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Characteristics, treatment patterns and retention with extended-release subcutaneous buprenorphine for opioid use disorder: A population-based cohort study in Ontario, Canada

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ABSTRACT

Background: Uptake and retention for opioid agonist treatment (OAT) remains low. Novel extended-release formulations may improve OAT accessibility by reducing the frequency of healthcare visits. Our aim was to examine uptake, characteristics, treatment patterns and retention of individuals initiating extended-release subcutaneous buprenorphine (BUP-ER), a monthly injectable OAT.

Methods: We conducted a population-based cohort study among adults aged 18+ initiated on BUP-ER between February 3, 2020 and March 31, 2022 in Ontario, Canada. Using administrative health data, we defined continuous BUP-ER use based on repeat injections within a 56-day period and used Kaplan-Meier curves to estimate time on treatment. Among new BUP-ER recipients, we described individual and prescriber characteristics, healthcare utilization and treatment patterns.

Results: 2366 individuals initiated BUP-ER. The median time to BUP-ER discontinuation was 183 days (interquartile range: 66–428 days) and 52.0% of individuals were co-prescribed buprenorphine/naloxone at least once throughout the period of BUP-ER receipt. Among individuals who initiated on a dose of 300 mg BUP-ER and had three or more injections, 18.8% continued to receive only 300 mg doses (N=276 of 1470). Furthermore, 28.6% of those whose dose was reduced to 100 mg (N=341 of 1194) had a subsequent dose increase to 300 mg.

Conclusions: On average, people initiating BUP-ER discontinue within the first 6 months of treatment. While BUP-ER is likely providing an important OAT option, the high occurrence of discontinuation, supplementation with buprenorphine/naloxone, and frequent dose increases suggest inadequacy of current dosing recommendations among a proportion of individuals.

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1. Introduction

In 2019, opioids accounted for 12.9 million years of healthy life lost from early death and disability, globally (UNODC, 2022). A rapid rise of opioid toxicity deaths in North America, driven by non-pharmaceutical fentanyl, reached record high levels during the COVID-19 pandemic (UNODC, 2022). Canada experienced a doubling in the rate of accidental opioid toxicity deaths in 2021 (vs. 2019), and rates remained elevated in 2022 (Special Advisory Committee on the Epidemic of Opioid Overdoses, 2023). Recent evidence suggests that up to two-thirds of individuals who died from an opioid toxicity had an opioid use disorder (OUD) (Gomes et al., 2022b), suggesting that many deaths may have been prevented through effective and accessible treatment.

Methadone and buprenorphine are commonly prescribed and effective opioid agonist treatments (OAT) that have been shown to reduce the risk of opioid-related and all-cause death among people with opioid use disorder (Larochelle et al., 2018; Pearce et al., 2020; Sordo et al., 2017). Despite the demonstrated effectiveness of OAT, treatment retention is a major challenge (Priest et al., 2019; Russell et al., 2022), with frequent pharmacy and physician visits being described as a hindrance for some individuals, especially those residing in more rural and remote areas (Pijl et al., 2022; Russell et al., 2022). This may place people at an increased risk for negative health and social outcomes, including opioid toxicity, when treatment is discontinued abruptly or never initiated. As a result, new long-acting formulations of buprenorphine have recently been approved, with the potential for reducing frequency of clinical interactions. One such formulation, extended-release subcutaneous buprenorphine (BUP-ER; brand name: Sublocade®), was approved by Health Canada on February 3, 2020 (Government of Canada, n.d.). BUP-ER is indicated for people with moderate to severe OUD who have been initiated and stabilized on a transmucosal buprenorphine-containing product for a minimum of seven days (Indivior UK Limited, 2022). The product monograph suggests that individuals receive a BUP-ER injection of 300 mg/month for two months, followed by 100 mg/month; however, they may be transitioned back to 300 mg/month if they do not demonstrate a satisfactory clinical response to the 100 mg dose (Indivior UK Limited, 2022). BUP-ER must be administered via abdominal subcutaneous injection by a healthcare provider, with a recommended dosing interval of 28 days (Indivior UK Limited, 2022; META:PHI, n.d.).

