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Evaluating the Impact of Increased Dispensing of Opioid Agonist Therapy Take-Home Doses on Treatment Retention and Opioid-Related Harm among Opioid Agonist Therapy Recipients: A Simulation Study

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Abstract: Modified opioid agonist therapy (OAT) guidelines that were initially introduced during the COVID-19 pandemic allow prescribers to increase the number of take-home doses to fulfill their need for physical distancing and prevent treatment discontinuation. It is crucial to evaluate the consequence of administering higher take-home doses of OAT on treatment retention and opioid-related harms among OAT recipients to decide whether the new recommendations should be retained post-pandemic. This study used an agent-based model to simulate individuals dispensed daily or weekly OAT (methadone or buprenorphine/naloxone) with a prescription over a six-month treatment period. Within the model simulation, a subset of OAT recipients was deemed eligible for receiving increased take-home doses of OAT at varying points during their treatment time course. Model results demonstrated that the earlier dispensing of increased take-home doses of OAT were effective in achieving a slightly higher treatment retention among OAT recipients. Extended take-home doses also increased opioid-related harms among buprenorphine/naloxone-treated individuals. The model results also illustrated that expanding naloxone availability within OAT patients' networks could prevent these possible side effects. Therefore, policymakers may need to strike a balance between expanding access to OAT through longer-duration take-home doses and managing the potential risks associated with increased opioid-related harms.

Keywords: agent-based modelling; opioid agonist therapy; COVID-19-related public health order; methadone; buprenorphine/naloxone; retention in opioid agonist therapy; opioid-related harms

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1. Introduction

Opioid agonist therapy (OAT) utilizes methadone or buprenorphine/naloxone to prevent withdrawal in individuals exhibiting opioid use disorder (OUD) [1–3] and elevate treatment retention, as achieving this goal is linked with a decreased risk of suffering from an overdose [3,4]. However, due to its low treatment retention rate, OAT is often underutilized [5–9]. OAT recipients are required to frequently visit their prescribing doctors until they qualify for an increased dispensing of opioid agonist therapy take-home doses. Under these circumstances, many patients either decline treatment or are not retained in the treatment for sufficiently long enough to secure approval for graduated numbers of their take-home doses [9,10].

In the context of COVID-19-related healthcare delivery modifications [11], in some jurisdictions, regular access to OAT and retention in treatment were further disrupted [12,13], raising the risk of overdose and death for individuals who discontinue OAT [3,13]. This pandemic experience calls for procedures and policies that guarantee constant access to OAT. New guidance for expanded access to OAT during the COVID-19 pandemic was approved across several countries, including in the US and Canada [14,15]. In Ontario,

this guidance supported an increase in the number of take-home doses for individuals who may have been eligible under the existing treatment guidelines [15]. Expanded access to OAT during the COVID-19 pandemic may lead to a high treatment adherence [16,17]. However, it is not clear whether this new guideline for administering higher take-home doses of OAT will still be beneficial as the world moves beyond the unique circumstances of the COVID-19 pandemic.

Methadone and buprenorphine/naloxone are both opioid agonist medications used in the treatment of opioid addiction. Methadone, a synthetic opioid agonist medication, has a long-lasting effect and helps alleviate withdrawal symptoms and reduce cravings [18]. Buprenorphine/naloxone is an oral medication that combines buprenorphine and naloxone, with a higher concentration of buprenorphine compared to naloxone. Buprenorphine acts as a partial opioid agonist, helping to reduce withdrawal symptoms and cravings, while the naloxone in buprenorphine/naloxone serves as a deterrent against misuse. When taken orally as prescribed, naloxone has a limited impact due to poor absorption in the gastrointestinal tract. However, if buprenorphine/naloxone is misused via injections, naloxone becomes active and can block the effects of other opioids as a result [19]. In emergency situations that require the rapid reversal of an opioid overdose, naloxone, as a potent opioid antagonist on its own, is typically administered via routes such as intranasal, intramuscular, intravenous, or subcutaneous means. These routes facilitate faster absorption rates and immediate effects, allowing for a more rapid response to the medication and effectively reversing the overdose. Hence, considering the differences in the concentrations of buprenorphine and naloxone within this combination and administration method, the naloxone present in buprenorphine/naloxone is insufficient to effectively reverse an overdose on its own [20].

Computational simulation models [21] are efficient tools for evaluating the possible effects of different intervention strategies and are used for better understanding the mechanisms underlying the observed trends. Agent-based modelling [22] is one of the primary types of computational simulation methods employed in the field of public health, with that choice being generally being dependent on the research question and the scope of the respective study. Agent-based models can highlight heterogeneous properties with ease, reflect individual-level behaviours, and generate potential health consequences and histories as a result of such behaviours. Although there are several simulation models that exist for studying OAT [23–29], the current study is the first agent-based model simulation to assess the impact of increased dispensing of take-home doses of OAT utilizing data sources from Canadian OAT recipients. In the present study, an agent-based model can capture a clear understanding of the trajectory of patients using methadone or buprenorphine/naloxone for OAT and investigate the potential effects of administering higher take-home doses of OAT on treatment retention and opioid-related harms among OAT recipients.

