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Systematic Literature Review

Economic Evaluation of Interventions to Address Opioid Misuse: A Systematic Review of Methods Used in Simulation Modeling Studies

Carolina Barbosa, PhD,* William N. Dowd, BA, Gary Zarkin

ABSTRACT

Objectives: Several evidence-based interventions exist for people who misuse opioids, but there is limited guidance on optimal intervention selection. Economic evaluations using simulation modeling can guide the allocation of resources and help tackle the opioid crisis. This study reviews methods employed by economic evaluations using computer simulations to investigate the health and economic effects of interventions meant to address opioid misuse.

Methods: We conducted a systematic mapping review of studies that used simulation modeling to support the economic evaluation of interventions targeting prevention, treatment, or management of opioid misuse or its direct consequences (ie, overdose). We searched 6 databases and extracted information on study population, interventions, costs, outcomes, and economic analysis and modeling approaches.

Results: Eighteen studies met the inclusion criteria. All of the studies considered only one segment of the continuum of care. Of the studies, 13 evaluated medications for opioid use disorder, and 5 evaluated naloxone distribution programs to reduce overdose deaths. Most studies estimated incremental cost per quality-adjusted life-years and used health system and/or societal perspectives. Models were decision trees (n = 4), Markov (n = 10) or semi-Markov models (n = 3), and microsimulations (n = 1). All of the studies assessed parameter uncertainty though deterministic and/or probabilistic sensitivity analysis, 4 conducted formal calibration, only 2 assessed structural uncertainty, and only 1 conducted expected value of information analyses. Only 10 studies conducted validation.

Conclusions: Future economic evaluations should consider synergies between interventions and examine combinations of interventions to inform optimal policy response. They should also more consistently conduct model validation and assess the value of further research.

Keywords: cost-effectiveness, economic evaluation, modeling, opioid misuse, simulation.

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Introduction

There is a crisis with regards to the inappropriate use of opioids and related morbidity and mortality. Globally, about 127 000 people died in 2015 as a result of opioid use disorder (OUD). Additionally, about 10.6 million people across the world who engage in injection drug use suffer from hepatitis C and human immunodeficiency virus (HIV).[1] In the United States, where a plurality of global opioid-related deaths have occurred in recent years, the opioid epidemic has resulted in high economic costs (up to $504 billion in 2015)[2] driven by premature death, crime, lost productivity, and health-related costs.

Several prevention, treatment, and harm reduction interventions have been employed to address the crisis.[3] Prevention initiatives including drug take-back programs,[4] educational initiatives targeting providers and the public,[5] and prescription drug monitoring programs[6–8] seek to limit the number of people inappropriately using opioids. Treatments include medication for opioid use disorder (MOUD)[9–12] and behavioral therapies, which have been shown to enhance the effectiveness of MOUD.[13] Harm reduction strategies, including overdose prevention with naloxone[14–16] and supervised injection facilities,[17] seek to limit the consequences of opioid use.

Identifying the optimal mix of interventions is complex, so community leaders need guidance on how to allocate resources to address the epidemic. Economic evaluations identify, measure, and value the costs and outcomes of alternative strategies to guide decisions.[18] A simulation model is an analytic approach that projects outcomes and costs associated with alternative strategies.[19] Simulation modeling draws information from multiple sources, offering an approach to integrate information on the trajectory of OUD and associated complications with the clinical and economic

* Address correspondence to: Carolina Barbosa, PhD, Behavioral Health Research Division, RTI International, 230 W. Monroe Street, Suite 2100, Chicago, IL, USA, 60606. Email: cbarbosa@rti.org

impact of public health strategies to inform the best response to the opioid crisis.[20] It offers several advantages, including (1) extrapolating beyond the data observed in a trial, (2) linking intermediate endpoints (eg, treatment retention) to final outcomes (eg, overdose death), (3) generalizing to other settings, (4) synthesizing head-to-head comparisons, (5) accounting for the synergistic effect of multiple interventions, and (6) informing decisions in the absence of data.[21] Simulation modeling offers the ideal framework to identify uncertainty around relevant variables and set priorities for further research.[22,23] In addition, long-term decision modeling can capture the multiplicity of outcomes characteristic of OUD, with periods of relapse and recovery accompanied by several comorbid conditions.

A recent study conducted a systematic review of the literature on economic evaluations of interventions for OUD.[24] This study found 43 economic evaluations conducted up to August 2015, with most of the studies focusing on MOUD with methadone maintenance treatment, and found strong support for the cost-effectiveness of methadone. This previous review did not focus on economic evaluations with a decision-analysis simulation-modeling approach, was limited to treatment only, and focused on the results of the individual studies rather than the methods used. In addition, several relevant economic evaluations have been published since 2015. Our study reviews the methods employed by economic evaluations that used simulation modeling to investigate the health and economic effects of interventions meant to address opioid misuse and appraises the approaches in the context of best practices.

Methods

Overview

We conducted a systematic mapping review to characterize the health economic evaluations of OUD interventions that used simulation techniques.[25] In general, a systematic mapping review involves a systematic search and the categorization of existing literature according to study design and other key features. We followed relevant Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in conducting and reporting the review.[26,27]

Search Strategy

The search strategy included search terms relating to 3 dimensions: (1) opioids (eg, heroin), interventions (eg, methadone), and related consequences (eg, dependence); (2) simulation and modeling (eg, Markov); and (3) economic evaluation (eg, cost-effectiveness). A research librarian reviewed the search terms and created tailored searches for the following databases: PubMed, Embase, PsycINFO, CINAHL, Web of Science, and EconLit (see Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2020.03.015). We restricted our search to full-text studies published in English between 2000 and the time of the search (January 2019).