BUP-ER may improve quality of life by reducing frequency of prescription renewals to only once per month, thus increasing convenience and reducing stigma associated with receiving OAT (Ling et al., 2019). BUP-ER also eliminates the need for take-home medications and daily administration, thus potentially facilitating improved access and adherence, particularly in rural and remote areas (Ling et al., 2019). Given the novelty of BUP-ER, there is a lack of real-world evidence evaluating use patterns. Of the few published BUP-ER studies in real-world settings, treatment gaps were often not considered, samples were highly restrictive (e.g., commercially-insured only, conducted at a single treatment program), and studies were based solely in the United States (Morgan et al., 2021; Stein et al., 2022). Using administrative health data with near complete population capture, we sought to assess BUP-ER uptake, retention and clinical patterns of use in a cohort of people initiating this new form of OAT in Ontario, Canada.

2. Material and methods

2.1. Setting

We conducted a population-based cohort study among adults aged 18+ initiating BUP-ER between February 3, 2020 and March 31, 2022 and residing in Ontario, Canada.

2.2. Data sources

All data used in this study are held in databases at ICES (formerly the Institute for Clinical Evaluative Sciences; https://www.ices.on.ca), an independent, non-profit research institute whose legal status under Ontario's health information privacy law allows it to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement.

We used the Narcotics Monitoring System (NMS) to capture all prescriptions for controlled substances (including OAT) dispensed from community pharmacies in Ontario (regardless of payer) and the Ontario Drug Benefit (ODB) Claims data to identify eligibility for the public drug plan. We used the Registered Persons Database (RPDB), a registry of all individuals eligible for the publicly funded Ontario Health Insurance Plan (OHIP), to obtain demographic information and vital statistics. We determined diagnoses and procedures captured during inpatient hospitalizations, emergency department (ED) visits, and mental health hospitalizations using the Canadian Institute for Health Information's Discharge Abstract Database (DAD), National Ambulatory Care Reporting System (NACRS), and Ontario Mental Health Reporting System (OMHRS), respectively. We captured outpatient visit data using the Community Health Centre (CHC) dataset (Ontario Ministry of Health and Long-Term Care, 2023) and the OHIP Claims Database, which together capture all outpatient primary care visits provided in Ontario. We determined prescriber information using the Corporate Provider Database and ICES Physician Database, and generated drug lists using the Drugs List database. Finally, data regarding neighborhood-level income quintile and rurality of community of residence were ascertained from the Postal Code Conversion File and reference file using Statistics Canada's standard geographical areas. These datasets were linked using unique encoded identifiers and analyzed at ICES.

2.3. Cohort definition

We identified a cohort of individuals initiating BUP-ER, defined as all those dispensed at least one BUP-ER pharmacy claim over the study period. We defined the index date as the date of first BUP-ER dispense, and excluded individuals aged <18 on index date and those who had been dispensed BUP-ER in the 90 days prior to index to confirm treatment initiation. Although this full cohort was used to present trends in BUP-ER uptake over time, we took additional steps to avoid misclassification of the BUP-ER initiation date for subsequent analyses related to clinical characteristics at treatment initiation, because in-hospital initiation cannot be captured accurately in our data. Specifically, in these analyses, we created a sub-cohort that further excluded individuals who were not dispensed buprenorphine/naloxone from a community pharmacy in the 30 days prior to index and those with more than one BUP-ER prescription dispensed on the same service date, noting the recommendation for induction with buprenorphine/naloxone for a minimum of 7 days prior to BUP-ER initiation (Indivior UK Limited, 2022). These exclusions were not applied to the analysis of trends because the exact date of initiation was less pertinent in this analysis. See Supporting Information, Figure S1 for a flowchart outlining the number of individuals excluded at each step.

2.4. Measures and analysis

2.4.1. Trends in uptake

We reported trends in monthly BUP-ER uptake as the number of individuals initiating BUP-ER and as a percentage of all OAT initiators between April 1st, 2020 and March 31st, 2022. Data is presented starting April 1st, 2020 to avoid small cell counts (N≤5) in earlier months.

2.4.2. Demographic and clinical characteristics

Within the sub-cohort of people initiating BUP-ER with no evidence

of inpatient initiation, we defined a number of demographic and clinical characteristics at the time of their first initiation of BUP-ER. Demographic characteristics included age, sex, income quintile of residence, location of residence (urban, rural, Northern, Southern) and whether or not the individual was a beneficiary of the provincial public drug program (ODB claim 180 days prior to BUP-ER initiation). Clinical characteristics prior to index included OAT (prescribed 180 days prior), health system utilization (one year prior), opioid toxicity hospitalizations (three years prior) and ED visits or hospitalizations for mental health or substance use disorder diagnoses (three years prior). Given that initiation of BUP-ER requires induction with buprenorphine/naloxone, we excluded buprenorphine/naloxone prescriptions that were dispensed 0–7 days prior to BUP-ER initiation for the OAT measure.

