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RESEARCH REPORT

ADDICTION SSA

Duration of use and outcomes among people with opioid use disorder initiating methadone and buprenorphine in Ontario: a population-based propensity-score matched cohort study

Tara Gomes[1,2,3,4] | Daniel McCormack[3] | Nikki Bozinoff[5,6] | Mina Tadrous[2,3,7] | Tony Antoniou[1,3,6,8] | Charlotte Munro[9] | Tonya Campbell[1] | J. Michael Paterson[3,4,10] | Muhammad Mamdani[1,2,3,4] | Beth Sproule[2,5,11]

[1]Li Ka Shing Knowledge Institute of St. Michael's Hospital, Toronto, Ontario, Canada

[2]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

[3]ICES, Toronto, Ontario, Canada

[4]Institute for Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada

[5]Centre for Addiction and Mental Health, Toronto, Ontario, Canada

[6]Department of Family and Community Medicine, University of Toronto, Toronto, Ontario, Canada

[7]Women's College Hospital, Toronto, Ontario, Canada

[8]Department of Family and Community Medicine, St. Michael's Hospital, Toronto, Ontario, Canada

[9]Ontario Drug Policy Research Network Lived Experience Advisory Group, St Michael's Hospital, Toronto, Ontario, Canada

[10]Department of Family Medicine, McMaster University, Hamilton, Ontario, Canada

[11]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

Correspondence
Tara Gomes, Li Ka Shing Knowledge Institute of St Michael's Hospital, 30 Bond Street, Toronto, Ontario M5B 1W8, Canada.
Email: tara.gomes@unityhealth.to

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Abstract

Aims: To characterize comparative risks and benefits of methadone versus buprenorphine/naloxone in a contemporary cohort where the unregulated drug supply is dominated by fentanyl.

Design, Setting and Participants: Population-based propensity-score matched cohort study conducted in Ontario, Canada among people aged 18+ initiating opioid agonist therapy (OAT) for an opioid use disorder between October 2016 and December 2018 (n = 18 880).

Intervention: Initiation of methadone versus buprenorphine/naloxone.

Measurements: The primary outcome was opioid overdose (fatal and non-fatal) while on treatment, with secondary outcomes including opioid overdose (first 30 days of treatment), treatment discontinuation, health-care interactions related to treatment of opioid use disorder, receiving a weekly supply of take-home doses and opioid overdose within 30 days of treatment discontinuation. Outcomes were assessed over 1 year.

Findings: Overall, 7517 people initiating buprenorphine were matched to an equal number of methadone-treated individuals. Risk of opioid overdose while on treatment [hazard ratio (HR) = 0.50; 95% confidence interval (CI) = 0.37–0.68] or within the first 30 days of treatment (HR = 0.51, 95% CI = 0.31–0.85) was lower among buprenorphine recipients compared to methadone recipients. In secondary analyses, people initiating buprenorphine had a higher risk of treatment discontinuation within the first year (median time to discontinuation 104 versus 265 days, HR = 1.43, 95% CI = 1.37–1.49), had lower rates of health-care interactions for OUD (186.4 versus 254.3 per person-year; rate ratio = 0.73; 95% CI = 0.72–0.75), and a higher rate of receiving weekly take-home doses (HR = 2.33; 95% CI = 2.20–2.46). Overdose rates in the period following

OAT discontinuation were higher than those observed while on treatment, but did not differ significantly by OAT type.

Conclusions: Although treatment retention is higher among methadone recipients, overdose risk is also elevated compared to buprenorphine recipients. These findings demonstrate the benefits of any OAT on avoidance of overdose, particularly following treatment discontinuation and with the increasingly unpredictable drug supply in North America.

KEYWORDS
Drug discontinuation | Health Services Research | opioid agonist therapy, opioid use disorder, overdose | persistence

INTRODUCTION

Opioid use disorder (OUD) is associated with significant health and economic burdens [1, 2], with more than 70 000 overdose-related deaths occurring in Canada and the United States in 2019 alone [3–5]. Opioid agonist therapy (OAT) using either methadone or buprenorphine/naloxone is a widely used and effective intervention for OUD, with strong evidence for reduced risks of hospital admissions for opioid-related harm and fatal overdose [6–8]. In Ontario, Canada, methadone and buprenorphine are both considered first-line options for the treatment of OUD [9]. Although methadone remains the most commonly prescribed form of OAT in Ontario (43 567 methadone recipients versus 27 258 buprenorphine recipients in 2019), buprenorphine use has more than tripled since its inclusion on the provincial drug formulary in 2012 [10].

