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Estimated effectiveness and cost-effectiveness of opioid use disorder treatment under proposed U.S. regulatory relaxations: A model-based analysis

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ABSTRACT

Aim: To assess the effectiveness and cost-effectiveness of buprenorphine and methadone treatment in the U.S. if exemptions expanding coverage for substance use disorder services via telehealth and allowing opioid treatment programs to supply a greater number of take-home doses of medications for opioid use disorder (OUD) continue (Notice of Proposed Rule Making, NPRM).

Design setting and participants: Model-based analysis of buprenorphine and methadone treatment for a cohort of 100,000 individuals with OUD, varying treatment retention and overdose risk among individuals receiving and not receiving methadone treatment compared to the status quo (no NPRM).

Intervention:

Buprenorphine and methadone treatment under NPRM.

Measurements:

Fatal and nonfatal overdoses and deaths over five years, discounted lifetime per person QALYs and costs.

Findings: For buprenorphine treatment under the status quo, 1.21 QALYs are gained at a cost of $19,200/QALY gained compared to no treatment; with 20% higher treatment retention, 1.28 QALYs are gained at a cost of $17,900/QALY gained compared to no treatment, and the strategy dominates the status quo. For methadone treatment under the status quo, 1.11 QALYs are gained at a cost of $17,900/QALY gained compared to no treatment. In all scenarios, methadone provision cost less than $20,000/QALY gained compared to no treatment, and less than $50,000/QALY gained compared to status quo methadone treatment.

Conclusions: Buprenorphine and methadone OUD treatment under NPRM are likely to be effective and cost-effective. Increases in overdose risk with take-home methadone would reduce health benefits. Clinical and technological strategies could mitigate this risk.

1. Introduction

In the U.S., COVID-19 reduced the safety of in-person care for patients with opioid use disorder (OUD), exacerbating a long-term issue of poor access to evidence-based OUD care (Alexander et al., 2020; Russell et al., 2021). These realities spurred a search for more flexible and accessible OUD treatment options (Mauro et al., 2022).

In March 2020, the Substance Abuse and Mental Health Services Administration (SAMHSA) issued an exemption (SAMSHA, 2020b) that expanded coverage for substance use disorder services delivered via telehealth and allowed opioid treatment programs (OTPs) to supply a greater number of take-home doses of medications for opioid use disorder (MOUD) (SAMSHA, 2020a). In December 2022, SAMSHA issued a Notice of Proposed Rule Making (NPRM) to make several of these regulatory relaxations permanent (SAMSHA, 2022). These include flexibilities in the provision of unsupervised doses of methadone (e.g., allowing take-home doses based on provider judgment and eliminating the requirement to consider the length of time an individual has been in

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treatment), the use of telehealth in initiating buprenorphine, and other measures intended to improve access to MOUD (e.g., broadening the set of individuals who can potentially prescribe MOUD to include practitioners outside of OTPs, and eliminating the requirement that an individual must have a one-year history of OUD before entering treatment).

The NPRM states that "A growing body of research has demonstrated that these flexibilities facilitate access to treatment and eliminate criteria that promote stigma and discourage people from accessing care from OTPs." (SAMSHA, 2022) The NPRM cited several studies and noted that "increases in take-home doses following the SMHSA exemption did not lead to worse treatment outcomes, higher overdose rates, or diversion of medication, but resulted in increased treatment engagement and improved patient satisfaction with care." For example, a cross-sectional survey study involving 183 participants from a methadone clinic found that even though the average number of take-home doses of methadone increased by nearly 200%, there was no significant change in either the number of individuals experiencing overdoses or the frequency of negative methadone urine drug tests (Amram et al., 2021). A survey of 104 patients at three North Carolina methadone clinics found varied experiences with take-home dosing by clinic and little evidence of dose diversion (Figgatt et al., 2021). A case study of OTPs in New York City serving over 3600 patients showed that despite significantly more take-home doses of methadone, the patients experienced no fatal overdoses (Joseph et al., 2021).

However, some studies have found relaxations in take-home methadone dosing to be associated with increased methadone-related deaths (Aldabergenov et al., 2022; Fugelstad, 2022; Kaufman et al., 2023; Kleinman and Sanches, 2023; Tjagvad et al., 2016). Moreover, the U.S. experience to date with regulatory flexibility in the treatment of OUD has primarily involved established and generally stable patients, i.e., those who were already in OUD treatment when COVID-19 struck. Despite the goal of increasing accessibility to care, national treatment enrollment dropped during the pandemic (Cantor et al., 2022); thus, assumptions about the effects of regulatory relaxation can be incorrect. Longer-term patients may not be representative of the broader population of individuals with OUD, and their behavior and outcomes may differ from new patients who enter care under a more relaxed regulatory regime. Further, health outcomes observed during the COVID-19 pandemic may not be the same as those attained in the future. Additionally, such flexibilities may come with attendant harms if take-home doses of MOUD are misused or diverted, as has been the experience of regulatory relaxation in multiple European countries (Frank et al., 2023).

We sought to assess the potential effectiveness and cost-effectiveness of MOUD under the proposed regulatory relaxations. We used a model-based analysis to estimate health outcomes and costs for both buprenorphine and methadone treatment, allowing for both potential benefits (increased retention in treatment) and harms (misuse or diversion of take-home doses).

2. Methods

2.1. Overview

We used a previously developed continuous-time dynamic compartmental model to estimate health outcomes and costs for simulated individuals who initiate MOUD treatment (Fairley et al., 2021). Individuals can transition between different health states including out of treatment, on treatment, abstinent (no illicit opioids) and not on treatment, and dead (Figure S1). Individuals using opioids can experience fatal or non-fatal overdoses. Full details of the model are provided elsewhere (Fairley et al., 2021).

We simulated a representative cohort of 100,000 individuals in the U.S. with OUD receiving MOUD in both the presence and absence of the proposed regulatory relaxations. We conducted separate analyses for buprenorphine and methadone treatment varying, as appropriate, rates of treatment retention and risk of overdose among individuals receiving and not receiving MOUD. Model parameter values are shown in Table 1 and Table S1.

2.2. Base case model

The model was originally calibrated prior to the expansion of fentanyl in illicit drug markets in the U.S. (Fairley et al., 2021). Fentanyl-involved overdose deaths accounted for 19.3% of total fatal opioid overdoses in 2014, rising to 87.8% in 2021 (National Safety Council, 2023). For our analyses, we updated rates of overdose and overdose death in the model to reflect the greater risks posed by fentanyl and other synthetic opioids (Carroll et al., 2017). Using data from the National Forensic Laboratory Information System we estimated that approximately 44% of opioid use would involve fentanyl (Lim et al., 2022) and adjusted the overall chances of fatal and non-fatal overdoses accordingly in our model. With these numbers, approximately twice as many opioid-related overdose deaths occurred among untreated individuals in our model compared to the previously calibrated model, reflecting observed trends (CDC, 2022) (further details in Supplement). In sensitivity analysis we considered higher levels of fentanyl prevalence and overdose deaths, reflecting a continuation of the recent trends.

2.3. Treatment retention

Multiple studies have found that telemedicine has the same or better efficacy in retaining patients in care compared to in-person buprenorphine treatment. A cross-sectional study of 17,182 patients in the Veterans Health Administration (VHA) found that patients receiving buprenorphine via telehealth had significantly higher retention in treatment than individuals receiving in-person buprenorphine, with adjusted odds ratios (AORs) of 1.31 (95% CI: 1.12–1.53) for care initiated prior to COVID-19-related changes and 1.23 (95% CI: 1.08–1.39) for care initiated after COVID-19-related changes (Frost et al., 2022). A nationwide study of Medicare beneficiaries comparing 70,538 individuals receiving OUD-related telehealth services to 105,240 individuals receiving primarily in-person services found increased odds of MOUD retention, with AOR 1.27 (95% CI: 1.14–1.41) (Jones et al., 2022b). A retrospective cohort study of 1590 Canadian patients initiating MOUD treatment found increased odds of MOUD retention for patients treated via telehealth versus in person, with AOR 1.27 (95% CI: 1.14–1.41) (Eibl et al., 2017). A retrospective cohort study of 28,791 VHA patients receiving buprenorphine for OUD found that treatment discontinuation was lower for patients treated via telehealth than those treated in person, with an adjusted hazard ratio of 0.69 (95% CI: 0.60–0.78) (Vakkalanka et al., 2022). Another retrospective cohort study analyzed Medicaid data from 41,266 individuals in Kentucky and 50,648 individuals in Ohio and found that enrollees who initiated buprenorphine treatment via telemedicine had higher odds of retention in treatment: the AOR was 1.13 (95% CI: 1.01–1.27) for individuals in Kentucky and 1.19 (95% CI: 1.06–1.32) for those in Ohio (Hammerslag et al., 2023). Based on these findings, we considered two cases in our analyses: (i) the treatment retention rate for buprenorphine would be the same as before the regulatory relaxations, (ii) the treatment retention rate would increase by 20%. In sensitivity analysis, we considered a 0–35% increase in the treatment retention rate.