We also defined characteristics of prescribers of BUP-ER, including clinician type (physician vs. nurse practitioner), main specialty of physicians, practice location, and frequency of BUP-ER initiations (<20 vs. 20+ new BUP-ER starts). See Supporting Information Table S2 for additional details.

2.4.3. Discontinuation

To accommodate patient variance in the timing of injections, we defined continuous use of BUP-ER as a prescription refill within 56 days of the date of the previous BUP-ER prescription (i.e., allowing for one missed dose). Individuals were censored if they switched to a different OAT (methadone, buprenorphine/naloxone, implantable buprenorphine or slow-release oral morphine [SROM]), died, or reached the maximum follow-up date (September 30th, 2022). Switching to methadone, implantable buprenorphine or SROM was defined as any dispense of these drugs during the BUP-ER continuous use period. Due to expectations of combined use of buprenorphine/naloxone and BUP-ER, individuals were only defined as having switched to buprenorphine/naloxone if they received this medication within 14 days of BUP-ER discontinuation.

2.4.4. Treatment patterns

Among all BUP-ER treatment courses, we defined several indicators related to treatment induction, including prevalence and dose of buprenorphine/naloxone in the week prior to BUP-ER initiation. We also defined a number of characteristics of BUP-ER treatment patterns, including starting dose (100 mg vs. 300 mg), subsequent claims for buprenorphine/naloxone, total number of BUP-ER dispenses, and time between doses. To assess dose changes over time, we conducted a subgroup analysis among those who were initiated on a 300 mg BUP-ER dose and had three or more injections to determine the prevalence of: continued 300 mg doses, dose reductions (to 100 mg), and initial dose reductions that were subsequently reversed (i.e., dose increase back to 300 mg). Among those whose dose was reduced to 100 mg, we characterized the time to dose reduction (e.g., second injection, third injection). We reported the median time between all BUP-ER doses at the individual-level, as well as the number of claims that occurred at various time intervals after the initial dose.

2.5. Analysis

We used descriptive statistics to summarize demographic and clinical characteristics, and treatment patterns among new BUP-ER recipients. We determined the median time to BUP-ER discontinuation using Kaplan Meier (KM) estimates, and in an analysis stratified by location of residence, used the log-rank test to determine whether there were significant differences between strata using a Type 1 error rate of 0.05 as the threshold. We conducted all analyses at ICES using SAS Enterprise Guide 7. Missing data are reported as separate categories where relevant.

2.6. Involvement of people with lived experience

We engaged with the Ontario Drug Policy Research Network's Lived Experience Advisory Group (LEAG), to inform the design, implementation and interpretation of this study. Three individuals with lived experience from the LEAG participated as research team members throughout the project, and are co-authors on this manuscript.

2.7. Ethics approval

Ontario's health information privacy law allows ICES to collect and analyze health care and demographic data, without consent, for health system evaluation and improvement. Use of these data was authorized under section 45 of the Ontario Personal Health Information Protection Act, which does not require review by a research ethics board.

3. Results

3.1. Trends in uptake

A total of 3069 individuals initiated BUP-ER from February 3, 2020 to March 31, 2022. We observed a steady increase in monthly BUP-ER initiation, with BUP-ER representing 5.8% of all new OAT use by March 2022 in Ontario (N=214 BUP-ER initiations; Fig. 1).

3.2. Demographic and clinical characteristics

After applying additional exclusions to remove people potentially initiating BUP-ER in a hospital setting, 2366 individuals remained in our final analytic cohort. The median age at BUP-ER initiation was 38 years, and 30.3% (N=716) of those who initiated BUP-ER (which contains a potential teratogen) were females of child-bearing age (18–44 years old) (Table 1). Most individuals resided in urban regions (81.7%), Southern Ontario (77.5%) and lower income neighborhoods (62.7% in the two lowest neighborhood income quintiles; Table 1). There were a total of 448 prescribers who prescribed BUP-ER over the study period, the majority of which were physicians (80.4%), most commonly family physicians (68.1%; Table 1). Of the prescribers who prescribed the initial BUP-ER dose (N=308), 30 (9.7%) initiated 20 or more people on BUP-ER over the study period, and were responsible for 49.2% of all BUP-ER initiations (Supporting Information, Table S1).