The primary objectives of this study were to evaluate the impact of increased dispensing of take-home doses of methadone and buprenorphine/naloxone on treatment retention and opioid-related harm among OAT recipients, and to examine the health consequences of whether the new guidelines for administering higher take-home doses of OAT should be continued in the future. Furthermore, this study aimed to investigate the effect of fostering a supportive environment within OAT communities. While previous research has documented varying effects of peers on individuals undergoing opioid agonist treatment, such as deterring prescription refills [30,31] or, conversely, providing assistance during overdose events to reduce opioid-related harm [32,33], the secondary objective of this study was to explore the effects of promoting a peer support network within OAT communities, with a specific focus on the involvement of naloxone-equipped peers during opioid overdose emergencies [34,35]. The remainder of this paper is organized as follows: Section 2 describes the model, including agent-based modelling, and the experimental design. Section 3 elucidates the results. Section 4 includes the corresponding discussion and concludes the paper.

2. Materials and Methods

The impact of the clinical decision to increase the number of take-home doses of OAT and patient outcomes among OAT recipients was investigated using an agent-based model. This study presents the dynamics of individuals' behaviors actively treated with OAT (methadone or buprenorphine/naloxone). Data for the agent-based model presented in this work was obtained from a detailed study from the Institute for Clinical Evaluative Sciences (ICES) [36], which captured many relevant health variables for Ontario residents [17]. The simulation software AnyLogic Version 8.8.0 [37] was used to create the model.

2.1. Agent-Based Modelling

The use of agent-based modelling in this study supports scenario-based assessments of the impact of the increase in the dispensing of OAT take-home doses on treatment retention and opioid-related harms among individuals receiving daily or weekly dispensed OAT. The model used in this study featured a single type of agent, representing an individual experiencing an opioid use disorder (OUD).

Within the model, individuals experiencing opioid use disorder were endowed with sociodemographic characteristics that influence their possible peer network, including the location of residence (urban or suburb) and neighborhood income quintile. OUD behaviour is governed using two state charts which are depicted in Figure 1. These state charts characterize the possible state space for individuals experiencing OUD whether they are undergoing treatment or not.

The treatment state chart represents the dynamics of the treatment options available for each individual experiencing an OUD. Individuals experiencing an OUD are out of treatment if they never choose a treatment or have discontinued the previous one. An individual who has never previously entered treatment can choose either methadone or buprenorphine/naloxone treatment. Further, patients are dispensed OAT in a daily or weekly manner, which is equivalent to a one-day supply or 5–6 days supply for all prescriptions, respectively. Individuals are classified among these four groups based on historical distributions [17]. During each visit to a physician for OAT, individuals who do not possess naloxone have the opportunity to obtain a naloxone kit, which can be used to assist their peers in the event of an opioid overdose.

Every patient in these four subsets of treatment have the potential to experience treatment disruption. The model treats such disruptions as being of two types: gaps in therapy from 5 to 14 days, respectively, are classed as interruptions, while those of more than 14 days are termed as treatment discontinuations and lead the patient to enter the out-of-treatment state. There are specific hazard rates governing individuals in each treatment type and leading to occurrence of an opioid overdose, opioid-related death, and all-cause death based on historical data [17]. Treatment retention is viewed as having been successfully achieved when the patient enters the post-treatment state after 6 months of therapy without any interruptions.

The illicit opioid use status state chart reflects the various illicit opioid use stages determined by treatment through which each OAT recipient progresses, including uncontrolled illicit opioid use, restricted opioid use while under treatment, and stopping illicit opioid use while in a post-treatment stage. While an OAT recipient is in an in-treatment restriction state, they have a probability of being deemed eligible for dispensing of increased take-home doses of OAT, based on historical distributions [17].