Extensive data are not available regarding the effect of telemedicine and take-home doses of methadone on methadone treatment retention. One study that considered telehealth effects on both methadone and buprenorphine treatment retention found values similar to those found by studies considering only buprenorphine (Jones et al., 2022b). Increased take-home doses of methadone, as would be allowed under NPRM, has also been shown to increase treatment retention rates. For example, a study of COVID-19-related relaxations of methadone take-home dosing in two rural U.S. treatment programs found that each percentage point increase in take-home dosing above what would be

Table 1
Base Case Parameter Values and Sources.

Parameter	Mean	Range	Source
Demographics			
Fraction male	0.511	–	(SAMSHA, 2019; U.S. Census Bureau, 2020)
Fraction female	0.489	–	(SAMSHA, 2019; U.S. Census Bureau, 2020)
Average male age	43.7	–	(SAMSHA, 2019; U.S. Census Bureau, 2020)
Average female age	45.3	–	(SAMSHA, 2019; U.S. Census Bureau, 2020)
Initial fraction with OUD who inject drugs	0.253	[0.214 – 0.294]	(SAMSHA)
Transitions			
Death and Overdose, annual rates per person			
Background mortality	CDC Life Tables	–	(Arias and Xu, 2019)
Non-overdose excess mortality due to OUD, out of treatment	0.00978	[0.00744 – 0.0125]	(Ma et al., 2019)
Non-overdose excess mortality due to OUD, in treatment	0.00318	[0.00238 – 0.00406]	(Ma et al., 2019)
Multiplier for increased all-cause mortality when inducted onto methadone	14.0	[1.08 – 62.16]	(Ma et al., 2019)
Overdose, out of treatment	0.155	[0.070 – 0.331]	(Kelty et al., 2019; Ma et al., 2019)
Overdose, in treatment	0.066	[0.0304 – 0.140]	(Kelty et al., 2019)
Overdose Survival Probability, per overdose	0.899	[0.799 – 0.954]	(Coffin and Sullivan, 2013)
Treatment Discontinuation, annual rates per person			
Discontinuation from methadone	1.051	[0.579 – 1.751]	(Hser et al., 2014; Neumann et al., 2013; Otiashvili et al., 2013; Potter et al., 2013)
Discontinuation from buprenorphine	1.609	[1.002 – 2.420]	(Hser et al., 2014; Lee et al., 2018; Neumann et al., 2013; Otiashvili et al., 2013; Potter et al., 2013; Ruger et al., 2012; Tanum et al., 2017)
Other Transitions, annual rates per person			
Re-entry into treatment (from out of treatment > 1 month)	0.426	[0.367 – 0.489]	(Krebs et al., 2018)
Becoming abstinent and leaving treatment	0.316	[0.296 – 0.337]	(Krebs et al., 2018)
Becoming abstinent, from out of treatment	0.0791	[0.00401 – 0.1551]	Estimated
Return to use from abstinence 1 year[a]	0.379	[0.331 – 0.430]	(Krebs et al., 2018)
Return to use from abstinence, year 10+	0.019	[0.00394 – 0.0342]	(Krebs et al., 2018)
Rate of initiating injection drug use	0.031	[0.020 – 0.043]	(Carlson et al., 2016)
Costs, 2022 USD[b]			
Annual background healthcare costs			
Baseline, male age 30[c]	2509	–	(Liu et al., 2012; Meara et al., 2004)
Excess cost for OUD out of treatment	8015	[7234 – 8836]	(Baser et al., 2014)
Excess cost for OUD in treatment[d]	6413	[3337 – 9667]	Estimated
Annual treatment costs			
Methadone	7795	[7035 – 8593]	(Department of Defense, 2016)
Buprenorphine	7115	[6421 – 7843]	(Department of Defense, 2016)
Healthcare cost per overdose	2882	[1239 – 5773]	(Coffin and Sullivan, 2013)
Quality-of-life Multipliers for Health States			
Out of treatment, month 1	0.670	[0.660 – 0.680]	(Krebs et al., 2018)
Out of treatment (IDU), month 1	0.660	[0.640 – 0.680]	(Krebs et al., 2018)
Out of treatment, month > 1	0.670	[0.660 – 0.680]	(Krebs et al., 2018)
Out of treatment (IDU), month > 1	0.660	[0.640 – 0.680]	(Krebs et al., 2018)
Induction into treatment	0.725	[0.700 – 0.750]	(Krebs et al., 2018)
Induction into treatment (IDU)	0.710	[0.700 – 0.720]	(Krebs et al., 2018)
On treatment	0.725	[0.700 – 0.750]	(Krebs et al., 2018)
On treatment (IDU)	0.710	[0.700 – 0.720]	(Krebs et al., 2018)
Abstinence: first year[e]	0.725	[0.700 – 0.750]	(Krebs et al., 2018)
Abstinence (IDU): first year	0.710	[0.700 – 0.720]	(Krebs et al., 2018)
Abstinence: year 10+	0.984	[0.970 – 0.996]	Calculated
Abstinence (IDU): year 10+	0.983	[0.969 – 0.996]	Calculated

Abbreviations: IDU = injection drug user; OUD = opioid use disorder.
[a]Rates of return to use from abstinence from years 2, …, 9 of abstinence were linear interpolations of the year 1 and year 10 values.
[b]All costs were updated to $2022 using the PCE Price Index (Agency for Health Care Research and Quality, 2023).
[c] Baseline healthcare costs were age- and sex-specific.
[d] Estimated based on the (conservative) assumption that patients with OUD who are on treatment incur 20% higher healthcare costs on average than those not on treatment due to increased access to healthcare.
[e]Utility values for years 2, …, 9 were linear interpolations of the year 1 and year 10+ utility values.

expected without COVID-19-related policy changes was associated with a 3% higher treatment retention rate (Hoffman et al., 2022). A retrospective study of methadone patients in a Pennsylvania OTP found that relaxation of regulations guiding take-home methadone doses was associated with increased 12-month treatment retention (72.9% for 229 patients treated pre-pandemic vs. 84.5% for 278 patients treated after take-home reforms) (Kawasaki et al., 2023). A retrospective observational study of 821 individuals across 9 geographically disperse OTPs found that 6-month treatment retention was the same for patients entering methadone treatment before vs. after take-home reforms (Williams et al., 2023). As for buprenorphine, we considered the cases that the treatment retention rate for methadone would be the same as before the regulatory relaxations or would increase by 20%. In sensitivity analysis we considered a 0–35% increase in the treatment retention rate.

2.4. Overdose risk

"Diversion" has been variously defined in the literature (Bell, 2010; Cairns et al., 1996; Shei et al., 2015). The most comprehensive definition incorporates not only the use of medication by individuals for whom it was not prescribed, but also the misuse of medication by current patients (e.g., co-injecting methadone with heroin) (Ritter and Di Natale, 2005).

We found no published evidence that buprenorphine prescribed via telemedicine leads to increased diversion or increased overdose risk. A retrospective study of 566 patients in England found no increase in buprenorphine-related overdoses after buprenorphine prescribing regulations were relaxed (Aldabergenov et al., 2022). We thus assumed that

individuals receiving telemedicine prescriptions for buprenorphine would have the same overdose risk as individuals prescribed buprenorphine through in-person care, and that the risk of overdose among individuals not prescribed buprenorphine would be unchanged.

Evidence about potential harms of take-home methadone is mixed. Methadone-related fatalities increased in Connecticut during COVID-19, although the rate of increase did not differ from that of fatal overdoses involving other opioids (Brothers et al., 2021). In contrast, in Spokane Washington, 183 patients receiving methadone from an OTP showed no increased risk of overdose after increased take-home methadone doses were allowed (Amram et al., 2021). An analysis of U.S. nationwide overdose data found that methadone overdoses increased overall after take-home dosing was expanded, but the percentage of overdose deaths involving methadone decreased (Jones et al., 2022a). A nationwide study of Medicare beneficiaries receiving MOUD before and during the COVID-19 pandemic reported a negative association between expanded use of telehealth and flexibilities in MOUD provision and odds of medically treated overdose (Jones et al., 2022b). Two analyses using data from the Centers for Disease Control and Prevention's WONDER (Wide-ranging Online Data for Epidemiologic Research) database found an increase in methadone-involved overdose deaths between 2020 and 2019 (Kaufman et al., 2023; Kleinman and Sanches, 2023), whereas a study of 14,529 methadone-involved overdose deaths in the U.S. between January 2018 and June 2022 using the same database found that take-home methadone was associated with reduced deaths for Black and Hispanic men, and no change in deaths among Black or Hispanic women or White men or women (Harris et al., 2023).

