Retention in care for persons with opioid use disorder transitioning from sublingual to injectable buprenorphine

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ABSTRACT

Introduction: In the current overdose epidemic, effective treatments for opioid use disorders (OUD), including innovations in medication delivery such as extended-release formulations, have the potential to improve treatment access and reduce treatment discontinuation. This study assessed treatment retention in a primary care–based, extended-release buprenorphine program.

Methods: The study recruited individuals (n = 92) who transitioned from sublingual buprenorphine to extended-release buprenorphine (BUP-XR) in 2018–2019. The study defined the primary outcome, treatment retention, as three or more consecutive, monthly BUP-XR injections following the transition to BUP-XR in this retrospective chart review.

Results: Participants’ mean age was 38 years old and 67% were male. The average duration of sublingual buprenorphine prior to transition was 17.1 (±28.1) months. Three months after transition, 48% of extended-release buprenorphine patients had discontinued BUP-XR treatment. Persons with chronic pain were more likely, and those who had used heroin in the past month less likely to continue BUP-XR. Mean months on sublingual buprenorphine prior to BUP-XR initiation was 24.3 (±32.5) months for people who received 3+ post-induction injections compared to only 8.9 (±19.5) months for those who did not (p = .009).

Conclusions: Extended-release buprenorphine discontinuation was high in a real-world setting. Retention continues to represent a major obstacle to treatment effectiveness, and programs need interventions with even newer MOUD formulations.

1. Introduction

Opioid use disorder (OUD) continues to be a global health concern, affecting more than 26 million individuals worldwide (Ahmad, Rossen, & Sutton, 2021; World Health Organization, 2018). In the United States, the Centers for Disease Control and Prevention estimates that 2.6 million Americans have an OUD and that between 1999 and 2017, approximately 400,000 people had died from opioid-related overdose (Scholl, Seth, Kariisa, Wilson, & Baldwin, 2018).

Office-based opioid treatment (OBOT) with buprenorphine has expanded rapidly in the past fifteen years, both in the United States and abroad (Alderks, 2013; Morgan, Schackman, Leff, Linas, & Walley, 2018). In 2002, the Food and Drug Administration approved the use of sublingual buprenorphine as an agonist alternative to methadone for the treatment of OUD. Commonly co-formulated with the opioid antagonist naloxone (NX), combination (BUP-NX) is designed to alleviate symptoms of opioid withdrawal and reduce craving, thus decreasing illicit opioid use, and prolonging survival. Since its inception as an OUD treatment, buprenorphine sales have increased exponentially: the number of milligrams of buprenorphine sold by pharmacies in the United States increased from almost 270 million in 2006 to more than 3.58 billion in 2018 (Department Of Justice Drug Enforcement Administration [DEA] Diversion Control Division).

The expansion of OBOT treatment and increase in availability of...
sublingual buprenorphine in the marketplace raised new concerns about medication diversion among policy-makers and providers (Butler, Black, Severtson, Dart, & Green, 2018; Johanson, Arfken, di Menza, & Schuster, 2012; Lofwall & Walsh, 2014). As with any oral medication used daily, sublingual buprenorphine adherence remained a concern as well, as nonadherence might signal a return to use of nonprescribed opioids. Indeed, Greiner et al. (2021) demonstrated that 39% of those stopping buprenorphine for OUD relapsed to regular opioid use within 12 weeks. In 2017, the FDA approved a subcutaneous, extended-release depot injection of buprenorphine (BUP-XR), comparable in safety and efficacy to BUP-NX (Haight et al., 2019), for persons who have first been stabilized with sublingual buprenorphine. In addition, proponents of the injectable formulation hypothesize that it is likely to address many of the concerns with take-home BUP-NX medications, including diversion, daily fluctuations in plasma concentrations (Greenwald et al., 2007), poor daily adherence (Fareed et al., 2014; Tkacz, Volpicelli, Un, & Ruetsch, 2014), medication misuse (Cicero, Ellis, Surratt, & Kurtz, 2014), accidental poisoning in children (Budnitz et al., 2016), and possibly provide improvements in treatment retention. In a randomized trial, Lofwall et al. (2018) compared sublingual buprenorphine to injection (weekly for twelve weeks and monthly for 12 weeks) and did not find a difference in retention in treatment, but did find modest advantage for the injections in measures of opioid use. This suggested that an extended-release injection may prevent discontinuation of treatment, but may avoid lapses of medication-taking for a few days (as may occur with daily sublingual use) that could lead to return to illicit opioid use. However, few studies have published on BUP-XR use and patient outcomes in real world settings.

Retention in treatment for medication for opioid use disorders (MOUD) is associated with better outcomes—reduced mortality, decreased drug use, and improved quality of life (Bart, 2012; Timko, Schultz, Cucchiare, Vittorio, & Garrison-Diehn, 2016). Research on discontinuation from MOUD treatment for those first starting medications has suggested that continued substance use (Fareed et al., 2014; Ferri, Finlayson, Wang, & Martin, 2014; Hser et al., 2014) is the paramount drop-out risk. Factors predicting treatment discontinuation have also included Black or Hispanic race (Hser et al., 2014), male gender (Ohlin, Fridell, & Nyhlen, 2015), younger age (Gryczynski et al., 2014), and greater psychiatric comorbidity (Fareed et al., 2014; Ferri et al., 2014; Hser et al., 2014; Savant et al., 2013) Research has not investigated patient factors associated with discontinuation of BUP-XR following a transition from prolonged prior sublingual buprenorphine use.

