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Economic Evaluation in Opioid Modeling: Systematic Review

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ABSTRACT

Objectives: The rapid increase in opioid overdose and opioid use disorder (OUD) over the past 20 years is a complex problem associated with significant economic costs for healthcare systems and society. Simulation models have been developed to capture and identify ways to manage this complexity and to evaluate the potential costs of different strategies to reduce overdoses and OUD. A review of simulation-based economic evaluations is warranted to fully characterize this set of literature.

Methods: A systematic review of simulation-based economic evaluation (SBEE) studies in opioid research was initiated by searches in PubMed, EMBASE, and EbscoHOST. Extraction of a predefined set of items and a quality assessment were performed for each study.

Results: The screening process resulted in 23 SBEE studies ranging by year of publication from 1999 to 2019. Methodological quality of the cost analyses was moderately high. The most frequently evaluated strategies were methadone and buprenorphine maintenance treatments; the only harm reduction strategy explored was naloxone distribution. These strategies were consistently found to be cost-effective, especially naloxone distribution and methadone maintenance. Prevention strategies were limited to abuse-deterrent opioid formulations. Less than half (39%) of analyses adopted a societal perspective in their estimation of costs and effects from an opioid-related intervention. Prevention strategies and studies' accounting for patient and physician preference, changing costs, or result stratification were largely ignored in these SBEEs.

Conclusion: The review shows consistently favorable cost analysis findings for naloxone distribution strategies and opioid agonist treatments and identifies major gaps for future research.

Keywords: economic evaluation, opioid overdose, opioid use disorder, simulation models, systematic review.

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Introduction

Overdose deaths involving opioids have increased fourfold in the United States between 1999 and 2017, and opioid-related overdose deaths and hospitalizations have risen sharply in the United States and worldwide.[1]

Death due to opioids is a leading cause of unintentional death for Americans and has contributed to a decrease in US life expectancy.[2] In 2018, a substantial number of deaths in the United States (estimated 128 people per day)[3] were attributed to an overdose involving opioids.[1,2,4,5] The opioid crisis is characterized by multilayered dimensionality, with many moving interconnected parts ranging from the individual to societal level.[6] Opioid-related illness has significant economic costs for healthcare systems and society. Costs to the US economy of the opioid epidemic—including healthcare, mortality, criminal justice activities, family assistance, and productivity loss—were estimated at $631 billon total over the 4-year interval 2015 to 2018.[7] Several medications are effective in improving opioid-related health outcomes, including naloxone to reverse an opioid overdose[8] and methadone, buprenorphine and buprenorphine-naloxone, and injectable naltrexone to treat opioid use disorder.[9]

Resource allocation in public health decision making is often guided by guesswork, leading to misappropriated resources. To better guide allocations, it is critical to assess the cost-effectiveness and efficiency of alternatives when considering strategic solutions. Evaluations include assessment of interventions directly targeted at individual patients and decisions about broader implementation strategies within a greater system.[10] Economic evaluations provide an analysis given current observable conditions. Yet conditions constantly change in a dynamic world, so an estimate of future costs given a set of assumptions about future conditions could prove even more useful. Simulation-based economic evaluations (SBEEs) (eg, Markov, agent-based, system dynamics, and compartmental models) represent a set of such tools that can assess allocative efficiency in opioid policies while accounting for weaknesses in standard economic evaluations.

Specifically, SBEEs extrapolate beyond short timeframes and can offer projections of future cost-effectiveness and utility.[11] In

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addition to the use of existing real-world data, their ability to accommodate gaps in data allows for the simulation of populations for more accurate estimates of population-level effects.[12] SBEEs are especially useful to model phenomena with rapidly changeable landscapes, such as the prescription and illicit opioid supply channels characteristic of the opioid crisis. Simulation models are increasingly used in public health to account for the systemic complexity of the opioid crisis,[13–17] but SBEEs represent only a fraction of a wider pool of economic evaluations, and their usefulness in answering public health policy questions deserves greater attention. SBEEs have the potential to aid decision makers in implementing strategies to ameliorate the impacts of the opioid crisis. Strategies that might be modeled using SBEEs include policies or interventions that alter the flow of people from the healthy population into disordered states—for example, using nonopioids to treat pain or abuse-deterrent formulations of opioid pain medications; treatment programs that move people with substance use disorders into remission; or strategies that reduce harm to people once they have developed substance use disorders such as reducing likelihood of fatal overdose. See Sharareh et al[17] for information about the benefits and weaknesses of different modeling methods in opioids research and Jalali et al[18] for the type of policy questions they can answer.

The current systematic review provides insight into SBEE research pertaining to interventions to reduce opioid use and related harm. The primary goal is to identify what has been studied in existing SBEE research and to review and evaluate characteristics of the published studies. A secondary objective is to synthesize the results when possible. This review will highlight weaknesses in the existing body of SBEEs and gaps in the scope and quality of these economic evaluations. Reviews of economic evaluations have been published in the area of opioid-related interventions before many relevant simulation models addressing the opioid crisis were developed[19] or which have a narrow scope focused on economic evaluations of a specific subtype of opioid misuse or use disorder treatment strategy.[17,20,21]. For example, a 2016 review[21] assessed a broad scope of any type of economic evaluation for opioid use disorder interventions, yet cut off the inclusion time window to post-2007 studies, which excludes some high-quality intervention efforts. A 2017 review[20] examined the limited scope of opioid agonist treatments among people with nonprescription opioid dependence; this criterion excludes elements included in the current review such as opioid antagonist (ie, naloxone and extended-release naltrexone) treatments and people with strictly prescription opioid dependencies who have not escalated to heroin use. A 2019 scoping review[17] included simulation and conceptual models for policies aimed to resolve the opioid epidemic but did not focus on economic evaluation. No publication exists to date that reviews modeling-based economic evaluations for opioid crisis interventions. The current review encompasses SBEEs that provide a cost-based analysis for an intervention aimed at addressing the opioid crisis, and the scope is not limited to any subtype of intervention strategy.

The rest of this article is organized as follows: we describe the process of the review in the Methods section; present the descriptive and technical characteristics in the Results section; and summarize and synthesize the results when possible in the Discussion section.

Method

Search Strategy and Selection Criteria

A multiphase search strategy was applied to collect economic evaluations of interventions to reduce opioid use and related harms based on simulation models. PubMed was first searched for non-animal research journal articles published in English from the inception of PubMed (1966) to September 2019. The following MeSH terms were used in the PubMed search: (analgesics, opioid, heroin, naloxone, methadone, opioid-related disorders, prescription drug misuse, OR fentanyl) AND (computer simulation/[education; economics; methods; statistics and numerical data; supply and distribution], Markov chains, OR systems analysis). The five MeSH term categories of "computer simulation/[ ]" ensured the inclusion of a wide range of simulation modeling approaches (agent-based, system dynamics, compartmental, and microsimulation, among others); however, decision tree and regression analyses were excluded. To complement the search and to ensure that all relevant journal articles were included in the initial sample, results from EBSCOhost and Embase were also included.

Cost Screening

Two independent reviewers conducted a general cost-related screen to filter out articles not conducting cost analyses. The reviewers excluded articles that did not analyze an intervention strategy with an outcome around opioid use or did not report a quantitative, cost-related result. Analyses of cost or price dynamics within drug markets were also excluded in this stage—for example, an article on the heroin epidemic in Baltimore[22] was excluded because its only cost analysis was related to prices of drugs in the market rather than the cost of an intervention to reduce opioid overdose deaths and use disorder.

For each of these screens, following best review practices,[23] a 10-article pilot test was performed to ascertain mutual understanding of the inclusion criteria among the reviewers. After each screen, the reviewers compared findings, recorded the percent agreement, and discussed discrepancies to arrive at a mutual agreement. In cases where the inclusion decision could not be made based on title and abstract, the article was escalated to full-text review. The full-text reviews were then conducted to ensure that the actual content of the studies aligned with the inclusion criteria. For any step of the screening, extraction, and abstraction processes in which a consensus between the 2 reviewers was not reached, a third reviewer was available to resolve discrepancies.