In Denmark, expansion of take-home dosing and reduced requirements for in-person visits, supervised dosing, and urine drug testing for methadone patients was followed by a decrease in heroin deaths but a corresponding and equally-sized increase in methadone-related overdose deaths among both treated individuals and others in the community (Tjagvad et al., 2016). In England, a retrospective study of methadone-related deaths during a three-month period after relaxation of MOUD prescribing regulations found a 22% increase in methadone-involved deaths among individuals with methadone prescriptions and a 74% increase among individuals without prescriptions (Aldabergenov et al., 2022). Similarly, Sweden experienced increased methadone-related deaths after relaxation of methadone prescribing regulations (Fugelstad, 2022). To reflect this uncertainty, we ranged methadone overdose risk among individuals receiving methadone treatment from the baseline level (which was calculated assuming that individuals receive MOUD with no regulatory relaxations) to 20% higher in our analyses.

In sensitivity analysis we considered increases in overdose risk among individuals not receiving methadone treatment. We assumed that each person who diverted their methadone medication would divert to one untreated person; thus, when assessing overdose risk due to diversion we assumed the same cohort size for individuals receiving diverted methadone as the number of individuals receiving methadone treatment. We ranged methadone overdose risk among individuals not receiving MOUD from the baseline level to 20% higher, and used the model to calculate incremental outcomes compared to baseline for this population of individuals. We added these incremental outcomes to the outcomes calculated for individuals receiving methadone treatment.

2.5. Outcomes

We took a healthcare system perspective and followed standard guidelines for conducting cost-effectiveness analysis (Sanders et al., 2016). We calculated the number of fatal and non-fatal overdoses and the number of deaths over a five-year time horizon per 100,000 individuals receiving MOUD, as well as discounted lifetime costs and quality-adjusted life years (QALYs) for the cohort. Costs and QALYs were discounted using a 3% annual rate (Sanders et al., 2016). We assumed that the cost for telemedicine provision of buprenorphine or methadone would be the same as the cost for in-person provision of these medications. We did not count costs of patient time and travel. We used previously estimated cost for in-person provision of buprenorphine and methadone (Fairley et al., 2021), updated to 2022 USD. Similarly, we used previously estimated values for quality-of-life multipliers (Fairley et al., 2021). We assumed probability distributions for all parameters (Table S1) and calculated 95% credible intervals for all outcomes. We also performed probabilistic sensitivity analysis, drawing 180,000 parameter samples for each treatment scenario.

To compare strategies, we calculated incremental cost-effectiveness ratios (ICERs). ICERs were calculated as the difference in cost between two possible treatment scenarios, divided by the difference in QALYs between the two scenarios. ICERs are a standard measure of value in healthcare: they represent the cost of achieving an additional unit of health benefit.

3. Results

3.1. Base case

If individuals receive no MOUD, we estimate that 60,052 overdoses (8082 fatal) and 16,414 deaths would occur over five years in a cohort of 100,000 individuals with OUD (Table 2). Discounted lifetime per person QALYs experienced and healthcare costs incurred would be 10.48 and $246,500, respectively.

3.1.1. Buprenorphine

If the buprenorphine treatment retention rate under NPRM is the same as under the status quo, we estimate that 47,073 overdoses (6335 fatal) and 13,863 deaths would occur over five years in the cohort (Table 2, Fig. 1a). This corresponds to reductions of 21.6% in total overdoses and 15.5% in deaths compared to no treatment. Discounted lifetime per person QALYs and healthcare costs increase by 1.21 (to 11.69) and $23,200 (to $269,700), respectively, yielding an ICER of $19,200 compared to no treatment.

If the buprenorphine treatment retention rate under NPRM is 20% higher than under the status quo, 45,445 overdoses (6116 fatal) and 13,545 deaths occur over five years. This corresponds to reductions of 24.3% in total overdoses and 17.5% in deaths compared to no treatment. Lifetime QALYs and healthcare costs increase to 11.85 and $272,400 per person, respectively. Compared to no treatment, 1.37 QALYs are gained at a net present cost of $25,900 per person, yielding an ICER of $18,900. In this case, buprenorphine treatment with NPRM dominates status quo buprenorphine treatment by extended dominance (it gains more QALYs at a lower cost per QALY gained). Strategies that are dominated would not be selected as the preferred policy because another policy is better from a value perspective.

3.1.2. Methadone

If the methadone treatment retention rate under NPRM is the same as under the status quo, and overdose risk does not increase, 50,332 overdoses (6774 fatal) and 15,243 deaths occur per 100,000 treated people over five years (Table 2, Fig. 1b). Lifetime per person QALYs and healthcare costs are 11.59 and $266,300, respectively. Compared to no treatment, 1.11 QALYs are gained at a net present cost of $19,800 per person, yielding an ICER of $17,900 per QALY gained. If the methadone treatment retention rate under NPRM is 20% higher than under the status quo, with no increase in overdose risk, 48,549 overdoses (6534 fatal) and 14,879 deaths occur in the cohort over five years. Lifetime per person QALYs and healthcare costs are 11.76 and $269,400, respectively. The ICER compared to no treatment is $17,900 (1.28 QALYs gained at a cost of $17,900).

If the methadone treatment retention rate under NPRM is the same as under the status quo, and overdose risk increases by 10% in treated individuals, then 8.1% more overdoses (54,404 total, 7322 fatal) and 3.4% more deaths (15,761) occur over five years compared to treatment

Table 2
Base Case Results: Health Outcomes and Costs (Mean Value and 95% Credible Interval).

	Over 5 Years, per 100,000 Individuals Treated for Opioid Use Disorder				Lifetime per Person Discounted Healthcare Costs and QALYs		ICER ($/QALY gained)[1]	
Treatment Option	**Fatal Overdoses**	**Nonfatal Overdoses**	**Total Overdoses**	**Deaths[2]**	**QALYs**	**Health Care Cost ($1000, 2022)**	**Compared to no treatment**	**Compared to treatment under status quo**
No treatment	8082 [5928, 10,747]	51,971 [20,052, 121,172]	60,052 [27,136, 129,910]	16,414 [13,713, 19,634]	10.48 [8.78, 12.03]	246.5 [223.9, 268.8]	–	–
Buprenorphine								
Status quo[3]	6335 [4692, 8368]	40,738 [15,739, 94,874]	47,073 [21,329, 101,829]	13,863 [11,798, 16,318]	11.69 [10.41, 12.87]	269.7 [245.0, 296.3]	$19,200	–
NPRM: 83.3% lower treatment discontinuation	6116 [4530, 8079]	39,329 [15,198, 91,596]	45,445 [20,588, 98,262]	13,545 [11,553, 15,920]	11.85 [10.61, 13.00]	272.4 [247.2, 299.6]	$18,900	Dominates[4]
Methadone								
No change in treatment discontinuation rate								
Status quo[3]	6774 [4601, 10,801]	43,559 [15,994, 105,749]	50,332 [21,510, 114,276]	15,243 [11,808, 23,230]	11.59 [9.60, 12.98]	266.3 [220.9, 300.9]	$17,900	–
NPRM: 10% higher overdose risk in treated individuals	7322 [4955, 11,706]	47,082 [17,247, 114,392]	54,404 [23,192, 123,684]	15,761 [12,152, 24,047]	11.44 [9.41, 12.85]	262.7 [216.7, 297.7]	$16,900	$24,100
NPRM: 20% higher overdose risk in treated individuals	7865 [5307, 12,598]	50,577 [18,509, 122,967]	58,442 [24,877, 132,860]	16,275 [12,493, 24,872]	11.29 [9.23, 12.73]	259.2 [212.6, 297.7]	$15,700	$23,800
83.3% lower treatment discontinuation rate								
NPRM: No change in overdose risk	6534 [4429, 10,486]	42,015 [15,395, 102,175]	48,549 [20,704, 110,453]	14,879 [11,542, 22,727]	11.76 [9.80, 13.11]	269.4 [224.2, 304.6]	$17,900	
NPRM: 10% higher overdose risk in treated individuals	7049 [4758, 11,354]	45,331 [16,583, 110,360]	52,381 [22,282, 119,292]	15,367 [11,862, 23,511]	11.62 [9.62, 13.00]	265.9 [220.0, 301.4]	$17,100	Dominates[5]
NPRM: 20% higher overdose risk in treated individuals	7561 [5084, 12,211]	48,621 [17,759, 118,487]	56,182 [23,860, 128,080]	15,851 [12,176, 24,291]	11.47 [9.44, 12.88]	262.6 [216.0, 298.3]	$16,200	$31,300

[1] Incremental cost-effectiveness ratio (ICER).
[2] From all causes.
[3] Status quo: No change in treatment discontinuation rate or overdose risk.
[4] Dominates by extended dominance: gains more QALYs and costs more than the status quo, but a lower ICER compared to no treatment.
[5] Dominates: gains more QALYs at a lower cost compared to the status quo.

