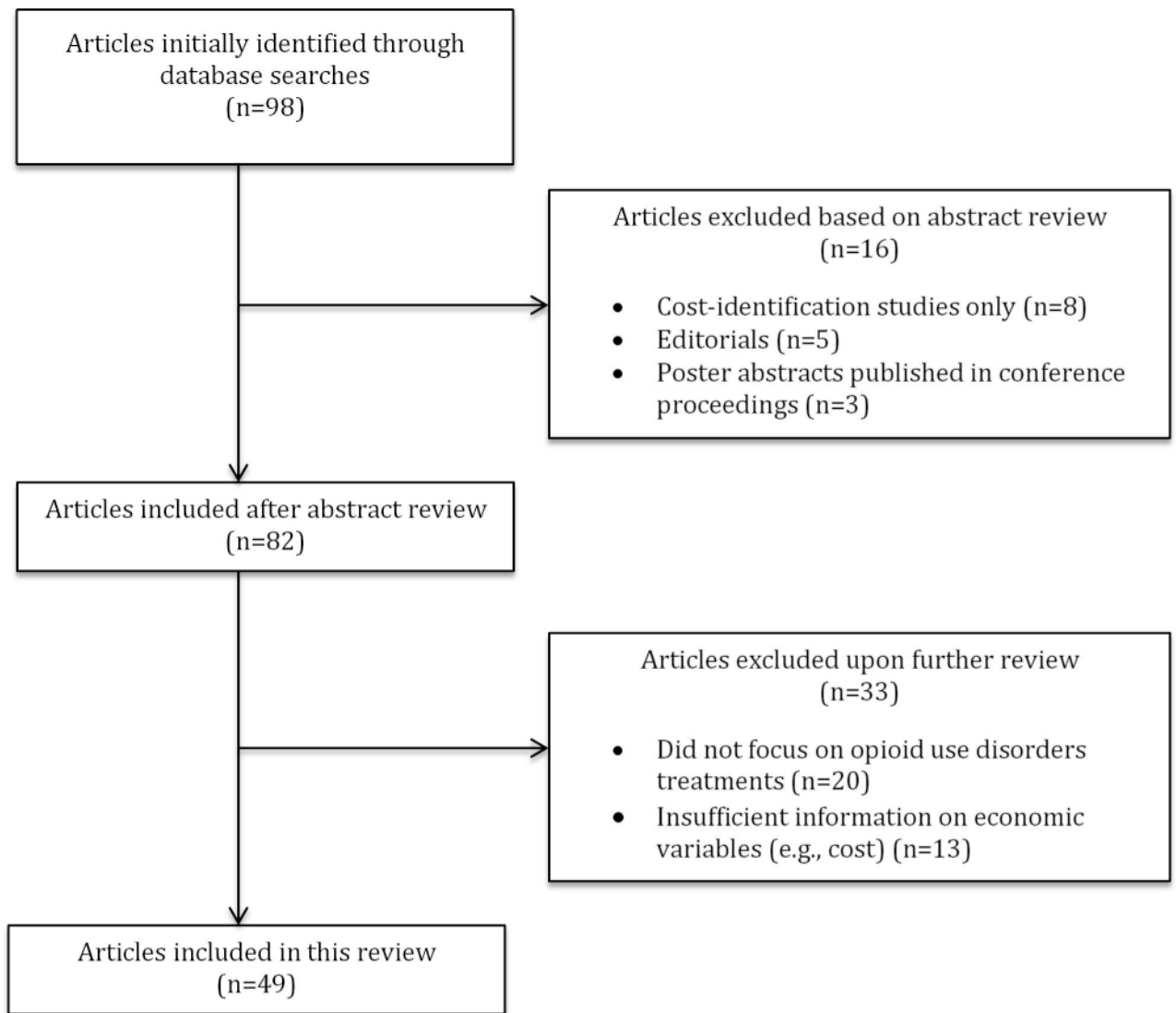


Figure 1.
Article selection process.