A high proportion of people initiating BUP-ER in our sample were

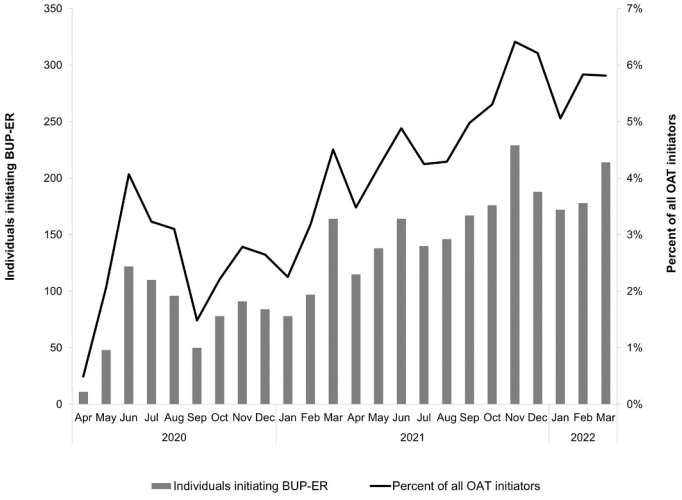

Fig. 1. Number of individuals initiating BUP-ER and percentage of all OAT initiators who initiated BUP-ER between April 1st, 2020 to March 31st, 2022 in Ontario. Data is presented starting April 1st, 2020 to avoid small cell counts (N≤5) in earlier months.

Table 1
Demographic characteristics among individuals initiating BUP-ER and their prescribers in Ontario between February 3, 2020 to March 31, 2022 in Ontario.

Characteristics of people initiating BUP-ER	
Number of unique people initiating BUP-ER (N)	**2366**
Age (Median, IQR)	38 (31–47)
Age group (N, %)	
18–24	151 (6.4%)
25–34	722 (30.5%)
35–44	774 (32.7%)
45–64	676 (28.6%)
65+	43 (1.8%)
Sex (N, %)	
Male	1383 (58.5%)
Female	983 (41.5%)
Females of child-bearing age* (N, %)	716 (30.3%)
Income quintile (Q) of residence (N, %)	
Q1 (lowest)	972 (41.1%)
Q2	510 (21.6%)
Q3	354 (15.0%)
Q4	268 (11.3%)
Q5 (highest)	239 (10.1%)
Missing	23 (1.0%)
Location of residence (urban/rural) (N, %)	
Urban	1932 (81.7%)
Rural	412 (17.4%)
Missing	22 (0.9%)
Location of residence (Northern/Southern) (N, %)	
Southern	1834 (77.5%)
Northern	532 (22.5%)
Provincial public drug beneficiary (N, %)	1688 (71.3%)
Prescriber characteristics	
Number of unique prescribers (N, %)	448
Physicians	360 (80.4%)
Nurse practitioners	86 (19.2%)
Physician main specialty (N, %)**	
General practitioner/family medicine	245 (68.1%)
Emergency medicine	29 (8.1%)
Psychiatry	19 (5.3%)
Internal medicine	9 (2.5%)
Other	14 (3.9%)
Missing	44 (12.2%)
Location of practice (urban/rural)	
Urban	276 (76.7%)
Rural	40 (11.1%)
Missing	44 (12.2%)

N: number; IQR: inter-quartile range.
*18–44 years old.
**11 physicians had missing information and were thus not included in the total.

dispensed any OAT in the six months prior (92.3%; excluding buprenorphine/naloxone claims dispensed within the seven-day induction period) (Table 2). Note that this is likely an overestimate given our exclusion of individuals who were not dispensed buprenorphine/naloxone from a community pharmacy in the 30 days prior to index for this analysis. Prior health services utilization in this population was relatively common, with 20.2% of individuals having one or more inpatient hospitalizations in the year prior to BUP-ER initiation, and 22.2% having an ED visit or inpatient hospitalization for opioid toxicity in the past 3 years (Table 2).