Eligibility Criteria

Included studies satisfied 3 criteria. First, the studies had to focus on prevention, treatment, or harm reduction interventions targeting opioid misuse and/or direct consequences of misuse (ie, overdose). Studies of needle exchange programs were not included because the outcomes reported did not directly target opioid misuse. Additionally, studies that described interventions targeting drug use in general for which methods and results could not be clearly subset to opioids were not included. Studies also had to be economic evaluations, meaning that they compared the costs and effects of at least 2 strategies.[18] Cost-effectiveness analyses (CEAs), cost-utility analyses (CUAs), and cost-benefit analyses (CBAs) were considered. Cost analyses that did not compare an intervention with another strategy were not included. Finally, studies had to use a simulation modeling technique. Economic evaluations based entirely on trials or observational data were not included.

Study Selection

Two authors screened titles and abstracts for inclusion. Each author was primarily responsible for half of the identified studies, checked 10% of the other author's list, and discussed studies that either author was unsure about. Studies were excluded if they clearly did not meet the inclusion criteria. Studies not excluded during title and abstract screening were reviewed in full.

Data Collection

We developed an extraction form that focused on the components of economic analysis and modeling (see Appendix 2 in Supplemental Materials). The extraction form followed the principles of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS)[28] and other guidelines for reporting economic evaluations and simulation models.[18,29,30] The extraction form captured details on the study population and intervention(s), outcomes and costs, modeling approach, and economic analysis characteristics.

Results

Search Results

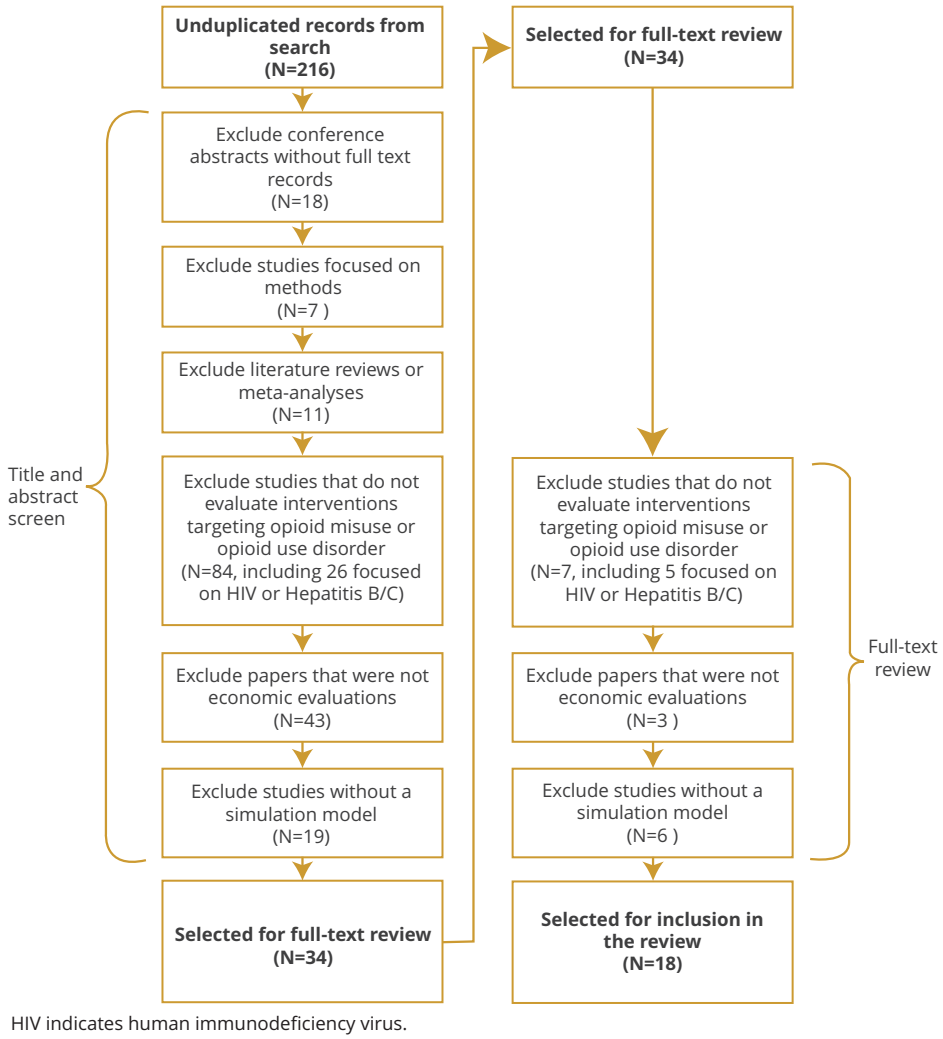
A total of 216 unduplicated records were identified (see Appendix 3 in Supplemental Materials). After the initial screening, 34 were selected for full-text review. Of those, 16 more were excluded (see Appendix 4 in Supplemental Materials) because they did not satisfy the inclusion criteria, leaving 18 studies for data extraction (Fig. 1).[31–48]

Study Population and Intervention

The included studies were conducted in the United States (n = 10; Table 1), the United Kingdom (n = 4), Canada (n = 3), and Russia (n = 1). Of the studies conducted in North America, 4 applied to specific states, provinces, or cities. Most studies (n = 13) evaluated MOUD, including methadone, buprenorphine, naltrexone, hydromorphone, and diacetylmorphine. In 12 studies, a medication was compared with nonpharmacologic treatments (eg, psychosocial support), other pharmacologic agents (eg, methadone vs buprenorphine), other formulations of the same pharmacologic agent (eg, implantable vs sublingual buprenorphine), other modalities (eg, maintenance vs detoxification), or no treatment. In one study, methadone maintenance was the comparator for deep-brain stimulation.[46] The remaining studies were economic evaluations of naloxone distribution (n = 5), and one of the naloxone studies evaluated naloxone with linkage to addiction treatment and/or pre-exposure prophylaxis.[47] Studies modeling MOUD focused on people with OUD, except for one[48] that focused on heroin users without a formal diagnosis. Studies modeling naloxone focused on people at risk of opioid overdose, usually heroin users.