Despite the availability of two effective forms of OAT, there are few population-based studies to guide clinicians with respect to treatment selection, and none that assess the longer-term comparative effectiveness of buprenorphine and methadone in preventing fatal overdose in the current context of an unregulated supply that predominantly contains fentanyl [6, 7, 11]. Although some evidence suggests that buprenorphine is associated with a lower risk of fatal overdose than methadone, particularly in the first 4 weeks of treatment [11, 12], this early advantage may be negated by higher treatment discontinuation with buprenorphine relative to methadone due to elevated risk of overdose when no longer on treatment [13–15]. Translation of these findings into clinical practice is complicated further by the appearance of unregulated fentanyl in community drug supplies since the time of their publication and the relative importance that clinicians and their clients may place on retention in treatment, given the known risks of overdose upon discontinuation of OAT. Additional research is therefore needed to clarify whether buprenorphine versus methadone should be offered as first-line therapy in the era of fentanyl.

We consequently undertook a large, population-based study with the aim of comparing treatment patterns and outcomes among people treated with methadone versus buprenorphine to help characterize the comparative risks and benefits of these first-line treatment options for OUD in Ontario, Canada.

METHODS

Setting and cohort definition

We performed a population-based cohort study of Ontario residents aged 18 years and older who were newly prescribed or re-initiating buprenorphine/naloxone or methadone between 1 October 2016 and 31 December 2018. All Ontario residents prescribed OAT were included in the study, all of whom were covered by the Ontario Health Insurance Plan (OHIP), which provides universal coverage of physician services and hospital care. We defined the index date as the date of the first prescription for either buprenorphine/naloxone or methadone during the study period. To limit the cohort to people newly treated with OAT and those re-initiating treatment after a prolonged period of no treatment, we excluded those with a buprenorphine/naloxone or methadone prescription in the 180 days preceding the index date and those who initiated both methadone and buprenorphine/naloxone on the same day. In the primary analysis, people were followed for up to 365 days with a maximum follow-up date of 31 December 2019.

Data sources

We obtained data from ICES (formerly Institute for Clinical Evaluative Sciences), an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyse health-care and demographic data, without consent, for health system evaluation and improvement. We identified prescriptions for methadone, buprenorphine/naloxone combination products and other controlled substances (i.e. other opioids, benzodiazepines, stimulants and barbiturates) using the Narcotics Monitoring System (NMS) database, which contains data on all prescriptions for controlled substances dispensed from community pharmacies in Ontario, regardless of payment mechanism. These data include drug identification number, date of dispense, quantity dispensed and prescription duration. We identified hospital encounters using the Canadian Institute for Health Information's Discharge Abstract Database, National Ambulatory Care Reporting System and Ontario Mental

Health Reporting System, which contain detailed diagnostic information from acute inpatient hospital admissions, emergency department visits and mental health-related hospitalizations, respectively. We used the OHIP database to identify outpatient claims for physician visits, and obtained basic demographic and vital status data from the Registered Persons Database (RPDB). We used the Drug and Drug–Alcohol Related Death (DDARD) database to identify confirmed opioid-related deaths. The DDARD is based on investigations by the Office of the Chief Coroner of Ontario and is generated using methods described elsewhere [16]. Opioid-related deaths are determined by a medical coroner as those deaths in which toxicological analyses identified opioid concentrations deemed high enough to cause death, either alone or in the presence of other drugs. In Ontario, coroners investigate all sudden and unexplained deaths and this database is considered to be of exceptionally high quality, and is used regularly for research purposes.