Table 1

Characteristics of cost and utilization studies

Study	Country	Participants	Intervention	Comparator	Study design	Perspectives	Outcomes	Findings
Baser et al., 2011 [28]	USA	Adult beneficiaries of a large U.S. healthcare plan, with a diagnosed opioid use disorder	Opioid-use-disorder pharmacotherapy	No opioid-use-disorder pharmacotherapy	Retrospective cohort analysis	Health insurer	Total healthcare costs and healthcare resource utilization	Participants receiving pharmacotherapy utilized fewer healthcare resources and had lower total healthcare costs.
Barnett, 2009 [29]	USA	Veteran's Health Administration patients treated with opioid agonist therapy	Buprenorphine/naloxone maintenance therapy (BMT)	Methadone maintenance therapy (MMT)	Retrospective cohort analysis	Veteran's Health Administration	Total healthcare costs; substance use and mental health services; ambulatory services; inpatient stays; and treatment retention	BMT patients utilized fewer healthcare resources, had lower total healthcare costs and had higher retention rates
McCarty et al., 2010 [37]	USA	Beneficiaries of a large Northwest HMO with 9 months of health plan eligibility and 2 encounters per year with a diagnoses of opioid dependence	MMT	1) No MMT and 2) outpatient addiction treatment visits, and 2) < 2 outpatient addiction treatment visits	Retrospective cohort analysis	Health insurer	Total healthcare costs; inpatient stays; and emergency department (ED), primary care, and other non-addiction visits	MMT patients utilized the fewest healthcare resources and had the lowest total healthcare costs.
Gourevitch et al., 2007 [38]	USA	Medicaid patients enrolled in MMT program who voluntarily participated in the HIV Epidemiologic Research on Outcomes Study	Long-term (6 months) MMT with on-site medical care	1) Long-term MMT, and 2) no long-term MMT	Retrospective cohort analysis	Medicaid	Total annual Medicaid expenditures; inpatient stays; and outpatient and ED visits	Long-term MMT with on-site medical care was associated with more outpatient visits, but fewer ED visits and hospitalizations, resulting in no significant difference in total healthcare costs.
Krebs et al., 2014 [39]	Canada	Illicit drug users who had accessed MMT and were involved in one of the following studies: At-Risk Youth Study, AIDS Care Cohort to evaluate Exposure to Survival Services, or the Vancouver Injection Drug Users Study	MMT with high effectiveness	1) MMT with low effectiveness, 2) opioid abstinence, and 3) relapse	Retrospective cohort analysis	Societal	Criminal-justice-system and victimization costs	Criminal costs averted were largest among those who remained abstinent, followed by those in the MMT-high-effectiveness group.

Buprenorphine/Naloxone Maintenance Therapy

Study	Country	Participants	Intervention	Comparator	Study design	Perspectives	Outcomes	Findings
Lynch et al., 2014 [40]	USA	Beneficiaries in 1 of 2 large health systems with 2 encounters with a diagnosis of opioid dependence	BMT with counseling	1) counseling only, and 2) little-to-no addiction treatment	Retrospective cohort analysis	Health system	Total healthcare costs; inpatient detoxification and residential treatment stays; and primary-care, ED, mental-health and other-medical visits	Relative to no-treatment, BMT-plus-counseling was associated with fewer primary-care, emergency and other medical services, and lower total healthcare costs. Relative to counseling-only, BMT-plus-counseling was associated with more inpatient detoxification visits, but fewer primary-care, other-medical, emergency and mental-health visits; total healthcare costs were not significantly different.
Tkacz et al., 2014 [41]	USA	Beneficiaries of large Northeast HMO with an opioid use disorder diagnosis and buprenorphine prescription	BMT-adherent	BMT-non-adherent	Retrospective cohort analysis	Health insurer	Total prescription fills and charges; opioid fills, days' supply and charges; inpatient hospital admissions, days and charges; ED visits and charges; outpatient visits and charges; total medical charges; total healthcare charges (medical + pharmacy)	BMT-adherent patients used fewer healthcare resources, aside from pharmaceuticals, and had significantly lower total healthcare charges.
Martínez-Raga, González-Saiz, Pascual, Casado and Sabater Torres, 2010 [42]	Spain	Targeted populations: 1) Patients needing medically assisted withdrawal prior to entering a relapse prevention program; 2) patients in high threshold programs; and 3) patients in low-intermediate threshold programs	BMT	MMT	Budget impact model	Societal	Total healthcare costs	Implementation of BMT would increase costs by €9 [2007 EUR], or less, per patient, relative to an MMT-only scenario.
Martínez-Raga, González-Saiz, Onate, Oyagüez, Sabater and Casado, 2012 [43]	Spain	Targeted populations: 1) Patients needing medically assisted withdrawal prior to entering a relapse prevention program; 2) patients in high threshold programs; and 3) patients in low-intermediate threshold programs	BMT	MMT	Budget impact model	Societal	Total healthcare costs	Implementation of BMT would increase costs by €10.58 [2010 EUR], or less, per patient, relative to an MMT-only scenario.