In general, studies evaluating MOUD found it to be cost-effective,[31,39,41,43,45,48] with methadone being more cost-effective than buprenorphine[37] and less cost-effective than hydromorphone and diacetylmorphine.[32,44] One study found that a

Figure 1. Flowchart of examined studies.



HIV indicates human immunodeficiency virus.

long-acting formulation of buprenorphine (implant) was less expensive and more effective than oral buprenorphine.[33] Four studies that evaluated naloxone distribution found it to be highly cost-effective.[35,36,42,47] The exception was a model of a naloxone distribution in high schools, which found that the cost-effectiveness of the program was heavily dependent on the overdose frequency among students.[34]

Characteristics of Economic Analyses

Health outcomes and economic analysis framework

Details on economic analyses are presented in Table 2. Most studies (n = 15) were CUAs using quality-adjusted life-years (QALYs) as the main health outcome, as recommended by US and international best practice guidelines.[19,49–51] Four studies were CEAs using natural units as the health outcome (eg, opioid-free days); one of these conducted a CUA and a CEA.[43] One study was a CBA, which is a less common approach for decision making in the healthcare field because of the difficulty and controversy inherent in placing a monetary value on health, including survival.[18,19,43] One study[48] valued life-years gained using lifetime earnings.[48]

Utility values varied among studies that used QALYs, but all had lower utilities associated with opioid use compared with not using opioids. One applied utility decrements based on frequency of heroin use,[43] 3 used utility values based on EuroQol 5-Dimension (EQ-5D) dimensions,[32,35,44,52] 5 used values based on SF-6D dimensions,[34,36,41,42,47,52,53] and 6 used utility values from a panel of 22 UK respondents using the standard gamble technique.[31,33,37,39,45,46,54] Seven used utilities generated in a country different from the country of analysis,[33–35,41,42,45,46] and 2 assumed the baseline utilities of substance users to be the same as for other conditions (eg, depression, HIV).[35,47] Several studies shared the same utility values (Fig. 2). Several CUA studies also reported on other outcomes, such as mortality[32,35,36,41,47] and drug use.[32,33,35–37,45,48]

Seven studies modeled time horizons of 1 year or less, 1 study used a time horizon of 2 years, 2 considered multiple time horizons up to 20 years or a lifetime, and 8 used a lifetime horizon. Studies with shorter time horizons were at risk of underestimating the benefits of interventions that may accrue later. Studies with time horizons longer than 1 year applied discount rates between 1.5% and 5% annually. Five studies estimated results for subgroups; 2 stratified by demographic characteristics,[32,34]

Table 1. Summary of studies included in the review: study population and interventions

Study	Country/state	Delivery setting	Target population	Intervention	Comparator
Adi et al,[31] 2007	UK	NHS	Detoxified patients who were previously opioid dependent	Oral naltrexone; psychosocial support	Psychosocial support only
Bansback et al,[32] 2018	British Columbia, Canada	Healthcare clinic	Patients with severe OUD	Injectable hydromorphone	Oral methadone maintenance; injectable diacetylmorphine
Carter et al,[33] 2017	USA	Office-based clinic	Opioid-dependent, clinically stable adults	Subdermal, implantable buprenorphine; psychosocial support	Sublingual buprenorphine; psychosocial support
Cipriano and Zaric,[34] 2018	Ontario, Canada	Toronto School District secondary schools	Students	Naloxone kits in schools	No naloxone
Coffin and Sullivan,[36] 2013	USA	Community	Heroin users	Naloxone distribution for lay administration to 20% of heroin users	No naloxone distribution
Coffin and Sullivan,[35] 2013	Russia	Community	Heroin users	Naloxone distribution for lay administration to 20% of heroin users	No naloxone distribution
Connock et al,[37] 2007	UK	NHS	Patients with OUD	Methadone or buprenorphine maintenance	No opioid substitution therapy or methadone compared with buprenorphine
Jackson et al,[38] 2015	USA	OTPs/primary care/ specialty care	Adult males initiating OUD treatment	Extended-release, injectable naltrexone	Methadone or buprenorphine maintenance
Kenworthy et al,[39] 2017	UK	NHS	Patients with OUD	Methadone or buprenorphine maintenance treatment	No opioid substitution therapy
King et al,[40] 2016	USA	OTPs/primary care	Adult patients with OUD	Office-based buprenorphine maintenance	Clinic-based methadone maintenance
Krebs et al,[41] 2018	California, USA	OTPs	Adults presenting for publicly funded OUD treatment (first treatment)	100% access to methadone treatment	Standard of care: 54.3% medically managed withdrawal, with 2 previous failures
Langham et al,[42] 2018	UK	NHS	Adults at risk of heroin overdose	Naloxone distribution (assumed 30% of heroin users)	No naloxone to adults at risk of heroin overdose
Masson et al,[43] 2004	USA	OTP	Adults with OUD	Methadone maintenance (14 months and 2-month detoxification); group therapy (1 hour/week for 6 months); individual therapy (1 hour/month)	Methadone detoxification (6 months); group therapy (2 hours/week); individual therapy (1 hour/week); education sessions (14 sessions in 6 months)
Nosyk et al,[44] 2012	Canada	Treatment facilities	Adults with chronic, refractory OUD (more than 5 years of use and 2 or more prior failed substitution treatment attempts)	Diacetylmorphine	Methadone maintenance
Schackman et al,[45] 2012	USA	Primary care	Clinically stable patients with OUD who had been in office-based buprenorphine-naloxone treatment for 6 months	Long-term office-based buprenorphine-naloxone treatment	No treatment
Stephen et al,[46] 2012	USA	Healthcare facilities	Patients with heroin dependence	Nucleus accumbens deep-brain stimulation	Methadone maintenance

