ADDICTION

SSA SOCIETY FOR THE STUDY OF ADDICTION

RESEARCH REPORT

doi:10.1111/add.14797

Cost-effectiveness of expanding the capacity of opioid agonist treatment in Ukraine: dynamic modeling analysis

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ABSTRACT

Background and aims Although opioid agonist treatment (OAT) for opioid use disorder (OUD) is cost-effective in settings where the HIV epidemic is concentrated among people who inject drugs, OAT coverage in Ukraine remains far below internationally recommended targets. Scale-up is limited by both OAT availability and demand. This study aimed to evaluate the cost-effectiveness of a range of plausible OAT scale-up strategies in Ukraine incorporating the potential impact of treatment spillover and the real-world demand for addiction treatment. **Design, setting and participants** Ten-year horizon (2016–25) modeling study of opioid addiction epidemic and treatment that accommodated potential peer effects in opioid use initiation and supply-induced treatment demand in three Ukrainian cities: Kyiv, Mykolaiv and Lviv, comprising a simulated population of people at risk of and with OUD. **Measurements** Incremental cost per quality-adjusted life-year gained in the simulated population. **Findings** An estimated 12.2-, 2.4- and 13.4-fold OAT capacity increase over 2016 baseline capacity in Kyiv, Mykolaiv and Lviv, respectively, would be cost-effective at a willingness-to-pay of one per-capita gross domestic product (GDP) per quality-adjusted life-year gained. This result is robust to parametric and structural uncertainty. Even under the most ambitious capacity increase, OAT coverage (i.e. the proportion of people with OUD receiving OAT) over a 10-year modeling horizon would be 20, 11 and 17% in Kyiv, Mykolaiv and Lviv, respectively, owing to limited demand. **Conclusions** It is estimated that a substantial increase in opioid agonist treatment (OAT) capacity in three Ukrainian cities would be cost-effective for a wide range of willingness-to-pay thresholds. Even a very ambitious capacity increase, however, is unlikely to reach internationally recommended coverage levels. Further increases in coverage may be limited by demand and would require addressing existing structural barriers to OAT access.

Keywords Buprenorphine, Eastern Europe, economic evaluation, injection initiation, methadone, opioid epidemic, people who inject drugs (PWID), treatment as prevention, treatment demand, treatment waiting-list.

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Submitted 5 February 2019; initial review completed 24 June 2019; final version accepted 23 August 2019
[Correction added on 7 November 2019, after first online publication: The author affiliations have been amended in this version.]

INTRODUCTION

Ukraine has one of the most severe HIV epidemics in the eastern European and central Asian region, with HIV prevalence exceeding 1% among adults aged 15–49 years and 22.6% among people who inject drugs (PWID) [1]. More than 80% of PWID identify opioids as their primary drug used [2]. Opioid agonist treatment (OAT) using methadone or buprenorphine remains the most effective [3,4] and highly cost-effective [5–7] for chronic opioid use disorder (OUD), yet coverage in Ukraine remains low, at approximately 3% of the estimated number of people with opioid use disorder (POUD) [2,8,9]. OAT was introduced in Ukraine in 2004 for HIV prevention but not for treatment of OUD, and is primarily available in specialty addiction treatment clinics with limited expansion to integrated care settings at HIV and tuberculosis clinics [8], which limits access to treatment. Many countries have successfully implemented OAT provision in primary health-care settings [10], and the feasibility of this intervention in Ukraine was recently demonstrated with high levels of retention and reduced stigma, suggesting a plausible route to expand capacity [11].

Most OAT scale-up modeling studies assume that demand for treatment will always exceed capacity [6,12]. Individual and structural barriers, however, may restrict demand for OAT in Ukraine [13,14]. The World Health Organization's (WHO) target of 40% coverage of all POUD is ambitious [15], yet even 20% coverage may be unattainable, regardless of whether or not capacity is increased, due to a lack of demand for OAT by POUD. The typical approach to model the epidemics of substance use disorders (SUDs) and their treatment assumes that an individual's risk of developing SUD and their likelihood of seeking treatment are independent of population-level drug use prevalence and treatment outcomes [5,12]. Some researchers argue, however, that drug use may exhibit peer effects, and therefore the drug use initiation rate may exhibit positive density-dependence [16–22], that the demand for treatment may be partly driven by supply [23,24] and that the dynamics of the waiting-lists should be taken into account in the assessment of addiction treatment capacity requirements [25].

In this study, we addressed these limitations and conducted a cost-effectiveness analysis (CEA) of OAT scale-up in three cities in Ukraine, considering increased capacity of both specialty (standard of care) and primary care (new) settings. We developed a generic dynamic model of substance abuse epidemics and adapted it to capture specific features of opioid epidemic and OAT in Ukraine. The model permits peer effects in drug use initiation and relapse, and allows demand for and retention in treatment to be capacity-dependent.

METHODS

Overview

We developed a deterministic compartmental dynamic model [26] of opioid epidemic to explore a range of different OAT capacity increase strategies, defined in terms of the number of treatment slots allocated within specialty and primary care settings. We examined three Ukrainian cities —Kyiv, Mykolaiv and Lviv—selected based on data availability for model parameterization and because these cities represent different epidemiological characteristics and structural barriers to accessing OAT. The Supporting information provides details about these locations.

The primary outcome of the CEA is incremental cost per unit change in quality-adjusted life-years (QALYs). In addition, we analyzed two secondary outcomes: averted injections and prevented opioid use initiations. Our model does not incorporate potential changes in HIV and hepatitis C (HCV) transmission as a result of increased OAT availability; however, secondary outcomes may serve as a proxy for prevention of blood-borne infections transmission. This analysis is intended to inform the public funding choice between alternative OAT scale-up strategies, including within primary care settings. Consequently, we restricted our attention to costs incurred in the provision of OAT services and measured these costs from the perspective of the payer (i.e. the government, as represented by the Ministry of Health and municipal authorities) [27]. The main analysis is presented in 2016 $US, and the respective Ukrainian *Hryvnya* equivalent is provided in the Supporting information. The modeling time horizon is a 10-year period between 2016 and 2025. We explored the robustness of the findings to parametric uncertainty, choice of time horizon and structural assumptions. The analysis was conducted and reported in conformity with the guidelines of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement [28].

Model and base case assumptions

Figure 1 shows the structure of the dynamic model. In the base case, we modeled problematic opioid use initiation and relapse rates as a sum of two components: a constant rate representing spontaneous initiation and development of OUD, and a 'peer effects' component, which is a function of the current prevalence of active opioid use defined as using non-prescription opioids in the last 30 days. People using recreationally and not developing OUD were assumed to remain susceptible. This approach allows capture of the indirect societal benefits from addiction treatment due to the potentially socially communicable nature of drug use (i.e. PWID often initiate others to inject drugs that may result in the development of SUD) [29–31].