Study	Country	Participants	Intervention	Comparator	Study design	Perspectives	Outcomes	Findings
Clay et al., 2014 [44]	USA	Continuously enrolled beneficiaries of commercial health insurance plan with a new buprenorphine/naloxone prescription and 1 refill	Buprenorphine / naloxone film	Buprenorphine / naloxone tablet	Retrospective cohort analysis	Health insurer	Total healthcare, pharmacy, hospital ED and outpatient costs; pharmacy claims; probability of hospitalization or ED visit; and outpatient visits	BMT-film was associated with higher retention rates; more outpatient visits, a lower likelihood of hospitalization, and fewer total healthcare costs.
Asche et al., 2015 [45]	USA	Patients with an opioid use disorder	Buprenorphine / naloxone film	Buprenorphine / naloxone tablet	Budget impact model	Medicaid	Total healthcare costs	BMT-film would result in an increased use of outpatient services, fewer ED and inpatient visits, and lower total healthcare costs.
Khemiri et al., 2014 [46]	USA	Continuously enrolled commercial-health-plan and Medicaid beneficiaries with a new buprenorphine/naloxone prescription and 1 refill	Buprenorphine / naloxone - high dose	Buprenorphine / naloxone - low dose	Retrospective cohort analysis	Health insurer	Total healthcare and nonpharmaceutical costs; pharmaceutical claims; inpatient care (psychiatric and nonpsychiatric); ED and outpatient visits	High-dose BMT was associated with better retention rates and higher pharmacy costs, but similar total healthcare costs.
Kaur, McQueen and Jan, 2008 [47]	USA	Continuously enrolled beneficiaries in a managed care organization, with a new buprenorphine/naloxone prescription	Buprenorphine / naloxone	No buprenorphine / naloxone	Retrospective pre-post analysis	Health insurer	Opioid pharmacy claims; daily dose; days supply; and opioid drug costs	New opioid pharmacy claims decreased; however, drug costs did not differ significantly after accounting for the cost of therapy.

Table 2

Drummond checklist for cost and utilization studies

Study	Research question	Description of competing alternatives	Establishment of intervention's effectiveness	Inclusion of relevant costs and consequences	Measurement of costs and consequences	Valuation of costs and consequences	Adjustment of costs and consequences for differential timing	Incremental analysis of costs and consequences	Sensitivity analyses	Discussion quality	Total	Rating
Baser et al., 2011 [28]	1	1	0	1	1	1	0	0	1	1	7	Average
Barnett, 2009 [29]	1	1	0	1	1	1	1	0	0	1	7	Average
Multiple Medications												
Methadone Maintenance Therapy												
McCarty et al., 2010 [37]	0	1	0	1	1	1	1	0	1	1	7	Average
Gourevitch et al., 2007 [38]	1	1	0	1	1	1	0	0	0	1	6	Average
Krebs et al., 2014 [39]	1	1	1	0	1	1	1	0	0	1	7	Average
Buprenorphine/Naloxone Maintenance Therapy												
Lynch et al., 2014 [40]	1	1	0	1	1	1	1	0	0	1	7	Average
Tkacz et al., 2014 [41]	0.5	0.5	0	1	1	1	0	0	0	1	5	Average
Martínez-Raga, González-Saiz, Pascual, Casado and Sabater Torres, 2010 [42]	1	1	0	0	1	1	1	0	1	1	7	Average
Martínez-Raga, González-Saiz, Oñate, Oyagüez, Sabater and Casado, 2012 [43]	1	1	0	0	1	1	1	0	1	1	7	Average
Clay et al., 2014 [44]	1	1	1	0	1	1	1	0	1	1	8	Good
Asche et al., 2015 [45]	1	1	0	0	1	1	1	0	1	1	7	Average
Khemiri et al., 2014 [46]	1	1	1	0	1	1	1	0	0	1	7	Average
Kaur, McQueen and Jan, 2008 [47]	1	0	1	0	0	0	0	0	0	1	3	Poor