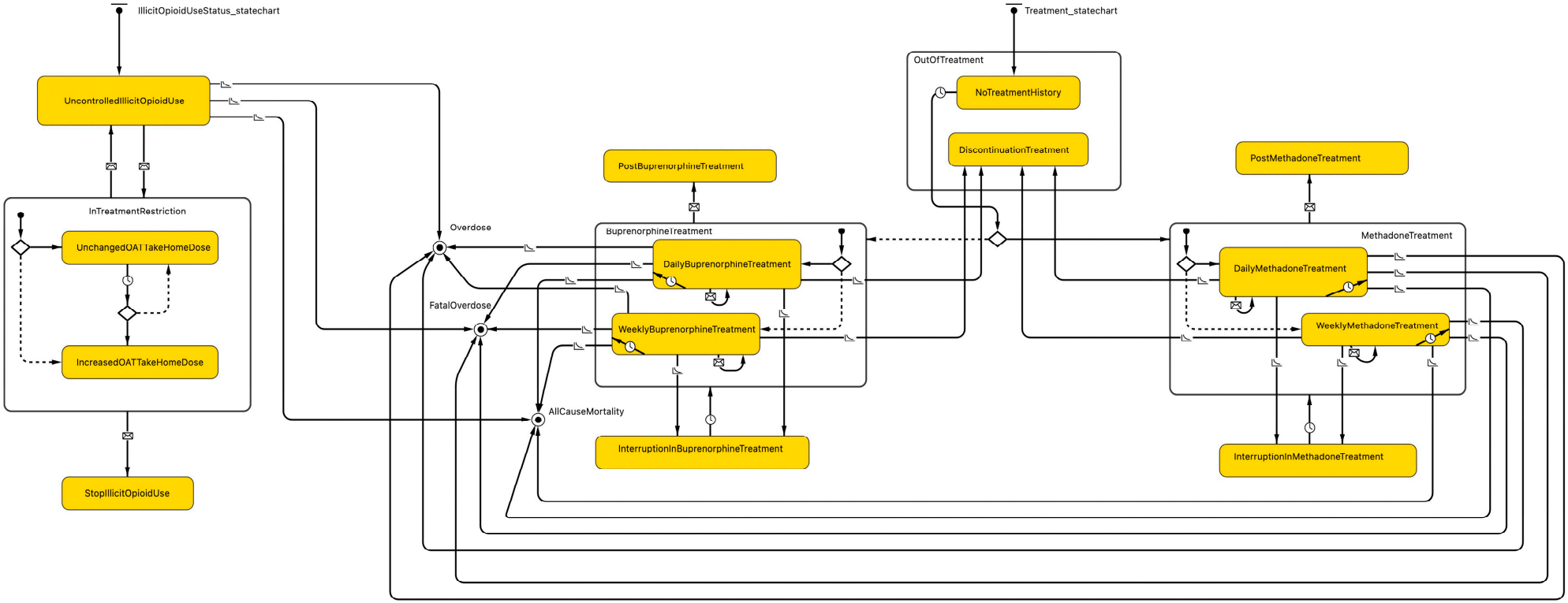

Figure 1. Patient receiving OAT state chart structure. When viewed in a landscape mode, the treatment state chart is positioned to the **right** while the illicit opioid use status state chart is to the **left**.

Among the daily buprenorphine/naloxone recipients without any change in their dose status, they are required to make daily visits to the clinic to receive their dispensed take-home doses. Additionally, for those with a change in their take-home dose status, their visits are scheduled every 14 days. Similarly, among the weekly buprenorphine/naloxone recipients with no change in their dose status, they are required to make weekly visits to the clinic to obtain their dispensed take-home doses. For individuals with a change in their take-home dose status, their visits are scheduled every 14 days. In a comparable manner, methadone daily recipients with no change in their dose status have daily visits to the clinic to receive their dispensed take-home doses. However, for those with a change in their take-home dose status, their visits occur every other day. Methadone weekly recipients without any change in their dose status make weekly visits to the clinic to receive their dispensed take-home doses. In contrast, for individuals with a change in their take-home dose status, their visits are scheduled every 14 days.

As policymakers may consider implementing targeted interventions or additional support measures for patients at a higher risk of opioid-related harms due to an increased dispensing of OAT, this study simulated the creation of a supportive peer network among patients to enhance the access to naloxone kits for overdose prevention. Therefore, considering agent heterogeneity and preferential attachment, a network was constructed with multiple disconnected components, wherein OAT recipients, regardless of changes in their take-home dose, have the potential to acquire a naloxone kit when attending to receive their dispensed OAT; that kit can then be used to reverse overdoses amongst other patients in their network.

2.2. Network

To simulate the possibility of a patient receiving naloxone administration from their peers in the case of an opioid overdose, a network exhibiting preferential attachment was implemented between patients. Within this network, it was assumed that an individual (ego) is always intended to connect with alters in the same location of residence, neighborhood income, and treatment type. In order to achieve this objective, the network construction process underwent two steps. First, an Erdos–Renyi network [38] was established connecting each ego with an average number of 15 candidate alters. Second, candidate alters that did not meet the desired criteria of having the same residence location, neighborhood income, and treatment type were then promptly removed, resulting in the formation of a network exhibiting a preferential attachment composed of multiple disconnected components. Figure 2 illustrates the distribution of the final network.

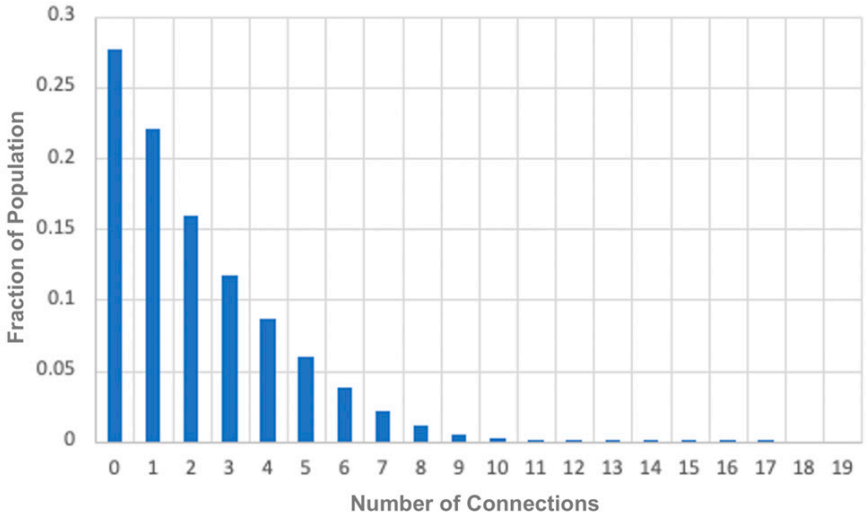

Figure 2. The degree distribution for each individual's social circle induced through the network construction process.

2.3. Outcome Measures

Primary model outcome measures were set as cumulative opioid overdoses, cumulative opioid-related deaths, and cumulative treatment retention among people treated with methadone or buprenorphine/naloxone over six months of treatment without any interruptions.

2.4. Parameterization and Validation

The model was parameterized with assumptions characteristic of the Ontario adult population experiencing OUDs and simulates a population of 50,000 individuals enrolled in OAT. The main source of data for parameterization was a published original investigation [17] which utilized the narcotics monitoring system database and the ICES repository to detect prescription claims for OAT in Ontario between March 2020 and October 2020, respectively.