We assumed that POUD join the OAT waiting-list when they are both eligible and willing to start OAT. While some OAT eligibility restrictions are present, the main barriers to OAT scale-up in Ukraine are lack of capacity and demand [13]. We applied a similar two-component approach to model the demand for OAT among POUD and treatment dropout. Each of these rates is a combination of constant and treatment capacity-dependent components, where the latter exhibits a saturation effect. The demand for treatment may increase with supply due to reduction of expected waiting times, lower enrollment thresholds, reduced stigma resulting from treatment becoming more common and changing attitudes based on observed peer experiences [13,14,24,32]. A detailed description of the dynamic model is provided in the Supporting information.

Parameters

Table 1 summarizes key parameter estimates used in the model. Aside from official demographic [33] and administrative OAT data [8], most parameter estimates were obtained from two studies recently conducted in Ukraine: a pilot study of integrating OAT into primary care settings [11] and a large, cross-sectional survey among opioid-dependent PWID [34]; and two routine OAT patient data

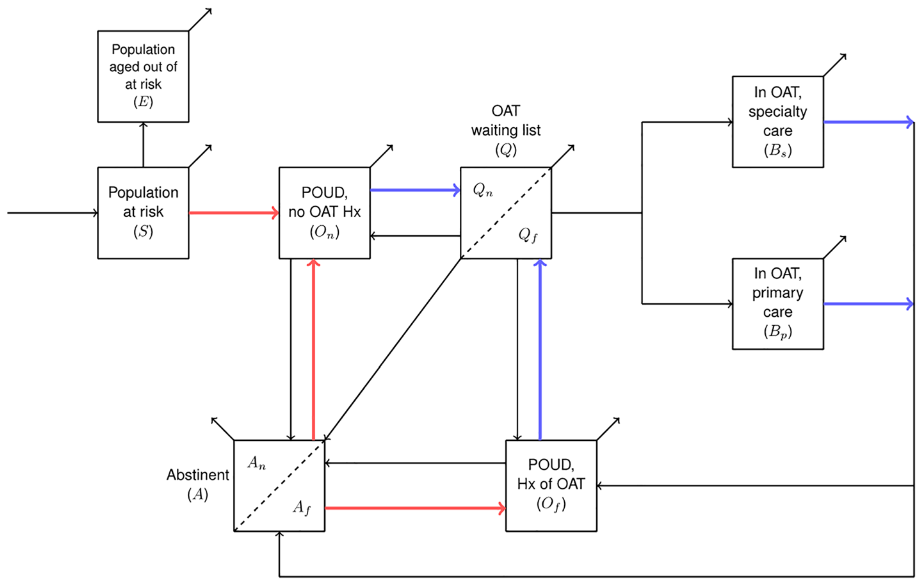

Figure 1 Schematic of the dynamic model of opioid epidemic, demand for and access to the treatment. The population is divided into eight compartments. The population at risk of developing opioid use disorder (OUD, compartment S) is represented by a proportion of the general population aged between 12–49 years, who either develop OUD (transition to compartment O_n), leave the population at risk (transition to E) or die. People with opioid use disorder (POUD) are divided into: those actively using drugs and not willing or ineligible to start opioid agonist treatment (OAT) with (O_f) and without (O_n) history of OAT; those actively using drugs and waiting to start OAT (Q); OAT patients in specialty (B_s) and primary (B_p) care and POUD, who are temporarily or permanently abstinent (A). Compartments Q and A include POUD with (Q_f and A_f) and without (Q_n and A_n) history of OAT. Active opioid use is defined as using non-prescription opioids in the last 30 days. POUD in compartments O_n and O_f may be ineligible for OAT, unwilling to enroll or both. Compartment S may include people who use opioids, but do not meet the criteria for OUD. Compartment A includes people with a history of OUD, who did not use opioids in the last 30 days. Incarcerated POUD are included in compartments O_n, O_f and A. Assumptions about peer effects affect the transition rates represented by the red and blue arrows. Red arrows correspond to the transition rates that increase with the number of people actively using opioids, and blue arrows—to the rates that increase with the OAT capacity. A more detailed version of this figure, with definitions of transition rates, appears in section 1 of the Supporting information. [Colour figure can be viewed at wileyonlinelibrary.com]

management systems [35,36]. All parent studies received Institutional Review Board (IRB) approval. When direct estimates from the data sets were unavailable we estimated parameters from the literature, including measures of uncertainty where available [2,9,37–40]. A detailed list of model parameters, data sources and underlying assumptions is provided in the Supporting information.

Strategies

We defined a strategy as the allocation of a specific number of treatment slots to specialty and primary care clinics. For each city, we first specified a maximum plausible number of treatment slots based on the estimates of OAT demand in that city. We then specified a range of different capacity increases between the current and the maximum number of slots, with different fractions allocated to specialty and primary care. In total, we evaluated 687, 161 and 229 different strategies in Kyiv, Mykolaiv and Lviv, respectively.

In keeping with accepted standards for CEA [41], we identified all efficient strategies (i.e. strategies that yield the greatest benefit for any given outlay), and then selected a subset of the most policy-relevant efficient strategies for further analysis. For each of these strategies, we computed incremental cost-effectiveness ratios (ICERs), measured in US dollars per QALY gained. These ICERs were compared to a reference value—the so-called willingness-to-pay (WTP) threshold—representing the most a decision-maker would be prepared to forgo in exchange for an additional unit of benefit. The largest of the efficient strategies whose ICER remained less than the WTP threshold was labeled the ‘cost-effective’ option. As there is no generally accepted approach to establishing the WTP threshold for health interventions [42], we present our findings for WTP thresholds ranging from $US 0 to 6555 (corresponding to three times the 2016 per-capita gross domestic product (GDP) for Ukraine [43]). For purposes of illustration, we used the one per-capita GDP as a benchmark threshold.

Uncertainty analysis

The joint distribution of model parameters, including transition rates, initial conditions, costs, health utility weights and injection frequency, gives rise to a distribution over model outcomes. Supporting information, Table S2

Table 1 Summary of the key model parameters: marginal means and 95% CI of the joint parameter distribution.