Table 3
Characteristics of cost-benefit and cost-effectiveness studies: MMT vs. residential or outpatient non-pharmacological therapy

Study	Country	Participants	Intervention	Comparator	Study design	Perspectives	Outcomes	Findings	Quality rating
Vanagas, Padaiga and Bagdonas, 2010 [48]	Lithuania	New outpatient methadone maintenance therapy (MMT) clients	MMT	No MMT	Prospective pre-post analysis Methadone Maintenance Therapy Pre-Post	Societal	Quality-adjusted life years (QALYs)	The cost-effectiveness ratio for MMT was €34,368 [2004 EUR] per QALY gained.	Average
Schwartz et al., 2014 [50]	USA	New outpatient MMT clients	MMT with drug-abuse counseling	MMT without drug-abuse counseling	Randomized controlled trial (RCT) Methadone Maintenance Therapy Alone Versus With Counseling	Societal	Benefit-cost ratio	The benefit-cost ratio did not differ significantly between groups.	Good
Basu et al., 2008 [51]	USA	Patients in residential and outpatient substance-abuse-treatment programs	Outpatient MMT	1) Residential short-term treatment, or 2) residential long-term treatment Methadone Maintenance Therapy Alone Versus Residential Treatment	Retrospective pre-post net-monetary benefit analysis	Societal	Robberies averted	For patients < 25 years of age, MMT resulted in the lowest cost-per-robbery-averted threshold required to achieve a net-monetary benefit. For patients younger than 25, the threshold was similar for all 3 modalities.	Good
Xing et al., 2012 [52]	China	Intravenous drug users (IDUs) seeking treatment in MMT clinics	MMT	No MMT	Retrospective cohort analysis Methadone Maintenance Therapy Versus Usual-Care Among HIV-Positive Drug Users	Provider	HIV infections averted	The cost-effectiveness ratio for MMT was \$3,705 [2007 USD] per HIV infection averted.	Good
Wammes, et al., 2012 [53]	Indonesia	IDUs, female sex workers and men having sex with men	MMT	Current practice	Modeled	Societal	HIV infections averted	The cost-effectiveness ratio for MMT was \$7,000 [2010 USD] per HIV infection averted.	Good
Alistar et al., 2011 [54]	Ukraine	Non-IDUs, IDUs using opiates and IDUs on MMT	MMT with increased access to antiretroviral therapy (ART)	1) MMT, 2) increased access to ART, or 3) current practice	Dynamic compartmental model	Provider	QALYs	Stand-alone MMT was most cost-effective, relative to current practice, with a cost-effectiveness ratio of \$530 per QALY gained.	Good
Tran and Nguyen, 2013 [55]	Vietnam	HIV-positive drug users seeking treatment at hospitals and health centers, who responded to the HIV Services Users Survey	MMT	No MMT	Retrospective cohort analysis	Patient	Health utility scores; out-of-pocket healthcare expenditures; and inpatient and outpatient services	MMT patients had higher levels of health utility and utilized fewer healthcare resources, resulting in lower out-of-pocket healthcare expenditures.	Average
Tran et al., 2012 [56]	Vietnam	HIV-positive patients seeking treatment for an opioid use disorder at a stand-alone MMT clinic	MMT	No MMT	Retrospective cohort analysis	Provider	QALYs	The cost-effectiveness ratio for MMT was \$3,551 [2009 USD] per QALY gained.	Good