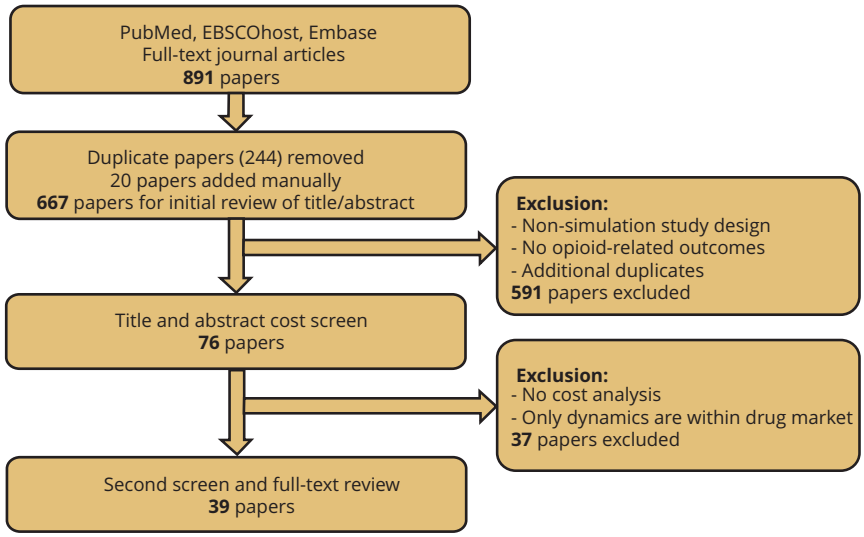
Data Extraction and Abstraction

For each study that met all inclusion criteria, 2 researchers independently read the full text and supplemental materials where applicable, and they abstracted and entered information into predefined 17-item extraction sheets adapted from systematic review data extraction tools.[24] The information items were selected to characterize the core characteristics of the analyses by observing trends of analyzed interventions over time; economic evaluation techniques and specifications; simulation modeling approaches underlying the economic evaluations; the core finding (cost-effectiveness or cost utility); and differences across strategies that drove the cost-related results. Each extraction item is described briefly in the Supplementary Materials found at https://doi.org/10.1016/j.jval.2020.07.013.

Quality Assessment

Each of the economic evaluations was appraised using the Drummond 10-point checklist.[25] The Drummond checklist, which has also been used by other systematic reviews of economic evaluations,[26-28] informs a quality appraisal of economic evaluations with consideration of a variety of methodological attributes and was selected for its ease of communication to a wider audience (Fig 1). This checklist has the advantage that it allows identification of the minimum acceptable standard for reporting of the

Figure 1. Quality assessment of economic evaluations.



general methods and results, and it allows direct comparison across economic evaluations and their results.[28] The tool enables reporting of each economic evaluation's fulfillment of 10 criteria items ranging from defining the research question, establishment of appropriate alternatives, effectiveness and costs, analytical approach, accounting for uncertainty, and presentation of results. One researcher identified whether each article met each criterion. In cases of ambiguity, the designation was escalated to a second researcher for further evaluation. It was permissible for a given item within the checklist to remain marked as partially met after the second review; this is reported in the results.

Results

Study Selection

Figure 2 represents the search strategy and results. The initial search produced 76 articles for simulation models of the opioid crisis, and they were uploaded into an online screening tool (Abstrackr[29]) to be screened for whether the title or abstract contained any mention of cost analysis or economic evaluation. There was 79% agreement in the designations given by the 2 reviewers. Following discussion between the reviewers, the consensus reached brought 39 studies into passage to inclusion from this screening.

The second screen assessed whether each of the 39 studies reported a cost-related result quantitatively and included an intervention strategy that was examined for an effect or outcome around opioid use. The 2 reviewers had an initial 85% agreement before reaching full consensus. Studies were excluded if the article did not report a cost-related finding quantitatively, did not model its effectiveness outcome in a manner directly related to opioids, or focused only on the transmission of human immunodeficiency virus (HIV) or hepatitis C virus (HCV) as the mechanism of effectiveness for the intervention. These exclusion criteria were adopted to avoid evaluation of articles targeting evaluation of strategies that were not primarily surrounding opioids-related interventions. For example, we included a study[30] that modeled

Figure 2. PRISMA flow diagram.

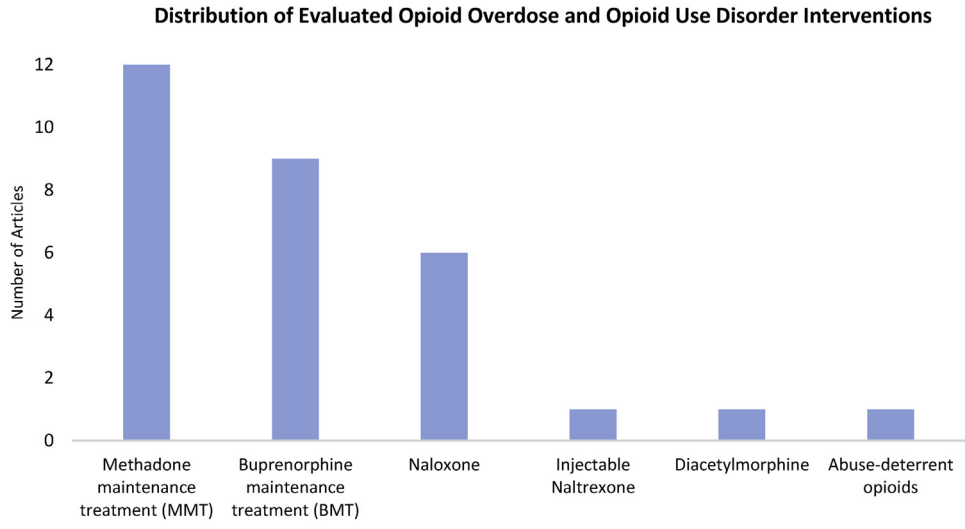


Table 1. Extracted items from 23 studies.

Study	Study characteristics		Cost and effectiveness estimation	Results
	Descriptive characteristics	Technical characteristics		
Asche 2015[36]	• **Perspective:** Medicaid • **Intervention and comparator:** sublingual film formulation vs tablet formulation of bup/nx combination • **Simulated population:** Medicaid patients with opioid dependence • **Treatment setting:** office-based • **Country/Currency (adj. year):** US; USD (2010-12) • **Cost source:** MarketScan Medicaid claims database • **Industry funding:** yes (Reckitt Benckiser Pharmaceuticals)	• **Modeling approach:** Markov model • **Economic evaluation (EE) method:** budget impact analysis • **Sensitivity analysis:** deterministic • **Time horizon:** 5 years • **Discounting:** 3% cost	• **Cost:** emergency care, medication, inpatient care • **Effectiveness:** impact on budget; transition probabilities between initiation, maintenance, discontinuation	• **Results:** sublingual bup/nx has 100% market share; cost = $6.4B sublingual film is progressively replaced by generic tablet; cost = $6.464B • **Most sensitive parameter:** The ratio of probabilities of nonpsychiatric hospitalization in the "off-treatment" state between film and tablet, and the price rebate for tablet • **Authors' conclusion:** Using the sublingual film formulation for more patients treated with bup/nx is predicted to increase outpatient care costs, but it would also generate savings in emergency care and hospitalizations. Total direct medical costs for Medicaid would be lower for sublingual-film-treated patients at current drug prices • **% EE assessment items fully satisfied:** 80%
Barnett 1999[37]	• **Perspective:** healthcare payer • **Intervention and comparator:** MMT vs "drug-free" treatment • **Simulated population:** 25-year-old people who use heroin • **Treatment setting:** clinic-based • **Country/Currency (adj. year):** US; USD (1996) • **Cost source:** literature • **Industry funding:** no	• **Modeling approach:** Markov model • **EE method:** cost-effectiveness analysis • **Sensitivity analysis:** deterministic • **Time horizon:** lifetime • **Discounting:** 3% cost and effects	• **Cost:** emergency care, medication, inpatient care • **Effectiveness:** Life-years gained; mortality rates	• **Results:** ICER = $5915 per LY gained • **Most sensitive parameter:** do not identify specifically; ICER found to be < $10k/life-year over wide range of modeling assumptions • **Author's conclusion:** giving opiate addicts access to methadone maintenance has an ICER of $5915 per life-year gained • **% EE assessment items fully satisfied:** 70%
Barnett 2001[38]	• **Perspective:** healthcare payer • **Intervention and comparator:** BMT vs MMT • **Simulated population:** adults in opiate dependence maintenance treatment • **Treatment setting:** clinic, office, and hospital • **Country/Currency (adj. year):** US; USD (1998) • **Cost source:** literature, RedBook, French national reporting • **Industry funding:** no	• **Modeling approach:** Compartmental model[†] • **EE method:** cost-utility analysis • **Sensitivity analysis:** deterministic • **Time horizon:** 10 years • **Discounting:** 3% cost and effects	• **Cost:** medication; urinalysis, physician evaluation, psychosocial interventions; costs associated with HIV/AIDS • **Effectiveness:** QALYs; number of injection drug users in maintenance	• **Results:** ICER = $14 000-$84 700 per QALY gained (low HIV prevalence); $10 800-$66 700 per QALY gained (high HIV prevalence). ICERS given across range of buprenorphine cost/dose, expansion strategy, and methadone status. • **Most sensitive parameter:** do not identify specifically; Tables 3 and 4 display how ICERs change in response to different quality of life adjustment assumptions • **Authors' conclusion:** Cost-effectiveness of buprenorphine maintenance depends on its price per dose. At $5 or less per dose, buprenorphine maintenance is cost-effective; at $15/dose it is cost-effective if its adoption does not lead to a net decline in methadone use or if a medium to high value is used to years of life for PWID and those in maintenance therapy; at $30/dose, it is cost-effective only under the most optimistic assumptions. • **% EE assessment items fully satisfied:** 60%