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Table 1. Continued

Study	Country/state	Delivery setting	Target population	Intervention	Comparator
Uyei et al,[47] 2017	Connecticut, USA	Syringe services programs	HIV-negative people who inject drugs	Four alternative strategies: (1) naloxone distribution, (2) naloxone distribution plus linkage to addiction treatment (referral to methadone program), (3) naloxone distribution plus PrEP, and (4) naloxone distribution plus linkage to addiction treatment and PrEP	No intervention
Zarkin et al,[48] 2005	USA	Methadone clinic	US adult population of heroin users and non-users	Increase of 100% in methadone treatment, increase of 25% in length of stay and no treatment	Current methadone treatment

NHS indicates National Health Service (UK); OUD, opioid use disorder; OTP, opioid treatment program (ie, facility permitted to deliver methadone for OUD in the United States); PrEP, preexposure prophylaxis.

and 3 stratified by opioid use characteristics, including novice versus experienced users,[36] heroin versus prescription opioids,[41] and route of administration (oral vs injection).[36,41,45] One study also stratified results by HIV serostatus.[41] Studies that stratify their populations into subgroups may uncover different responses to interventions from different segments of the population. This can have important policy implications, but conducting stratified analysis requires data unique to specific subgroups, which can present a challenge to modelers.

Included costs and study perspective

All of the studies included the costs of strategies. For MOUD strategies, costs included the full costs of the drugs (ie, medication costs and staff time for medication management) and the costs of associated services (eg, laboratory tests or psychotherapy as appropriate). Two studies relied on reimbursement rates from state Medicaid fee schedules and the Centers for Medicare & Medicaid Services Physician Fee Schedule, respectively,[38,40] 1 used a detailed microcosting approach,[43] and the remaining 15 drew intervention costs from published studies or government reports.

Thirteen studies self-described as adopting a societal perspective as the primary perspective or a secondary perspective, and all 13 applied higher costs to health states or scenarios resulting in opioid use compared with abstinence from opioids.[31–37,39,41,42,44,46,48] All 13 included healthcare costs beyond intervention costs, and all but 1 included costs from other sectors.[34] Healthcare costs in studies of MOUD included all healthcare utilization whether it was directly related to opioid use or not. Twelve of the 13 studies that adopted a societal perspective included criminal activity or the criminal justice system costs. With the exception of 1 study that assumed criminal justice costs due to lack of available data,[35] all studies include costs incurred by crime victims in addition to costs incurred by the criminal justice system. Of the 13 studies with a societal perspective, 3 included productivity costs,[33,46,48] and only 1 included patient out-of-pocket healthcare costs.[33]

Of 5 studies that did not adopt a societal perspective, 1 adopted a healthcare system perspective,[43] 2 US–based studies were conducted from the payer perspective,[38,40] 1 focused on the treatment system and included patient costs (eg, time costs in treatment),[45] and 1 adopted a narrow perspective focusing on costs relating to consequences addressed by its interventions (eg, costs related to overdose and HIV treatment).[47]

Modeling Approach

Model structure

Four studies used decision trees to track costs and outcomes for 1 year or less (Table 3).[31,37,39,46] Thirteen studies used a cohort Markov model approach, which tracks a cohort's progression through defined health states over discrete time cycles.[55] Of the Markov studies, 3 integrated a decision tree to model overdose events, which occur over a short period and are suitably modeled as a decision tree,[35,36,42] and 3 incorporated history by defining health states in terms of time in state and treatment history.[32,41,44] One study[48] was a microsimulation that defined transitions and probabilities of events based on age and gender, heroin use, history of criminal activity and employment, and the success or failure of the last treatment episode. Generally, the decision tree models represented intervention effects as differences in treatment retention. The 3 studies that embedded decision trees into Markov models evaluated naloxone and applied differences in overdose mortality as the intervention effect. Other Markov model studies represented the intervention effect by varying transition probabilities across strategies. Among the 18 studies included in the review, 9 shared major model structure characteristics with at least one other (see Fig. 2). Fourteen studies reported the software used: R (n = 5), TreeAge Pro (n = 4), Excel (n = 4), and Arena (n = 1).

Uncertainty

All of the studies reported conducting deterministic or probabilistic sensitivity analysis (PSA) to evaluate parameter uncertainty, and 14 reported both, as recommended by the ISPOR-SMDM Modeling Good Research Practices Task Force.[56] Fifteen studies used one-way sensitivity analyses on some or all parameters, and 9 conducted multiway sensitivity analyses (ie, varying 2 or more parameters simultaneously while holding the rest constant) to test best- or worst-case scenarios or alternative assumptions on a combination of input parameters. Two studies conducted conditional PSAs, which held select parameters constant and conducted the PSA on the remaining parameters.[41,45] Four studies[35,36,44,48] reported formal calibration to generate model parameters.[35,36,44,48,56] For example, one study[35,36] calibrated both models to epidemiologic outcomes using a trial-and-error algorithm until it hit all targets simultaneously. Two studies examined structural uncertainty in their models[41,44]; for example, one study[41] relaxed an assumption that transition from relapse or medically managed withdrawal to

Table 2. Summary of studies included in the review: health outcomes, costs, and economic analysis.

