Treatment Retention with Monthly Buprenorphine Extended-Release Injection: Results From a Canadian Rapid Access Addiction Medicine Clinic: 21 Month Data

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Abstract

The primary objective of this cohort analysis was to elucidate the factors associated with continued attendance at the Rapid Access Addiction Medicine (RAAM) clinic in London, Canada in participants who were receiving a monthly buprenorphine extended-release injection (BUP ER SC). Data was collected between October 2019 and June 2021 (21 months).

It has been established that longer retention in Opioid Agonist Treatment (OAT) correlates with increased treatment success in terms of reducing illicit opiate use and apparent opiate toxicity deaths (AOTD).

Introduction

The opioid crisis in Canada has taken an increasingly greater toll during the Covid-19 outbreak, with the number of AOTD doubling compared to the same period of time before the pandemic, and reaching the highest levels since national surveillance began in 2016.[1]

Some of the factors worsening the opioid crisis are: an increasingly toxic drug supply, compound stressors, and limited ability to access addiction services.

In Canada in 2020, there were about 17 AOTD per day, almost all of which were unintentional.

Over 80% of the AOTD were due to fentanyl, and 99% of fentanyl used was non-pharmaceutical in origin.

Almost 85% of apparent stimulant toxicity deaths (ASTD) in Canada in 2020 involved an opioid.

One of the strategies to combat AOTD is to use opioid partial agonists such as buprenorphine, which have a wider margin of safety than full agonists. A further step in the quest to decrease the potential for prescription diversion and to increase medication participation rates is to administer buprenorphine as an extended-release monthly injection (BUP ER SC).

A rapid access addiction medicine (RAAM) clinic is a low-barrier, walk-in clinic that people can attend to get help for a substance use disorder without an appointment or formal referral. RAAM clinics provide time-limited medical addiction care (including pharmacotherapy, brief counselling, and referrals to community services).[2]

Prerequisite for Entrance into the Study

Participants had different start dates and stayed in the cohort analysis for variable periods of time over the 21 months of data collection. Data for the first 75 people who were able to access the BUP ER SC are reported here.

Ethics Approval

The Western University Health Science Research Ethics Board (HSREB) reviewed and approved the data collection for this cohort analysis (Western University is located in London, Canada).

Participant Characteristics

In order to make this cohort analysis as "real world" as possible, the only inclusion criterion was the ability to access the BUP ER SC. There were no exclusion criteria. The first 75 people who were able to access the injection at the London RAAM Clinic participated in this analysis. Their demographic details are summarized in Table 1.

Table 1. Participant Demographics

Variable		
Age	Mean (SD)	39y (11)
	Median (range)	38y (16-62)
Gender	Female, n (%)	29 (38.7%)
	Male, n (%)	46 (61.3%)
Opioid of Choice	Fentanyl, n (%)	33 (44%)
(some used	Heroin, n (%)	3 (4%)
combinations)	Other, n (%)	70 (93.3%)
Sublingual Buprenorphine-Naloxone Stabilization Dose	Mean (SD)	15mg (7)
	Median (range)	16mg (8 – 48)
Previous Opioid Agonist Therapy (OAT)	Yes, n (%)	75 (100%)
Non-fatal opioid toxicity history	Yes, n (%)	27 (36%)

Cohort Analysis Design

Participants were stabilized on sublingual buprenorphine/naloxone (ᴺSuboxone®) (BUP/NLX SL) at a minimum of 8mg for seven days (as per the product monograph for ᴺSublocade™).[3] Initial BUP ER SC dosing was 300mg for the first two doses (as per the Canadian product monograph).[3] Beyond this, the dosing was flexible based on participant reports of withdrawal symptoms, craving, expressed wishes, etc.

Participants were not told what dose their next injection was going to be — that determination made at the time of the next clinic.

Outcome Definitions

The Canadian product monograph for treatment with buprenorphine extended-release injection (ᴺSublocade™) specifies administration every four weeks. Delays of up to 2 weeks are not deemed to significantly impact treatment.[3] Since participants can be unpredictable in their clinic attendance, it is often advantageous to have a flexible approach to the resumption of BUP ER SC therapy.

A previous investigation[4] defined **retention** and **discontinuation** from treatment in three different ways:

- **6-Week Treatment Gaps**
Study subjects were considered to have discontinued treatment if there was a gap of longer than six weeks between injections,

- **8-Week Treatment Gaps**
Study subjects were considered to have discontinued treatment if there was a gap of longer than eight weeks between injections, and

- **Flexible Re-Entry Approach**
Study subjects are permitted to return to the injection program at any time.

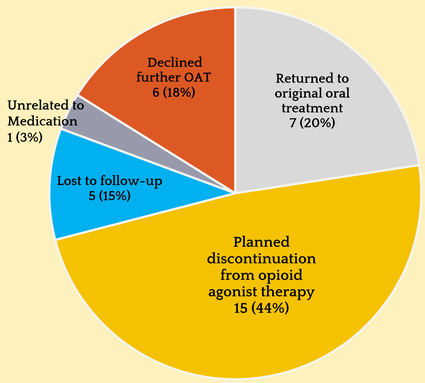
Discontinuation Details

There were seven different pathways that participants could take once in the program:

1. **Stayed in the program**
2. **Returned to original oral treatment**
   - ✓ Returned to methadone or BUP/NLX SL generally seeking better pain reduction, but remaining in Opioid Agonist Therapy (OAT)
3. **Planned discontinuation from OAT**
   - ✓ Wished to taper off all OAT; some used BUP ER SC for a gradual, steady taper believing that they had "graduated" from OAT
4. **Moved away**
   - ✓ Stayed on BUP ER SC in another program
5. **Drop-out unrelated to BUP ER SC/OAT**
   - ✓ Alcohol-related seizures, hospitalization or incarceration were reasons for drop-out
6. **Opioid preference**
   - ✓ Preferred to keep using illicit fentanyl
7. **Lost to follow-up**
   - ✓ No known explanation provided for departure