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Table 1. Continued

Study	Study characteristics		Cost and effectiveness estimation	Results
	Descriptive characteristics	Technical characteristics		
Carter 2017[39]	• **Perspective:** societal • **Intervention and comparator:** subdermal implantable vs sublingual buprenorphine • **Simulated population:** people seeking treatment for OUD • **Treatment setting:** office based • **Country/Currency (adj. year):** US; USD (2016) • **Cost source:** literature, insurance claims reports • **Industry funding:** yes (Braeburn Pharmaceuticals)	• **Modeling approach:** Markov model • **EE method:** cost-utility analysis • **Sensitivity analysis:** univariate and probabilistic • **Time horizon:** 12 months • **Discounting:** no	• **Cost:** direct medical costs and non-medical costs; clinical and societal penalties of relapse and illicit opioid use (criminal justice, work lost) • **Effectiveness:** QALYs; number of abstinent patients, retained patients	• **Results:** subdermal implantable buprenorphine costs $4386 less and gives 0.031 more QALYs than sublingual buprenorphine • **Most sensitive parameter:** relative monthly probability of relapse while on treatment • **Authors' conclusion:** subdermal injectable buprenorphine preferred over sublingual buprenorphine from health-economic perspective for treatment • **% EE assessment items fully satisfied:** 100%
Chalmers 2012[40]	• **Perspective:** healthcare payer(s) and patient • **Intervention and comparator:** subsidized vs unsubsidized MMT • **Simulated population:** patients enrolled in MMT therapy • **Treatment setting:** clinic based • **Country/Currency (adj. year):** Australia; AUS $ (2006/2007) • **Cost source:** NEPOD database, survey data • **Industry funding:** no	• **Modeling approach:** System dynamics model • **EE method:** other cost analysis (estimating cost burden if subsidy policy adopted) • **Sensitivity analysis:** deterministic • **Time horizon:** cyclical model with monthly and annual estimates • **Discounting:** no	• **Cost:** medication, prescribing and dispensing; and proportionate bearers of the cost • **Effectiveness:** Cost estimation of methadone maintenance treatment; behavioral effects of entry and retention to treatment	• **Results:** Annual cost to subsidize MMT = $94M to $175.8M • **Most sensitive parameter:** do not identify specifically; cost estimation depends on behavior effects assumptions of how patients stay longer in treatment and treatment-naive patients enter treatment sooner • **Authors' conclusion:** if Australian government(s) were to provide dispensing fee subsidies for methadone maintenance patients, it would be costly, but these additional costs are offset by the social and health gains achieved from the programs • **% EE assessment items fully satisfied:** 60%
Cipriano 2018[51]	• **Perspective:** societal • **Intervention and comparator:** distributing naloxone kits in secondary schools vs no naloxone distribution • **Simulated population:** secondary school students at risk of overdose • **Treatment setting:** secondary schools • **Country/Currency (adj. year):** Canada; Can $ (2017) • **Cost source:** literature, Toronto School Board data, Canadian Red Cross data, Canadian Institute for Health Information • **Industry funding:** no	• **Modeling approach:** Decision-analytic model • **EE method:** cost-utility analysis • **Sensitivity analysis:** deterministic and probabilistic • **Time horizon:** lifetime • **Discounting:** 1.5% cost and effects	• **Cost:** naloxone kits, program setup, training, administration, maintenance; emergency medical care, long-term healthcare costs • **Effectiveness:** QALYs; mortality in event of overdose	• **Results:** Scenarios in which the program would be cost-effective • **Most sensitive parameter:** most sensitive to cost and intensity of staff training, lifetime costs of person who overdoses, and intensity of naloxone training program • **Authors' conclusion:** making naloxone available in schools is cost-effective if there are at least 2 overdoses/year in the school • **% EE assessment items fully satisfied:** 100%
Coffin 2013 (1)[52]	• **Perspective:** societal • **Intervention and comparator:** naloxone distribution for lay administration vs no naloxone distribution • **Simulated population:** people who use heroin averaging 28-38 years of age • **Treatment setting:** community based • **Country/Currency (adj. year):** Russia; USD, converted from Russian currency (2010) • **Cost source:** Russian Federation data, program reports, media • **Industry funding:** no	• **Modeling approach:** Markov model • **EE method:** cost-utility analysis • **Sensitivity analysis:** deterministic and probabilistic • **Time horizon:** lifetime • **Discounting:** 5% cost and effects	• **Cost:** naloxone kits; emergency and hospital care; transport costs; heroin user cost to society • **Effectiveness:** QALYs; mortality in event of overdose	• **Results:** ICER = $71 USD per QALY gained • **Most sensitive parameter:** efficacy of lay-administered naloxone at preventing overdose death and the cost of naloxone • **Authors' conclusion:** naloxone distribution to heroin users for lay overdose reversal is highly likely to reduce overdose deaths in target communities and is robustly cost-effective • **% EE assessment items fully satisfied:** 100%