Despite the uncertainties associated with the data values presented by the authors of [17], due to the restrictions in the study population, the potential influence of pandemic-related factors, and the possibility of changes in take-home dose dispensing patterns [17], these data deliver a significant level of value in informing for the current study. Table A1 presents a summary of the parameters for the patients receiving methadone or buprenorphine/naloxone treatment either on a daily or weekly basis and considers their eligibility for changes in take-home doses of OAT. The parameters were reported in terms of the rates per year and include opioid overdose, discontinuation and interruption of therapy, all-cause mortality, and opioid-related deaths that are based on the parameterizations postulated by the authors of [17]. Table A1 shows that—with the notable exception of weekly methadone patients eligible for increased take-home doses—methadone patients generally have higher opioid overdose rates compared to buprenorphine/naloxone patients. This suggests that buprenorphine/naloxone may have a lower risk of overdose compared to methadone, potentially due to its partial agonist properties. Table A1 also indicates that buprenorphine/naloxone patients exhibit higher rates of therapy discontinuation and interruption compared to methadone patients across different settings. This could be attributed to buprenorphine/naloxone being less effective for certain individuals in managing their opioid dependency along with the limited availability of buprenorphine/naloxone treatment providers and clinics. Additionally, within Table A1, in cases where the number of deaths among recipients was small ($\leq$5), either all-cause mortality or opioid-related mortality was treated as 0.001. However, the all-cause mortality and opioid-related death rates generally appeared to be higher for methadone patients, particularly for those who were not eligible for increased take-home doses. The data presented in Table A1 was then utilized to specify the transition rates, such as the opioid overdose rate, discontinuation rate of therapy, interruption rate in therapy, all-cause mortality rate, and opioid-related death rate, for each of the two different methadone or buprenorphine/naloxone recipient sub-state charts depicted in Figure 1.

Table A2 provides insights into the socio-demographic factors related to the patients of interest, including their urban location of residence and neighborhood income quintile [17]. This table showcases the distribution of patients residing in urban areas across various treatment groups and their eligibility for increased take-home doses. The data presented in Table A2 reveals that the majority of patients, irrespective of the medication type, reside in urban areas. This may suggest a higher number of opioid users living under urban settings and potentially indicates that opioid treatment programs may be more accessible and concentrated in these areas. Further, in most cases (except for weekly methadone patients not eligible for increased take-home doses) methadone patients have a higher percentage of individuals from urban areas compared to buprenorphine/naloxone patients. This may reflect accessibility or availability advantages in securing methadone treatment across urban settings. Table A2 also highlights the distribution of patients based on their eligibility for increased take-home doses. In general, patients who are eligible for increased take-home doses tend to exhibit higher levels of urban dwelling compared to those who are not eligible. This finding suggests that increased take-home doses may be more commonly provided to patients living in urban settings, potentially indicating a higher likelihood of meeting

the criteria for extending take-home doses among patients in urban areas. Additionally, Table A2 presents the distribution of patients based on neighborhood income levels. The declining percentage of patients as one moves from the lowest to the highest income category implies a potential lower prevalence of extensive opioid use and/or individuals seeking opioid agonist treatment in higher-income neighborhoods. When interpreting this result, it is important to consider the difference between the total population residing in the urban areas and rural areas. Additionally, the distribution of individuals across the different neighborhood income levels should also be considered. The data presented in Table A2 was utilized to define the custom distributions for the residence location and neighborhood income of the diverse agents in the model.

Table A3 provides an overview of the remaining parameters, which involve different treatment types, varying disposal timings, and the potential for changes in the disposal time [17]. The parameters listed in Table A3 were utilized as custom distributions to initialize the model and as parameters for implementing the interventions during model simulation. Furthermore, Table A3 includes parameters that are specifically relevant to opioid users outside OAT settings, for which the assumptions have been grounded in the relevant literature. These parameters, such as the opioid overdose rate per year, all-cause mortality rate per year, and opioid-related death rate per year, have been utilized to determine the transition rates in the illicit opioid use state chart, depicted as a sub-state chart in Figure 1.

Finally, the model underwent a thorough verification and validation process to assess its accuracy. Firstly, the assumptions made within the model were visually represented using state charts and possible transitions. This visual representation allowed for a clearer understanding of the assumptions and facilitated their evaluation for accuracy and coherence. The model's assumptions were then carefully articulated and validated against its code logic, ensuring that there were no discrepancies or errors between the assumptions and the code. Secondly, the model's emergent behavior was compared to real-world data to assess its accuracy. This step ensured that the model's outcomes closely matched the observed outcomes in the real world [17], increasing confidence in its validity. Thirdly, the coefficient of variation for treatment retention was found to be less than 0.05 for both treatment types, indicating a relatively low level of variation. Similarly, the coefficient of variation for opioid overdose in both treatment types and opioid-related deaths in the methadone treatment group was less than 0.20. However, due to the limited number of opioid-related deaths amongst the buprenorphine recipients ($\leq$5), the coefficient of variation did not provide informative insights for this outcome in the buprenorphine group. By fulfilling these requirements, this model successfully passed our tests by demonstrating the clarity of its assumptions provided by the state charts and its alignment with real-world data [17].

2.5. Scenarios

Alongside the baseline scenario that examined the no extended take-home doses for OAT recipients across the 6-month treatment horizon, three scenarios were defined to explore the differential results of providing extended take-home doses for OAT recipients starting at various times of treatment. The number of eligible OAT recipients for extended take-home doses remained constant within these three scenarios, while the time of implementation of the extended take-home doses policy varied to begin with after the second, third, and fourth month of treatment, respectively. Furthermore, these three scenarios were combined with varying probabilities of OAT patients obtaining a naloxone kit during a physician visit (i.e., 5%, 10%, and 15%, respectively) to assess the impact of naloxone disposal within OAT patients' networks. For each scenario, an ensemble of 100 realizations was run, each with varying random seeds. Finally, percentage changes from the baseline for all three outcomes of interest were reported over the six-month treatment horizon.