Notation	*Parameter*	*Kyiv*	*Mykolaiv*	*Lviv*
Opioid use initiation and demand for OAT				
λ	Rate of initiation of problematic opioid use per susceptible individual at time zero	0.028 (0.019–0.038)	0.049 (0.032–0.068)	0.025 (0.013–0.044)
λ_0	Spontaneous component of λ	0.011 (0.002–0.022)	0.024 (0.009–0.043)	0.010 (0.001–0.022)
λ_1	Coefficient of peer effects component of λ	0.099 (0.059–0.138)	0.099 (0.059–0.138)	0.099 (0.059–0.138)
α_f	Rate of transition to OAT waiting-list per POUD actively using drugs with a history of OAT at time zero	0.122 (0.112–0.132)	0.138 (0.125–0.153)	0.202 (0.161–0.261)
$\alpha_0^{(f)}$	Spontaneous component of α_f	0.116 (0.105–0.127)	0.125 (0.106–0.142)	0.198 (0.158–0.256)
$\alpha_1^{(f)}$	Coefficient of peer effects component of α_f	0.062 (0.025–0.129)	0.062 (0.025–0.129)	0.062 (0.025–0.129)
α_n/α_f	Rate ratio for transition to OAT waiting-list among OAT-naive POUD to POUD with a history of OAT	0.601 (0.446–0.789)	0.186 (0.101–0.297)	0.233 (0.146–0.342)
Dropout from the OAT waiting-list and opioid use cessation and relapse				
δ	Rate of dropout per individual in the OAT waiting-list due to transitioning to non-waiting-list active opioid use	0.208 (0.158–0.264)	0.148 (0.116–0.186)	0.168 (0.119–0.229)
δ_a	Rate of dropout per individual in the OAT waiting-list due to transitioning to abstinence	0.099 (0.076–0.127)	0.093 (0.065–0.125)	0.099 (0.074–0.130)
γ_n, γ_f	Rate of quitting opioid use (for at least 30 days) per POUD actively using drugs (for reasons other than OAT initiation)	0.099 (0.076–0.127)	0.093 (0.065–0.125)	0.099 (0.074–0.130)
ρ_n	Rate of relapse to active opioid use per abstinent POUD with no history of OAT at time zero	0.267 (0.217–0.326)	0.290 (0.231–0.362)	0.264 (0.209–0.331)
$\rho_0^{(n)}$	Spontaneous component of ρ_n	0.221 (0.173–0.277)	0.221 (0.173–0.277)	0.221 (0.173–0.277)
$\rho_1^{(n)}$	Coefficient of peer effects component of ρ_n	0.277 (0.160–0.454)	0.277 (0.160–0.454)	0.277 (0.160–0.454)
ρ_f	Rate of relapse to active opioid use per abstinent POUD with a history of OAT at time zero	0.301 (0.261–0.351)	0.324 (0.274–0.388)	0.298 (0.252–0.357)
$\rho_0^{(f)}$	Spontaneous component of ρ_f	0.256 (0.216–0.302)	0.256 (0.216–0.302)	0.256 (0.216–0.302)
$\rho_1^{(f)}$	Coefficient of peer effects component of ρ_f	0.277 (0.160–0.454)	0.277 (0.160–0.454)	0.277 (0.160–0.454)
Retention in OAT and site preferences				
μ_s	Rate of treatment dropout (excluding mortality) per OAT patient in specialty care at time zero	0.151 (0.139–0.166)	0.190 (0.155–0.239)	0.145 (0.128–0.167)
$\mu_0^{(s)}$	Spontaneous component of μ_s	0.122 (0.105–0.140)	0.122 (0.105–0.140)	0.122 (0.105–0.140)
$\mu_1^{(s)}$	Coefficient of capacity-dependent component of μ_s	0.319 (0.107–0.600)	0.319 (0.107–0.600)	0.319 (0.107–0.600)
μ_p/μ_s	Rate ratio for treatment dropout among OAT patients in primary to specialty care	0.780 (0.644–0.936)	0.780 (0.644–0.936)	0.780 (0.644–0.936)
u	Probability of at least 30 days of abstinence among people dropping out of OAT	0.320 (0.270–0.372)	0.320 (0.270–0.372)	0.320 (0.270–0.372)

(*Continues*)

Table 1. (Continued)

Notation	*Parameter*	*Kyiv*	*Mykolaiv*	*Lviv*
p	Proportion of POUD in the waiting-list who prefer getting OAT in primary (versus specialty) care	0.535 (0.499–0.571)	0.535 (0.499–0.571)	0.535 (0.499–0.571)
Demographic rates				
υ	Rate of entry into susceptible population (absolute)	5353	667	1053
ξ	Rate of aging out per susceptible individual	0.0236	0.0281	0.0270
m_S	Mortality rate per susceptible individual	0.0021	0.0029	0.0025
m_E	Mortality rate per individual who aged out of susceptible population and did not develop OUD	0.0268	0.0379	0.0322
m_{DU}	Mortality rate among POUD actively using drugs	0.120 (0.092–0.153)	0.120 (0.092–0.153)	0.120 (0.092–0.153)
m_{OAT}	Mortality rate among OAT patients	0.037 (0.031–0.044)	0.037 (0.031–0.044)	0.037 (0.031–0.044)
m_A	Mortality rate among abstinent POUD	0.029 (0.023–0.034)	0.029 (0.023–0.034)	0.029 (0.023–0.034)
Initial conditions (size of compartments at time zero)				
$S(t_0)$	Number of susceptible individuals	144 355 (134341–154 139)	20 483 (17563–23 365)	38 432 (31756–42 813)
$E(t_0)$	Number of individuals who aged out of susceptible population and did not develop OUD	111 878 (111205–112 536)	21 642 (21446–21 836)	31 111 (30662–31 405)
$O_n(t_0)$	Number of POUD with no OAT history, who actively use drugs, and are not in the OAT waiting-list	19 222 (14242–24 466)	6263 (4412–8149)	5386 (2884–9192)
$O_f(t_0)$	Number of POUD with a history of OAT, who actively use drugs, and are not in the OAT waiting-list	1938 (1145–2895)	634 (366–948)	163 (21–370)
$Q(t_0)$	Number of POUD in the OAT waiting-list	9915 (6909–13 369)	792 (443–1232)	1893 (963–3331)
$A(t_0)$	Number of abstinent POUD	10 432 (7315–13 952)	2319 (1435–3303)	2547 (1280–4515)
$B(t_0)$	Number of OAT patients (specialty/primary care)	829 (829/0)	508 (478/30)	142 (142/0)
Health-related quality of life utility weights				
QoL_S	Among susceptible individuals	0.833 (0.830–0.835)	0.833 (0.830–0.835)	0.833 (0.830–0.835)
QoL_E	Among individuals who aged out of susceptible population and did not develop OUD	0.781 (0.777–0.785)	0.781 (0.777–0.785)	0.781 (0.777–0.785)
QoL_A	Among abstinent POUD	0.735 (0.702–0.767)	0.735 (0.702–0.767)	0.735 (0.702–0.767)
QoL_{DU}	Among POUD actively using drugs (compartments O_n, O_f, Q)	0.636 (0.627–0.645)	0.636 (0.627–0.645)	0.636 (0.627–0.645)
ΔQoL_{OAT}	Increase in utility score when receiving OAT compared to active opioid use	0.045 (0.027–0.063)	0.045 (0.027–0.063)	0.045 (0.027–0.063)
Average annual number of injections (zero for compartments S, E and A)				
INJ_{On}	Among POUD with no OAT history who actively use drugs and are not in the OAT waiting-list (compartment O_n)	458 (395–530)	615 (510–744)	525 (461–602)
INJ_{Of}	Among POUD with OAT history who actively use drugs and are not in the OAT waiting-list (compartment O_f)	327 (262–404)	440 (342–559)	376 (304–460)