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Table 1. Continued

Study	Study characteristics		Cost and effectiveness estimation	Results
	Descriptive characteristics	Technical characteristics		
Coffin 2013 (2)[53]	• **Perspective:** societal • **Intervention and comparator:** naloxone distribution for lay administration vs no naloxone distribution • **Simulated population:** 21-year-old new US people who use heroin (base model) to ages 31 and 41 • **Treatment setting:** community based • **Country/Currency (adj. year):** US; USD (2012) • **Cost source:** literature, CDC data • **Industry funding:** no	• **Modeling approach:** Markov model • **EE method:** cost-utility analysis • **Sensitivity analysis:** deterministic and probabilistic • **Time horizon:** lifetime • **Discounting:** 3% cost and effects	• **Cost:** naloxone kits; EMS visits and transport to hospital; emergency department care; heroin user cost to society • **Effectiveness:** QALYs and life-years gained; absolute and relative overdose death rates	• **Results:** ICER = $438 per QALY gained • **Most sensitive parameter:** cost effectiveness result was robust to range of inputs; most sensitive to efficacy of lay-administered naloxone and cost of naloxone. • **Authors' conclusion:** the intervention to distribute naloxone to heroin users would likely reduce overdose deaths, increase QALYs, and be highly cost-effective • **% EE assessment items fully satisfied:** 100%
Jackson 2015[41]	• **Perspective:** state-level addiction treatment payers • **Intervention and comparator:** injectable XR-NTX vs MMT vs BMT • **Simulated population:** adult 18-65-year-old males ages enrolled in treatment for opioid dependence in the United States • **Treatment setting:** office based and clinic based • **Country/Currency (adj. year):** US; USD (2015*) • **Cost source:** literature, CMS data • **Industry funding:** no	• **Modeling approach:** Markov model • **EE method:** cost-effectiveness analysis • **Sensitivity analysis:** deterministic • **Time horizon:** 168 days (approx. 0.5 year) • **Discounting:** no	• **Cost:** medication, counseling, medication management and oversight • **Effectiveness:** opioid-free days; transition probabilities between abstinence, opioid use, retention in treatment	• **Results:** ICER for XR-NTX relative to MMT = $72.42 per opioid-free day gained; BMT is dominated • **Most sensitive parameter:** cost-effectiveness of XR-NTX compared to MMT is sensitive to effectiveness inputs and may be altered by uncertainty in relative costs • **Authors' conclusion:** XR-NTX is a cost-effective medication for treating opioid dependence if state addiction treatment payers are willing to pay at least $72 per opioid-free day • **% EE assessment items fully satisfied:** 80%
King 2016[42]	• **Perspective:** third-party payers in the US • **Intervention and comparator:** office-based BMT vs clinic-based MMT • **Simulated population:** 1,000 adult, opioid-dependent patients with no history of treatment within 30 days • **Treatment setting:** office based and clinic based • **Country/Currency (adj. year):** US; USD (2014) • **Cost source:** expert input, Redbook, CMS data • **Industry funding:** no	• **Modeling approach:** Markov model • **EE method:** cost-effectiveness analysis • **Sensitivity analysis:** deterministic and probabilistic • **Time horizon:** 1 year • **Discounting:** no	• **Cost:** medication, counseling, medication management and oversight • **Effectiveness:** Number of drug-free weeks and additional patient in treatment; probabilities of retention	• **Results:** ICER for MMT vs BMT is $10 437 per additional patient in treatment gained and $8515 per additional opioid abuse-free week gained • **Most sensitive parameter:** weekly cost of MMT had the largest impact on cost-effectiveness when retention in treatment was the outcome • **Authors' conclusion:** MMT is a cost-effective alternative to BMT for newly initiated opioid-dependent adults for opioid maintenance treatment in the United States from the perspective of a third-party payer • **% EE assessment items fully satisfied:** 90%
Krebs 2018[43]	• **Perspective:** societal • **Intervention and comparator:** OAT for all treatment recipients vs observed standard of care (54% treatment initiation with medically managed withdrawal) • **Simulated population:** patients presenting with OUD; base model patient is 35 years old • **Treatment setting:** publicly funded opioid use disorder treatment facilities • **Country/Currency (adj. year):** US; USD (2016) • **Cost source:** literature, legislative reporting • **Industry funding:** no	• **Modeling approach:** Semi-Markov cohort model • **EE method:** cost-utility analysis • **Sensitivity analysis:** probabilistic • **Time horizon:** lifetime • **Discounting:** 3% cost and effects	• **Cost:** healthcare resource use and criminal activity • **Effectiveness:** QALYs; survival probability, HIV incidence, rate of incarceration	• **Results:** Initial OAT strategy gives higher QALYs (12.93 vs 12.52) at a lower cost (946,804 vs 1,025,061) • **Most sensitive parameter:** OAT healthcare costs while not directly in treatment • **Authors' conclusion:** OAT delivered to all patients presenting for treatment provides greater health benefits and cost savings than the observed standard of care. This strategy maximizes the value of publicly funded treatment of opioid use disorder in California • **% EE assessment items fully satisfied:** 100%

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Table 1. Continued

Study	Study characteristics		Cost and effectiveness estimation	Results
	Descriptive characteristics	Technical characteristics		
Langham 2018[54]	• **Perspective:** public health system; societal perspective in sensitivity analysis • **Intervention and comparator:** distribution of naloxone for use by nonmedical responders vs no naloxone distribution • **Simulated population:** Adults at risk of heroin overdose • **Treatment setting:** community based • **Country/Currency (adj. year):** United Kingdom; Pound sterling £ (2016) • **Cost source:** Royal Pharmaceutical Society, National Health Service • **Industry funding:** yes (Mundipharma International Ltd.)	• **Modeling approach:** Markov model • **EE method:** cost-utility analysis • **Sensitivity analysis:** deterministic and probabilistic • **Time horizon:** lifetime • **Discounting:** 3.5% cost and effects	• **Cost:** medication, training/education, kit distribution, emergency care • **Effectiveness:** QALYs; mortality in event of overdose	• **Results:** ICER = 899 pounds per QALY gained • **Most sensitive parameter:** rate of first overdose; proportion of witnessed overdoses; efficacy of naloxone; proportion of witnessed overdoses when naloxone is available; social network modifier • **Authors' conclusion:** Distribution of take-home naloxone decreased OD deaths by 6.6% and was cost-effective. ICER is 899 pounds per QALY gained, well below the 20 000 set by UK decision makers • **% EE assessment items fully satisfied:** 100%
Masson 2004[44]	• **Perspective:** long-range perspective of the healthcare system • **Intervention and comparator:** MMT and 1 hour/week psychosocial therapy during first 6 months vs 180-day detoxification, 3 hours/week of psychosocial therapy, and 14 education sessions during the first 6 months • **Simulated population:** 196 adults with diagnosed opioid dependence • **Treatment setting:** research clinic in an established drug treatment program • **Country/Currency (adj. year):** US; USD (2004*) • **Cost source:** public health system administrative database • **Industry funding:** no	• **Modeling approach:** Markov model • **EE method:** cost-utility analysis • **Sensitivity analysis:** deterministic • **Time horizon:** 16 months with projection to 10-20 years • **Discounting:** 3% cost and effects	• **Cost:** health service utilization and psychosocial therapy/education • **Effectiveness:** QALYs; years in opioid use health state	• **Results:** ICER = $16 967 per LY gained; ICER < $20 000 per QALY gained • **Most sensitive parameter:** do not identify specifically; table shows how $/LY and $/QALY change in response to a set of 1-way inputs • **Authors' conclusion:** methadone maintenance is a cost-effective treatment relative to 180-day-long methadone detoxification • **% EE assessment items fully satisfied:** 100%
Morozova 2019[45]	• **Perspective:** payer (Ministry of Health and municipal authorities) • **Intervention and comparator:** scale-up strategies for OAT for OUD vs current capacity • **Simulated population:** people at risk of and with OUD • **Treatment setting:** clinic based • **Country/Currency (adj. year):** Ukrainian cities; USD, converted from Ukrainian currency (2016) • **Cost source:** private and national reports • **Industry funding:** no	• **Modeling approach:** Compartmental model • **EE method:** cost-utility analysis • **Sensitivity analysis:** probabilistic • **Time horizon:** 10 years • **Discounting:** 3% cost and effects	• **Cost:** costs associated with increased opioid agonist therapy capacities • **Effectiveness:** QALYs; access, initiation, retention in treatment	• **Results:** increased OAT capacity (12.2-, 2.4-, and 13.4-fold) would be cost-effective at WTP for QALYs gained of one GDP/capita. ICER given across strategies for each city • **Most sensitive parameter:** do not identify specifically • **Authors' conclusion:** A substantial increase in opioid agonist treatment (OAT) capacity in 3 Ukrainian cities would be cost-effective for a wide range of willingness-to-pay thresholds • **% EE assessment items fully satisfied:** 100%