3. Results

The baseline scenario posits approximately 10,500 individuals, which represents 20.8% of the OAT population receiving the six-month buprenorphine/naloxone treatment, while approximately 39,700 individuals comprising 79.1% of the OAT population receive the six-month methadone treatment, respectively.

Among the people treated with buprenorphine/naloxone, 1600 individuals representing 15.2% of this population received daily dispensed buprenorphine/naloxone while others received weekly dispensed buprenorphine/naloxone. Among people treated with methadone, 13,900 individuals representing 35.0% of this population received daily dispensed methadone, and the rest of the individuals received weekly dispensed methadone. With no additional interventions applied, the baseline scenario yielded approximately 80 opioid overdoses and 10 opioid-related deaths with the six-month buprenorphine/naloxone treatment, accounting for 0.7% and 0.09% of this population, respectively; in contrast, methadone treatment gave rise to a higher burden, with approximately 750 opioid overdoses and 70 opioid-related deaths having occurred during the six-month treatment period, accounting for 1.8% and 0.1% of this population, respectively. Finally, out of the population receiving the six-month buprenorphine/naloxone treatment, 7900 individuals, representing 75.4%, continued treatment without interruption and discontinuation for six months, thereby achieving a six-month retention with buprenorphine/naloxone treatment; in contrast, 30,800 individuals, which was equivalent to 77.5%, achieved six-month retention with methadone treatment. These results demonstrate the baseline distribution of OAT recipients across distinct types of treatment and disposal methods based on empirical data [17].

3.1. Individuals Receiving Methadone Treatment

Among the methadone-treated individuals receiving daily dispensed OAT, 8200 individuals, equivalent to 58.8% of this population, were eligible to transition to take-home doses, and among the methadone-treated individuals receiving weekly dispensed OAT, 18,700 individuals, representing 72.5%, were eligible to extend to 13 take-home doses.

3.1.1. Providing Extended Take-Home Doses among the People Treated with Methadone

Table 1 shows the six-month outcomes of interest for providing extended take-home doses among people treated with methadone within the successive time frames. Earlier permission for the provision of extended methadone take-home doses to eligible patients was found to exhibit a beneficial impact on all three outcomes of interest. Providing extended take-home doses among people treated with methadone increased treatment retention (by 2.8%, 2.0%, and 1.4% when permission for extended take-home doses was granted within the second month of treatment, the third month of treatment, and the fourth month of treatment, respectively). Furthermore, providing extended take-home doses among people treated with methadone decreased both the total number of opioid overdoses by 7.3%, 6.1%, and 3.5%, and the total number opioid-related deaths by 13.0%, 10.7%, and 6.9%, when permission for extended take-home doses was granted within the second month of treatment, the third month of treatment, and the fourth month of treatment, respectively. These results suggest that ensuring a guaranteed access to take-home doses of methadone as early as the second month of treatment can lead to higher treatment retention rates and reduce the harms related to opioids. This positive outcome may be attributed to reducing the barriers to accessing suitable methadone doses, providing relief from withdrawal symptoms and reducing cravings for methadone recipients.

Table 1. Results of providing extended take-home doses among people treated with methadone: six-month outcome percentage change from the baseline.

Policy	Change in Opioid Overdose (%)	Change in Opioid-Related Deaths (%)	Change in Treatment Retention (%)
Providing Extended Take-Home Doses after the			
Second month	−7.3%	−13.0%	+2.8%
Third month	−6.1%	−10.7%	+2.0%
Fourth month	−3.5%	−6.9%	+1.4%

3.1.2. Providing Extended Take-Home Doses and Expanding Naloxone Availability among People Treated with Methadone

Table 2 characterizes the six-month outcomes of interest arising from providing extended take-home doses and expanding naloxone availability among the people treated with methadone. Across all outcomes, the greatest impact was achieved with a 15% naloxone expansion combined with permission for the provision of extended methadone take-home doses granted within the second month of treatment. These results highlight the significant reduction in opioid-related harms when methadone recipients within the peer support network were empowered with readily available naloxone. By having naloxone readily available, methadone recipients can promptly intervene during an opioid overdose emergency for their peers, potentially saving lives and reducing the severity of harm.

Table 2. Results of providing extended take-home doses and expanding naloxone availability among the people treated with methadone: six-month outcome percentage change from the baseline.

Policy		Change in Opioid Overdose (%)	Change in Opioid-Related Deaths (%)	Change in Treatment Retention (%)
Providing Extended Take-Home Doses after the	**Expanding Naloxone Availability by**			
Second month	5%	−46.8%	−47.5%	+2.8%
Second month	10%	−58.5%	−61.4%	+2.7%
Second month	15%	−65.4%	−66.4%	+2.8%
Third month	5%	−46.8%	−47.8%	+2.0%
Third month	10%	−58.4%	−60.9%	+2.0%
Third month	15%	−65.3%	−66.2%	+2.0%
Fourth month	5%	−46.2%	−48.3%	+1.4%
Fourth month	10%	−58.3%	−59.9%	+1.2%
Fourth month	15%	−64.9%	−66.1%	+1.3%

3.2. Individuals Receiving Buprenorphine/Naloxone Treatment

Among the buprenorphine/naloxone-treated individuals receiving daily dispensed OAT, 700 individuals, representing 43.8% of this population, were eligible to transition to take-home doses, and among the buprenorphine/naloxone-treated individuals receiving weekly dispensed OAT, 6600 individuals, representing 74.3% of this population, were eligible to extend to 13 take-home doses.