3.3. Discontinuation

The median time to BUP-ER discontinuation was 183 days (IQR: 66–428 days), with no significant differences according to location of residence (urban/rural or Northern/Southern) (Table 3; Figures S2, S3, S4). In a subgroup analysis among individuals who discontinued treatment (N=1554), we observed that 502 people (32.3%) were re-initiated on BUP-ER after discontinuation, with half (50.0%; N=251 of 502) being dispensed BUP-ER 29–56 days after discontinuation (data not shown). Among those who were censored due to switching to a different OAT (N=403), most switched to buprenorphine/naloxone (85.1%, N=343; data not shown).

Table 2
Health service utilization prior to BUP-ER initiation among individuals initiating BUP-ER in Ontario between February 3, 2020 to March 31, 2022 in Ontario (N=2366).

Prescription use	
OAT prescribed 180 days prior (N, %)	
Any OAT*	2183 (92.3%)
Buprenorphine/naloxone*	2049 (86.6%)
Methadone	619 (26.2%)
Slow-release oral morphine (SROM)	131 (5.5%)
Implantable buprenorphine	0 (0.0%)
Health service utilization	
Health system utilization in the 1 year prior	
1+ inpatient hospitalizations (N, %)	477 (20.2%)
Number of outpatient physician visits (Median, IQR)	36 (17–60)
Number of outpatient physician visits for OUD reasons (not including CHC visits**) (Median, IQR)	9 (4–12)
Number of ED visits (Median, IQR)	3 (1–5)
Opioid toxicity in the 3 years prior (N, %)	
Hospitalized for opioid toxicity	526 (22.2%)
ED visits or hospitalizations for mental health or substance use disorder diagnoses 3 years prior (N, %)	
Any mental health or addictions diagnoses	1183 (50.0%)
Substance-related disorders	987 (41.7%)
Deliberate self-harm	245 (10.4%)
Trauma/stressor-related disorders	243 (10.3%)
Mood disorders	197 (8.3%)
Anxiety disorders	177 (7.5%)
Schizophrenia and other psychotic disorders	120 (5.1%)
Personality disorders	65 (2.7%)
Other mental health disorders	50 (2.1%)
OCD and related disorders	<=5

CHC: Community Health Centre; ED: Emergency department; N: number; OCD: Obsessive compulsive Disorder; IQR: inter-quartile range.
*Given that initiation of BUP-ER requires induction with buprenorphine/naloxone, buprenorphine/naloxone prescriptions dispensed 0–7 days prior to BUP-ER initiation were excluded for this measure. Any OAT and buprenorphine/naloxone prescribed 180 days prior to BUP-ER initiation is likely overestimated given the inclusion criteria requiring a claim for buprenorphine/naloxone in 30 days prior to BUP-ER initiation in this analysis.
**Cannot capture OUD as a reason for outpatient visit using CHC claims; therefore, CHC visits were omitted.

3.4. Treatment patterns

The vast majority of people were dispensed buprenorphine/naloxone in the week before BUP-ER initiation (91.4%), and nearly all were initiated on a 300 mg BUP-ER dose (98.1%; Table 4). Further, just over half (52.0%) of individuals initiated on BUP-ER had a claim for buprenorphine/naloxone after their BUP-ER initiation date, with most having claims more than 14 days after initiation (67.2%) (Table 4). Moreover, among individuals who initiated on a dose of 300 mg of BUP-ER and had three or more injections, 18.8% continued to receive only 300 mg doses (276 of 1470; Table 4). Furthermore, 28.6% of those whose dose was reduced to 100 mg (341 of 1194) had a subsequent dose increase to 300 mg.

The median time between doses was 28 days (IQR: 28–33 days). Half (50.8%) of BUP-ER claims occurred within a recommended treatment interval (26–30 days), while 2.2% occurred within less than 15 days, 13.7% occurred between 15 and 25 days, 29.3% occurred between 31 and 44 days, and 4.1% occurred past 44 days (Table 4).

4. Discussion

In this population-based study, we found that uptake of BUP-ER increased steadily since Health Canada approval in February 2020,

Table 3
BUP-ER discontinuation among individuals initiating BUP-ER between February 3, 2020 to March 31, 2022 in Ontario (N=2366).