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Table 1. Continued

Study	Study characteristics		Cost and effectiveness estimation	Results
	Descriptive characteristics	Technical characteristics		
Nosyk 2012[46]	• **Perspective:** societal; Ministry of Health and third-party payer in sensitivity analysis • **Intervention and comparator:** diacetylmorphine (heroin) vs methadone maintenance • **Simulated population:** people with chronic opioid dependence refractory to treatment • **Treatment setting:** clinic based • **Country/Currency (adj. year):** Canada; Can$ (2009) • **Cost source:** North American Opiate Medical Initiative, court records • **Industry funding:** no	• **Modeling approach:** Markov model • **EE method:** cost-utility analysis • **Sensitivity analysis:** deterministic and probabilistic • **Time horizon:** 1-, 5-, 10-year and lifetime • **Discounting:** 5% effects	• **Cost:** medication, human resources, overhead, drug treatments for HIV and HCV infection, nonmedical costs: criminal activity (charges, justice system, victimization) • **Effectiveness:** QALYs; transition probabilities between treatment, abstinence, relapse	• **Results:** ICER for diacetylmorphine versus MMT in Can$ per QALYs gained is cost saving and more effective across all time horizons • **Most sensitive parameter:** the only scenarios where diacetylmorphine is not strictly cost saving and they report ICER numerically is the Ministry of Health perspective and when they apply mortality estimates from Gronbladh et al • **Authors' conclusion:** A treatment strategy featuring diacetylmorphine may be more effective and less costly than methadone maintenance treatment among people with chronic opioid dependence refractory to treatment. Societal costs would decrease via reduction in crime, and both duration and quality of life of the treatment recipients would increase. • **% EE assessment items fully satisfied:** 90%
Ritter 2016[47]	• **Perspective:** societal • **Intervention and comparator:** comparing residential rehabilitation, opioid substitution treatment, counseling only, in-prison treatment strategies to one another • **Simulated population:** people who use heroin between ages of 18 and 60 each with various genders, HIV and HCV statuses, and treatment histories • **Treatment setting:** various (clinic based, residential treatment, prison) • **Country/Currency (adj. year):** Australia; AUS$ (2012) • **Cost source:** literature, DOH data, Medical Benefits data, NSW committee data, experimental • **Industry funding:** no	• **Modeling approach:** Microsimulation model • **EE method:** other cost analysis (microsimulation model building and validation) • **Sensitivity analysis:** no • **Time horizon:** 42 years • **Discounting:** 3% effects	• **Cost:** treatment provision, healthcare services, criminal activity, life-years lost, family benefit of treatment, HIV/HCV treatment • **Effectiveness:** life-years saved; transition probabilities between abstinence, irregular and regular use, withdrawal, treatment states and mortality rates	• **Results:** estimated costs over heroin use careers; reported itemized costs by heroin use state, crime event, etc. • **Most sensitive parameter:** n/a • **Authors' conclusion:** authors were able to build a stable, tractable model and verified all parameters. Validation against external data sources revealed high validity. While there are limitations associated with any model, the heroin career model now has the potential to be used for simulations of alternate policy scenarios. • **% EE assessment items fully satisfied:** 40%
Schackman 2012[48]	• **Perspective:** healthcare payer and patient • **Intervention and comparator:** long-term office-based buprenorphine-naloxone (bup/nx) vs no treatment for clinically stable opioid-dependent patients • **Simulated population:** clinically stable patients with opioid dependence who already completed 6 months of office-based bup/nx treatment • **Treatment setting:** office based • **Country/Currency (adj. year):** US; USD (2010) • **Cost source:** literature, USDOL data, CMS data, state data (CT) • **Industry funding:** no	• **Modeling approach:** Decision-analytic model • **EE method:** cost-utility analysis • **Sensitivity analysis:** deterministic and probabilistic • **Time horizon:** 2 years • **Discounting:** 3% cost and effects	• **Cost:** medication, treatment delivery • **Effectiveness:** QALYs; transition probabilities between in/off treatment and on/off drugs states	• **Results:** ICER = $35,100 per QALY gained (bup/nx, compared to no treatment) • **Most sensitive parameter:** quality-of-life weight assumptions • **Authors' conclusion:** office-based bup/nx for this set of patients can be a cost-effective alternative to no treatment at an accepted threshold of $100 000/QALY • **% EE assessment items fully satisfied:** 100%

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Table 1. Continued

Study	Study characteristics		Cost and effectiveness estimation	Results
	Descriptive characteristics	Technical characteristics		
Townsend 2019[55]	• **Perspective:** societal and health sector • **Intervention and comparator:** comparing 8 naloxone distribution strategies to one another • **Simulated population:** people at risk of opioid-related overdose death • **Treatment setting:** community based • **Country/Currency (adj. year):** US; USD (2017) • **Cost source:** literature, pharmaceutical data, SAHMSA data, DOJ data, USDOL data, USGAO data • **Industry funding:** no	• **Modeling approach:** Decision-analytic model • **EE method:** cost-utility analysis • **Sensitivity analysis:** probabilistic • **Time horizon:** lifetime with 5-year social cost • **Discounting:** 3% cost and effects	• **Cost:** naloxone kits; training; time costs of naloxone training; ambulance and emergency department visits; productivity costs of OUD and overdose; costs to criminal justice system **Effectiveness:** QALYs; mortality rates and QOL due to less hypoxia and reduction in misuse	• **Results:** high layperson / high police and fire / high EMS distribution strategy is dominant from the societal perspective with an ICER of $15 950 per QALY gained • **Most sensitive parameter:** probability that police and fire arrive before EMS • **Authors' conclusion:** evidence supports increased naloxone distribution to laypeople, police/fire, and EMS; under resource constraints laypeople and EMS should be the priority • **% EE assessment items fully satisfied:** 100%
Uyei 2017[56]	• **Perspective:** healthcare sector • **Intervention and comparator:** comparing no treatment; naloxone distribution alone; with linkage to addiction treatment; with PrEP; and with linkage to addiction treatment and PrEP strategies to one another • **Simulated population:** people at risk of opioid-related overdose death via injection. Starting cohort is 22 years of age and HIV-negative • **Treatment setting:** community and hospital based • **Country/Currency (adj. year):** US; USD (2015) • **Cost source:** literature, state CMS data (CT) • **Industry funding:** no	• **Modeling approach:** Decision analytical Markov model • **EE method:** cost-utility analysis • **Sensitivity analysis:** probabilistic • **Time horizon:** 5, 10, and 20 years • **Discounting:** 3% cost	• **Cost:** cost of naloxone distribution, addiction treatment, emergency care, HIV care • **Effectiveness:** QALYS; overdoses averted, survival, life expectancy, HIV-related deaths averted	• **Results:** naloxone distribution plus PrEP and linkage to addiction treatment has an ICER at 20 years of $95 337 per QALY gained relative to naloxone distribution plus linkage to addiction treatment. The other 3 strategies were dominated • **Most sensitive parameter:** ICERs for the fifth (all-inclusive) strategy were most sensitive to variation • **Authors' conclusion:** naloxone distribution through syringe service programs is cost-effective compared with syringe distribution alone, but when combined with linkage to addiction treatment is cost saving compared with no additional services. A strategy that combines naloxone distribution, PrEP, and linkage to addiction treatment results in greater health benefits in people who inject drugs and is also cost-effective at the $100 000 per QALY gained willingness to pay threshold. • **% EE assessment items fully satisfied:** 90%
Yenikomshian 2017[35]	• **Perspective:** healthcare payer and physician • **Intervention and comparator:** ER ADOs vs ER non-ADOs • **Simulated population:** 10 000 adult chronic pain patients • **Treatment setting:** physician decision in primary care • **Country/Currency (adj. year):** US; USD (2015) • **Cost source:** literature, CMS data • **Industry funding:** yes (Pfizer Inc.)	• **Modeling approach:** Markov process model • **EE method:** other cost analysis (impacts of prescribing decision non-incrementally) • **Sensitivity analysis:** deterministic • **Time horizon:** 12 months • **Discounting:** no	• **Cost:** prescribing, medication, cost associated with abuse or misuse events • **Effectiveness:** misuse and/or abuse-related events and NNH; reduced misuse or abuse events	• **Results:** patients prescribed ER ADOs had 87 to 417 fewer misuse- and/or abuse-related events than patients prescribed ER non-ADOs with a savings of $8 to $35 per patient. NNH ranged from 185 to 40. • **Most sensitive parameter:** results range by population (commercial, Medicaid, Medicare, VA) and were sensitive to decreases in the probability of misuse and/or abuse-related events but showed reductions in most scenarios • **Authors' conclusion:** a physician's decision to prescribe ER ADOs rather than ER non-ADOs could lead to large reductions in misuse and/or abuse-related events and associated costs across many patient populations • **% EE assessment items fully satisfied:** 100%