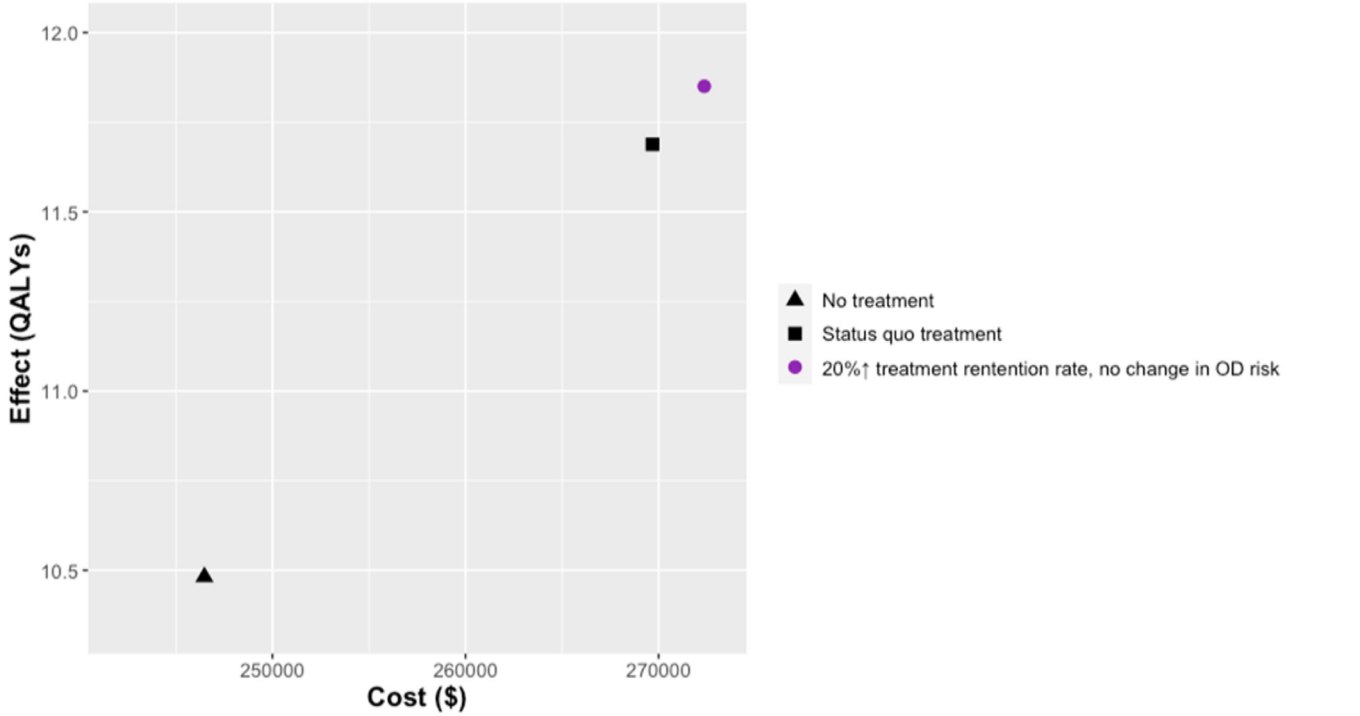
under the status quo. Lifetime QALYs and costs are both lower: 11.44 QALYs and a cost of $262,700 per person. Per person QALYs are lower because more individuals die from overdose, and healthcare costs are lower because individuals who die no longer incur healthcare costs. The ICER compared to no treatment is $16,900, and the ICER for moving to the status quo is $24,100. Even with these increased risks, if NPRM relaxations enable methadone treatment coverage that is at least 1.3% higher than under the status quo, then this strategy becomes dominant because the total QALYs gained are greater than or equal to the status quo while total costs are less than or equal to the status quo (1.013×11.44 QALYs $= 11.59$ QALYs accrue per person and cost per person is $1.013 \times \$262{,}700 \quad \$266{,}300$).

If the overdose risk in treated individuals increases by 20%, overdoses increase by 16.1% compared to the case of no overdose risk (58,442 total, 7865 fatal) and 6.8% more deaths (16,275) occur. Per person QALYs and costs are 11.29 and $259,200, respectively. The ICER compared to no treatment is $15,700, and the ICER for moving to the status quo (which yields more QALYs at higher cost) is $23,800. Even with these increased risks, if NPRM relaxations enable coverage of MOUD that is at least 2.7% higher than under the status quo, then this strategy becomes dominant because the total QALYs gained are greater than or equal to the status quo while total costs are less than or equal to the status quo (1.027×11.29 QALYs $= 11.59$ QALYs; $1.027 \times \$259{,}200 \quad \$266{,}300$).

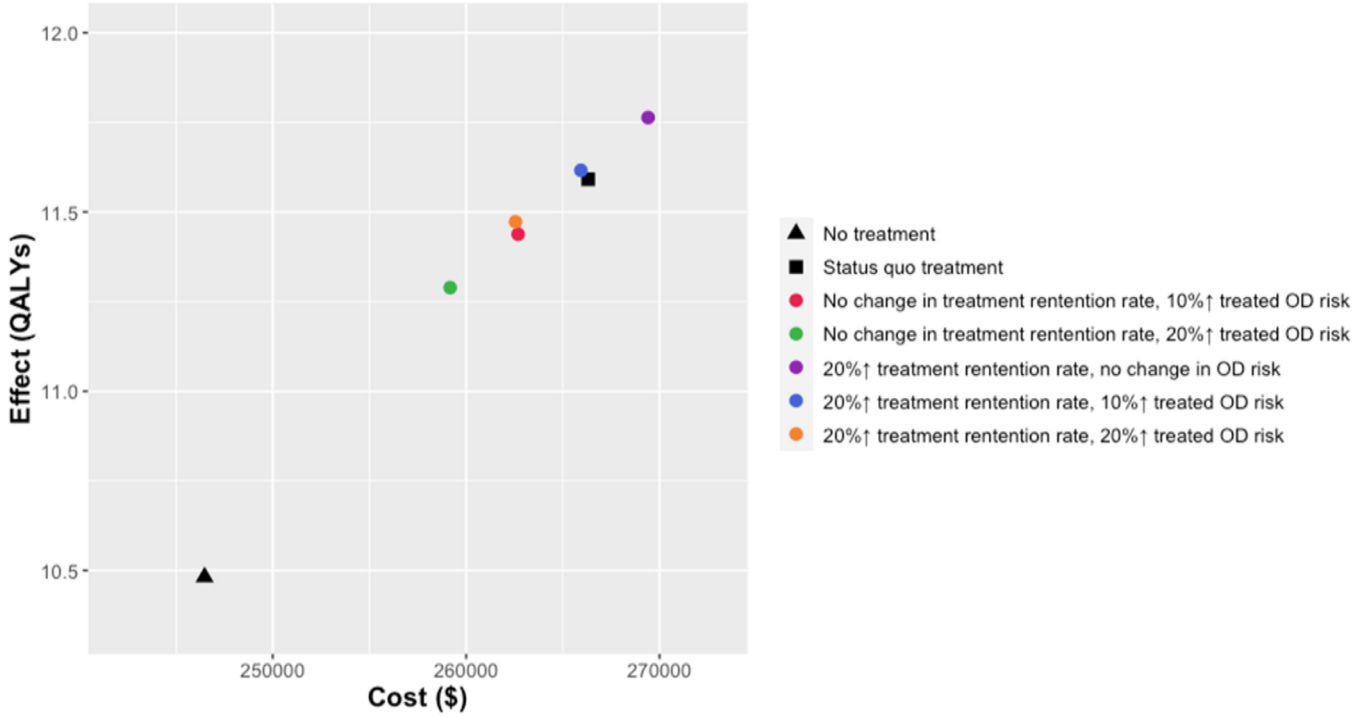
If the methadone treatment retention rate under NPRM is 20% higher than under the status quo, and overdose risk increases by 10% in treated individuals, then 7.9% more overdoses (52,381 total, 7049 fatal) and 3.3% more deaths (15,367) occur over five years. The ICER compared to no treatment is $17,100. Treatment in this scenario dominates treatment under the status quo (more QALYs gained at a lower cost). If the overdose risk in treated individuals increases by 20%, overdoses increase by 15.7% compared to the case of no overdose risk (56,182 total, 7561 fatal) and deaths increase by 6.5% (15,851). Per person costs and QALYs are 11.47 and $262,600, respectively. The ICER compared to no treatment is $16,200.