3.2.1. Providing Extended Take-Home Doses among the People Treated with Buprenorphine/Naloxone

Table 3 shows the six-month outcomes of interest for providing extended take-home doses among the people treated with buprenorphine/naloxone within the successive time frames. Earlier granting of permission for the provision to extend buprenorphine/naloxone take-home doses to eligible patients has a small beneficial impact on treatment retention and a large undesirable impact on opioid overdose and opioid-related deaths. Providing extended take-home doses among people treated with buprenorphine/naloxone increases treatment retention (by 1.5%, 1.0%, and 0.7% when permission for extended take-home doses was applied within the second month of treatment, the third month of treatment

and the fourth month of treatment, respectively). However, providing extended take-home doses among people treated with buprenorphine/naloxone also increased both the total number of opioid overdoses by 8.9%, 7.7%, and 3.9%, and the total number of opioid-related deaths by 3.4%, 7.2%, and 6.3%, when permission to use extended take-home doses was granted within the second month of treatment, the third month of treatment and the fourth month of treatment, respectively. These results suggest that ensuring a guaranteed access to take-home doses of buprenorphine/naloxone as early as the second month of treatment can lead to higher treatment retention rates. This finding suggests that when patients have the opportunity to receive take-home doses, they are more likely to remain engaged in their treatment program. However, this greater flexibility and convenience in managing their medication comes with some drawbacks for buprenorphine/naloxone recipients. The opioid-related harms tend to increase among this group, which may be attributed to the lack of direct monitoring of patients receiving buprenorphine/naloxone in OAT. Unlike methadone, buprenorphine/naloxone may be less effective in providing a long-term stability due to its pharmacological properties [39]; while not directly represented in the model, such factors may contribute to patterns reflected in the empirical data that are used to parameterize the model. Furthermore, individuals receiving buprenorphine/naloxone treatment who are experiencing a change in their take-home dose status are scheduled for visits every 14 days. This extended interval between visits may result in a loss of contact with healthcare providers, which could potentially contribute to an increase in opioid-related harms.

Table 3. Results of providing extended take-home doses among people treated with buprenorphine/naloxone: six-month outcome percentage change from the baseline.

Policy	Change in Opioid Overdose (%)	Change in Opioid-Related Deaths (%)	Change in Treatment Retention (%)
Providing Extended Take-Home Doses after			
Second month	+8.9%	+3.4%	+1.5%
Third month	+7.7%	+7.2%	+1.0%
Fourth month	+3.9%	+6.3%	+0.7%

3.2.2. Providing Extended Take-Home Doses and Expanding Naloxone Availability among People Treated with Buprenorphine/Naloxone

Table 4 shows the six-month outcomes of interest for providing extended take-home doses and expanding naloxone availability among the people treated with buprenorphine/naloxone. Even with a 5% naloxone expansion, a beneficial impact relative to the baseline would be achieved over all three different time frames of providing extended take-home doses. Achieving the best treatment retention and reducing both opioid overdose and opioid-related deaths has been made by a 15% naloxone expansion combined with an early (second treatment month) grant of permission for the provision of extended buprenorphine/naloxone take-home doses. When naloxone is easily accessible within the peer support network, it can be promptly administered during an overdose emergency. The timely administration of naloxone effectively counteracts the effects of opioids and restores normal respiration, thus reducing the risk of fatal outcomes associated with overdose incidents. Therefore, through empowering buprenorphine/naloxone recipients within the peer support network with readily available naloxone, the potential for reducing opioid-related harms is enhanced.

Table 4. Results of providing extended take-home doses and expanding naloxone availability among people treated with buprenorphine/naloxone: six-month outcome percentage change from the baseline.

Policy		Change in Opioid Overdose (%)	Change in Opioid-Related Deaths (%)	Change in Treatment Retention (%)
Providing Extended Take-Home Doses after the	**Expanding Naloxone Availability by**			
Second month	5%	−10.2%	−10.2%	+1.4%
Second month	10%	−19.9%	−21.7%	+1.6%
Second month	15%	−23.3%	−22.6%	+1.4%
Third month	5%	−13.6%	−15.8%	+1.4%
Third month	10%	−21.5%	−26.5%	+1.1%
Third month	15%	−25.9%	−32.8%	+1.2%
Fourth month	5%	−15.9%	−17.2%	+0.8%
Fourth month	10%	−24.4%	−21.9%	+1.1%
Fourth month	15%	−28.5%	−20.8%	+0.8%

4. Discussion

This simulation study of individuals receiving OAT in a context inspired by data from Ontario, Canada, suggests that facilitating methadone or buprenorphine/naloxone recipients' transition to take-home doses or receiving extended take-home doses would result in a higher treatment retention compared with the status quo. A crucial finding of this study was that expanding the access to take-home doses earlier during the subsequent six-month treatment period among OAT recipients is likely to elevate treatment retention. Th results further suggest that the use of these extended take-home doses would decrease the occurrence of opioid overdose and opioid-related deaths among methadone recipients. Meanwhile, among those prescribed buprenorphine/naloxone, the results suggest that extended take-home doses might increase the risk of opioid overdose and opioid-related deaths. Furthermore, these results suggest that expanding naloxone availability can mitigate the adverse effect of increased take-home doses guidance on opioid overdose and opioid-related deaths among buprenorphine/naloxone recipients.