We identified comorbidities using validated case definitions for human immunodeficiency virus (HIV) [17], diabetes [18], chronic obstructive pulmonary disease (COPD) [19] and asthma [20]. We used the ICES Physician Database to calculate the linear distance between the centroid of each person's residential postal code and that of the postal code of the office of the prescriber of their initial OAT prescription, and the Ontario Drug Benefit (ODB) database to identify both eligibility for the provincial public drug plan and claims for naloxone kits, which are dispensed free of charge from Ontario pharmacies. These data sets were available during the entire study period, and were linked using unique encoded identifiers and analysed at ICES (www.ices.on.ca).

Exposure

We defined ongoing use of methadone and buprenorphine/naloxone on the basis of successive refills with no gap in therapy exceeding 14 days. This definition of treatment discontinuation is aligned with recently published literature [21, 22] and was selected because a gap in treatment exceeding 14 days would reflect a clinically meaningful break in therapy requiring the re-initiation of OAT. When this condition was not satisfied, people were deemed to have discontinued treatment. The date of discontinuation was defined as the date on which the final prescription would have been fully consumed (i.e. the dispensing date plus the duration of the final dispensed prescription). We did not consider buprenorphine single products (i.e. those not in combination with naloxone) in our exposure definition because the sublingual formulation is not approved to treat OUD in Canada unless in exceptional circumstances, and therefore is rarely used in Ontario. Newer single-ingredient long-acting formulations were not yet approved in Canada during our study period.

Outcomes

The primary outcome was a composite of opioid overdose while on treatment, defined as an inpatient hospitalization or emergency department visit for opioid toxicity (International Classification of Diseases, 10th revision, diagnosis codes T40.0–T40.4 or T40.6) or an opioid-related death confirmed using coronial records and occurring between the dates of treatment initiation and discontinuation. We followed each person for up to 365 days from their index date until the first occurrence of the outcome, OAT discontinuation, switch between methadone and buprenorphine or non-opioid related death, whichever occurred first.

Secondary outcomes were time to first opioid overdose in the first 30 days of treatment, time to treatment discontinuation, rate of health-care interactions for OUD and time to first receipt of a weekly supply of take-home doses (defined as one or more OAT dispenses on a given day with a total duration of 7 days or greater). We defined a health-care interaction for OUD in two ways. First, we defined health-care interactions as outpatient physician visits for OUD using specific OHIP billing codes for the assessment or management of people with OUD (K682, K683, K684, A957, K680, G040, G041, G042, G043). Secondly, we expanded this definition to include either interactions with a physician related to OUD or a pharmacy dispensing OAT to more clearly characterize the frequency of all interactions required by OAT recipients. When multiple outpatient health-care interactions were observed on the same day, only one was counted.

Finally, in a secondary analysis to characterize the risk of opioid overdose soon after treatment discontinuation, we restricted our main cohort to individuals who discontinued therapy during the 1-year follow-up, and further classified those who discontinued prior to (i.e. OAT duration ≤ 30 days) or following (i.e. OAT duration > 30 days) treatment stabilization. Within each group, we assessed the risk of opioid overdose within 30 days of OAT discontinuation, with a maximum follow-up date of 31 January 2020.

Cohort characteristics

We determined demographic characteristics for the study cohort at baseline, including age, sex, neighbourhood income quintile, urban or rural location of residence, residence in northern Ontario (as frequent pharmacy visits associated with methadone therapy make it more challenging to administer in remote locations), receipt of an OAT prescription through the publicly funded drug plan and linear distance to the physician writing the initial OAT prescription. Missing data (income quintile and rurality) were categorized separately, and due to low prevalence (≤ %) and potential for informative missingness were included as separate categories in the propensity score model. There were 434 individuals (2.9%) with missing information on distance to provider. Because we could not determine distance to provider, a continuous variable for all individuals, we did not include this variable in the propensity score model and calculated the median distance only for those individuals with available information.