3.2. Sensitivity analyses

In sensitivity analysis we examined outcomes when methadone overdose risk increases among both treated and untreated individuals. To do so, we separately calculated outcomes associated with potential methadone diversion to individuals not receiving methadone treatment, assuming 5%, 10%, and 20% increased risk of overdose among such individuals (Table 3). If risk of overdose is 5% higher among untreated individuals due to methadone diversion, we estimate that 2856 additional overdoses (384 fatal) will occur over five years in untreated individuals per 100,000 individuals receiving methadone treatment, with 366 additional deaths. The total number of incremental deaths is lower than the number of incremental fatal overdoses because deaths captures all-cause mortality during the five-year time period, and some individuals who might have died from other causes when there is no drug diversion die earlier due to a fatal overdose when drug diversion occurs.



a. Buprenorphine treatment



b. Methadone treatment

Fig. 1. Cost-effectiveness planes. a. Buprenorphine treatment. b. Methadone treatment.

These incremental health outcomes lead to 0.10 fewer lifetime discounted QALYs per untreated person and healthcare cost savings of $2400 per person. Per person healthcare costs are lower when overdose risk increases because individuals who die no longer incur healthcare costs. For larger increases in the risk of overdose due to diversion, more overdoses and deaths occur among untreated individuals, larger per person QALY decrements occur, and larger per person cost savings accrue. These changes are approximately linear in the overdose risk increase.

We added these outcomes for untreated individuals to outcomes for

Table 3
Results: Estimates of Incremental Health Outcomes and Costs among Untreated Individuals due to Methadone Diversion Compared to Status Quo[a] (Mean Value and 95% Credible Interval).

	Incremental Health Outcomes Over 5 Years, per 100,000 Untreated Individuals with Opioid Use Disorder				Incremental Discounted Lifetime per Person Costs and QALYs	
Risk of Overdose Compared to Status Quo	**Fatal Overdoses**	**Nonfatal Overdoses**	**Total Overdoses**	**Deaths[b]**	**QALYs**	**Health Care Cost ($1000, 2022)**
5% higher	384 [286,504]	2472 [960, 5742]	2856 [1300, 6165]	366 [273,478]	-0.10 [0.12, 0.08]	-2.4 [3.1, 1.7]
10% higher	767 [571, 1005]	4932 [1915, 11,454]	5699 [2595, 12,297]	729 [544,953]	-0.20 [0.23, 0.16]	-4.7 [6.0, 3.5]
20% higher	1527 [1138, 1997]	9818 [3814, 22,796]	11,345 [5169, 24,467]	1452 [1085, 1894]	-0.38 [0.45, 0.32]	-9.2 [11.8, 6.8]

[a] Status quo for these individuals is no treatment and no increase in risk of overdose due to methadone diversion under NPRM
[b] From all causes

individuals receiving methadone treatment to calculate population health outcomes when methadone diversion increases overdose risk in both treated and untreated individuals (Table 4). In every scenario we considered, per person QALYs and costs are less than would accrue under status quo methadone treatment, and the ICER compared to no treatment is less than the ICER of status quo treatment compared to no treatment.

Table 4 also shows the ICER for moving to the status quo. In all cases, it would be cost-effective to move from methadone provision under NPRM to status quo provision of methadone, as more QALYs would be gained at an ICER less than $50,000. However, even in the extreme scenario where NPRM provision of methadone does not increase the retention rate and increases overdose risk by 20% for both treated and untreated individuals, if NPRM relaxations enable methadone coverage that is at least 6.3% higher than under the status quo, then this strategy becomes dominant because the total QALYs gained are greater than or equal to the status quo while total costs are less than or equal to the status quo (1.063 × 10.90 QALYs = 11.59 QALYs; 1.063 × $249,900 $266,300).

To account for the uncertainty surrounding the prevalence of fentanyl in the U.S illicit drug market, in one-way sensitivity analysis we varied fentanyl prevalence between 22% and 66%. In all cases, the ICER for both methadone and buprenorphine provision compared to no treatment was less than $19,000.

We also explored the impact of the increased treatment retention rate attributable to NPRM, varying the increase between 0% and 35%. In all cases, the ICER for both buprenorphine and methadone provision compared to no treatment was less than $20,000.

In probabilistic sensitivity analysis, no treatment was dominated beyond a willingness-to-pay threshold of $20,000 in all scenarios we considered (Figures S2, S3). At a willingness-to-pay threshold of $100,000, no treatment was preferred in only approximately 6% of simulations.

4. Discussion

Our analysis finds that provision of both buprenorphine and methadone for treatment of OUD under NPRM would be effective and cost-effective. Compared to no treatment, we estimate that buprenorphine provision would cost $19,200/QALY gained if the treatment retention rate under NPRM is unchanged, and $18,900/QALY gained if the retention rate increases by 20%. In all the scenarios we considered, methadone provision cost less than $20,000/QALY gained compared to no treatment, and cost less than $50,000/QALY gained compared to status quo methadone treatment.

Economic evaluations are increasingly important in medicine and public health as healthcare and public health budgets are stressed by rising costs (Center for the Evaluation of Value and Risk in Health, 2023; Neumann et al., 2016). Especially for large-scale programs that have substantial budgetary implications, achieving the maximum health benefit efficiently (maximum health improvement for each dollar spent) is critical. This can be accomplished in healthcare and public health contexts by choosing interventions whose incremental cost-effectiveness ratios are as close to but below a willingness-to-pay threshold (typically $100,000/QALY gained in the context of health and medicine (Neumann et al., 2016; Sanders et al., 2016)). In light of this, our finding that both methadone and buprenorphine provision under NPRM are likely to achieve health benefits at a cost per QALY gained (ICER) that is low relative to the typical willingness-to-pay threshold implies that we should continue with such relaxation policies to achieve maximal health benefit in a way consistent with health budgets.

Previous analyses using the same model but without reflecting the increasing prevalence of fentanyl and other synthetic opioids estimated that, without NPRM, buprenorphine provision would yield 1.07 incremental QALYS per person (Fairley et al., 2021; Qian et al., 2023) and methadone provision would yield 1.02 QALYs per person compared to no treatment (Fairley et al., 2021); we estimated that with NPRM these values would be 1.21 and 1.11 QALYs, respectively. Similarly, the previous analyses estimated ICERs on the order of $18,000-$19,000 (in 2022 USD) for methadone provision and $17,400 for methadone compared to no treatment; we estimated that with NPRM these values would be $19,200 and $19,800, respectively. The higher QALYs estimated for buprenorphine and methadone treatment in the current study reflect higher numbers of overdoses and deaths averted – overdoses and deaths that would have been caused by the increased prevalence of fentanyl. The higher costs incurred reflect costs for treating increased numbers of non-fatal overdoses.

Our analyses model a cohort of individuals who all enter treatment, so we have made no assumptions about the fraction of individuals who enter treatment under NPRM; instead, our model calculates the per-person costs and health outcomes that accrue for each person who enters treatment. We calculated that with 20% higher methadone treatment retention, then even when overdose risk increases by 20% among treated and untreated individuals, if NPRM relaxations enable methadone coverage that is at least 6.3% higher than under the status quo then this strategy yields more QALYs at lower cost than the status quo. Such an increase is likely achievable if NPRM relaxations continue: a cohort comparison study of 19,648 Kaiser Permanente patients in California before COVID-19 with drug use problems and 16,949 patients at COVID-19 onset found that OUD treatment engagement increased (AOR 1.20 [95% CI: 1.14–1.25]) as did telehealth treatment initiation (AOR 1.13 [95% CI: 1.03–1.24]) (Palzes et al., 2023).

We have shown that overdose risks associated with take-home methadone can reduce the health benefits of MOUD provision. Efforts are needed to reduce these potential risks. These could include, for example, careful assessment of factors such as a patient's drug use history, medical comorbidities, and housing stability when prescribing (or, more precisely, ordering and dispensing) take-home methadone doses, and systematic follow-up to track adverse events (Suen et al., 2022). Technological solutions might include remotely observed or monitored

Table 4
Results of Sensitivity Analysis on Increased Overdose Rates Among Untreated Individuals due to Methadone Diversion: Health Outcomes and Costs (Mean Value and 95% Credible Interval).