Days to BUP-ER discontinuation	Median (IQR)	p-value
Overall	183 (66–428)	
Location of residence (Urban/Rural)		0.72
Urban	185 (67–434)	
Rural	172 (63–399)	
Location of residence (Northern/ Southern)		0.36
Southern	191 (67–433)	
Northern	161 (63–414)	
Ongoing use of BUP-ER at the following time periods after initiation	**N (%)**	
60 days	1583 (77.1%)	
90 days	1351 (67.7%)	
182 days	949 (50.1%)	
365 days	400 (29.5%)	

N: number; IQR: inter-quartile range.
22 individuals were excluded in the rural/urban stratification due to missing information.
P-values were obtained using the log-rank test.
Number and percent of people with ongoing use of BUP-ER since initiation was calculated using Kaplan Meier estimates.

with a total of 2366 individuals initiating BUP-ER up to March 31, 2022. Almost two-thirds of adults starting BUP-ER treatment were between 25 and 44 years of age, and just under 60% were male. Health service utilization and mental health conditions were relatively common among those initiating BUP-ER, with one-fifth hospitalized as an inpatient at least once in the prior year, and half experienced an ED visit or hospitalization for mental health or substance use disorder. Approximately two-thirds of BUP-ER prescribers were general practitioners, and only 10% initiated 20 or more individuals on therapy. Overall, the median time to BUP-ER discontinuation was six months; however, although most discontinued after one year, approximately one-third of those who discontinued subsequently re-initiated BUP-ER treatment. While treatment patterns were generally aligned with recommendations, some exceptions were observed. For instance, half concurrently received buprenorphine/naloxone, and 28.6% of individuals eligible for a dose reduction either increased their dose or only ever received the highest dose.

On average, individuals initiating BUP-ER in our study discontinued treatment within six months. The one-year BUP-ER retention rate in our real-world study (29.5%) was lower than clinical trials, which ranged from 50.5% (Andorn et al., 2020) to 75% (Farrell et al., 2022). This likely reflects the controlled conditions of clinical trials compared to real-world settings, and our research advances the literature by examining real-world use. In contrast, compared to other real-world BUP-ER studies conducted in the U.S. (Morgan et al., 2021; Stein et al., 2022), retention in our study was higher, with Morgan et al. (2021) reporting a median of 47 days until discontinuation, and Stein et al. (2022) reporting that 52% of individuals had three or more consecutive monthly BUP-ER injections, compared to 67.7% in our study. This is likely attributable to less strict retention requirements in our study, as we allowed for a longer treatment gap of 28 days (i.e., one missed dose). This may also be due to variation in the structural facilitators and barriers to treatment across regions and in data capture across studies. For instance, the study by Morgan et al. (2021) included only commercially insured individuals in the U.S., and therefore those who appeared lost to treatment could have experienced changes or lapses in insurance coverage, transitioned to paying for BUP-ER out-of-pocket, or truly discontinued. In contrast, our study captured all outpatient BUP-ER prescriptions dispensed in Ontario, regardless of insurance status or method of payment, enabling a more accurate assessment of retention. Additionally, the higher retention observed in our study may be influenced by the high rate of concurrent treatment with buprenorphine/-naloxone in our cohort, as individuals may have been less likely to discontinue treatment due to inadequate dosing and withdrawal symptoms. Moreover, comparing our results to another real-world observational study using the same administrative datasets (Gomes et al., 2022a) suggests that retention in BUP-ER treatment (median: 183 days) may be slightly longer than that for buprenorphine/naloxone (median: 104 days), yet shorter than that for methadone (median: 265 days).

Table 4
Treatment patterns among individuals initiating BUP-ER between February 3, 2020 to March 31, 2022 in Ontario.