Study	Main health outcome(s)	Other health out-come(s)	Intervention costs	Perspective(s)	Costs included in addition to intervention costs	Time horizon	Discount rate	Year and currency	Analytical frame-work
Adi et al,[31] 2007	QALYs (standard gamble)	-	Drug costs, counseling, laboratories	Health system,* societal	NHS and PSS, CJS† and crime victimization†	12 months	n/a	2004 GBP	Cost utility
Bansback et al,[32] 2018	QALYs (EQ-5D)	Drug use, mortality	Drug costs, medication management	Societal,* health system	Healthcare, CJS, and crime victimization	Lifetime	5.0%	2015 CAD	Cost utility
Carter et al,[33] 2017	QALYs (standard gamble)	Treatment retention, drug use	Drug costs, medication management	Societal	Healthcare, productivity, CJS, crime victimization, patient out of pocket	12 months	n/a	2016 USD	Cost utility
Cipriano and Zaric,[34] 2018	QALYs (SF-6D)	Overdoses, overdose deaths, life-years	Naloxone costs and training costs	Described as societal, but healthcare perspective was adopted	Medical costs associated with overdose and age-adjusted future healthcare costs based on epidemiological data	Lifetime	1.5%	2017 CAD	Cost utility
Coffin and Sullivan,[36] 2013	QALYs (SF-6D)	Overdose deaths, mortality, heroin use, relapse	Naloxone costs and distribution	Societal	Costs related to overdoses (ED/EMS costs), "excess" health and CJS/ victimization costs	Lifetime	3.0%	2012 USD	Cost utility
Coffin and Sullivan,[35] 2013	QALYs (EQ-5D)	Overdose deaths, mortality, heroin use, relapse	Naloxone costs and distribution	Societal	Costs related to overdoses (ED/EMS costs), "excess" health and CJS costs (assumed)	Life-time	5.0%	2010 USD	Cost utility
Connock et al,[37] 2007	QALYs (standard gamble)	Treatment retention, drug use	Drug costs, counseling, laboratories	Health system,* societal	NHS and PSS, CJS† and crime victimization costs†	12 months	n/a	2004 GBP	Cost utility
Jackson et al,[38] 2015	Opioid-free days	-	Drug costs, counseling, medication management	Payer	None	6 months	n/a	USD (year not described)	Cost-effectiveness
Kenworthy et al,[39] 2017	QALYs (standard gamble)	-	Drug costs, counseling, laboratories	Health system,* societal	NHS and PSS, costs associated with HIV and HCV infection, CJS† and crime victimization costs†	12 months	n/a	2016 GBP	Cost utility
King et al,[40] 2016	Opioid abuse-free weeks	Treatment retention	Drug costs, medication management, counseling, laboratories	Payer	None	12 months	n/a	2014 USD	Cost-effectiveness
Krebs et al,[41] 2018	QALYs (SF-6D)	HIV sero-conversion, mortality	Direct and indirect costs of methadone maintenance including medication management	Societal,* health system	Healthcare costs, CJS, crime victimization	Lifetime	3.0%	2016 USD	Cost utility
Langham et al,[42] 2018	QALYs (SF-6D)	Overdose deaths	Naloxone, distribution, and training	Health system,* societal	Costs related to overdoses (ED/EMS costs), CJS†, and crime victimization†	Lifetime	3.5%	2016 GBP	Cost utility

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Table 2. Continued

Study	Main health outcome(s)	Other health outcome(s)	Intervention costs	Perspective(s)	Costs included in addition to intervention costs	Time horizon	Discount rate	Year and currency	Analytical frame-work
Masson et al,[43] 2004	Life-years gained; QALYs (assumed utility decrements)	-	Costs of treatment arms through microcosting	Health system	Healthcare costs (hospital stays, ED visits, ambulatory care, and behavioral health treatment)	Life-time	3.0%	USD (year not described)	Cost effectiveness and cost utility
Nosyk et al,[44] 2012	QALYs (EQ-5D)	-	Drug costs, medication management	Societal,* health system	Healthcare, CJS, crime victimization	1, 5, and 10 years, and lifetime	5.0%	2009 CAD	Cost utility
Schackman et al,[45] 2012	QALYs (standard gamble)	Treatment retention, drug use	Drug costs, medication management, laboratories	Health system and patient	Patient costs: time spent, transportation	24 months	3.0%	2010 USD	Cost utility
Stephen et al,[46] 2012	QALYs (standard gamble)	-	Reimbursement cost for methadone, and surgery with follow-up for DBS	Societal	Healthcare, productivity, CJS, crime victimization,	6 months	n/a	2011 USD	Cost utility
Uyei et al,[47] 2017	QALYs (SF-6D)	Survival, life expectancy, overdose deaths, HIV-related deaths	Naloxone and distribution, PrEP costs (medication, staffing, laboratories)	Health system	Healthcare costs (EMS/ED, HIV antiretroviral costs)	5, 10, and 20 years	3.0% (applied to costs only)	2015 USD	Cost utility
Zarkin et al,[48] 2005	Years using heroin, life-years saved	-	Direct and indirect costs of methadone maintenance including medication, management	Societal	Healthcare, employment, CJS	Lifetime	3.0%	2001 USD	Cost benefit

CAD indicates Canadian dollar; CJS, criminal justice system; DBS, deep-brain stimulation; ED, emergency department; EMS, emergency medical services; GBP, Great Britain pound; HCV, hepatitis C virus; n/a, not applicable; NHS, National Health Service; PrEP, pre-exposure prophylaxis; PSS, Personal Social Services; QALY, quality-adjusted life-year; USD, United States dollar.
*Main study perspective
†Costs included in secondary perspective

abstinence was impossible. One study performed expected value of partially perfect information analysis.[45]