	Over 5 Years, per 100,000 Individuals Treated for Opioid Use Disorder				Lifetime per Person Discounted Healthcare Costs and QALYs		ICER ($/QALY gained)[1]	
Treatment Option	**Fatal Overdoses**	**Nonfatal Overdoses**	**Total Overdoses**	**Deaths[2]**	**QALYs**	**Health Care Cost ($1000, 2022)**	**Compared to no treatment**	**Compared to treatment under status quo**
No treatment	8434 [6199, 11,196]	54,243 [20,943, 126,413]	62,678 [28,351, 135,608]	16,750 [13,975, 20,056]	10.48 [8.78, 12.03]	246.5 [223.9, 268.8]	–	–
No change in treatment discontinuation rate								
Status quo[3]	7049 [4806, 11,171]	45,334 [16,675, 109,795]	52,384 [22,437, 118,627]	15,542 [12,018, 23,725]	11.59 [9.60, 12.98]	266.3 [220.9, 300.9]	$17,900	–
10% higher overdose risk in treated individuals								
NPRM: 5% higher overdose risk in untreated individuals	8019 [5493, 12,544]	51,566 [19,032, 124,483]	59,585 [25,603, 134,412]	16,461 [12,688, 24,979]	11.34 [9.31, 12.76]	260.3 [214.2, 295.4]	$16,100	$23,800
NPRM: 10% higher overdose risk in untreated individuals	8417 [5808, 12,991]	54,128 [20,069, 130,255]	62,544 [27,003, 140,550]	16,839 [12,996, 25,383]	11.24 [9.21, 12.68]	258.0 [211.7, 293.2]	$15,100	$23,00
NPRM: 20% higher overdose risk in untreated individuals	9208 [6431, 13,885]	59,213 [22,120, 141,549]	68,421 [29,792, 152,746]	17,591 [13,605, 26,190]	11.05 [9.01, 12.51]	253.5 [206.9, 288.9]	$12,200	$23,700
20% higher overdose risk in treated individuals								
NPRM: 5% higher overdose risk in untreated individuals	8582 [5861, 13,462]	55,192 [20,343, 133,351]	63,774 [27,362, 144,034]	16,994 [13,044, 25,811]	11.19 [9.13, 12.64]	256.8 [210.0, 292.2]	$14,600	$23,800
NPRM: 10% higher overdose risk in untreated individuals	8981 [6175, 13,903]	57,754 [21,377, 139,062]	66,734 [28,770, 150,067]	17,373 [13,352, 26,219]	11.09 [9.02, 12.56]	254.5 [207.6, 290.0]	$13,100	$23,800
NPRM: 20% higher overdose risk in untreated individuals	9772 [6800, 14,799]	62,839 [23,425, 150,403]	72,611 [31,548, 162,295]	18,125 [13,962, 27,026]	10.90 [8.82, 12.39]	249.9 [202.7, 285.8]	$8200	$23,800
83.3% lower treatment discontinuation rate								
10% higher overdose risk in treated individuals								
NPRM: 5% higher overdose risk in untreated individuals	7552 [5158, 11,934]	48,568 [17,881, 117,522]	56,120 [24,066, 126,939]	15,792 [12,200, 24,056]	11.52 [9.51, 12.91]	263.6 [217.5, 299.2]	$16,500	$37,200
NPRM: 10% higher overdose risk in untreated individuals	7951 [5475, 12,373]	51,130 [18,918, 123,219]	59,080 [25,461, 133,084]	16,171 [12,511, 24,460]	11.42 [9.41, 12.82]	261.2 [215.1, 296.9]	$15,700	$29,700
NPRM: 20% higher overdose risk in untreated individuals	8741 [6099, 13,258]	56,215 [20,965, 134,583]	64,957 [28,244, 145,260]	16,923 [13,124, 25,263]	11.23 [9.21, 12.65]	256.7 [210.3, 292.6]	$13,600	$26,700
20% higher overdose risk in treated individuals								
NPRM: 5% higher overdose risk in untreated individuals	8062 [5483, 12,793]	51,844 [19,047, 125,610]	59,906 [25,631, 135,639]	16,275 [12,512, 24,827]	11.37 [9.34, 12.79]	260.2 [213.5, 296.1]	$15,400	$28,200
NPRM: 10% higher overdose risk in untreated individuals	8460 [5800, 13,223]	54,405 [20,098, 131,228]	62,866 [27,033, 141,839]	16,653 [12,827, 25,232]	11.28 [9.23, 12.71]	257.9 [211.0, 293.9]	$14,300	$26,900
NPRM: 20% higher overdose risk in untreated individuals	9251 [6426, 14,116]	59,491 [22,138, 142,691]	68,742 [29,801, 153,936]	17,405 [13,441, 26,033]	11.09 [9.03, 12.54]	253.3 [206.2, 289.6]	$11,300	$25,800

[1] Incremental cost-effectiveness ratio (ICER).
[2] From all causes.
[3] Status quo: No change in treatment discontinuation rate or overdose risk.

dosing (Dunn et al., 2021; Hallgren et al., 2022) and greater use of depot formulations of MOUD which cannot be diverted.

In 2019, only about 28% of individuals in the U.S. with OUD received MOUD (Mauro et al., 2022). NPRM relaxations, particularly the use of telehealth, may allow some individuals (e.g., those in rural areas or those served by geographically dispersed provider hubs such as the VHA) who would not have been able to access MOUD without telehealth to receive MOUD (Frost et al., 2022; Hughto et al., 2021; Moore et al., 2021; Nordeck et al., 2021; Palzes et al., 2023). Efforts to increase access to MOUD, including relaxations provided by NPRM, Medicaid expansion (Hinde et al., 2019), and efforts to increase the supply of providers trained in addiction medicine (Humphreys et al., 2022) are critically needed. Increases in the number of individuals receiving MOUD would improve health and reduce complications of OUD and associated costs. A future analysis could examine these potential aggregate benefits.

Because modelling the future is a hypothetical process, the conclusions of our study should not make us forget past experiences in some countries, such as Denmark, Sweden, and the UK, where relaxation of regulations has been followed by increased MOUD-related deaths. We recommend that the Government Accountability Office or an equally credible research organization conduct an extended evaluation of the new regulations' impact, examining aspects such as accessibility and retention in MOUD care, medication diversion, and overdose deaths among individuals receiving and not receiving MOUD, as well as assessment of how care providers interpret and apply the term "stable patients" in their monitoring practices.

Our analysis has several limitations. Uncertainty exists regarding the extent to which NPRM relaxations may lead to increased overdoses among treated and untreated individuals, particularly for methadone treatment. We therefore considered a range of potential values for the level of increased overdose (including no increase). With relaxed regulations in methadone dispensing, some patients currently receiving buprenorphine might instead opt for methadone (Luty, 2018). Our study shows that although methadone is slightly less cost-efficient than buprenorphine, it is still cost-effective compared to no treatment. Our analysis takes a healthcare system perspective. We did not include the cost of patient time and travel, nor did we include criminal justice system costs. If we include savings in criminal justice system costs associated with MOUD treatment, buprenorphine and methadone will be cost-saving in all the scenarios we considered. Finally, continued changes in the supply of illicit opioids may change overdose risk, potentially to higher values than we have estimated.

Despite these uncertainties, we conclude that the provision of both buprenorphine and methadone for the treatment of OUD under NPRM is likely to be effective and cost-effective. Increases in overdose risk that may be associated with take-home methadone reduce health benefits; thus, efforts to mitigate this risk are critical.

Author Disclosures

None

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Qian Gary Lurui: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Brandeau Margaret L.:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Funding acquisition, Data curation, Conceptualization. **Goldhaber-Fiebert Jeremy D.:** Writing – review & editing, Conceptualization. **Humphreys Keith:** Writing – review & editing, Writing – original draft, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors have no conflicts of interest to declare.

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Declaration of interests

None to declare.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2024.111112.

References

Agency for Health Care Research and Quality, 2023. Using appropriate price indices for analyses of health care expenditures or income across multiple years. https://meps.ahrq.gov/about_meps/Price_Index.shtml#t2a1.

Aldabergenov, D., Reynolds, L., Scott, J., Kelleher, M.J., Strang, J., Copeland, C.S., Kalk, N.J., 2022. Methadone and buprenorphine-related deaths among people prescribed and not prescribed opioid agonist therapy during the COVID-19 pandemic in England. Int. J. Drug Policy 110, 103877.

Alexander, G.C., Stoller, K.B., Haffajee, R.L., Saloner, B., 2020. An epidemic in the midst of a pandemic: opioid use disorder and COVID-19. Ann. Intern Med. 173 (1), 57–58.

Amram, O., Amiri, S., Panwala, V., Lutz, R., Joudrey, P.J., Socias, E., 2021. The impact of relaxation of methadone take-home protocols on treatment outcomes in the COVID-19 era. Am. J. Drug Alcohol Abus. 47 (6), 722–729.

Arias, E., Xu, J., 2019. United States life tables, 2017. Natl. Vital.-. Stat. Rep. 68 (7), 1–65.

Baser, O., Xie, L., Mardekian, J., Schaaf, D., Wang, L., Joshi, A.V., 2014. Prevalence of diagnosed opioid abuse and its economic burden in the Veterans Health Administration. Pain. Pract. 14 (5), 437–445.

Bell, J., 2010. The global diversion of pharmaceutical drugs: opiate treatment and the diversion of pharmaceutical opiates: a clinician's perspective. Addiction 105 (9), 1531–1537.

Brothers, S., Viera, A., Heimer, R., 2021. Changes in methadone program practices and fatal methadone overdose rates in Connecticut during COVID-19. J. Subst. Abus. Treat. 131, 108449.