(***Continues***)

Table 1. (Continued)

Notation	*Parameter*	*Kyiv*	*Mykolaiv*	*Lviv*
INJ_Q	Among POUD in the OAT waiting-list (compartment Q)	443 (390–504)	514 (437–607)	530 (469–603)
INJ_{OAT}	Among OAT patients	36 (19–55)	122 (70–184)	82 (20–163)
Annual cost of OAT slot (2016 $US)				
$cost_s^{(b)}$	Occupied OAT slot in specialty care	306 (186–426)	306 (186–426)	306 (186–426)
$cost_p^{(b)}$	Occupied OAT slot in primary care	392 (239–548)	392 (239–548)	392 (239–548)
$cost_s^{(i)}$	Unoccupied OAT slot in specialty care	66 (40–92)	66 (40–92)	66 (40–92)
$cost_p^{(i)}$	Unoccupied OAT slot in primary care	80 (49–112)	80 (49–112)	80 (49–112)
r	Discount rate for costs and outcomes in the economic evaluation	0.030 (0.016–0.052)	0.030 (0.016–0.052)	0.030 (0.016–0.052)

CI = confidence interval; OAT = opioid agonist treatment; OUD = opioid use disorder; POUD = people with opioid use disorder. All rates are annual; for rates that combine spontaneous and peer effects or capacity-dependent components, the value of the sum corresponds to the size of relevant compartments and OAT capacity at time zero; most of the demographic parameters are entered as constants.

provides detailed description of parameter distributions, assumptions and data sources.

In accordance with recommended practice [44], we assessed uncertainty in economic findings using both cost-effectiveness acceptability frontiers (CEAFs, which depict the probability that the optimal strategy is cost-effective at any given WTP threshold) and cost-effectiveness acceptability curves (CEACs, which show how likely each strategy is to be cost-effective at a given WTP threshold). We examined how our findings vary with OAT cost and PWID population size in each city. CEACs are provided in the Supporting information.

The sensitivity analysis evaluates which model inputs are most important in determining the outcomes. We evaluated the relationship between inputs and outcomes using random forest variable importance estimation [45] and partial rank correlation coefficient [46] methods. Section 6 of the Supporting information provides a description of these methods.

Scenario analysis

We investigated how the CEA results change under the alternative structural assumptions about peer effects in opioid use initiation and relapse, as well as treatment demand keeping these transition rates constant at their baseline values. We refer to this structural model assumption as ‘no peer effects’. In the scenario analysis, we did not relax the conservative assumption of capacity dependence of treatment retention [35,38,47]. We identified the efficient strategies under no peer effects and showed how they relate to the efficient strategies in the base case analysis. The uncertainty analysis under no peer effects was performed for the same capacity increase strategies as the base case.

In the base case, we assumed that the potential contribution of OAT patients to the opioid use initiation and relapse is captured by the constant components of the respective rates. However, insufficient OAT doses may result in concurrent drug injecting [48], suggesting that some OAT patients may exhibit opioid use peer effects. We investigated this scenario assuming a 50% reduction in the intensity of peer effects among OAT patients compared to untreated POUD [31].

To investigate the impact of choosing a 10-year modeling horizon, we additionally performed the CEA over 5- and 20-year periods.

RESULTS

Base case efficient strategies

Among all evaluated OAT capacity increase strategies, 22, 12 and 13 strategies were efficient in Kyiv, Mykolaiv and Lviv, respectively. Figure 2 illustrates the set of evaluated and efficient strategies for Lviv (labeled L1–L13). The next efficient strategy after the current capacity of 142 slots at the beginning of 2016 (L1) corresponds to a maximum capacity of 400 slots at specialty care and current capacity of zero slots at primary care (L2). All capacity increase strategies between L2 (400 slots) and L3 (1750 slots: 400 in specialty and 1350 in primary care) are dominated; however, the ICERs of some of the intermediate increase strategies are only slightly higher than that of L3. Among the intermediate increase strategies of the same total capacity, those allocating the maximum number of slots to specialty care dominate moving some slots to primary care (see lower right corner of Fig. 2). When the overall capacity reaches the level that allows elimination of the waiting-list during the entire modeling period, however, moving some of the slots from specialty to primary care becomes efficient (strategies L7–L13 in the upper left corner of Fig. 2). The largest of the efficient strategies in Lviv (L13) corresponds to 2000 slots, which is a 14-fold