Induction with buprenorphine/naloxone in the seven days prior to BUP-ER initiation (N=2366)	
Claim for buprenorphine/naloxone* (N, %)	2163 (91.4%)
Number of days covered with buprenorphine/naloxone* (Median, IQR)	7 (4–7)
Dose of buprenorphine/naloxone (mg) on the latest buprenorphine/naloxone claim prior to BUP-ER initiation** (Median, IQR)	16 (10–20)
BUP-ER initiation dose (N=2366)	
Starting dose of BUP-ER (N, %)	
100 mg	46 (1.9%)
300 mg	2320 (98.1%)
Post-BUP-ER initiation patterns during the BUP-ER continuous use period (N=2366)	
Claim for buprenorphine/naloxone after BUP-ER initiation (N, %)	1230 (52.0%)
Claim for buprenorphine/naloxone >14 days after BUP-ER initiation	826 (34.9%)
Number of prescriptions for BUP-ER (N, %)	
1	585 (24.7%)
2+	1781 (75.3%)
Total who initiated on 300 mg and had 3+ injections (N, %)	1470 (62.1%)
Only ever received 300 mg doses†	276 (18.8%)
Dose reduction from 300 mg to 100 mg†	1194 (81.2%)
Injection where the dose was reduced***	
Injection 2‡	58 (4.9%)
Injection 3‡	984 (82.4%)
Injection 4‡	82 (6.9%)
Injection 5‡	28 (2.3%)
Injection 6‡	20 (1.7%)
Dose increase from 100 mg to 300 mg‡	341 (28.6%)
Time between doses	
Time between doses (Median, IQR), individual-level (N=2366)	28 (28–33)
Time between doses (N, %), claims-level (N=13,501)	
≤14 days	295 (2.2%)
15–25 days	1846 (13.7%)
26–30 days	6859 (50.8%)
31–44 days	3952 (29.3%)
>44 days	549 (4.1%)

N: number; IQR: inter-quartile range.
*Accounting for prior dispenses that overlap into this period.
**Reported only among those with buprenorphine/naloxone in the 7 days prior to BUP-ER initiation.
***Injection 7–20 were not included in the table due to small cells (N<=5).
†Denominator is total who initiated on 300 mg and had 3+ injections (N=1470).
‡Denominator is total who initiated on 300 mg and had 3+ injections and had a dose reduction from 300 mg to 100 mg (N=1194).

However, it is important to note that higher healthcare needs among individuals initiating BUP-ER compared to methadone and buprenorphine/naloxone (Gomes et al., 2022a) as well as other characteristics associated with selection into different treatment options, such as prior experience with OAT, severity of opioid use disorder, other concurrent mental health conditions, and rurality of the region of residence (Gomes et al., 2022a; Homayra et al., 2020), may explain these differences in retention. Therefore, future research is needed to directly compare treatment retention between various types of OAT, including BUP-ER, adjusting for demographic and clinical characteristics of those accessing treatment.

Although many individuals discontinued BUP-ER in our study, one-third of those who discontinued were subsequently re-initiated on BUP-ER treatment, suggesting that some individuals may be receiving BUP-ER intermittently rather than completely stopping treatment. Furthermore, switching to a different type of OAT occurred in 17.0% of our sample, with the majority of individuals switching to buprenorphine/naloxone, a finding that is similar to other BUP-ER initiation studies conducted in the U.S. (Morgan et al., 2021; Stein et al., 2022). Relatively low BUP-ER retention rates observed in our study in comparison to those from clinical trials, in combination with frequent re-initiation of BUP-ER among those who discontinue may reflect barriers to accessing BUP-ER in some communities, withdrawal symptoms due to inadequate dosing, and side effects that have been reported with BUP-ER (Haight et al., 2019; Indivior UK Limited, n.d.). Given that retention in opioid agonist treatment is associated with a reduced risk of mortality and opioid-related acute care (Gomes et al., 2022a; Larochelle et al., 2018; Pearce et al., 2020; Sordo et al., 2017; Wakeman et al., 2020), more research is needed to understand the drivers of BUP-ER discontinuation and inform opportunities for improved retention, particularly for people living in more rural and remote areas who often experience challenges accessing more traditional forms of OAT that require frequent healthcare interactions (Pijl et al., 2022). There is also a need for future research to examine health outcomes, such as all-cause and opioid-specific mortality and quality of life among people who discontinue BUP-ER, in order to help develop and guide clinical and social support services.