Cairns, A., Roberts, I.S., Benbow, E.W., 1996. Characteristics of fatal methadone overdose in Manchester, 1985-94. BMJ 313 (7052), 264–265.

Cantor, J.H., Whaley, C.M., Stein, B.D., Powell, D., 2022. Analysis of substance use disorder treatment admissions in the US by sex and race and ethnicity before and during the COVID-19 pandemic. JAMA Netw. Open 5 (9), e2232795.

Carlson, R.G., Nahhas, R.W., Martins, S.S., Daniulaityte, R., 2016. Predictors of transition to heroin use among initially non-opioid dependent illicit pharmaceutical opioid users: A natural history study. Drug Alcohol Depend. 160, 127–134.

Carroll, J.J., Marshall, B.D.L., Rich, J.D., Green, T.C., 2017. Exposure to fentanyl-contaminated heroin and overdose risk among illicit opioid users in Rhode Island: A mixed methods study. Int. J. Drug Policy 46, 136–145.

CDC, 2022. Drug Overdose Deaths in the United States, 2001–2021. https://www.cdc.gov/nchs/products/databriefs/db457.htm. (Accessed May 5 2023).

Center for the Evaluation of Value and Risk in Health, 2023. CEA Registry. https://cevr.tuftsmedicalcenter.org/databases/cea-registry.

Coffin, P.O., Sullivan, S.D., 2013. Cost-effectiveness of distributing naloxone to heroin users for lay overdose reversal. Ann. Intern Med. 158 (1), 1–9.

Department of Defense, 2016. TRICARE; Mental Health and Substance Use Disorder Treatment, 81. Federal Register, pp. 61068–61098.

Dunn, K.E., Brooner, R.K., Stoller, K.B., 2021. Technology-assisted methadone take-home dosing for dispensing methadone to persons with opioid use disorder during the Covid-19 pandemic. J. Subst. Abus. Treat. 121, 108197.

Eibl, J.K., Gauthier, G., Pellegrini, D., Daiter, J., Varenbut, M., Hogenbirk, J.C., Marsh, D. C., 2017. The effectiveness of telemedicine-delivered opioid agonist therapy in a supervised clinical setting. Drug Alcohol Depend. 176, 133–138.

Fairley, M., Humphreys, K., Joyce, V.R., Bounthavong, M., Trafton, J., Combs, A., Oliva, E.M., Goldhaber-Fiebert, J.D., Asch, S.M., Brandeau, M.L., Owens, D.K., 2021. Cost-effectiveness of treatments for opioid use disorder. JAMA Psychiatry 78 (7), 767–777.

Figgatt, M.C., Salazar, Z., Day, E., Vincent, L., Dasgupta, N., 2021. Take-home dosing experiences among persons receiving methadone maintenance treatment during COVID-19. J. Subst. Abus. Treat. 123, 108276.

Frank, R.G., Humphreys, K., Huskamp, H.A., 2023. Comments on medications for the treatment of opioid use disorder. https://www.brookings.edu/opinions/comments-on-medications-for-the-treatment-of-opioid-use-disorder/. (Accessed June 5 2023).

Frost, M.C., Zhang, L., Kim, H.M., Lin, L.A., 2022. Use of and retention on video, telephone, and in-person buprenorphine treatment for opioid use disorder during the COVID-19 pandemic. JAMA Netw. Open 5 (10), e2236298.

Fugelstad, A., 2022. What lessons from Sweden's experience could be applied in the United States in response to the addiction and overdose crisis? Addiction 117 (5), 1189–1191.

Hallgren, K.A., Darnton, J., Soth, S., Blalock, K.L., Michaels, A., Grekin, P., Saxon, A.J., Woolworth, S., Tsui, J.I., 2022. Acceptability, feasibility, and outcomes of a clinical pilot program for video observation of methadone take-home dosing during the COVID-19 pandemic. J. Subst. Abus. Treat. 143, 108896.

Hammerslag, L.R., Mack, A., Chandler, R.K., Fanucchi, L.C., Feaster, D.J., LaRochelle, M. R., Lofwall, M.R., Nau, M., Villani, J., Walsh, S.L., Westgate, P.M., Slavova, S., Talbert, J.C., 2023. Telemedicine buprenorphine initiation and retention in opioid use disorder treatment for Medicaid enrollees. JAMA Netw. Open 6 (10), e2336914.

Harris, R.A., Long, J.A., Bao, Y., Mandell, D.S., 2023. Racial, ethnic, and sex differences in methadone-involved overdose deaths before and after the US Federal policy change expanding take-home methadone doses. JAMA Health Forum 4 (6), e231235.