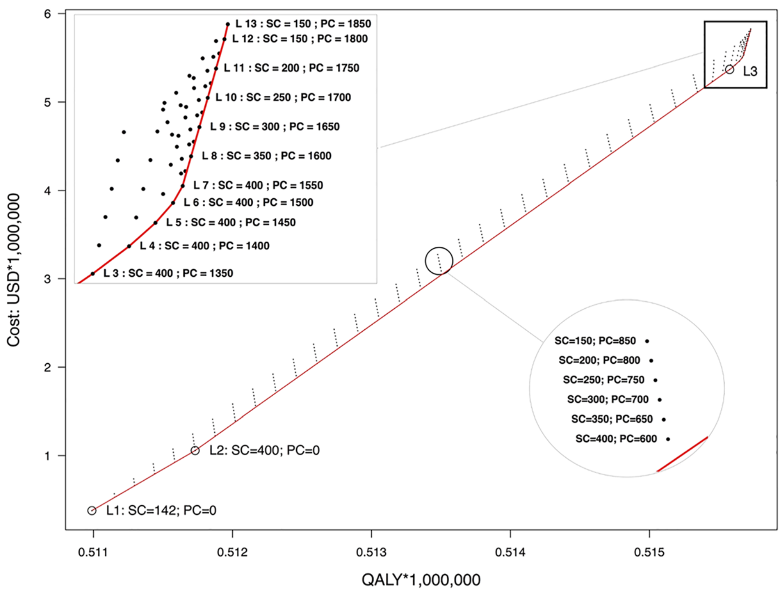

Figure 2 Total cost and quality-adjusted life-years (QALYs) gained for 229 opioid agonist treatment (OAT) capacity increase strategies in Lviv. Each point represents a strategy defined by the number of OAT slots allocated to both specialty (SC) and primary (PC) care. Every cluster of six strategies located between strategies L2 and L3 corresponds to the same total capacity, but different allocation of slots between specialty and primary care (see lower right corner). Horizontal distance between these clusters of strategies is an artifact created by our chosen increment of 50 slots. Red line connects the efficient strategies labeled L1–L13. These labels also provide a cross-reference to the Supporting information, which details the outcomes associated with each efficient strategy, including costs, QALYs gained, injections averted, opioid use initiations prevented, as well as projected coverage of POUD with OAT and capacity utilization. The subset of five strategies selected for further analysis includes: L1 (current capacity), L2 (maximum SC), L3 (minimum efficient mix), L6 (GDP-optimal) and L13 (maximum efficient). [Colour figure can be viewed at wileyonlinelibrary.com]

increase relative to the current capacity. The efficiency frontier plots for Kyiv and Mykolaiv demonstrate a pattern similar to Fig. 2, and are provided in the Supporting information (Figs S2 and S3). The largest efficient strategy in Kyiv corresponds to 10 600 slots (13-fold increase relative to current capacity), and 1300 slots (2.6-fold increase) in Mykolaiv.

In further analyses, we focused on a subset of five efficient strategies in each location: (1) current capacity; (2) maximum SC (increasing capacity to its maximum level at the specialty care facilities, keeping primary care capacity at its current level); (3) minimum efficient mix (increasing capacity to its maximum level in specialty care, while increasing primary care capacity to its lowest efficient level); (4) GDP-optimal (increasing capacity to the fullest extent possible while achieving an ICER that remains below one per-capita GDP WTP threshold); and (5) maximum efficient (increasing capacity to the fullest feasible extent). To illustrate, these five strategies correspond to strategies L1, L2, L3, L6 and L13 in Lviv. We chose these strategies because they span the range of the efficiency frontier and have policy relevance to the decision-makers. The current capacity represents the *status quo*, the maximum SC represents what could maximally be achieved if OAT was only provided in a standard-of-care way, the minimum efficient mix represents the smallest 'intermediate' increase that is efficient, the GDP-optimal represents the optimal choice at the intuitive one per-capita GDP WTP threshold and the maximum efficient represents the most ambitious of all efficient strategies. Table 2 provides a summary of selected strategies by city.

Tables S6–S8 in the Supporting information provide details concerning the estimated outcomes for every efficient strategy by city. Under the assumption of peer effects, the GDP-optimal strategy may prevent 5415 opioid use initiations and may avert approximately 36.4 million injections during 10-year period in Kyiv, 315 initiations and approximately 2.8 million injections in Mykolaiv, and 1049 initiations and approximately 7.4 million injections in Lviv. This strategy corresponds to a 12.2-, 2.4-, and 13.4-fold OAT capacity increase over 2016 baseline in Kyiv, Mykolaiv, and Lviv, respectively.

While all efficient strategies would begin with 100% capacity utilization, for most of these strategies we projected that utilization would eventually drop. In Kyiv, alone, the capacity increase may allow reaching the minimum recommended OAT coverage level of 20% by the end of the modeling period owing to a higher estimated treatment demand relative to Mykolaiv and Lviv. Even under maximum efficient capacity, limited treatment demand is expected to result in OAT coverage of 11 and 17% by the end of 2025 in Mykolaiv and Lviv, respectively.

Uncertainty analysis

Figure 3 summarizes the uncertainty analysis in Lviv. The top row shows the optimal strategy and the probability that this strategy is cost-effective under the base case

Table 2 Summary of the selected opioid agonist treatment (OAT) capacity increase strategies.

	Kyiv				*Mykolaiv*				*Lviv*			
Strategy	*Slots in specialty care*	*Slots in primary care*	*ICER/QALY, $US (peer effects)*	*ICER/QALY, $US (no peer effects)*	*Slots in specialty care*	*Slots in primary care*	*ICER/QALY, $US (peer effects)*	*ICER/QALY, $US (no peer effects)*	*Slots in specialty care*	*Slots in primary care*	*ICER/QALY, $US (peer effects)*	*ICER/QALY, $US (no peer effects)*
Current capacity	829	0	–	–	478	30	–	–	142	0	–	–
Maximum SC	1500	0	919	1449	600	30	937	1368	400	0	917	1454
Minimum efficient mix	1500	7800	1109	2753	600	525	1199	2512	400	1350	1119	2237
GDP-optimal	1500	8600	2011	not efficient	600	625	2025	4279	400	1500	1904	5816
Maximum Efficient	900	9700	12 424	not efficient	500	800	14 631	not efficient	150	1850	7824	not efficient

ICER = incremental cost-effectiveness ratio; QALY = quality-adjusted life-year; SC = specialty care; PC = primary care. ICER is reported as $US per QALY. Costs and QALYs were discounted at an annual rate of 3%. Strategies: (1) current capacity, L1; (2) maximum SC, L2 (increases capacity to its maximum level in specialty care facilities, keeping primary care capacity at its current level); (3) minimum efficient mix, L3 (increases capacity to its maximum level in specialty care facilities, while increasing primary care capacity to its lowest efficient level); (4) GDP-optimal, L6 (increases capacity to the fullest extent possible while achieving an ICER that remains below one per-capita gross domestic product (GDP) willingness-to-pay (WTP) threshold); and (5) maximum efficient, L13 (increases capacity to the fullest feasible extent).