Validation

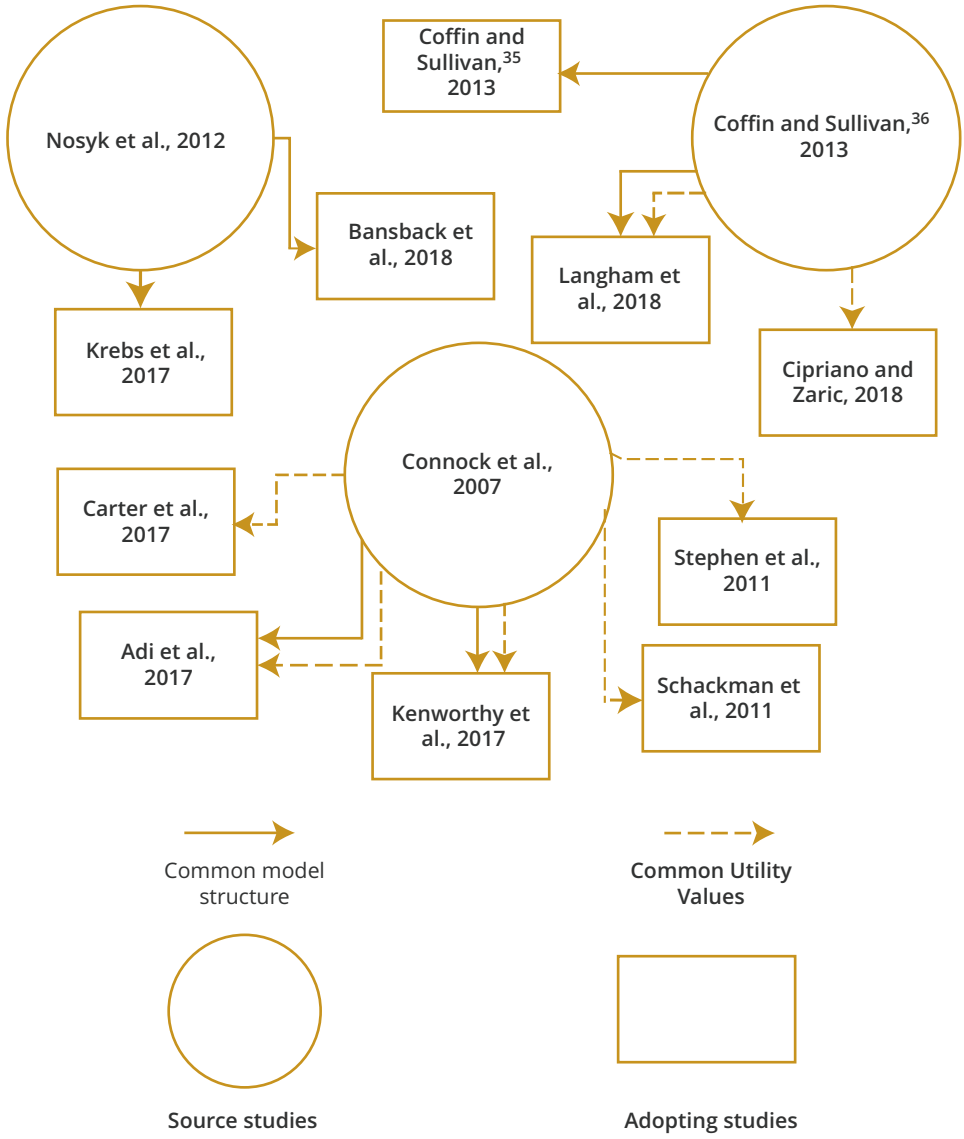
Validation represents the extent to which a model reproduces reality.[57] Only 10 studies included a validation approach, and only 2 used multiple types (ie, internal and external validation).[32,44] Two studies cross-validated their model against earlier models also included in the review,[39,42] but the authors of the original models did not report their approach to validation,[36,37] thus limiting the importance of cross-validation. Two studies conducted internal validation by comparing base case results from trials that informed key parameter sources to model results.[32,44] Of the 8 studies[32,33,35,41,43,44,47,48] that reported conducting external validation, 5 validated against a single parameter type (eg, mortality rates) and thus did not validate multiple components of the model.[57]

Discussion

We conducted a systematic review of the methods employed by economic evaluations that used simulation modeling to assess the health and economic impacts of interventions to address opioid misuse. We reviewed the studies' methods to understand current practice and to identify gaps that need to be addressed to better inform the optimal deployment of resources to combat the opioid crisis.

Simulation modelers face several interrelated decisions among alternative model structures, perspectives, valuation approaches, and methods to address uncertainty and validation. The choice of model structure depends on the decision problem, individual versus cohort unit of analysis, the time horizon, and data availability.[19,20,58,59] Decision trees are best applied to situations with no or few recurrent events and in which the time horizon is short and fixed.[18] Because of the chronic nature of OUD, which is characterized by recurrent relapse and recovery and multiple treatment episodes,[55] a long-term horizon, ideally lifetime, can better capture all of the relevant consequences of the strategies under consideration. Thus, for decision problems related to OUD, Markov models with long time horizons are superior to decision trees because they are particularly adept for decision problems involving disease progression or the potential for alternating episodes of recovery and relapse. Other common modeling

Figure 2. Links between included studies. *Solid arrow* denotes common model structure. *Dashed arrow* denotes common utility values. *Rectangles* represent studies that adopted model structure characteristics or utility values from source studies, which are represented by circles.



approaches include dynamic compartmental models, which compartmentalize the population assuming homogeneity and use a system of equations representing stocks and flows of people among compartments over time, and agent-based models, which permit interaction between simulated people. Although both approaches have been used for opioid use and OUD,[60–64] no study using these approaches met our inclusion criteria.

Modelers also need to determine the appropriate unit of analysis for their model. Of the 18 studies in our review, 17 were cohort models and 1 was an individual-level simulation.[48] Although there are clear advantages to using individual-level models in that they permit the model to capture variability by individual-level characteristics—including individual histories—they require data to support parameterization, calibration, and validation at the individual level and are often more computationally intensive than models with higher-level units of analysis.[20] Individual-level models should be considered when data and computational resources are available to support them, but failing that, cohort models are appropriate tools to analyze many policies and often reach similar conclusions to those of individual-level models.[20] When an individual-level model cannot be supported, modelers should consider conducting a subgroup analysis to provide more granular detail about costs and the effectiveness of interventions for different groups. Several studies included in the review did this,[32,34,36,41,45] whereas others acknowledged the value in doing so but cited data limitations as a barrier.[31,42] Because calibration can be used to estimate parameters that are not directly observable,[56] it should be considered to overcome data limitations to subgroup analysis.