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Table 1. Continued

Study	Study characteristics		Cost and effectiveness estimation	Results
	Descriptive characteristics	Technical characteristics		
Zaric 2000 (1)[30]	• **Perspective:** healthcare payer • **Intervention and comparator:** expanded MMT vs current level of MMT • **Simulated population:** IDUs and non-IDUs with varying HIV status, 18 to 44 years of age • **Treatment setting:** clinic based • **Country/Currency (adj. year):** US; USD (1998) • **Cost source:** literature, census data, national report • **Industry funding:** no	• **Modeling approach:** Compartmental model • **EE method:** cost-utility analysis • **Sensitivity analysis:** deterministic • **Time horizon:** 26 years • **Discounting:** 3% cost and effects	• **Cost:** health care costs with and without MMT expansion for both HIV- and non-HIV-related medical needs • **Effectiveness:** QALYs; treatment availability, reduced risky behavior and spread of HIV, mortality	• **Results:** ICER = $8200 per QALY gained (high HIV prevalence) and $10 900 per QALY gained (low HIV prevalence). Under various other assumptions the ICER ranges from $10 000 to $38 300 per QALY gained (high HIV prevalence) and from $15 200 to $36 100 per QALY gained (low HIV prevalence) • **Most sensitive parameter:** do not identify specifically; the expanded MMT capacity remains cost-effective even if it is twice as expensive and half as effective as current MMT slots • **Authors' conclusion:** expansion of MMT is cost-effective on the basis of commonly accepted criteria for medical interventions • **% EE assessment items fully satisfied:** 60%
Zaric 2000 (2)[49]	• **Perspective:** healthcare payer • **Intervention and comparator:** expanded MMT vs current level of MMT • **Simulated population:** IDUs and non-IDUs with varying HIV status, 18 to 44 years of age • **Treatment setting:** clinic based • **Country/Currency (adj. year):** US; USD (1998) • **Cost source:** literature, census data, national report • **Industry funding:** no	• **Modeling approach:** Compartmental model • **EE method:** cost-utility analysis • **Sensitivity analysis:** deterministic • **Time horizon:** 26 years with 10-year forward projection • **Discounting:** 3% cost and effects	• **Cost:** non-HIV healthcare, HIV care, methadone maintenance by HIV and IDU status • **Effectiveness:** LYs and QALYs; treatment availability and HIV infections averted	• **Results:** ICER of 10% MMT expansion is $10 900/$8400/$6300/$8200 per QALY gained for 5%/10%/20%/40% HIV-prevalence communities, respectively • **Most sensitive parameter:** do not identify specifically; incremental MMT slots are likely to be cost-effective even if they cost twice as much and are half as effective in reducing risky behavior as current MMT programs • **Authors' conclusion:** expanding existing MMT programs is a cost-effective healthcare intervention that can play an important role in slowing the spread of HIV and improving the length and quality of life for IDUs; expansion is cost-effective even in populations with low HIV prevalence among IDUs • **% EE assessment items fully satisfied:** 90%
Zarkin 2005[50]	• **Perspective:** societal • **Intervention and comparator:** methadone treatment vs no intervention • **Simulated population:** heroin users aged 18-60 in general population • **Treatment setting:** clinic based • **Country/Currency (adj. year):** U.S.; USD (2001) • **Cost source:** literature, national report, FBI data, USDOJ data, USDHHS data, census data • **Industry funding:** no	• **Modeling approach:** Monte Carlo simulation • **EE method:** cost-benefit analysis • **Sensitivity analysis:** yes; deterministic • **Time horizon:** approximating lifetime by modeling ages 18-60 (42 years) • **Discounting:** 3% cost and benefits	• **Cost:** heroin use, treatment, criminal behavior, employment, and healthcare use; crime, incarceration, and loss of employment • **Effectiveness:** outcomes converted to monetary terms; mortality, crime, employment loss	• **Results:** lifetime benefit-to-cost ratio = 37.73 (dynamic model) and 4.86 (static model) • **Most sensitive parameter:** lifetime crime costs and mean per-individual economic benefit depends highly on probability of committing a crime. Life-years, number of years using heroin, and mean lifetime crime costs depend highly on the mortality rate of heroin users • **Authors' conclusion:** increasing access to treatment significantly increased treatment benefits and costs and dominates the alternative strategy of improving treatment process by lengthening stay in treatment • **% EE assessment items fully satisfied:** 60%

Note. Cost-benefit analysis: comparison of interventions and their consequences where both are expressed in monetary terms. Cost-effectiveness analysis: economic analysis that compares the relative costs and outcomes of 2 or more alternatives. Budget impact analysis: economic assessment that estimates the financial consequences of adopting an intervention. Cost-utility analysis: economic analysis that compares the relative costs and quality-adjusted outcomes of 2 or more alternatives.

adj., year indicates year to which costs were adjusted; ADO, abuse-deterrent opioid; BMT, buprenorphine maintenance treatment; bup/nx, buprenorphine-naloxone; EE, economic evaluations; ER, extended release; ICER, incremental cost-effectiveness ratio; IDU, injection drug user; LY, life-year; MMT, methadone maintenance treatment; NNH, number needed to harm; NTX, naltrexone; OAT, opioid agonist treatment; OUD, opioid use disorder; QALY, quality-adjusted life-year.
*Year of currency adjustment not explicitly stated in article; year of publication shown instead for context in comparing costs across studies.
†Model details in prior work.[51]

interventions as explicitly affecting non-HIV costs and utilities but excluded a study[31] that had a primary focus on HIV transmission. Inclusion of studies that focus primarily on HIV would further increase the heterogeneity of study design, research methods, and findings of the final collection of studies. Following the full-text review and conflict resolution discussions after each screening, 23 studies were finally included. Ten studies were published in substance abuse journals, 7 in health economic and management journals, and 6 in general medicine and public health journals.

Descriptive Characteristics of Studies

Seven major descriptive characteristics were extracted, discussed below, and presented in detail in Table 1.

Perspective

The perspective of an economic evaluation depends on the research question and which costs and effectiveness measures the analysis considers. We divided these primary perspectives into 3 general categories: healthcare sector, payers, and societal. Healthcare sector perspectives account for "formal health care sector (medical) costs borne by third-party payers or paid for out-of-pocket by patients," including "current and future health costs, related and unrelated to the condition under consideration."[32] Payer perspectives account for the subset of healthcare sector costs covered by the payer. The societal perspective accounts for medical-related costs and factors such as an intervention's effects on reduced criminal activity or worker productivity and wages lost.[32,33] The Second Panel on Cost Effectiveness in Health and Medicine[34] recommends use of the healthcare sector and societal perspectives as reference case analyses. Less than half (9 articles; 39%) of the studies adopted a societal perspective in their primary analysis. The others (14 articles; 61%) were limited to a healthcare sector or specific payer perspective for healthcare costs.

Intervention and comparator

Interventions and accompanying comparators of interest included one prevention strategy (abuse-deterrent opioids),[35] treatment strategies (opioid agonist, partial agonist, or antagonist maintenance therapies),[30,36–50] and strategies involving naloxone distribution (distribution to laypeople; emergency medical services (EMS), police and fire workers; and secondary schools).[51–55] One study considered multiple sets of strategy combinations.[56] The focus of economic evaluations has shifted over time as the incidence of overdose has escalated. Analyses of opioid agonist or partial agonist therapies (methadone and buprenorphine maintenance) were the predominant strategy evaluated between 1999 and 2005, and these continue to be relevant through the present day. Evaluations of naloxone distribution strategies increased beginning in 2013,[51–56] coinciding with the rapid rise in overdose deaths and increasing fentanyl contamination of the heroin supply.

As shown in Figure 3, methadone maintenance treatment (MMT) is covered with the highest frequency, followed by buprenorphine maintenance treatment (BMT) and naloxone (the only explicit harm reduction strategy explored). Injectable naltrexone,[41] prescription injectable diacetylmorphine[46] (ie, the active ingredient in heroin) for opioid use disorder, and abuse-deterrent opioid formulations[35] were each evaluated only once.

Simulated population

The simulated populations varied in age, and some models had initial conditions where nonusers could transition into opioid-related states. Modeled individuals were commonly defined by drug use status (7 articles; 30%—eg, individuals who actively use heroin), disorder status (8 articles; 35%—eg, chronic pain patients, people with opioid use disorder), treatment status (4 articles; 17%); or event risk status (4 articles; 17%—eg, people at risk of opioid-related overdose death).

Treatment setting

Treatment or strategy setting of models underlying the economic evaluations were clinic-based (10 articles; 43%), office-based (4 articles; 17%), both clinic- and office-based comparatively (3 articles; 13%), or community-based (6 articles; 26%).

Country and currency

Eighteen studies (78%) were based on North American (US or Canada) models, so costs for most of the economic evaluations are expressed in US dollars (USD). The remaining 5 (22%) were based on models for Australia (2), the UK (1), Ukraine (1), and Russia (1); these studies' costs are expressed in the given country's currency or converted to USD.

Cost source

Eighteen studies (78%) used cost data from national or state data, often supplemented by literature and private data; the remaining 5 used only literature or industry sources to determine costs.

Industry funding

Four studies (17%) were funded by the pharmaceutical industry; the rest were unfunded or funded by NIH Institutes, the Department of Veteran Affairs, the Connecticut Department of Public Health, or philanthropic organizations.

Technical Characteristics of Studies

Five major technical characteristics are extracted, discussed below, and presented in detail in Table 1.