Study	Country	Participants	Intervention	Comparator	Study design	Perspectives	Outcomes	Findings	Quality rating
Tran et al., 2012 [58]	Vietnam	HIV-positive patients seeking treatment for an opioid use disorder at a stand-alone MMT clinic	Integrated MMT and ART	1) Separate-site MMT and ART; or 2) ART alone.	Decision analytic model	Provider	QALYs	Separate-site MMT and ART was most cost-effective with a cost-effectiveness ratio of \$569 [2009 USD] per QALY gained, relative to ART alone.	Good
Tran et al., 2012 [59]	Vietnam	HIV-positive patients seeking treatment for an opioid use disorder at a stand-alone MMT clinic	MMT	No MMT	Decision analytic model	Healthcare system	QALYs and HIV cases averted	The cost-effectiveness ratios for MMT were \$964 [2009 USD] per QALY gained and \$3,324 per HIV case averted.	Good
Stephen et al., 2012 [60]	USA	Participants from 15 trials administering 6 months of MMT and participants from 45 trials of deep-brain stimulation for movement disorders	Deep-brain stimulation	MMT	Decision analytic model	Societal	QALYs	Deep-brain stimulation was dominated up to a success rate of 36.5% and would not be considered cost-effective at a threshold of \$200,000 [2011 USD] per QALY gained until a success rate of 50%.	Good
Moore et al., 2007 [62]	AU	Individuals seeking treatment for heroin dependence at a drug treatment agency	Buprenorphine/naloxone maintenance therapy (BMT) or MMT	1) Residential rehabilitation, or 2) prison	Retrospective cohort analysis	Societal	Abstinent years	BMT/MMT produced the lowest cost-per-abstinent-year ratio, \$500 [2002 AUD].	Good
Clark, Baxter et al., 2015 [63]	USA	Massachusetts Medicaid beneficiaries with an opioid use disorder	BMT or MMT	Drug-free opioid-addiction therapy	Retrospective cohort analysis	Medicaid	Time to relapse and total healthcare costs	BMT/MMT was associated with a lower likelihood of relapse and lower healthcare costs.	Average
Clark, Samnaliev et al., 2011 [30]	USA	Massachusetts Medicaid beneficiaries with an opioid use disorder	BMT or MMT	1) Drug-free opioid-addiction therapy, or 2) no therapy	Retrospective cohort analysis	Medicaid	Relapse-related mortality and total healthcare costs	BMT/MMT was associated with lower total healthcare costs and mortality rates. MMT was associated with the lowest relapse rates, followed by BMT.	Average

Table 4
Drummond checklist for cost-benefit and cost-effectiveness studies: MMT vs. residential or outpatient non-pharmacological therapy

Study	Research question	Description of competing alternatives	Establishment of intervention's effectiveness	Inclusion of relevant costs and consequences	Measurement of costs and consequences	Valuation of costs and consequences	Adjustment of costs and consequences				Total	Rating	
							for differential timing	Incremental analysis of costs and consequences	Sensitivity analyses	Discussion quality			
Vanagas, Padaiga and Bagdonas, 2010 [48]	1	0	0.5	0.5	1	1	1	1	0	0	1	7	Average
Methadone Maintenance Therapy Pre-Post													
Methadone Maintenance Therapy Alone Versus With Counseling													
Schwartz et al., 2014 [50]	1	1	1	1	1	1	1	0.5	1	1	0	8.5	Good
Methadone Maintenance Therapy Alone Versus Residential Treatment													
Basu et al., 2008 [51]	1	1	1	1	1	1	0	1	1	1	1	9	Good
Methadone Maintenance Therapy Versus Usual-Care Among HIV-Positive Drug Users													
Xing et al., 2012 [52]	1	0	1	1	1	1	1	1	1	1	1	9	Good
Wammes, et al., 2012 [53]	1	0.5	1	1	1	1	1	1	1	1	1	9.5	Good
Alistar et al., 2011 [54]	1	1	1	1	1	0.5	1	1	1	1	1	9.5	Good
Tran and Nguyen, 2013 [55]	0.5	0.5	1	1	0.5	1	1	0	0	0	1	6.5	Average
Tran et al., 2012 [56]	1	1	1	1	1	1	1	1	1	1	1	10	Good
Tran et al., 2012 [58]	1	1	1	1	1	1	1	1	1	1	1	10	Good
Tran et al., 2012 [59]	1	1	1	1	1	1	1	1	1	1	1	10	Good
Methadone Maintenance Therapy Versus Deep-Brain Stimulation													
Stephen et al., 2012 [60]	1	1	1	1	1	1	1	1	1	1	1	10	Good
Methadone Maintenance Therapy Versus Rehabilitation Or Prison													
Moore et al., 2007 [62]	1	1	1	1	1	1	0	1	1	1	0	8	Good
Methadone Maintenance Therapy Versus Drug-Free Therapy													
Clark, Baxter et al., 2015 [63]	1	1	1	1	1	1	0	0	0	0	1	7	Average
Clark, Sannaliev et al., 2011 [30]	1	1	1	1	1	1	0	0	0	0	1	7	Average

Table 5
Characteristics of cost-benefit and cost-effectiveness studies: Multiple pharmacological therapies, CM and implementation strategies