We defined several indicators of comorbidity, including any prior diagnosis of HIV, diabetes, COPD or asthma, and calculated the Deyo–Charlson Comorbidity Index [23] using hospital data from the 3 years prior to the index date. We also captured alcohol use disorder

based on outpatient physician services and hospital visits, and hospital visits for substance-related disorders, schizophrenia and other psychotic disorders, mood disorders, anxiety disorders, deliberate self-harm and other mental health disorders in the previous 3 years. Finally, we defined several indicators of medication use and health-care utilization in the year before OAT initiation, including prescriptions for non-OAT opioids, stimulants, benzodiazepines, barbiturates and pharmaceutical cannabinoids (e.g. nabilone), emergency department visits for opioid toxicity, naloxone dispensing, non-OUD outpatient physician visits and emergency department visits and inpatient hospitalizations for any reason. Diagnosis codes used to define measures of comorbidity can be found in the Supporting information.

Statistical analysis

We compared baseline characteristics of people treated with buprenorphine to those treated with methadone using standardized differences, with values lower than 0.10 suggesting adequate balance between groups [24]. We generated a propensity score by fitting a non-parsimonious logistic regression model that included the type of OAT as the dependent variable and all baseline characteristics, with the exception of distance to prescriber of initial OAT (due to missing data), as independent variables. People treated with buprenorphine were matched 1:1 to methadone-treated individuals on sex, age (within 2 years) and their propensity score (within 0.2 standard deviations). In the secondary analysis of overdose risk among people who discontinued OAT after becoming stabilized on therapy, we also matched on duration of OAT therapy (within 14 days). All matching was performed without replacement using the greedy nearest-neighbour method, meaning that once a match is made it is not reconsidered in the matching algorithm. This approach has been shown in simulations to be the preferred method for propensity-score matching [25].

We constructed Kaplan–Meier curves to compare time to treatment discontinuation between people initiating buprenorphine and methadone, and used conditional Cox proportional hazards regression to estimate hazard ratios (HR) and 95% confidence intervals (CI) comparing treatment discontinuation, opioid overdose and receipt of weekly take-home doses. We checked the proportional hazards assumption assessing time-varying covariates, log-negative–log survival plots and martingale residuals (Supporting information). For the outcomes of health-care interactions for OUDs, we calculated rates per person-year of follow-up and used conditional Poisson regression to generate rate ratios (RR) and 95% CI. All analyses were conducted at ICES using SAS Enterprise Guide version 7.1.

Ethics approval

The use of the data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act (PHIPA) and did not require review by a Research Ethics Board.

RESULTS

During the accrual period, we identified 18 880 people with new use of OAT (n= 9404 with new use of methadone and n= 9476 with new use of buprenorphine) who met our eligibility criteria. Within this cohort, 7517 (79.3%) people initiating buprenorphine were matched to a methadone-treated individual (Supporting information). Prior to matching, people treated with buprenorphine/naloxone were more likely to live in a rural or northern area, less likely to have received an OAT prescription through a low-income or disability support public drug plan and had a higher number of non-OUD-related physician visits compared to those initiating methadone. After matching, baseline characteristics of methadone and buprenorphine recipients were well balanced, with median ages of 35 years [interquartile range (IQR) = 28–44 years] and a majority of each group (65.5%) being male (Table 1).

In the primary analysis, people initiating buprenorphine had a significantly lower hazard of an opioid overdose while on treatment [n = 60 (1.9 per 100 person-years) versus n = 149 (3.6 per 100 person-years); HR = 0.50, 95% CI = 0.37–0.68; Table 2] compared to those initiating methadone. Among methadone-treated individuals, 6.7% of overdoses were fatal, compared to 3.3% among buprenorphine-treated individuals. We observed similar results in the analysis of overdose risk within the first 30 days of treatment (HR = 0.51, 95% CI = 0.31–0.85), although absolute risks of overdose were higher in both treatment groups (9.4 and 4.9 overdoses per 100 person-years, methadone and buprenorphine, respectively).

In secondary analyses, people initiating buprenorphine had a significantly higher hazard of treatment discontinuation within the first year compared to methadone-initiated individuals (median time to discontinuation = 104 days versus 265 days, HR = 1.43, 95% CI = 1.37 to 1.49). Further, people initiating buprenorphine had lower rates of outpatient physician visits for OUD (55.3 versus 69.1 per person-year; RR = 0.80, 95% CI = 0.78–0.82) and health-care interactions for OUD (186.4 versus 254.3 per person-year; RR = 0.73, 95% CI = 0.72–0.75) and a higher rate of receiving weekly take-home doses (HR = 2.33, 95% CI = 2.20–2.46).