Modeling approach

The sample of studies represents a wide variety of modeling approaches. Thirteen (57%) were Markov-based models (Markov, semi-Markov, Markov process, or decision-analytical Markov model). The next most common modeling approaches were other compartmental (4 articles; 17%) and decision-analytic models (3 articles; 13%). Finally, the studies included 1 (4%) each of a system dynamics, microsimulation, and Monte Carlo model.

Economic evaluation (EE) method

EE methods were mostly cost-utility (15 articles; 65%) or cost-effectiveness analyses (3 articles; 13%); there was 1 (4%) budget impact analysis and 1 (4%) cost-benefit analysis, and 3 (13%) cost analyses that do not fit a predefined economic evaluation framework ("other cost analysis" in Table 1). We labeled economic evaluations that report a cost-effectiveness result incrementally using a quality-adjusted outcome (eg, QALY) as a "cost-utility"

analysis, even in cases where "cost-effectiveness" was applied in the article title.[30,38,39,43–46,49,48,51,52–56] This designation does not represent an error or shortcoming on the part of the original studies because the terminology has become common in health economic literature. Quality adjustments are done by accounting for the quality of life associated with various health states using utilities ranging from 0 (death) to 1 (perfect health). Economic evaluation approaches reflected their respective aims, which most often (18 articles; 78%) were to contrast the cost-effectiveness of multiple interventions. As shown in Appendix Figure 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.07.013, cost-utility analyses were employed most frequently.

Sensitivity analysis

Twenty-two studies (96%) performed sensitivity analyses. Ten (43%) performed a deterministic sensitivity analysis only, and 12 (52%) performed a probabilistic sensitivity analysis, often in addition to a deterministic sensitivity analysis. More recent publications were more likely to be probabilistic (median publication year 2017, vs 2005 for deterministic approaches). A singular most sensitive parameter was not usually identified, but cost-effectiveness results often varied depending on the inputs. The magnitude of the dependence was not consistently reported. Authors' conclusions were typically qualitative interpretations of the main cost-related result.

Time horizon

Time horizons specified by the model ranged from 1 year or less (5 articles; 22%) to lifetime or approximating lifetime (10 articles; 43%).

Discounting

The most common discount rate chosen was 3% (14 articles; 61%) but ranged from 1.5% to 5%. All studies applied discounting except in cases with 1 year or smaller time horizons, where it would not apply.

These characteristics inform the context of conclusions decision makers may draw from the results of the economic evaluations. This gauging of technical attributes of SBEEs may expedite identification of appropriate areas of future research. If, for example, a decision maker is particularly interested in learning about interventions' impact on budget, this section shows that current SBEE literature is limited to only one budget impact analysis (ie, Asche 2015[36]), and research investments might be made in that area. Additionally, data collection efforts need to be aligned with research investments in order to develop better models for better decisions. Our study offers insights into what types of health and cost data are still needed across the diverse interventions for OUD.

Cost and Effectiveness Estimation

Input costs for all studies typically included healthcare costs associated with the intervention directly such as cost of medication, administrative costs, and treatment delivery costs. Seven (30%) studies accounted for costs associated with adverse events such as emergency care in the event of overdose. Some input cost components appeared only within the context of specific types of interventions. For example, pharmacotherapy maintenance[38] usually entails urinalysis testing, and training and education costs often incurred within naloxone distribution strategies.[51,54] Costs for comorbid conditions such as HIV and HCV were accounted for in 7 (30%) studies. When a perspective beyond the healthcare system is adopted, as in the case for societal perspectives, input costs such as the costs associated with criminal activity (8 articles; 35%) and worker productivity (6 articles; 26%) were also considered.

The effectiveness measures extraction item gives the summary outcomes unit and notes the driving factor for differences in effectiveness between intervention strategies. Summary effectiveness units were usually life-years (3 articles; 13%) or quality-adjusted life-years (QALYs) (15 articles; 65%) in accordance with most economic evaluation approaches being cost-effectiveness or cost-utility analyses. The important distinction—in economic evaluation generally and in the context of SBEEs specifically—between cost-utility and cost-effectiveness analysis is ultimately the presence of quality adjustment; cost-utility studies account for the difference in quantified estimates of quality of life gained, not just simply unadjusted count of life-years gained.[57]

Incremental Cost-Effectiveness Ratios and Other Cost Analysis Findings

Although the heterogeneity of the studies precluded a meta-analysis, some cost-effectiveness results may be summarized in

Figure 3. Distribution of evaluated interventions. Studies could have more than one evaluated intervention. Diacetylmorphine is the active ingredient in heroin.

cases where economic evaluations analyzed common alternatives or framed their findings in similar ways. Two studies[55,56] analyzed multiple mixed strategies and found an all-inclusive strategy of naloxone distribution, pre-exposure prophylaxis (PrEP), and addiction treatment was the cost-effective alternative to subcombinations of naloxone distribution, PrEP, and addiction treatment or each approach alone, at an incremental cost-effectiveness ratio (ICER) of $95 337 per QALY gained.[56] A particular naloxone distribution strategy combination (high levels of distribution to laypeople, police, fire workers, and EMS) was cost-effective against the other combinations with an ICER of $15 950 per QALY gained.[55] The intersection of sensitivity analysis results and intervention type point to how interventions might perform amid changing conditions. A trend that emerged for the most sensitive parameters across multiple studies[51,52,53,54,58] relates to the uncertainty around lay naloxone distribution: these results tended to be sensitive to cost and intensity of training, efficacy, and proportion of witnessed overdoses.

Incremental cost-effectiveness ratio (ICER) results are displayed under the results column in Table 1. Economic evaluations showed favorable cost-effectiveness results under a commonly accepted willingness to pay threshold of $50 000 per QALY for naloxone distribution strategies against the alternative of no naloxone distribution[52,53,54] and for opioid antagonist therapies (MMT or BMT) against an alternative of no treatment[37,44,48] or against a current standard of care.[43] The economic evaluations contained strong evidence that MMT is cost-effective against BMT[41,42] or no treatment[37] with one mixed result[38] that is discussed herein.

In the budget impact analysis,[37] the total cost incurred by scaling up a health intervention in terms of market share was compared to the alternative of smaller or 0% market shares. A general cost analysis[40] investigated government payer or patient share of cost burden under MMT subsidy policy implementation and found subsidizing methadone would reduce the cost burden on patients and costs are offset by social and health gains. Other studies analyzed health and cost impacts of the abuse-deterrent opioid prescribing decision separately rather than incrementally[35] or estimated costs over heroin use.[47]

Only 1 study[41] examined injectable naltrexone and compared it with MMT or BMT, and it was considered cost-effective against MMT if policymakers were willing to pay an additional $72 per patient per opioid-free day. One study[46] examined prescribed diacetylmorphine (ie, heroin), and it was found to be cost-effective relative to MMT. Additionally, cost findings were in favor of the sublingual over the tablet formulation of buprenorphine-naloxone from a public payer perspective[36] and the subdermal implantable over the sublingual version of buprenorphine. Three studies that looked specifically at scale-up of interventions for buprenorphine or methadone maintenance therapies[30,45,49] showed evidence in favor of cost-effectiveness.

Quality Assessment

Eleven (48%) of the 23 studies met the full 10 checklist criteria (see the overall score (%) in Table 1 and details in Appendix Table 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.07.013). Figure 1 shows the proportion of items that were fully or partially satisfied.

Discussion

Summary of Findings: Quality, Scope, and Gaps

We identified 23 studies that conducted simulation-based economic evaluations (SBEEs), analyzing the cost of various interventions to address opioid overdose and use disorder. The quality assessment indicated that the economic evaluations were of moderate to high quality, with most studies fully satisfying at least 90% of the quality assessment items. It appears particularly difficult for researchers to identify the important and relevant costs and consequences for each alternative, which could be due to the challenges of data availability and complexity. This challenge is especially present when attempting to model a population, such as people who use heroin, whose behaviors are parameterized with high uncertainty over a long time horizon.[37,47] Other cost-related challenges appeared, for instance, in measuring the quantities of drug-free therapy and detoxification services received,[37] differences in cost estimation methods between methadone and buprenorphine treatments,[42] and missing societal-relevant costs such as lost wages in the societal perspective.[47] When performed, sensitivity analyses help resolve these concerns in part by showing that varying the cost inputs did not alter the results drastically[37]—although interpretation is complicated by the lack of a standard, generally acceptable threshold of willingness to pay for some outcomes such as additional patients retained in treatment.[42]

The topical scope of the studies covered 6 main analyses of cost-effectiveness: methadone expansion; comparisons of different medications for opioid use disorder (methadone, buprenorphine, injectable naltrexone, and, in one study, medically prescribed diacetylmorphine [ie, the active ingredient in heroin]); comparisons of modes of medication delivery (eg, sublingual vs subdermal buprenorphine-naloxone); comparisons of medications to treatment without medications; abuse-deterrent versus non–abuse-deterrent opioid prescribing; and comparisons of different naloxone distribution strategies. The most common comparisons involved opioid agonist treatments, particularly methadone, a full agonist, and buprenorphine, a partial agonist.