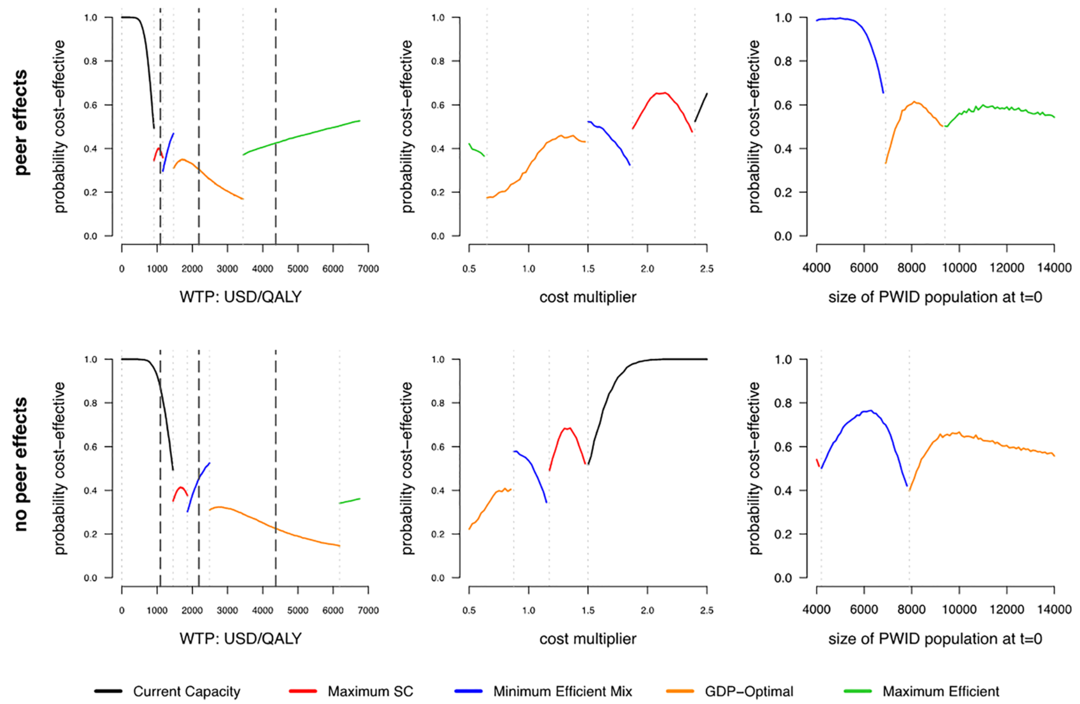

Figure 3 Optimal strategies in Lviv under the assumption of 'peer effects' (top row) and 'no peer effects' (bottom row). The plots show the cost-effectiveness acceptability frontier: the probability that the optimal strategy is cost-effective at a given willingness-to-pay (WTP) threshold. Left column shows optimal strategies as a function of the WTP per quality-adjusted life-year (QALY) (long-dashed lines correspond to the half, one and two per-capita gross domestic product (GDP) WTP thresholds). Middle column shows the optimal strategies as a function of opioid agonist treatment (OAT) cost (the same multiplier is applied to four OAT cost point estimates from Table 1). Right column shows the optimal strategies as a function of people who inject drugs (PWID) population size at time zero (set to 7400 in the base case analysis). In the middle and right columns, the WTP threshold was set to one per-capita GDP ($US 2185 in 2016). OAT capacity corresponding to each strategy is given in Table 2. Similar plots for Kyiv and Mykolaiv are presented in sections 4 and 5 of the Supporting information. [Colour figure can be viewed at wileyonlinelibrary.com]

assumptions of peer effects in opioid use initiation and relapse, and capacity dependence of treatment demand and retention. The left column shows how the optimal strategy changes as a function of the WTP threshold, the middle column as a function of OAT cost at one per-capita GDP threshold, and the right column as a function of baseline PWID population size at the same WTP. Figures S5–S7 in the Supporting information provide similar analysis at a half and two GDP thresholds, include all three cities and show CEACs as a function of the WTP in addition to CEAF shown in Fig. 3.

For WTP values greater than half per-capita GDP, the optimal choice is generally between three substantial capacity increase strategies: minimum efficient mix, GDP-optimal and maximum efficient, while maximum SC and current capacity strategies only become plausible policy options at the very low WTP thresholds. A combination of cost per OAT slot and the WTP threshold have the most substantial impact on the choice of optimal strategy (Supporting information, Fig. S6). Uncertainty concerning the size of the PWID population would only lead the decision-maker to choose between the minimum efficient mix, GDP-optimal and maximum efficient strategies unless the WTP threshold is very low (Supporting information, Fig. S7).

The sensitivity analysis shows that the outcomes of different strategies are sensitive to different inputs (see section 6 of the Supporting information for details). The outcomes of maximum SC and minimum efficient mix strategies are most sensitive to the peer effects component of the opioid use initiation rate, mortality among POUD, improvement in health utility when in OAT and the discount rate. The outcomes of minimum efficient mix, GDP-optimal and maximum efficient strategies are primarily influenced by the OAT demand and the PWID population size. Outcomes of all strategies are sensitive to the OAT cost.

Scenario analysis: no peer effects, role of OAT patients and modeling horizon

In the absence of peer effects, the attractiveness of more aggressive strategies is diminished. The ICER of the minimum efficient mix strategy under no peer effects is approximately twice that under the base case assumptions, and the maximum efficient strategy no longer belongs to the efficiency frontier (Table 2 and Tables S9–S11 in the Supporting information).

The bottom row of Fig. 3 shows the results of the uncertainty analysis in Lviv under no peer effects, and Supporting information, Figs S11–S13 provide details for other cities. Under no peer effects, a wide range of WTP thresholds yields minimum efficient mix or GDP-optimal strategy as optimal, and the minimum efficient mix has the highest probability of being cost-effective at both one and two per-capita GDP thresholds (Supporting information, Fig. S11). At the half GDP threshold and constant rates, the current capacity strategy would be optimal for any PWID population size (Supporting information, Fig. S13), and unless the actual OAT cost is approximately 25% lower than our point estimate (Supporting information, Fig. S12).

When we assumed that OAT patients might exhibit some peer effects in opioid use, but those effects were less important relative to untreated POUD, the cost-effectiveness of OAT scale-up strategies landed somewhere between the base case peer effects and no peer effects assumptions. Supporting information, Tables S12–S14 show the efficient strategies under this scenario.

Our choice of a 10-year modeling horizon was intended to balance between allowing enough time to observe the long-term intervention effects and making reasonable assumptions about some parameter values being constant over time. Using 5- and 20-year modeling horizons did not substantially change the results. Longer modeling horizons resulted in the intermediate increase strategies being more cost-effective. The ICER of the GDP-optimal strategy showed little sensitivity to the choice of modeling horizon (see section 5 of the Supporting information).