The differences in the pharmacological properties of methadone and buprenorphine/naloxone may contribute to variations in the treatment outcomes that were seen in the empirical data used for model parameterization. Factors such as the duration of action, receptor binding affinity, and pharmacokinetic profiles could impact the treatment response and the risk of adverse events [39]. For example, the longer duration of action and higher receptor binding affinity of methadone [18] may result in a greater stability and decreased risk of overdose among those receiving extended take-home doses.

Alternatively, buprenorphine/naloxone has a shorter duration of action and a lower receptor binding affinity compared to methadone, which could reduce its effectiveness in providing a long-term stability. As potential contributors to relevant patterns in the empirical data used to evidence the model, these factors may contribute to the current observation in that an increased availability of the buprenorphine/naloxone outside of the clinic without close supervision may lead to a higher risk of opioid misuse, overdose, and their related deaths. Additionally, it is important to note that individual patient characteristics, such as tolerance levels, treatment history, and support systems, can influence these outcomes. The stability of patients in their treatment can also impact their response to the take-home doses.

Moreover, it is important to emphasize that individuals undergoing buprenorphine/naloxone treatment and undergoing a change in their take-home dose status are only required to attend clinic visits every 14 days. This prolonged gap between visits for all individuals undergoing buprenorphine/naloxone treatment with a change in their take-home dose poses a concern, as it may reduce the frequency of contact with their healthcare providers. The potential consequences of limited contact include a diminished opportunity to address any emerging challenges or concerns promptly, such as adjusting their medication dosage or addressing new risk factors.

The creation of supportive peer networks and the availability of naloxone have demonstrated promising results in preventing opioid overdose incidents due to several reasons. Firstly, supportive peer networks provide individuals in OAT with a sense of belonging and mutual support, which may enhance their treatment engagement and reduce the risk of relapse. Secondly—and in an effect captured in the model presented here—the availability of naloxone, a medication used to reverse opioid overdose, plays a critical role in harm reduction. When naloxone is readily accessible—including through such peer networks—it can be promptly administered during an overdose emergency, reducing the risk of fatal outcomes. By having naloxone readily available, one can act quickly to intervene and potentially save lives. The combination of supportive peer networks and naloxone availability creates a complementary approach to preventing opioid overdose incidents.

Patient-centered care for OAT recipients involves adapting the treatment and support services to meet the unique needs and preferences of each individual [12]. This study examined various aspects of patient-centered care, including the implementation of flexible take-home doses and the establishment of supportive peer networks. Reflecting the ability of patients to exercise a greater level of control over their treatment through flexible take-home doses and reduced challenges in weaving their dose administration into daily scheduling, this model captured a resulting increase in the treatment retention. Moreover, the creation of supportive peer networks, coupled with the availability of naloxone, demonstrated the potential to prevent opioid overdose incidents. In this context, concern has been raised in that the storage of a large quantity of OAT medication at home, particularly methadone, might place other family members or other co-domiciliaries at risk of opioid overdoses—a consideration that suggests the importance of promoting safe storage. Furthermore, there are specific criteria that must be met before providing patients with new or higher take-home doses, which adds to the complexity of these clinical decisions.

Several limitations of this study need to be noted. First, while the implemented agent-based model monitors the behavior of OAT recipients over a six-month treatment period informed using reported data and investigates the patterns of changes between the baseline and subsequent scenarios, it is essential to recognize that it does not employ a conceptual framework with distinct evidence-based rules for the full diversity of the causal mechanisms involved; indeed, the current state of evidence falls well short of what would be required to support such a representation. It is therefore particularly important to acknowledge that the main data source used in this model may still be subject to residual confounding, which can impact the reported results. Thus, it is advisable to interpret these findings with caution. Partly to support the incorporation of evolving evidence, the implemented model is accessible online. Beyond incorporating the updated parameter estimates, the availability of the model can further aid in refining the model structural assumptions with a refined theory. Second, it is important to note that the model simplifies the complexity of implementing and maintaining a peer support network among OAT patients in real-world settings. Establishing and maintaining a successful peer support network in practice requires a significant amount of effort and consideration of the diversity within the OAT population. Third, while the literature [3,40] suggests a potential for an elevated risk of overdose and mortality during the initial stages of methadone treatment, it bears emphasis that this model has not been parameterized to reflect this aspect of the context and does not report the timing of the events within the six-month treatment time frame. This limitation is primarily attributed to the constraints imposed by the currently utilized data sources. Finally, additional evaluations may be required to validate the findings thoroughly. For instance, in accordance with the empirical data, opioid-related rates, including overdose and deaths, were not excluded from the all-cause death rate for OAT recipients. Moreover, due to the potential changes in the levels of tolerance among OAT recipients over time, there are uncertainties regarding opioid-related harm rates outside of OAT. However, since these rates remained constant across all scenarios and that the amounts of opioid-related harm outside of OAT were not among the outcomes of interest for the current study, these limitations are expected to have only a minimal

impact on the overall results. Moreover, the model was simplified by greatly limiting its representation of agent heterogeneity by virtue of employing overall empirical data, and the model does not account for disparities in the access to treatment services.

The findings of this study are in accordance with that of several other previous case studies [41–46] in suggesting that benefits can be secured if the modified guidance for administering higher take-home doses of OAT continues beyond the COVID-19 pandemic. Through implementing longer-duration take-home doses in methadone treatment programs, there is a potential to decrease the occurrence of opioid overdose and opioid-related deaths. To further address overdose incidents and prevent fatalities among OAT recipients, while also enhancing treatment retention, promoting the usage of naloxone among peers [34,35], and facilitating its accessibility without a prescription [47] may be effective.