Finally, in analyses of overdose risk among people discontinuing OAT prior to or following treatment stabilization, we identified 2118 matched methadone/buprenorphine pairs who discontinued OAT within the first 30 days of therapy and 1688 matched pairs discontinuing OAT after 30 days of therapy. Overall, rates of overdose in the period following OAT discontinuation were higher than those observed while on treatment, but did not differ significantly by OAT type (Table 3). Specifically, among people not stabilized on therapy, similar rates of overdose were observed within 30 days of discontinuation among methadone and buprenorphine-treated individuals (23.4 versus 20.3 per 100 person-years, respectively; HR = 0.87, 95% CI = 0.56–1.36). Among those stabilized on OAT before discontinuation rates of overdose were slightly higher for buprenorphine-initiated individuals, but the difference was not statistically significant (18.9 versus 13.1 per 100 person-years, respectively; HR = 1.45, 95% CI = 0.79–2.65).

TABLE 1 Characteristics of individuals initiated on opioid agonist therapy in Ontario after matching

	Buprenorphine/naloxone *n* = 7517	Methadone *n* = 7517	Standardized difference
Age, years			
Median (IQR)	35 (28–44)	35 (28–44)	0.00
18–24	977 (13.0%)	952 (12.7%)	0.01
25–34	2741 (36.5%)	2769 (36.8%)	0.01
35–44	1952 (26.0%)	1924 (25.6%)	0.01
45–64	1776 (23.6%)	1804 (24.0%)	0.01
65+	71 (0.9%)	68 (0.9%)	0.00
Male (*n*, %)	4922 (65.5%)	4922 (65.5%)	0.00
Location of residence			
Urban	6475 (86.1%)	6440 (85.7%)	0.01
Rural	976 (13.0%)	1012 (13.5%)	0.01
Missing	66 (0.9%)	65 (0.9%)	0.00
Residence in northern Ontario	866 (11.5%)	879 (11.7%)	0.01
Neighbourhood income quintile			
1 (lowest)	2717 (36.1%)	2803 (37.3%)	0.02
2	1710 (22.7%)	1720 (22.9%)	0.00
3	1251 (16.6%)	1224 (16.3%)	0.01
4	930 (12.4%)	922 (12.3%)	0.00
5 (highest)	837 (11.1%)	775 (10.3%)	0.03
Missing	72 (1.0%)	73 (1.0%)	0.00
Eligible for low-income or disability support public drug plan	1597 (21.2%)	1547 (20.6%)	0.02
Charlson Comorbidity Index			
No hospitalizations	5657 (75.3%)	5703 (75.9%)	0.01
0	1430 (19.0%)	1379 (18.3%)	0.02
1	252 (3.4%)	257 (3.4%)	0.00
2	80 (1.1%)	85 (1.1%)	0.01
3+	98 (1.3%)	93 (1.2%)	0.01
HIV	60 (0.8%)	60 (0.8%)	0.00
Diabetes	476 (6.3%)	454 (6.0%)	0.01
COPD	239 (3.2%)	241 (3.2%)	0.00
Asthma	1278 (17.0%)	1277 (17.0%)	0.00
ED visit or hospital admission for mental health diagnoses (previous 3 years)			
Substance use disorders	1845 (24.5%)	1800 (23.9%)	0.01
Schizophrenia spectrum and other psychotic disorders	228 (3.0%)	214 (2.8%)	0.01
Mood disorders	526 (7.0%)	482 (6.4%)	0.02
Anxiety disorders	849 (11.3%)	810 (10.8%)	0.02
Deliberate self-harm	623 (8.3%)	598 (8.0%)	0.01
Other mental health disorders	212 (2.8%)	196 (2.6%)	0.01
Alcohol use disorder (previous 3 years)	1156 (15.4%)	1132 (15.1%)	0.01
Opioid toxicity-related ED visit (previous year)	387 (5.1%)	371 (4.9%)	0.01
Prescribed medications (previous year)			
Opioids	3184 (42.4%)	3092 (41.1%)	0.02
Stimulants	446 (5.9%)	408 (5.4%)	0.02