DISCUSSION

A large body of evidence confirms that OAT is a cost-effective strategy for treating OUD [5]. OAT has additional benefits, including reducing blood-borne infections such as HIV and HCV through reducing drug injection [4] and enhancing treatment as prevention efforts [49,50]. However, OAT scale-up has been suboptimal in Ukraine (and throughout eastern Europe and central Asia), a financially challenged country with multiple individual and structural barriers to OAT access that, if removed, would greatly benefit public health [51]. In this study, we conducted a CEA of the OAT scale-up in three diverse regions of Ukraine—Kyiv, Mykolaiv and Lviv—using a novel dynamic model of opioid use initiation, demand for and receipt of OAT. The potential peer effects related to opioid use and recent evidence of the effectiveness of OAT in reducing injection initiations motivated the adoption of a 'treatment as prevention' approach to address opioid epidemics [30,31]. To our knowledge, we have made the first attempt to incorporate a 'treatment as prevention' paradigm to dynamically model OUD and conduct the CEA of OAT, extending potential benefits of addiction treatment from the individual to the community level via reduction in drug use initiation and relapse. Three key findings emerged from our analyses.

First, given the current structural and cultural barriers to accessing OUD treatment, increasing OAT capacity from an overall low average of 3 to 24, 12 and 19% of the estimated number of POUD in Kyiv, Mykolaiv and Lviv, respectively, would fully satisfy the demand for OAT within less than a year. Although some treatment slots would remain unoccupied for most of the modeling horizon, this strategy would be optimal at the WTP threshold of one per-capita GDP per QALY gained. At the end of a 10-year modeling period, 20, 11 and 17% of POUD would be receiving OAT in Kyiv, Mykolaiv and Lviv, respectively. WHO defines mid-level OAT coverage to be 20–40%; the recommended high-level coverage exceeds 40% of POUD [15]. Even mid-level OAT coverage may be unattainable in Ukraine unless stigma is reduced and barriers such as name-based registries, daily supervision requirements, inconvenience and police harassment are eliminated [13,14,34,52]. Some of these barriers, such as stigma, inconvenience and police harassment, may be overcome by expanding OAT to primary care settings. Moreover, even modest OAT capacity increases are not feasible if only specialty addiction clinics provide treatment. It is therefore essential that OAT be expanded to primary care settings—an intervention shown to be effective in many countries [10] and both legal and feasible in the Ukrainian context [11].

Secondly, OAT scale-up planning requires city-specific estimation of demand, which drives the differences in recommended scale-up strategies between regions in our analysis. Utilization of treatment slots is determined by the dynamics of waiting-lists, including demand, waiting-list dropout rate and retention in treatment. Better estimates of slot utilization are necessary inputs for evaluating the cost-effectiveness of treatment capacity increase strategies. Our analysis shows that, despite waiting-list dropouts, the capacity increases under the minimum efficient mix strategy that is expected to eliminate the waiting-lists in approximately 2–3 years, correspond to 84, 79 and 89% of the estimated unsatisfied demand at baseline in Kyiv, Mykolaiv and Lviv, respectively. Several regions of Ukraine have recently introduced prescription-based, take-home OAT for stable patients [8]. While the potential changes in OAT demand as a result of better OAT accessibility remain unknown, it would probably make the results of our analysis more conservative.

Finally, policy recommendations resulting from our analysis are robust to parametric uncertainty and structural assumptions related to density dependence. Despite the uncertainty around the model inputs, in all three locations the optimal choice is between the minimum efficient mix, the GDP-optimal and the maximum efficient strategies for a wide range of WTP thresholds under either structural model assumptions. These three strategies are similar in terms of the number of slots, costs and benefits, which results in a straightforward policy recommendation at a given WTP threshold. If peer effects are absent or weak, the estimated ICER under the minimum efficient mix strategy is approximately $US 2200–2700 per QALY gained—just above the 2016 Ukraine per-capita GDP. If, however, peer effects exist the OAT scale-up interventions become even more cost-effective, and the minimum efficient mix strategy may result in as low as approximately $US 1100–1200 per QALY gained. This makes this strategy a safe and conservative capacity increase option for a decision-maker. Budget limitations, however, may prohibit the implementation of the minimum efficient mix strategy unless some or all the costs are transferred to the consumer. In this case, any intermediate capacity increase between the maximum SC and the minimum efficient mix would be a reasonable decision. Allocation of the maximum feasible number of slots to specialty care and as many as the budget allows to primary care would result in the ICER that is only slightly bigger than that of the minimum efficient mix strategy.

Findings from this study are informative to multiple stakeholders. In Ukraine, the Ministry of Health is responsible for financing and regulations regarding government-sponsored OAT provision and must address the burgeoning opioid epidemic by increasing OAT capacity and eliminating structural barriers to OAT access. Regional Health Departments are responsible for evaluating the OAT capacity need and identifying settings to provide treatment. Our analysis shows that efficient OAT delivery requires expansion to primary care clinics, as has been performed effectively elsewhere [10]. For international donors such as the President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), who continue supporting HIV treatment and prevention efforts, linking continued funding to attainment of OAT scale-up goals is crucial. Globally, strategies that guide OAT scale-up have important implications beyond Ukraine to countries with HIV epidemics driven by PWID that have failed to achieve prevention targets (e.g. Malaysia, Indonesia) and emerging HIV epidemics in PWID (e.g. Tanzania, Kenya).

Despite many important findings, there remain several limitations. Structural assumptions about potential peer effects in opioid use initiation and treatment demand are intended to capture the population dynamics of opioid addiction more effectively. The spillover effects of individual decisions, however, extend beyond these areas. More comprehensive analyses could incorporate the heterogeneity among individuals who do and do not access treatment, and the behavioral and risk implications of changing network characteristics in response to the actions of others. While we attempted to calibrate the model using the best available empirical data from recent studies in Ukraine and from the literature, parameter estimates could be biased. Further inquiry is needed to understand both the structure and the dynamics of this complex system more clearly.

Overall, our model represents a conservative approach. While our estimated cost of OAT provision does not include downstream costs related to diagnosis and treatment of HIV and other infections, we assume that the cost of an untreated individual is zero. This is a conservative assumption, given costs associated with higher rates of overdose and emergency room utilization among untreated POUD compared to those receiving OAT [37] and, while our model includes societal benefits related to opioid use initiation and relapse, it does not directly capture averted HIV and HCV infections. Thus, our analysis probably underestimates the full potential benefits of OAT. Future studies might incorporate a wider range of costs and benefits, including criminal activity, employment and transmission of blood-borne infections.

In conclusion, this modeling study provides city-specific estimates of the cost-effectiveness of OAT scale-up in three cities of Ukraine. While this study supports a substantial scale-up for a wide range of WTP thresholds across all locations, specific recommendations differ by city due to differences in treatment demand. Achieving internationally recommended OAT coverage targets would require addressing structural barriers to OAT access beyond the capacity limitations.