Economic evaluation results depend on many specifications—including geographies represented, choice of input parameters, model structures, assumptions inherent to the underlying models, and various reported outcomes—that make it difficult to arrive at blanket conclusions across a given extraction category. Because of high heterogeneity among the studies, additional synthesis in the form of a quantitative aggregation of results was ruled out. Nonetheless, results were consistent enough to give a reliable framework for discussion of overall findings.

The only harm reduction strategy evaluated across studies was naloxone distribution; other harm reduction strategies not treated in this collection of SBEEs—which may be an area for future research—include syringe exchange, safe consumption sites, fentanyl test strips, and education programs that teach how to use more safely.[59-61] The inclusion and exclusion criteria were set up such that they would have captured SBEEs on harm reduction strategies other than naloxone distribution. Economic evaluations that compared a naloxone distribution strategy against no naloxone distribution consistently arrived at a favorable cost-effective result for naloxone distribution with ICERs under a willingness-to-pay threshold of $50 000 per QALY.[52-54] The study[55] that addressed the question of which persons should be targeted to carry naloxone recommends prioritization of distribution to laypeople likely to experience or witness an overdose and first responders.

Economic evaluations for opioid antagonist therapies (MMT or BMT) against an alternative of no treatment[37,44,48] or against a current standard of care[43] were also found to be cost-effective at the $50 000 threshold. The cost-effectiveness comparison of MMT with BMT was mixed: in a model[38] with HIV effects, one extreme scenario found BMT to be cost-effective relative to MMT at a willingness-to-pay threshold of $100 000 (ICERs ranged from $84

700 to $10 800 per QALY). This study[38] was published in 2001, at the earliest part of the time window for economic evaluations represented in the review, and contained high uncertainty because the treatment was not introduced in the US market until 2002.[62] A more recent analysis[42] found MMT cost-effective over BMT if the decision maker is willing to pay $10 437 per additional patient in treatment or $8515 per additional opioid-free week gained. It is not surprising that MMT was found more effective given its superior clinical results in patient retention relative to buprenorphine or naltrexone[63,64]; its cost-effectiveness depends on the relevant decision maker's willingness to pay for the given outcomes. Notably, the one study evaluating prescription diacetylmorphine found it less costly and more effective than MMT, which is consistent with clinical studies finding superior outcomes in patients prescribed diacetylmorphine (often in addition to methadone).[65-67]

The one study[41] examining injectable naltrexone should be considered in light of additional research that has been conducted since 2015. First, studies in the United States have expanded, finding significant induction failure (ie, very early relapse[68]) and greater rates of discontinuation,[69] albeit equivalent success rates if people can be successfully inducted. Moreover, the FDA has issued a warning letter to Alkermes, the manufacturer of Vivitrol, for withholding information about the opioid overdose risk associated with its drug.[70] Thus, the limitation pointed out by Jackson et al[41] (that there is a "relative lack of evidence on the effectiveness") is less true now, and additional economic evaluations should be conducted taking into account these recent findings. The results of the review demonstrate a dearth of economic evaluations of prevention strategies for the opioid crisis, as only 1 study[35] addressed this angle.

To the end of using the results of this collection of economics evaluations to guide allocative efficiency, we can arrive at a broad conclusion that naloxone distribution and methadone-assisted treatment are options with consistently favorable cost-effectiveness results. Each study should be considered within its own context of relevant alternatives. Responsible interpretation of the economic evaluations' results will take into account each study's sensitivity analysis approach and input ranges and whether the inputs are varied in a manner that reflects the practical context for the decision makers' application. The SBEE studies reviewed did not typically take account of patient and prescriber preferences or acceptability of an intervention. Only 2 studies compared different formulations of buprenorphine, finding that the relative value of sublingual or tablet form was dependent on contextual factors that have since changed. Specifically, sublingual formulations were estimated to have lower total direct costs than tablets at drug prices as of the study[36] published in 2015, which was before the FDA's approval in 2018 of cheaper, generic formulations of sublingual buprenorphine-naloxone.[71] Implantable buprenorphine, a relatively new form of the medication that was only approved in 2016,[72] was found cost-effective relative to the sublingual formulation, but recent studies find that patients still generally prefer sublingual and other short-acting forms over injectable or implantable buprenorphine.[73-75] Patient preferences could preclude realization of any projected cost savings if patients are reluctant to use the product. This challenge of accounting for patient preference has been an active area of improving cost-effectiveness research.[76]

Besides making an intervention potentially irrelevant, low acceptability can mask costs of rapid scale-up for interventions that go underutilized. Feedback dynamics are largely unaccounted for, and, simply, preferences can change. Increasingly, urgent policy questions surround the rising costs of medications due to manufacturers' increased perception of demand and willingness to pay. Failing to account for rising prices can dramatically reduce cost-effectiveness and limit access to life-saving medications, particularly for treatments requiring prolonged use of medication, which is often the case in treatments for opioid use disorder. Cost inputs were cited as among the most sensitive parameters in studies across a variety of intervention types: opioid agonist therapies (ie, methadone and buprenorphine maintenance),[42,43,50,77] extended-release naltrexone,[41] and naloxone distribution strategies;[51-53] changing costs has the potential to present a shift in cost-effectiveness across a multitude of strategies.

Seven of the 23 studies cite cost as among the most sensitive inputs to the cost-effectiveness of treatment; rising prices of a central input to treatment costs may play an important role in using modeling insights to generate effective policy strategies.

Finally, only 2 studies[37,50] stratified results by age and gender; stratification by other factors such as socioeconomic status, ethnicity, or urban versus rural locality was not performed by any of the reviewed study. Stratification importantly provides insight into patient heterogeneity, reflecting how results for the so-called average patient may not represent patients in a given subgroup, thus informing the degree of appropriate generalizability of each study's conclusions.

Limitations and Future Research

This review was limited to journal articles published in English. Economic evaluations such as those conducted alongside a clinical trial or based on retrospective data without a simulation extension were excluded.

The quality assessment of economic evaluations was limited to the Drummond checklist. This checklist is one of multiple economic tools that exist, each with advantages and disadvantages, designed to aid quality assessment of economic evaluations. The primary advantage in this application is its offering of familiarity, ease of understanding, and accessibility to a general audience; however, the checklist cannot identify weaknesses in the underlying simulation model. The assessment informs how well the study has included the minimum quality aspects for economic evaluation. If a simulation model was of poor methodological quality, relied on weak or invalid assumptions, or was not calibrated, the economic evaluation could still attain a perfect quality score as long as the components of the economic evaluation were met. The Quality of Health Economic Studies (QHES) instrument is an example of a more specific quality assessment instrument that might be employed for future research assessing the quality and rigor of the simulation modeling methods included in this review.[78] A potential area for future research can also include reviewing the models retrospectively to assess their accuracy in predicting cost-effectiveness based on now observable historical trends. Areas that merit further attention as a topic for future research include understanding the tradeoff between making opioids available for pain versus restricting opioids and facing possible effects of undertreated pain; syringe exchange programs; and supervised consumption sites.

Conclusions

This systematic review identified 23 simulation-based economic evaluations (SBEEs) in the opioid literature. The characteristics of this set of studies reflect the heterogeneity and complexity behind this public health crisis and the large set of decisions required in attempting to model it. Despite slight declines in fatal opioid overdoses in 2018 and 2019,[79] Americans are still dying at unprecedented rates from opioids. In addition to the tremendous human toll that these deaths take, there are significant societal and healthcare system costs. Many of these

healthcare costs will remain, if not rise, as people with opioid use disorder access treatment and initiate medication maintenance. By making the best available use of limited data, SBEEs can help account for the chronic nature of the opioid crisis and the effects of various interventions within a greater dynamic system.

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