(Continues)

TABLE 1 (Continued)

	Buprenorphine/naloxone *n* = 7517	Methadone *n* = 7517	Standardized difference
Benzodiazepines	1997 (26.6%)	1903 (25.3%)	0.03
Barbiturates	≤ 5*	≤ 5*	0.01
Pharmaceutical cannabinoids	161 (2.1%)	162 (2.2%)	0.00
Naloxone dispensed (previous year)	507 (6.7%)	491 (6.5%)	0.01
Health system utilization (previous year)			
Number of non-OUD-related physician visits (median, IQR)	10 (4–22)	9 (3–21)	0.10
Number of ED visits (median, IQR)	1 (0–2)	1 (0–2)	0.04
Number of hospitalizations (mean, SD)	0.19 ± 0.67	0.19 ± 0.66	0.01
Distance to prescriber of initial OAT (km)**	25 (7–74)	31 (8–80)	0.06

IQR = interquartile range; HIV = human immunodeficiency virus; COPD = chronic obstructive pulmonary disease; ED = emergency department; OUD = opioid use disorder; SD = standard deviation.
*Suppressed to protect patient privacy;
**excluding data from 434 individuals (2.9%) without geographic data available.

TABLE 2 Association between opioid agonist therapy type and study outcomes

Exposure group	Outcome (*n*)[a]	Rate(per 100 person-years)[a]	Unmatched* HR (95% CI)	Matched* HR (95% CI)
Time to first opioid overdose while on treatment				
Methadone	149	3.6	–	–
Buprenorphine/naloxone	60	1.9	0.48 (0.37, 0.63)	0.50 (0.37, 0.68)
Time to first opioid overdose in first 30 days on treatment				
Methadone	49	9.4	–	–
Buprenorphine/naloxone	23	4.9	0.46 (0.30, 0.72)	0.51 (0.31, 0.85)
Time to treatment discontinuation				
Methadone	4022	97.3	–	–
Buprenorphine/naloxone	4828	153.1	1.46 (1.40, 1.51)	1.43 (1.37, 1.49)
Time to weekly take-home supply				
Methadone	2364	76.5	–	–
Buprenorphine/naloxone	2794	166.9	2.37 (2.26, 2.50)	2.33 (2.20, 2.46)

Exposure group	Outcome (*n*)[a]	Rate(per person-year)[a]	Unmatched* RR (95% CI)	Matched* RR (95% CI)
Number of outpatient physician visits for OUD				
Methadone	285 769	69.1	–	–
Buprenorphine/naloxone	174 338	55.3	0.79 (0.78, 0.80)*	0.80 (0.78, 0.82)*
Number of outpatient visits for OUD and pharmacy visits				
Methadone	1 051 397	254.3	–	–
Buprenorphine/naloxone	587 938	186.4	0.74 (0.74, 0.75)*	0.73 (0.72, 0.75)*

[a]Matched cohort.
HR = hazard ratio; CI = confidence interval; OUD = opioid use disorder.
*In unmatched analysis, methadone *n* = 9404, buprenorphine/naloxone *n* = 9476. In matched analysis, *n* = 7517 in each group.

TABLE 3 Association between opioid agonist therapy type overdose within 30 days of treatment discontinuation

Exposure group	Outcome (*n*)[a]	Rate(per 100 person-years)[a]	Unmatched* HR (95% CI)	Matched* HR (95% CI)
People discontinuing within ≤ 30 days of OAT initiation				
Methadone	40	23.4	–	–
Buprenorphine/naloxone	35	20.3	0.56 (0.37, 0.85)	0.87 (0.56, 1.36)
People discontinuing after > 30 days of OAT initiation				
Methadone	18	13.1	–	–
Buprenorphine/naloxone	26	18.9	1.22 (0.75, 1.98)	1.45 (0.79, 2.65)

[a]Matched cohort.
HR = hazard ratio; CI = confidence interval; OAT = opioid agonist therapy.
*Among people discontinuing OAT within ≤ 30 days, there were *n* = 2340 methadone recipients and *n* = 3389 buprenorphine/naloxone recipients. In matched analysis, there were *n* = 2118 in each group. Among people discontinuing OAT after > 30 days, there were *n* = 2762 methadone recipients and *n* = 2821 buprenorphine/naloxone recipients. In matched analysis, there were *n* = 1688 in each group.