The Second Panel on Cost-Effectiveness in Health and Medicine recommended that all CEAs report 2 reference case analyses: one with a healthcare sector perspective and another with a societal perspective, and the use of an "impact inventory" table that contains all consequences.[19,65] Most of the studies included, however, were published before the Second Panel recommendations were released in 2016, and the recommendations from the original

Table 3. Summary of studies included in the review: modeling approach.

Study	Model structure	Intervention effect	Modeling software	Approach to uncertainty/ sensitivity Analysis	Validation approach
Adi et al,[31] 2007	Decision tree	Treatment retention varied across strategies.	TreeAge Pro 2005	PSA; 1-way SA for key parameters	Not described.
Bansback et al,[32] 2018	Cohort semi-Markov	TPs varied across treatment strategies; utilities varied across treatment states.	R	PSA; multiway SA using alternative transition rates	Internal validation: compared results of base case model with results from the underlying trial. External validation: compared mortality rate with published study.
Carter et al,[33] 2017	Cohort Markov	Initiation of opioid use while in treatment varied by strategy.	Not described	PSA; 1-way SA of all parameters	External validation: compared total direct medical cost of the sublingual cohort with a cost of illness study.
Cipriano and Zaric,[34] 2018	Cohort Markov	Applied a reduction in mortality associated with overdose for naloxone.	Excel	PSA; series of 3-way SAs varying 2 key parameters with every other parameter one at a time	Not described.
Coffin and Sullivan,[36] 2013	Cohort Markov with integrated decision tree	Applied a reduction in mortality associated with overdose for naloxone.	Excel	PSA; 1-way SA of all parameters; multi-way SA representing best and worst cases; calibrated parameters and parameter structure to epidemiological data using trial-and-error search algorithm	Not described.
Coffin and Sullivan,[35] 2013	Cohort Markov with integrated decision tree	Applied a reduction in mortality associated with overdose for naloxone.	Excel with TreePlan add-in	PSA; 1-way SA with extreme values of all parameters; calibrated parameters and model structure to epidemiological data using trial-and-error search algorithm	External validation: compared model predictions with estimates from other studies (eg, rate of overdose).
Connock et al,[37] 2007	Decision tree	Treatment retention varied across strategies.	TreeAge Pro 2005	PSA; multi-way sensitivity analyses with alternative utility values and buprenorphine prescribing policies	Not described.
Jackson et al,[38] 2015	Cohort Markov	Transition out of treatment and probability of opioid use while in treatment varies across strategies.	Not described	Multi-way SA based on best- and worst-case parameter sets; 1-way SA focused on key parameters	Not described.
Kenworthy et al,[39] 2017	Decision tree	Treatment retention varied across strategies; utilities varied across treatment states.	R	PSA; 1-way SA on key parameters, including removal of crime victimization costs	Cross validation: outputs were validated against the related Excel model previously published.[37]
King et al,[40] 2016	Cohort Markov	Transition out of treatment and probability of opioid use while in treatment varies across strategies.	Not described	PSA; 1-way SA on key parameters; 2-way SA for drug costs	Not described.
Krebs et al,[41] 2018	Cohort semi-Markov	Access to opioid agonist treatment varies by strategy. The alternative approach (medically managed withdrawal) has a higher associated probability of relapse and a higher probability of death than methadone treatment.	R	PSA; conditional PSA (PSA with select parameters held constant); 1-way SA on key parameters; multi-way SA on transition parameters relating to out-of-treatment states, and analyses of structural uncertainty (eg, relaxation of structural assumptions)	External validation: compared projected mortality, HIV incidence, and proportion of time in treatment with observed outcomes.
Langham et al,[42] 2018	Cohort Markov with integrated decision tree	Applied a reduction in mortality associated with overdose for naloxone and accounted for the probability that it is available and used.	R	PSA; 1-way SA of all parameters	Cross-validation: confirmed that the model was replicated correctly by comparing outcomes with published outcomes from a related model.[36]
Masson et al,[43] 2004	Cohort Markov	Mortality (a function of heroin use) varied across strategies.	Not described	1-way SA on key parameters	External validation: model produced mortality rates in line with observed rates.

continued on next page

Table 3. Continued

Study	Model structure	Intervention effect	Modeling software	Approach to uncertainty/ sensitivity Analysis	Validation approach
Nosyk et al,[44] 2012	Cohort semi-Markov	Access to diacetylmorphine varies by strategy. The alternative approach (methadone maintenance) has a higher associated probability of relapse than diacetylmorphine.	R	PSA; 1-way SA on key parameters; analyses of structural uncertainty (eg, relaxation of structural assumptions); calibrated Weibull parameters representing time to discontinuation of abstinence to fit external data	Internal validation: compared model results with underlying trial data. External validation: compared modeled mortality with published data.
Schackman et al,[45] 2012	Cohort Markov	Probability of relapse varies by strategy.	TreeAge Pro 2009	PSA; EVPPI analysis; 1- and 2-way SA on key parameters; conditional PSA (holding select parameters at chosen value and varying all other parameters using PSA)	Not described.
Stephen et al,[46] 2012	Decision tree	Decision tree end nodes vary by strategy and are specific to that strategy.	TreeAge Pro 2009	1-way SA for all parameters; 2-way SA for most influential parameters (based on 1-way SA)	Not described.
Uyei et al,[47] 2017	Cohort Markov	Applied a reduction in mortality associated with overdose for naloxone and accounted for the probability that it is available and used. Treatment linkages increased the probability of entering treatment and discontinuing injection drug use.	Excel	PSA; 1-way SA on key parameters	External validation: compared modeled no-intervention scenario with published epidemiologic studies for 4 targets: 5-year mortality, 10-year mortality, HIV incidence, and HIV prevalence.
Zarkin et al,[48] 2005	Individual-level microsimulation	Vary by strategy and are explicit. Interventions are modeled by changing baseline parameters to represent the strategy under consideration.	Arena	1-way SA for parameters based on assumption or limited data; calibrated transition to abstinence and probability of crime parameters so that model outputs would match external data	External validation: compared findings from single-treatment episode scenario with a previously published CBA.