The breakdown is summarized in Chart 2

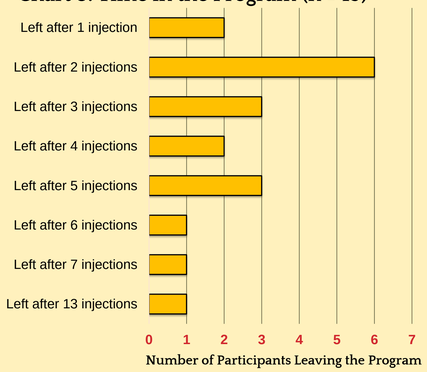
Chart 2: Departures From the Program



Calculation of Retention Time

Participant time in the program was calculated based on the first missed injection. For example, someone who received injections 1 and 2, but not the third, was deemed to be a drop-out at 3 months (since the BUP ER SC was considered to be active for the additional month). The distribution of number of injections received is summarized in Chart 3.

Chart 3: Time in the Program (n = 19)



Data Collection Specifics

Participants were enrolled in this cohort analysis as soon as the first BUP ER SC dose was given. Follow-up injections were booked at 28-day intervals. Data were analyzed using the above three definitions of retention:

If participants presented longer than 6 weeks but less than 8 weeks since the last injection, they were assessed and either re-initiated on BUP /NLX SL or given BUP ER SC (depending on clinical circumstances, such as ongoing illicit opioid use).

If participants presented longer than 8 weeks since the last injection, they were re-initiated on BUP/NLX SL up to a minimum dose of 8mg for one week and then were re-started on BUP ER SC as per the Canadian product monograph.

Analysis of Retention Rates

Retention rates varied depending on which definition/time frame was used, with the more stringent definitions showing lower values. Kaplan-Meier plots were generated to estimate retention. A summary of the retention rates appears in Table 2.

Table 2. Program Retention Details at 21 Months

Definition	Retention n (%)	Median Retention Time (days)	Kaplan-Meier Estimate at End of Study
6-Week Gap	40 (53.3%)	379	39.6%
8-Week Gap	44 (58.7%)	Not calculable	50.6%
Overall Retention	56 (74.7%)	Not calculable	71.1%

Overall, 19 of 75 participants discontinued taking BUP ER SC. Using the flexible re-entry approach, 71% remained in the program. The distribution of retention times was similar for all three definitions of retention.

Focus on Fentanyl Users

33 of the 75 participants (44%) were using fentanyl at the time of presentation to the RAAM Clinic. The overall retention rates were slightly higher in the fentanyl group, but these differences were not of statistical significance. A summary of retention rates on BUP ER SC by treatment gap definition and use of fentanyl.

Table 3. Program Retention By Retention Definition and Fentanyl Use (adjudicated for planned transitions)

Retention Definition	Fentanyl Use?	Retention n (%)	Median Retention Time (days)	Kaplan-Meier Estimate
6-Week Gaps	**No**	23 (54.8%)	401	41.0%
	Yes	17 (51.5%)	379	38.0%
8-Week Gaps	**No**	25 (59.5%)	Not calculable	54.2%
	Yes	19 (57.6%)	379	43.6%
Overall Retention	**No**	31 (73.4%)	Not calculable	69.2%
	Yes	25 (75.8%)	Not calculable	74.6%

Fentanyl Participant Pathway

People using fentanyl may have a different pathway in a clinic that administers BUP ER SC:

- They are more prone to leaving the program after the second injection of BUP ER SC, possibly because they anticipate the dosage to decrease
- They are more likely to request the 300mg dosage of BUP ER SC for maintenance
- Use of fentanyl while taking BUP ER SC is reported to have little euphoric effect, and usually causes sedation or fatigue
- The stability of life on BUP ER SC does resonate, as the retention rates are virtually the same as with the non-fentanyl user group

What Happened Between 15 to 21 Months?

With the flexible re-entry approach taken by the London RAAM, some of the participants who left before the 15 month point returned to the clinic at some point in the next 6 months to resume treatment with BUP ER SC. All of the participants who returned were fentanyl users. Only 40% of the participants received all of their injections on time.

Conclusions and Key Findings

There is a significant retention advantage to "flexible re-entry" into the BUP ER SC program. If the 6 or 8 week cut-off was waived, participants can easily be re-started on BUP ER SC with a view to resuming the injection after a short period of stabilization. The retention cohort jumped from 50 to 60 to > 70% with the 6 week vs. 8 week vs. flexible re-entry criteria (respectively).

There were no deaths due to overdose/ apparent opioid toxicity in the participants who remained on BUP ER SC. The analysis has expanded beyond the 75 initial participants and the June 30th 2021 data cut-off for this analysis, and this positive safety signal still holds.

The two main factors that appeared to be related to requests for the higher maintenance dose of 300mg of BUP ER SC were the presence of **chronic pain** and **prior use of fentanyl**. Sixteen participants of the 75 in the analysis requested 300mg as the maintenance dose, and of this number, 6 experienced chronic pain and 7 had used illicit fentanyl. The stabilizing dose of BUP/NLX SL prior to the initiation of BUP ER SC was not a strong predictor of requests for the 300mg dosage as maintenance since participants were generally transitioned to the BUP ER SC as soon as possible.

References

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