DISCUSSION

In this population-based study of approximately 15 000 new OAT recipients, people treated with buprenorphine had a slightly lower risk of overdose while on treatment, a higher rate of receiving weekly take-home doses and lower rates of OUD-related health-care interactions compared to those initiating methadone. However, risk of treatment discontinuation was 43% higher among buprenorphine-treated individuals, with a median time to discontinuation of approximately 3 months compared to almost 9 months for those starting methadone. Importantly, irrespective of OAT type, rates of overdose were 4–10 times higher in the 30 days after treatment discontinuation compared with during treatment, reinforcing the benefits of OAT in this population, as well as the importance of informing people of the serious risks following treatment discontinuation.

Our findings are similar to those of two cohort studies from the United Kingdom and Australia that showed a lower risk of overdose among buprenorphine-treated individuals relative to those receiving methadone and higher risks of fatal overdose during the first 4 weeks of treatment and the initial 4 weeks following discontinuation [11, 13, 14]. Although other studies have not directly compared risks of non-fatal overdose between methadone and buprenorphine, our findings of periods of elevated risk also generally align with patterns of all-cause and drug-specific toxicity among OAT recipients reported elsewhere in Canada and internationally [6, 7, 15]. In particular, a Canadian study found a 3.4 times higher risk of death while off OAT [6], which is consistent with our finding of at least a fourfold risk of overdose within 30 days of discontinuing OAT. Our study builds upon these findings by demonstrating additional benefits of buprenorphine, including reduced clinical interactions for OUD and higher rates of take-home doses. Furthermore, our study provides novel direct comparisons of multiple outcomes among recipients of methadone and buprenorphine using real-world data in a contemporary cohort with high fentanyl exposure, using rigorous methods for control of confounders, thus representing an important contribution to the existing literature in the context of the evolving unregulated drug supply.

Despite limited real-world data comparing retention between methadone and buprenorphine, our finding of higher treatment retention with methadone is consistent with the results of clinical trials and observational studies [26–29]. However, in general, many clinical trials suggest higher OAT retention compared to our findings and other real-world data, indicating that other factors, such as clinician knowledge, individual-level characteristics, negative treatment experiences, lack of resources, convenience, stigma and OAT setting and delivery may influence retention outside of strict clinical trial settings [28, 30–32]. This is reinforced by the findings of qualitative research and surveys that describe the important role of prior history of OAT use, severity of OUD, distance to pharmacies and client preference on selection of, and retention, in treatment [30, 33]. Interestingly, a recent observational study from Australia demonstrated improved retention for buprenorphine over time, reaching a high median time to discontinuation of 269 days by 2015 (versus 282 days for methadone). In contrast, although methadone retention was very similar in our study among a cohort treated with OAT from 2016 onwards (median 265 days), we found that buprenorphine retention was much lower (104 days). This could reflect differences in buprenorphine uptake and integration into primary care, degree of public funding and more stringent training requirements among prescribers in Australia [28, 34]. The implications of this finding are complex, as they may suggest lower effectiveness of buprenorphine among people with high levels of tolerance due to illicit fentanyl use and a need to individualize treatment approaches to meet people's needs. Therefore, there is an important opportunity in Ontario to improve provider training in provision of all forms of OAT such that there can be a low threshold for treatment rotation in cases of poor buprenorphine response.