Study	Country	Participants	Intervention	Comparator	Study design	Perspectives	Outcomes	Findings	Quality rating
Nosyk et al., 2012 [64]	Canada	Participants in the North American Opiate Medication Initiative trial	Injectable diacetylmorphine (heroin)	Methadone Maintenance Therapy Versus Injectable Heroin Methadone maintenance therapy (MMT)	Semi-Markov cohort model	Societal	Quality-adjusted life years (QALYs)	Injectable diacetylmorphine dominated MMT.	Good
Byford et al., 2013 [65]	England	Individuals with chronic heroin addiction, receiving oral MMT	Injectable diacetylmorphine (heroin)	1) Injectible MMT, or 2) oral MMT	Randomized controlled trial (RCT)	Societal, health and social-services	QALYs	From a societal perspective, both injectable treatments dominated oral MMT, but injectable MMT was most cost-effective. Both injectable treatments were cost-ineffective from a health and social service perspective.	Good
Connock et al., 2007 [21]	England	Individuals with an opioid use disorder	Buprenorphine/naloxone maintenance therapy (BMT)	1) MMT, or 2) no pharmacotherapy	Decision analytic model	National Health Services (NHS)/ Personal-Social Services (PSS)	QALYs	MMT dominated BMT and generated a cost-effectiveness ratio of £13,697 [2004 GBP] relative to no pharmacotherapy.	Good
Jones et al., 2009 [31]	USA	Patients receiving outpatient MMT	Office-based BMT	1) Clinic-based MMT, or 2) office-based MMT	RCT	Provider and patient	Abstinence rates	Clinic-based MMT was least expensive, while abstinence rates were similar.	Average
Maas et al., 2013 [66]	UK	Patients seeking treatment for an opioid use disorder at a urban community drug service clinic	BMT	MMT	Non-equivalent group design	Provider	1) Treatment retention for 6 months, and 2) opioid abstinence	MMT dominated BMT using the outcome retention. For abstinence, the BMT cost-effectiveness ratio was £903 [2010-2011 GBP] per individual abstained from opiates.	Good
Geitona et al., 2012 [32]	Greece	Individuals in an opioid addiction therapy program	Buprenorphine / naloxone	1) MMT, or 2) buprenorphine monotherapy	Budget impact model	National Health System	1) Treatment completion, and 2) number of avoided deaths	Buprenorphine/naloxone was the dominant form of therapy.	Good
Jackson et al., 2015 [67]	USA	Males initiating pharmacotherapy for an opioid use disorder	Extended-release naltrexone (XR-NTX)	1) MMT, or 2) BMT	Markov model	State addiction treatment payers	Opioid-free days	The cost-effectiveness ratio for XR-NTX, relative to the next most effective treatment, MMT, was \$72 [~2014 USD] per opioid-free day.	Good

Buprenorphine/Naloxone Maintenance Therapy Versus No Treatment

Study	Country	Participants	Intervention	Comparator	Study design	Perspectives	Outcomes	Findings	Quality rating
Schackman et al., 2012 [68]	USA	Individuals with an opioid use disorder who had completed 6 months of BMT in a primary care setting	BMT	No therapy	Decision analytic model	Societal	QALYs	The cost-effectiveness ratio for BMT was \$35,000 [2010 USD] per QALY gained.	Good
Polsky et al., 2010 [69]	USA	Adolescents seeking treatment for an opioid use disorder at a community outpatient treatment program	BMT	Buprenorphine detox	RCT	Payer, provider and societal	1) QALYs, and 2) abstinent years	The cost-effectiveness ratios for BMT were \$1,376 [2006 USD] per QALY gained from a payer perspective, and \$25,049 per QALY gained from a provider perspective. Total net social costs were not significantly different.	Good
Ruger et al., 2012 [70]	Malaysia	Detoxified heroin-dependent patients from an outpatient research clinic and detoxification program	BMT	Naltrexone	RCT	Societal	Primary: days in treatment, maximum consecutive days of heroin abstinence, days to first heroin use and days to heroin relapse. Secondary: treatment retention, injection drug use, illicit opiate use, AIDS Risk Inventory total score, and drug risk and sex risk subscores.	BMT generated cost-effectiveness ratios below \$50 [2004 USD] for the primary outcomes and approximately \$350 for the secondary outcomes.	Good
Adi et al., 2007 [19]	England	Detoxified individuals with a prior opioid use disorder	Naltrexone	Standard treatment	Decision analytic model	NHS/PSS	QALYs	The cost-effectiveness ratio for naltrexone was £42,500 [2004 GBP] per QALY gained.	Good
Olmstead and Petry, 2009 [33]	USA	Cocaine- or heroin-dependent patients from an outpatient substance abuse treatment program	CM with vouchers	1) CM with prizes, or 2) standard treatment	RCT	Clinic	1) Longest duration of abstinence, and 2) number of negative specimens	Relative to standard treatment, prize-based CM was most cost-effective with a ratio of \$166 per abstinent week.	Good
Sinderlar et al., 2007 [34]	USA	Patients with a stimulant, alcohol or opioid use disorder, seeking treatment in a methadone maintenance community treatment program	CM with prizes	Standard treatment	RCT	Clinic	1) Longest duration of abstinence, and 2) number of negative specimens	The cost-effectiveness ratio for prize-based CM was \$141 [2001-2003 USD] per additional week of abstinence and \$70 per additional stimulant-negative urine sample.	Good
							Implementation		