Based on these results, policymakers may need to consider several factors when formulating or revising policies related to OAT. Policymakers may need to strike a balance between expanding access to OAT through longer-duration take-home doses and managing the potential risks associated with increased opioid-related harms, suggesting the value of conducting a thorough risk assessment and considering additional safety measures to ensure the well-being of patients. Moreover, policymakers may acknowledge that the benefits of longer-duration take-home doses vary among patients. They may underscore the significance of modifying treatment plans to tailor to individual needs and consider factors such as gender, income level, residential location, and treatment history when assessing a patient's stability and risk profile. This information might aid in determining the most suitable treatment duration and level of supervision for each patient. To achieve this aim, policymakers might place an emphasis on establishing robust monitoring and surveillance systems to closely monitor the outcomes and safety of OAT patients receiving longer-duration take-home doses. This could involve regular check-ins, adherence monitoring, and systems to promptly identify and respond to any concerning trends or adverse events. Finally, this study highlights that policymakers may benefit from collaboration among systems scientists, healthcare providers, and data custodians to further investigate the impact of longer-duration take-home doses on treatment outcomes and opioid-related harms. Such collaborations facilitate research and studies that aim to identify context-specific policy recommendations that are highly dependent on patient populations, local regulations, and existing guidelines.

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Appendix A

Table A1. Summary of the opioid-related parameters for methadone and buprenorphine/naloxone treatment based on the study published by the authors of [17] used in the model parametrization: daily and weekly dispensing of OAT and eligibility for changes in take-home doses.

Parameter	Opioid Overdose rate (1/Year)	Discontinuation Rate of Therapy (1/Year)	Interruption Rate in Therapy (1/Year)	All-Cause Mortality Rate (1/Year)	Opioid-Related Death Rate (1/Year)
Daily methadone patients not eligible for increased take-home doses	0.095	0.636	0.239	0.013	0.005
Weekly methadone patients not eligible for increased take home doses	0.018	0.196	0.074	0.011	0.003
Daily methadone patients eligible for increased take-home doses	0.069	0.510	0.190	0.015	0.006
Weekly methadone patients eligible for increased take-home doses	0.014	0.141	0.051	0.008	0.001 *
Daily buprenorphine/naloxone patients not eligible for increased take-home doses	0.035	0.932	0.293	0.001 *	0.001 *
Weekly buprenorphine/naloxone patients not eligible for increased take-home doses	0.014	0.308	0.129	0.008	0.001 *
Daily buprenorphine/naloxone patients eligible for increased take-home doses	0.065	0.851	0.253	0.001 *	0.001 *
Weekly buprenorphine/naloxone patients eligible for increased take-home doses	0.017	0.260	0.095	0.008	0.001 *

* To deal with the statistical variability associated with small sample counts, a value of 0.001 is used when the reported number of deaths among recipients is less than or equal to 5.

Table A2. Summary of the socio-demographic parameters for methadone and buprenorphine/naloxone Treatment based on the study published by the authors of [17] used in the model parametrization: daily and weekly dispensing of OAT and eligibility for changes in take-home doses.

Parameter	Location of Residence	Neighborhood Income				
	Urban	One (Lowest)	Two	Three	Four	Five (Highest)
Daily methadone patients not eligible for increased take-home doses	88.7%	48.2%	21.5%	13.4%	10.2%	6.8%
Weekly methadone patients not eligible for increased take home doses	85.5%	41.3%	22.1%	16.0%	11.6%	9.1%
Daily methadone patients eligible for increased take-home doses	89.9%	39.4%	23.8%	16.0%	13.0%	7.8%
Weekly methadone patients eligible for increased take-home doses	88.1%	38.0%	24.4%	17.3%	12.3%	8.0%
Daily buprenorphine/naloxone patients not eligible for increased take-home doses	80.9%	48.8%	16.3%	15.6%	11.9%	7.4%

Table A2. *Cont.*

Parameter	Location of Residence	Neighborhood Income				
	Urban	One (Lowest)	Two	Three	Four	Five (Highest)
Weekly buprenorphine/naloxone patients not eligible for increased take-home doses	86.5%	34.0%	22.9%	18.6%	14.3%	10.2%
Daily buprenorphine/naloxone patients eligible for increased take-home doses	88.2%	39.5%	24.1%	14.9%	11.8%	9.6%
Weekly buprenorphine/naloxone patients eligible for increased take-home doses	86.5%	34.8%	24.4%	17.9%	12.6%	10.3%

Table A3. Summary of Remaining Parameters in the Model Parametrization.

Parameter	Values	Reference
OAT recipients' population size	50,000	Assumed
The number of OAT recipients in each treatment type (methadone and buprenorphine/naloxone)	Custom distribution	Parametrized [17]
The number of OAT recipients in each disposal timing (daily or weekly) across different treatment types	Custom distribution	Parametrized [17]
The number of OAT recipients considering their eligibility for changes in take-home doses across different treatment types and disposal timings	Custom distribution	Parametrized [17]
Rate of the opioid overdose per year for opioid users outside the OAT	Uniform distribution between 0.009 and 0.048, respectively	Assumed [17]
Rate of opioid-related death per year for opioid users outside the OAT	Uniform distribution between 0.0179 and 0.0562, respectively	Assumed [48]
Rate of non-opioid-related death per year for opioid users outside the OAT	0.001	Assumed [49]

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