CBA indicates cost-benefit analysis; EVPPI, expected value of partial perfect information; PSA, probabilistic sensitivity analysis; SA, sensitivity analysis; TP, transition probability.

panel[66,67] did not include an impact inventory table and recommended only a societal perspective. Studies that adopted a societal perspective presented a subset of all the possible consequences of the intervention(s) they evaluated. They omitted important consequences such as out-of-pocket patient costs (which should also be included in the healthcare perspective); caregiver time costs; the health-related quality-of-life impact on family, friends, and crime victims; and the cost of unpaid productivity. Nevertheless, it should be noted that the inclusion of a broad societal perspective that encompasses all possible consequences might not be practical because of data availability and might make the analysis too cumbersome, particularly for narrow research questions.

The choice of outcome and method of valuation in a health economic evaluation is of paramount importance because alternative choices can lead to different appraisals of an intervention. The Second Panel recommends that all CEAs use QALYs to incorporate morbidity and mortality in measuring health consequences.[19] Several studies identified the dearth of information on utility values for relevant health states as a limitation, and most made strong assumptions regarding these values. Among included studies, valuation approaches varied (eg, some studies relied on EQ-5D values, whereas others relied on Short Form 6-Dimension [SF-6D] values), which might lead to differences in utility values and hinder comparisons.[53] A recent study published US–representative utilities for health states for prescription and illicit drug misuse,[68] providing an important contribution to future economic evaluations of interventions to address opioid misuse.

An important feature of health economic models is the ability to measure the impact of uncertainty. Models provide insight into phenomena or policy scenarios that cannot be directly observed; thus model parameters are often selected with considerable uncertainty.[20] Consistent with best practices,[56] all of the studies conducted sensitivity analyses, and 14 of 18 conducted deterministic and probabilistic sensitivity analyses. Only one study, however, conducted value of information analysis,[45] an approach to establish the value of additional research compared with making decisions with current information.[69] Because many parameter values are largely uncertain in models involving OUD, value of sample information can be a valuable tool to prioritize future research,[70] and future studies should include it.

Finally, all models should address validation (ie, how well the model reproduces reality).[57,71] Only 10 of 18 studies in our review reported their validation approach, and only 2 conducted multiple types of validation. External validation is particularly challenging in models of opioid use because of data limitations.[72] Studies in the review that conducted external validation compared model outputs with epidemiologic data on mortality or disease incidence. Future modeling studies should put more effort into internal validation, external validation, and cross-validation.[73]

A common feature of the models included in this review is that they focused on a narrow set of interventions delivered at

individual stages of the continuum of care, rather than a more comprehensive response. Changing the course of the opioid crisis will require a multipronged approach,[74] which requires evaluating combinations of different interventions. A recent study[75] developed a dynamic compartmental model of pain status, opioid use status, and substance use disorder status to project the effect of policies aimed at reducing deaths in the United States. The study concluded that no single policy is likely to have a large enough effect to substantially reduce opioid-related deaths over 5 or even 10 years, and a portfolio of interventions is likely needed. Another recent study[76] developed a hierarchical latent Markov process model to estimate the individual and combined effect of large-scale opioid overdose interventions implemented in British Columbia in response to the overdose crisis. Neither study, however, accounted for the broader societal consequences of opioid misuse, its economic implications, or the cost of the interventions. Despite the resources now devoted to the opioid epidemic, funding is limited, and decision makers need to account for the effectiveness and cost of strategies. A necessary next step in refining those recently developed models is the incorporation of costs so they can guide resource allocation decisions, such as selecting an optimal set of interventions from a portfolio of possible investments.

Our review has 3 main limitations. First, there is a lack of diversity in the types of interventions represented in the models in our review. Most studies in the review evaluated MOUD, and about one-quarter evaluated naloxone distribution. No economic evaluation using simulation modeling has assessed the cost-effectiveness of prevention interventions, and although our review included studies that examined naloxone distribution, other harm reduction strategies (eg, supervised injection facilities [SIFs]) were not included. Important work has been done to examine the cost-effectiveness of SIFs,[60,77] but these studies were excluded because they focused on the impact of SIFs on HIV and hepatitis C transmission, without reporting outcomes related to the impact of the intervention on opioid misuse. Second, we did not conduct a formal quality assessment of the studies included in this review. Although formal quality appraisal is appropriate in systematic reviews that evaluate specific interventions, we adopted a review method that does not require a quality assessment of each study[25] because our goal was not to synthesize evidence for a particular intervention, but rather to examine methods used to evaluate different but related interventions. Finally, because some models included in our review were adapted and reused in later studies included in the review, the frequencies describing methodological choices in the results of this review should not be considered representative of modeling practice.

Conclusions

Cost-effectiveness simulation models can guide and inform clinical and public health responses to the opioid crisis and can be used to improve complex decision making about opioid policy. Future models should assess the effect of a combination of interventions and consider synergies across interventions in the continuum of OUD prevention, harm reduction, and treatment. Policy makers need guidance on how to combine interventions efficiently. Despite data challenges, future models should account for the heterogeneity in the characteristics of the opioid epidemic at state and local levels.[78–82] The cost-effective set of alternatives for one community could differ from that of another community. Future models should also more consistently report on validation, account for uncertainty in model parameters, and assess the value of further research.

Supplemental Material

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Author Affiliations: Behavioral Health Research Division, RTI International, Chicago, IL, USA (Barbosa); Behavioral Health Research Division, RTI International, Research Triangle Park, NC, USA (Dowd, Zarkin)

Author Contributions: *Concept and design:* Barbosa, Dowd, Zarkin
Acquisition of data: Barbosa, Dowd
Analysis and interpretation of data: Barbosa, Dowd
Drafting of the manuscript: Barbosa, Dowd
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