Study	Country	Participants	Intervention	Comparator	Study design	Perspectives	Outcomes	Findings	Quality rating
Barnett et al., 2010 [71]	USA	Patients seeking treatment for an opioid use disorder in a Department of Veterans Affairs opioid substitution program	Programs highly concordant with clinical MMT practice guidelines	Less concordant MMT programs	Retrospective cohort analysis	Payer	1) Opiate-free days, 2) healthcare utilization, and 3) health-related quality-of-life utility weights	Highly concordant programs were more expensive, but also more effective with regard to therapy sessions attended, abstinence rates, and health-related quality-of-life.	Good
Bell et al., 2007 [36]	Australia	Patients seeking treatment for heroin dependence at an outpatient drug treatment center	Observed BMT	Unobserved BMT	RCT	Payer plus patient travel	1) Retention in treatment, and 2) abstinence at 3 months	Observed BMT was more expensive, but not significantly more effective than unobserved BMT.	Good
Hayhurst et al., 2015 [25]	England	Criminal-justice-involved opiate- or crack-using individuals	Diversion and aftercare programs	No program	Decision analytic model	Societal	QALYs	Neither costs nor QALYs differed significantly between groups.	Good

Table 6
Drummond checklist for cost-benefit and cost-effectiveness studies: Multiple pharmacological therapies, CM and implementation strategies

Study	Research question	Description of competing alternatives	Establishment of intervention's effectiveness	Inclusion of relevant costs and consequences	Measurement of costs and consequences	Valuation of costs and consequences	Adjustment of costs and consequences for differential timing	Incremental analysis of costs and consequences	Sensitivity analyses	Discussion quality	Total	Rating
Nosyk et al., 2012 [64]	1	1	1	1	1	1	1	1	1	1	10	Good
Byford et al., 2013 [65]	1	1	1	1	1	1	1	1	1	1	10	Good
Connock et al., 2007 [21]	1	1	1	1	1	1	1	1	1	1	10	Good
Jones et al., 2009 [31]	1	1	0	1	1	1	1	0	0	1	7	Average
Maaß et al., 2013 [66]	1	1	0	1	1	1	1	1	0	1	8	Good
Geitona et al., 2012 [32]	1	1	1	1	1	1	1	1	1	1	10	Good
Jackson et al., 2015 [67]	1	1	0	1	1	1	1	1	1	1	9	Good
Schackman et al., 2012 [68]	1	1	1	1	1	1	1	1	1	1	10	Good
Polsky et al., 2010 [69]	1	1	1	1	1	1	1	1	1	1	10	Good
Ruger et al., 2012 [70]	1	1	0	1	1	1	1	1	1	1	9	Good
Adi et al., 2007 [19]	1	1	1	1	1	1	1	1	1	1	10	Good
Olmstead and Petry, 2009 [33]	1	1	0.5	1	1	1	1	1	0	1	8.5	Good
Sinderlar et al., 2007 [34]	1	1	1	1	1	1	1	1	0.5	0.5	9	Good
Barnett et al., 2010 [71]	1	1	1	1	1	1	1	0	0	1	8	Good
Bell et al., 2007 [36]	1	1	0	1	1	1	1	0	1	1	8	Good
Hayhurst et al., 2015 [25]	1	1	1	1	1	1	1	1	1	1	10	Good