Declaration of interests

All authors receive grants from the US National Institutes of Health. F.L.A. additionally receives grants from SAMHSA and HRSA. F.L.A. receives consulting fees and speaker honoraria from Gilead Sciences, Merck, Clinical Care Option and Simply Speaking HIV, all of which are not related to any content of this research.

Acknowledgements

This study was supported by the National Institute on Drug Abuse grants: R36 DA042643 (OM), K24 DA017072 (F.L. A.), R01 DA033679 (F.L.A.), R01 DA043125 (F.L.A.), and R01 DA015612 (A.D.P., Principal Investigator: Douglas K. Owens); National Institute of Mental Health grant R01 MH105203 (A.D.P.); and NIH Office of Director grant DP2 HD091799 (F.W.C.). Computational support was provided by Yale Center for Research Computing. The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript. We thank Sergii Dvoryak (Ukrainian Institute on Public Health Policy, UIPHP), Kostyantyn Dumchev (UIPHP), Iryna

Pykalo (UIPHP) and Sergii Filippovich (Alliance for Public Health) for providing additional data that made this analysis possible and for local expertise on the Ukrainian context. We are grateful to Jeremy Goldhaber-Fiebert, Edward H. Kaplan, Reza Yaesoubi, Alexei Zelenev, Natalia R. Kunst and Jorge Alfaro Murillo for helpful comments and discussion.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

[Correction added on 7 November 2019 after first online publication: The Supporting Information has been amended in this version.]

Replication code for the analysis presented in this paper, as well as a sample from the joint distribution of model parameters are available at https://github.com/olyamorozova/oat-capacity.

Figure S1 Schematic of the dynamic model of opioid epidemic, and demand for and access to treatment.
Figure S2 Set of 687 analyzed strategies (black dots) and the efficiency frontier (red line) in Kyiv under base case assumptions.
Figure S3 Set of 161 analyzed strategies (black dots) and the efficiency frontier (red line) in Mykolaiv under base case assumptions.
Figure S4 Set of 229 analyzed strategies (black dots) and the efficiency frontier (red line) in Lviv under base case assumptions.
Figure S5 CEACs (top row) and CEAF (bottom row) of the current and four OAT capacity increase strategies as a function of the WTP per incremental QALY gain under the base case modeling assumptions.
Figure S6 CEAF of the current and four OAT scale-up

strategies as a function of the OAT cost at the WTP threshold of USD 1093 (top row); USD 2185 (middle row), and USD 4370 (bottom row) under the base case modeling assumptions.

Figure S7 CEAF of the current and four OAT capacity increase strategies as a function of the baseline PWID size estimate at the WTP threshold equal to USD 1093 (top row); USD 2185 (middle row), and USD 4370 (bottom row) under the base case modeling assumptions.

Figure S8 Projected dynamics of the selected model features in Kyiv under the base case modeling assumptions.

Figure S9 Projected dynamics of the selected model features in Mykolaiv under the base case modeling assumptions.

Figure S10 Projected dynamics of the selected model features in Lviv under the base case modeling assumptions.

Figure S11 CEACs (top row) and CEAF (bottom row) of the current and four OAT scale-up strategies as a function of the willingness-to-pay (WTP) per QALY gain, when peer effects are not assumed.

Figure S12 CEAF of the current and four OAT capacity increase strategies as a function of the OAT cost under no peer effects assumption. Three WTP thresholds are considered: half per capita GDP of USD 1093 (top row); one per capita GDP of USD 2185 (middle row), and two per capita GDP of USD 4370 (bottom row).

Figure S13 CEAF of the current and four OAT capacity increase strategies as a function of the baseline PWID size estimate when peer effects are not assumed. Three WTP thresholds are considered: half per capita GDP of USD 1093 (top row); one per capita GDP of USD 2185 (middle row), and two per capita GDP of USD 4370 (bottom row).

Figure S14 Relative importance of model parameters calculated using random forest variable importance estimation.

Figure S15 Model parameter sensitivity using partial rank correlation coefficient.

Table S1 Model parameters notation

Table S2 Summary of the 'first-level' modeling parameters

Table S3 Characteristics of the selected locations

Table S4 Summary of candidate OAT capacity increase strategies

Table S5 Selected OAT capacity increase strategies

Table S6 Efficiency frontier with respect to QALYs gain of OAT capacity increase strategies in Kyiv: base case analysis

Table S7 Efficiency frontier with respect to QALYs gain of OAT capacity increase strategies in Mykolaiv: base case analysis

Table S8 Efficiency frontier with respect to QALYs gain of OAT capacity increase strategies in Lviv: base case analysis

Table S9 Efficiency frontier with respect to QALYs gain of OAT capacity increase strategies in Kyiv assuming no peer effects.

Table S10 Efficiency frontier with respect to QALYs gain of OAT capacity increase strategies in Mykolaiv assuming no peer effects.

Table S11 Efficiency frontier with respect to QALYs gain of OAT capacity increase strategies in Lviv assuming no peer effects.

Table S12 Efficiency frontier with respect to QALYs gain of OAT capacity increase strategies in Kyiv assuming that OAT patients exhibit peer effects in opioid use initiation and relapse.

Table S13 Efficiency frontier with respect to QALYs gain of OAT capacity increase strategies in Mykolaiv assuming that OAT patients exhibit peer effects in opioid use initiation and relapse.

Table S14 Efficiency frontier with respect to QALYs gain of OAT capacity increase strategies in Lviv assuming that OAT patients exhibit peer effects in opioid use initiation and relapse.

Table S15 Efficiency frontier with respect to QALYs gain of OAT capacity increase strategies in Kyiv under the base case structural model assumptions and a 5 - year modeling horizon.

Table S16 Efficiency frontier with respect to QALYs gain of OAT capacity increase strategies in Kyiv under the base case structural model assumptions and a 20 - year modeling horizon.

Table S17 Efficiency frontier with respect to QALYs gain of OAT capacity increase strategies in Mykolaiv under the base case structural model assumptions and a 5 - year modeling horizon.

Table S18 Efficiency frontier with respect to QALYs gain of OAT capacity increase strategies in Mykolaiv under the base case structural model assumptions and a 20 - year modeling horizon.

Table S19 Efficiency frontier with respect to QALYs gain of OAT capacity increase strategies in Lviv under the base case structural model assumptions and a 5 - year modeling horizon.

Table S20 Efficiency frontier with respect to QALYs gain of OAT capacity increase strategies in Lviv under the base case structural model assumptions and a 20 - year modeling horizon.