Hinde, J.M., Mark, T.L., Fuller, L., Dey, J., Hayes, J., 2019. Increasing access to opioid use disorder treatment: assessing state policies and the evidence behind them. J. Stud. Alcohol Drugs 80 (6), 693–697.
Hoffman, K.A., Foot, C., Levander, X.A., Cook, R., Terashima, J.P., McIlveen, J.W., Korthuis, P.T., McCarty, D., 2022. Treatment retention, return to use, and recovery support following COVID-19 relaxation of methadone take-home dosing in two rural opioid treatment programs: A mixed methods analysis. J. Subst. Abus. Treat. 141, 108801.
Hser, Y.I., Saxon, A.J., Huang, D., Hasson, A., Thomas, C., Hillhouse, M., Jacobs, P., Teruya, C., McLaughlin, P., Wiest, K., Cohen, A., Ling, W., 2014. Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. Addiction 109 (1), 79–87.
Hughto, J.M.W., Peterson, L., Perry, N.S., Donoyan, A., Mimiaga, M.J., Nelson, K.M., Pantalone, D.W., 2021. The provision of counseling to patients receiving medications for opioid use disorder: Telehealth innovations and challenges in the age of COVID-19. J. Subst. Abus. Treat. 120, 108163.
Humphreys, K., Shover, C.L., Andrews, C.M., Bohnert, A.S.B., Brandeau, M.L., Caulkins, J.P., Chen, J.H., Cuellar, M.F., Hurd, Y.L., Juurlink, D.N., Koh, H.K., Krebs, E.E., Lembke, A., Mackey, S.C., Larrimore Ouellette, L., Suffoletto, B., Timko, C., 2022. Responding to the opioid crisis in North America and beyond: recommendations of the Stanford-Lancet Commission. Lancet 399 (10324), 555–604.
Jones, C.M., Compton, W.M., Han, B., Baldwin, G., Volkow, N.D., 2022a. Methadone-involved overdose deaths in the US before and after federal policy changes expanding take-home methadone doses from opioid treatment programs. JAMA Psychiatry 79 (9), 932–934.
Jones, C.M., Shoff, C., Hodges, K., Blanco, C., Losby, J.L., Ling, S.M., Compton, W.M., 2022b. Receipt of telehealth services, receipt and retention of medications for opioid use disorder, and medically treated overdose among Medicare beneficiaries before and during the COVID-19 pandemic. JAMA Psychiatry 79 (10), 981–992.
Joseph, G., Torres-Lockhart, K., Stein, M.R., Mund, P.A., Nahvi, S., 2021. Reimagining patient-centered care in opioid treatment programs: Lessons from the Bronx during COVID-19. J. Subst. Abus. Treat. 122, 108219.
Kaufman, D.E., Kennalley, A.L., McCall, K.L., Piper, B.J., 2023. Examination of methadone involved overdoses during the COVID-19 pandemic. Forensic Sci. Int 344, 111579.
Kawasaki, S.S., Zimmerman, R., Shen, C., Zgierska, A.E., 2023. COVID-19-related flexibility in methadone take-home doses associated with decreased attrition: Report from an opioid treatment program in central Pennsylvania. J. Subst. Use Addict. Treat. 155, 209164.
Kelty, E., Joyce, D., Hulse, G., 2019. A retrospective cohort study of mortality rates in patients with an opioid use disorder treated with implant naltrexone, oral methadone or sublingual buprenorphine. Am. J. Drug Alcohol Abus. 45 (3), 285–291.
Kleinman, R.A., Sanches, M., 2023. Methadone-involved overdose deaths in the United States before and during the COVID-19 pandemic. Drug Alcohol Depend. 242, 109703.
Krebs, E., Enn, B., Evans, E., Urada, D., Angli, M.D., Rawson, R.A., Hser, Y.-I., Nosyk, B., 2018. Cost-effectiveness of publicly funded treatment of opioid use disorder in California. Ann. Intern Med 168 (1), 10–19.
Lee, J.D., Nunes, E.V., Jr, Novo, P., Bachrach, K., Bailey, G.L., Bhatt, S., Farkas, S., Fishman, M., Gauthier, P., Hodgkins, C.C., King, J., Lindblad, R., Liu, D., Matthews, A.G., May, J., Peavy, K.M., Ross, S., Salazar, D., Schkolnik, P., Shmueli-Blumberg, D., Stablein, D., Subramaniam, G., Rotrosen, J., 2018. Comparative effectiveness of extended-release naltrexone versus buprenorphine-naloxone for opioid relapse prevention (X:BOT): a multicentre, open-label, randomised controlled trial. Lancet 391 (10118), 309–318.
Lim, T.Y., Stringfellow, E.J., Stafford, C.A., DiGennaro, C., Homer, J.B., Wakeland, W., Eggers, S.L., Kazemi, R., Glos, L., Ewing, E.G., Bannister, C.B., Humphreys, K., Throckmorton, D.C., Jalali, M.S., 2022. Modeling the evolution of the US opioid crisis for national policy development. Proc. Natl. Acad. Sci. USA 119 (23), e2115714119.
Liu, S., Cipriano, L.E., Holodniy, M., Owens, D.K., Goldhaber-Fiebert, J.D., 2012. New protease inhibitors for the treatment of chronic hepatitis C: a cost-effectiveness analysis. Ann. Intern Med 156 (4), 279–290.
Luty, J., 2018. Treatment preferences of opiate-dependent patients. Psychiatr. Bull. 28 (2), 47–50.
Ma, J., Bao, Y.P., Wang, R.J., Su, M.F., Liu, M.X., Li, J.Q., Degenhardt, L., Farrell, M., Blow, F.C., Ilgen, M., Shi, J., Lu, L., 2019. Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis. Mol. Psychiatry 24, 1868–1883.
Mauro, P.M., Gutkind, S., Annunziato, E.M., Samples, H., 2022. Use of medication for opioid use disorder among US adolescents and adults with need for opioid treatment, 2019. JAMA Netw. Open 5 (3), e223821.
Meara, E., White, C., Cutler, D.M., 2004. Trends in medical spending by age, 1963-2000. Health Aff. (Millwood) 23 (4), 176–183.
Moore, D.T., Wischik, D.L., Lazar, C.M., Vassallo, G.G., Rosen, M.I., 2021. The intertwined expansion of telehealth and buprenorphine access from a prescriber hub. Prev. Med 152 (Pt 2), 106603.
National Safety Council, 2023. Drug overdoses. https://injuryfacts.nsc.org/home-and-community/safety-topics/drugoverdoses/data-details/. (Accessed May 5 2023).
Neumann, A.M., Blondell, R.D., Jaanimagi, U., Giambrone, A.K., Homish, G.G., Lozano, J.R., Kowalik, U., Azadfard, M., 2013. A preliminary study comparing methadone and buprenorphine in patients with chronic pain and coexistent opioid addiction. J. Addict. Dis. 32 (1), 68–78.
Neumann, P.J., Sanders, G.D., Russell, L.B., Siegel, J.E., Ganiats, T.G., 2016. Cost-Effectiveness in Health and Medicine, 2nd ed. Oxford University Press, New York.
Nordeck, C.D., Buresh, M., Krawczyk, N., Fingerhood, M., Agus, D., 2021. Adapting a low-threshold buprenorphine program for vulnerable populations during the COVID-19 pandemic. J. Addict. Med 15 (5), 364–369.
Otiashvili, D., Piralishvili, G., Sikharulidze, Z., Kamkamidze, G., Poole, S., Woody, G.E., 2013. Methadone and buprenorphine-naloxone are effective in reducing illicit buprenorphine and other opioid use, and reducing HIV risk behavior–outcomes of a randomized trial. Drug Alcohol Depend. 133 (2), 376–382.
Palzes, V.A., Chi, F.W., Metz, V.E., Sterling, S., Asyyed, A., Ridout, K.K., Campbell, C.I., 2023. Overall and telehealth addiction treatment utilization by age, race, ethnicity, and socioeconomic status in California after COVID-19 policy changes. JAMA Health Forum 4 (5), e231018.
Potter, J.S., Marino, E.N., Hillhouse, M.P., Nielsen, S., Wiest, K., Canamar, C.P., Martin, J.A., Ang, A., Baker, R., Saxon, A.J., Ling, W., 2013. Buprenorphine/naloxone and methadone maintenance treatment outcomes for opioid analgesic, heroin, and combined users: findings from starting treatment with agonist replacement therapies (START). J. Stud. Alcohol Drugs 74 (4), 605–613.
Qian, G., Rao, I., Humphreys, K., Owens, D.K., Brandeau, M.L., 2023. Cost-effectiveness of office-based buprenorphine treatment for opioid use disorder. Drug Alcohol Depend. 243, 109762.
Ritter, A., Di Natale, R., 2005. The relationship between take-away methadone policies and methadone diversion. Drug Alcohol Rev. 24 (4), 347–352.
Ruger, J.P., Chawarski, M., Mazlan, M., Ng, N., Schottenfeld, R., 2012. Cost-effectiveness of buprenorphine and naltrexone treatments for heroin dependence in Malaysia. PLoS One 7 (12), e50673.
Russell, C., Ali, F., Nafeh, F., Rehm, J., LeBlanc, S., Elton-Marshall, T., 2021. Identifying the impacts of the COVID-19 pandemic on service access for people who use drugs (PWUD): A national qualitative study. J. Subst. Abus. Treat. 129, 108374.
SAMSHA, 2019. National Survey on Drug Use and Health 2018 (NSDUH-2018-DS0001). https://www.datafiles.samhsa.gov/study-dataset/national-survey-drug-use-and-health-2018-nsduh-2018-ds0001-nid18758. (Accessed June 14 2020).
SAMSHA, 2020a. Leveraging Existing Health and Disease Management Programs to Provide Mental Health and Substance Use Disorder Resources During the COVID-19 Public Health Emergency (PHE). https://www.samhsa.gov/coronavirus. (Accessed May 6 2023).
SAMSHA, 2020b. Methadone Take-Home Flexibilities Extension Guidance. https://www.samhsa.gov/medications-substance-use-disorders/statutes-regulations-guidelines/methadone-guidance. (Accessed May 6 2023).
SAMSHA, 2022. Medications for the Treatment of Opioid Use Disorder: Notice of Proposed Rule Making. Federal Register, pp. 77330–77365.
Sanders, G.D., Neumann, P.J., Basu, A., Brock, D.W., Feeny, D., Krahn, M., Kuntz, K.M., Meltzer, D.O., Owens, D.K., Prosser, L.A., Salomon, J.A., Sculpher, M.J., Trikalinos, T.A., Russell, L.B., Siegel, J.E., Ganiats, T.G., 2016. Recommendations for conduct, methodological practices, and reporting of cost-effectiveness analyses: Second Panel on Cost-Effectiveness in Health and Medicine. JAMA 316 (10), 1093–1103.
Shei, A., Rice, J.B., Kirson, N.Y., Bodnar, K., Birnbaum, H.G., Holly, P., Ben-Joseph, R., 2015. Sources of prescription opioids among diagnosed opioid abusers. Curr. Med Res Opin. 31 (4), 779–784.
Suen, L.W., Castellanos, S., Joshi, N., Satterwhite, S., Knight, K.R., 2022. The idea is to help people achieve greater success and liberty: a qualitative study of expanded methadone take-home access in opioid use disorder treatment. Subst. Abus 43 (1), 1143–1150.
Tanum, L., Solli, K.K., Latif, Z.E., Benth, J.S., Opheim, A., Sharma-Haase, K., Krajci, P., Kunoe, N., 2017. Effectiveness of injectable extended-release naltrexone vs daily buprenorphine-naloxone for opioid dependence: a randomized clinical noninferiority trial. JAMA Psychiatry 74 (12), 1197–1205.
Tjagvad, C., Skurtveit, S., Linnet, K., Andersen, L.V., Christoffersen, D.J., Clausen, T., 2016. Methadone-related overdose deaths in a liberal opioid maintenance treatment programme. Eur. Addict. Res 22 (5), 249–258.
U.S. Census Bureau, 2020. American Community Survey 2018, 5-year estimates – public use microdata sample. https://data.census.gov/mdat/#/search?ds=ACSPUMS5Y2018&cv=SEX&rv=AGEP&wt=PWGTP. (Accessed May 6 2023).
Vakkalanka, J.P., Lund, B.C., Ward, M.M., Arndt, S., Field, R.W., Charlton, M., Carnahan, R.M., 2022. Telehealth utilization is associated with lower risk of discontinuation of buprenorphine: a retrospective cohort study of US veterans. J. Gen. Intern Med 37 (7), 1610–1618.
Williams, A.R., Krawczyk, N., Hu, M.C., Harpel, L., Aydinoglo, N., Cerda, M., Rotrosen, J., Nunes, E.V., 2023. Retention and critical outcomes among new methadone maintenance patients following extended take-home reforms: a retrospective observational cohort study. Lancet Reg. Health Am. 28, 100636.