Importantly, our study accrual period corresponds with a time in which unregulated fentanyl had supplanted prescription opioids as the leading cause of overdose fatalities in Canada, with rates of fentanyl-related deaths nearly quadrupling between 2015 and 2017 in Ontario [4, 5, 35, 36]. In this context of a dangerous unregulated drug supply, a lower overdose risk with buprenorphine relative to methadone must be balanced against higher retention rates with

methadone, particularly when viewed in light of our finding of a high risk of overdose soon after OAT discontinuation. However, regulatory requirements have historically acted as disincentives to methadone prescribing in Ontario, limiting access to this form of OAT. In 2021, the College of Physicians and Surgeons of Ontario rescinded its policy on methadone prescribing, effectively allowing any physician in Ontario to prescribe methadone. These changes provide an opportunity to expand access to methadone, for example, through primary care and emergency department settings. The differential risks of overdose, treatment retention and frequency of engagement with health-care providers that are observed between methadone and buprenorphine reinforce the importance of shared decision-making between clinicians and their clients [37, 38] to personalize OAT selection and identify opportunities to optimize treatment retention.

Limitations

Strengths of this study include its use of real-world, population-based data to capture all people initiating methadone or buprenorphine for OAT in Ontario over a contemporary period during which the majority of fatal overdoses were caused by unregulated fentanyl rather than prescription opioids. However, several limitations merit discussion. First, despite our use of propensity score methods to balance known confounders between exposure groups, it is possible that unmeasured confounders or selection bias influenced our findings (e.g. client preference, severity of OUD). Secondly, hospital discharge records do not identify the specific opioids involved in the toxicity event. Therefore, we do not know whether the overdoses we observed directly involved the OAT, other opioids or a combination of both. Thirdly, access to OAT, integration into primary care and level of prescriber training vary widely across jurisdictions, all of which may influence retention in treatment and frequency of interactions with the health-care system. Accordingly, our findings may not be generalizable to settings outside Ontario. Fourthly, we relied upon pharmacy claims data to define OAT discontinuation, defining this as a gap in treatment longer than 14 days. Therefore, individuals with shorter gaps in therapy were not defined as having discontinued treatment in this study. Similarly, we defined new use of OAT on the basis of having not received treatment in the previous 180 days. This ensured that we studied a population with no recent treatment, but allowed inclusion of people who may have attempted treatment in the more distant past. This decision was made to improve the generalizability of our findings to the population of people with OUD currently exposed to the unregulated drug supply in Ontario, as many have had prior exposure to treatment. Fifthly, although we can determine frequency of health-care interactions related to OUD, we cannot determine specific individual's need and quality of care. Therefore, future work is needed to determine whether lower rates of health services utilization among buprenorphine recipients are safe and appropriate. Finally, our study was not designed to differentiate between risks following treatment discontinuation among people who tapered their OAT versus those who discontinued abruptly. Future research is needed to elucidate these risks.

CONCLUSIONS

As the opioid crisis escalates across North America, OAT is a crucial, evidence-based intervention that has demonstrated effectiveness at reducing risks of overdose. However, retention in treatment remains a challenge, with many factors cited as reasons for discontinuation, including physician-level factors and client preferences which differ between treatment options [30–32]. Our study provides a direct comparison between methadone and buprenorphine, and highlights improved retention but higher on-treatment overdose risk for methadone. However, our finding of a high-risk period for overdose following OAT discontinuation reinforces the benefits of treatment with any OAT, particularly in the context of a potent, unpredictable unregulated drug supply. Ongoing engagement with clinicians and people who use drugs is therefore needed to identify opportunities for improving OAT access, supporting retention in treatment and ensuring safe tapering and access to harm reduction services for people choosing to discontinue therapy.

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DECLARATION OF INTERESTS

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AUTHOR CONTRIBUTIONS

Tara Gomes: Conceptualization-Lead; Funding acquisition-Lead; Project administration-Lead; Writing - original draft-Lead. **Daniel McCormack:** Formal analysis; methodology. **Nikki Bozinoff:** Conceptualization; methodology. **Mina Tadrous:** Conceptualization; methodology. **Tony Antoniou:** Conceptualization; methodology. **Charlotte Munro:** Conceptualization; methodology. **Tonya Campbell:** Conceptualization; methodology. **Michael Paterson:** Conceptualization; methodology; project administration. **Muhammad Mamdani:** Conceptualization; methodology. **Beth Sproule:** Conceptualization; methodology.

ORCID

Tara Gomes https://orcid.org/0000-0002-1468-1965

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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