In our study, over half of people initiating BUP-ER were concurrently treated with buprenorphine/naloxone (52.0%), a practice which is not described in the product monograph (Indivior UK Limited, 2022) but has been suggested in guidance documents for patients whose withdrawal symptoms return before the next injection date (META:PHI, n.d.). Furthermore, over one-quarter of individuals eligible for a dose reduction either increased their dose back to the highest dose (300 mg) or only ever received the highest dose. These findings are similar to a retrospective case series in a US clinic, which found that 55% of BUP-ER initiators required supplementation with sublingual buprenorphine (Peckham et al., 2021) and a US study using administrative data which found that over one-quarter of individuals did not have a reduction on their third dose as recommended (26%) (Morgan et al., 2021). Together, our findings of preference for higher BUP-ER doses and supplementation with buprenorphine/naloxone suggests possible treatment inadequacy with current manufacturer guidelines. Reasons for these findings could include higher drug tolerance caused by the increase of fentanyl in the unregulated drug supply (Canadian Centre on Substance Use and Addiction, 2022; Ontario Agency for Health Protection and Promotion Public Health Ontario, 2023; UNODC, 2022) and difficulties in shifting habits from daily to monthly doses (META:PHI, n.d.). Individuals with lived experience who contributed as co-authors on this study also described these as important factors influencing their own patterns of buprenorphine/naloxone supplementation. Further, more healthcare visits are likely required to address withdrawal concerns and OAT supplementation, which may limit the convenience of BUP-ER and hinder accessibility in rural and remote areas. These findings suggest the potential benefits of increased dosing options beyond the 100 mg and 300 mg forms of BUP-ER currently available which may allow for better response to withdrawal symptoms, more gradual transitions from 300 mg to 100 mg, and increased dose options for people who may benefit from sustained treatment at doses above 100 mg. Future research should explore the effectiveness of various BUP-ER doses among people exposed to fentanyl to best support people who would benefit from BUP-ER treatment.

While our study provides preliminary insight into BUP-ER use at the population-level using pharmacy claims data from Ontario, Canada's most populous province, they may not be generalizable to other jurisdictions – particularly those without publicly funded healthcare systems and listing of BUP-ER on public drug formularies. Second, because we do not have data on medications provided during inpatient hospitalizations or in correctional facilities, we cannot capture BUP-ER initiation in hospital settings or correctional institutions. It is therefore possible that some individuals within the studied cohort were initiated in those settings and may therefore have an earlier initiation date than reported in our study, although our exclusion of those not recently inducted on buprenorphine/naloxone from community pharmacies may mitigate this issue. It is important to note that because we excluded those not recently dispensed buprenorphine/naloxone, any OAT and buprenorphine/naloxone prescription use is likely an overestimate of prior use. Similarly, we were unable to censor continuous use of BUP-ER upon incarceration, and therefore individuals who became incarcerated during the study period may have been misclassified as having discontinued treatment. However, we expect that this would affect only a small proportion of the study population. Third, while our report captures the dispensing of BUP-ER prescriptions, it cannot quantify the extent to which people used the dispensed medication (i.e., it is unknown whether the individual attended their appointment to receive the injection), although given standard clinical practice related to BUP-ER administration, it is likely that the injection was administered in most cases. It is also possible that prescribers are reducing 300 mg doses of BUP-ER off-label, to allow for doses that range between 100 mg to 300 mg. This was described as occurring by an individual with lived experience on the study team during their time on BUP-ER treatment. Thus, there may be a proportion of doses administered that are lower than reported, although it is impossible to assess this practice using the current data. Also, our analysis was restricted to those who used a provincial health card at the dispensing pharmacy (3.2% of claims were excluded because a different identification type was used), and therefore excludes any First Nations people using a First Nations status card. We therefore anticipate that a large proportion of First Nations people dispensed BUP-ER are not included in this analysis. Future research with First Nations populations is thus warranted. Lastly, the analysis was not pre-registered, thus the results should be considered exploratory.

5. Conclusion

Our study provides timely and new insight into the uptake, retention and treatment patterns of BUP-ER, a novel treatment option for OUD, at the population-level. Our results demonstrate that BUP-ER retention in a real-world setting is relatively low; on average, people discontinue BUP-ER within the first 6 months of treatment. Furthermore, our findings suggest that dose adjustments recommended by the manufacturer may not be meeting the needs of individuals accessing BUP-ER in the community. Finally, frequent supplementation with buprenorphine/naloxone warrants further investigation on safety and effectiveness. While BUP-ER is likely providing an important alternative OAT option to people with OUD – particularly among those living in rural and remote areas – more research is urgently needed to understand factors influencing long-term retention and dosing patterns in the real-world and in the context of fentanyl use.

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CRediT authorship contribution statement

All authors were involved in study conception, design and interpretation. Tianru Wang led data acquisition and conducted the analysis. Tara Gomes supervised and secured funding for the project. Anita Iacono drafted the manuscript and all other authors critically reviewed the manuscript and have approved the submitted version.

Declaration of Competing Interest

None to declare.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2023.111032.

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