In this first study of the transition from sublingual (SL) BUP-NX to injectable BUP XR in a primary care office-based setting, our aim was to quantify BUP-XR retention and examine predictors of retention. We hypothesized that longer prior MOUD treatment, less illicit opioid use in the period prior to transition, and fewer psychiatric comorbidities would predict better BUP-XR continuation rates.

2. Methods

2.1. Participants

We reviewed the electronic health records of 92 consecutive persons with OUD who transitioned to BUP-XR treatment from sublingual BUP-NX at Stanley Street Treatment and Resources (SSTAR) in Fall River, Massachusetts, and received a first injection there between July 2018 and December 2019. To receive a first injection, patients had to be stabilized on a BUP-NX dose between 8 and 24 mgs per day, have health insurance that would reimburse for the administration of BUP-XR, and agree to the injectable formulation. BUP-XR was administered at the same program, by the same staff that had prescribed sublingual BUP-NX. The initial two doses (month 1 and month 2) of BUP-XR were 300 mg followed by a reduction to 100 mgs per month (starting in month 3). In the first months of treatment, if the patient experienced withdrawal or cravings, they could be supplemented with small doses (2–4 mg/d) of sublingual BUP-NX. If the need for supplementation continued, the BUP-XR dose was continued at 300 mgs per month.

2.2. Measures

We assessed demographic information, self-report drug use and treatment history using electronic medical records. Demographic sample descriptors included age, gender, and race/ethnicity. The study defined chronic pain as having an EMR-listed diagnosis. Drug use variables included lifetime history of injection drug use (yes/no), overdose in the past year, and months receiving sublingual buprenorphine prior to BUP-XR initiation. Finally, we determined the number of consecutive, monthly injections received. The Butler Hospital Institutional Review Board approved this study.

2.3. Analyses

The study followed patients for six months after induction. Our primary outcome was proportion of persons receiving at least 3 injections (yes/no) following the initial dose, suggesting clinical stability on the new buprenorphine formulation. We summarize sample characteristics using t-tests and chi-square tests to check for statistically significant differences in subject characteristics between the two groups. Because of the small n, statistical power is relatively low, and this study also reports Cohen’s d and h statistics giving standardized differences in means and proportions, respectively.

3. Results

Participants averaged 37.6 (±7.9) years of age, 67.4% were male, 90.2% were White, and 13.0% were Latinx (Table 1). Twenty-two (23.9%) had a chronic pain diagnosis, 34 (39.1%) had used heroin in

Table 1

<table>
<thead>
<tr>
<th>Background characteristics by completion of BUP-XR treatment protocol. cell entries are mean (±SD) or n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3+ BUP-XR injections</strong></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Years age</td>
</tr>
<tr>
<td>Sex (Male)</td>
</tr>
<tr>
<td>Race (White)</td>
</tr>
<tr>
<td>Ethnicity (Latinx)</td>
</tr>
<tr>
<td>Chronic pain diagnosis (yes)</td>
</tr>
<tr>
<td>Used heroin in 3 M before initiation (yes)</td>
</tr>
<tr>
<td>Injection drug use (yes)</td>
</tr>
<tr>
<td>Months on buprenphine</td>
</tr>
<tr>
<td>Major depression or bipolar disorder (yes)</td>
</tr>
<tr>
<td>Anxiety disorder (yes)</td>
</tr>
<tr>
<td>Psychotic disorder (yes)</td>
</tr>
<tr>
<td>Any mental health diagnosis (yes)</td>
</tr>
</tbody>
</table>

*a* Pearson χ² test of independence or t-test for difference in means.

b* Cohen’s standardized difference in means.

c* Cohen’s standardized difference in proportions.
the month prior to baseline, and 72.8% had a lifetime history of injection drug use. On average, participants had been on BUP-NX for 17.1 (±28.1) months. About 34.8% had major depression or bipolar disorder, 35.9% an anxiety disorder, 3.3% had schizophrenia or another psychotic disorder, and 67.4% had a positive diagnosis for any of the above disorders. Following the initial BUP-XR injection, 12% received no additional injections, 22% received one additional injection, 14% received two additional injections, and 52% received three or more injections.

A higher percentage of persons who had 3+ BUP-XR injections following the induction dose had chronic pain (33.3% vs 15.9%, p = .027). About 54.8% of persons who did not reach three post–induction injections had used heroin in the 3 months prior to induction, compared to 24.4% for persons who did have 3+ injections (p = .004). Mean months of sublingual buprenorphine prior to BUP-XR initiation was 24.3 (±32.5) months for persons who received 3+ post–induction injections compared to only 8.9 (±19.5) months for those who did not (p = .009). Between group differences on other background characteristics compared in Table 1 were generally small substantively. At the time of their last (for this study) injection, 11.4% of persons with <3 shots were positive for opioids on a urine toxicological screen. Among those with 3+ shots, 4.2% tested positive when screened prior to their third injection.

Most persons who did not complete 3+ BUP-XR injections returned to sublingual buprenorphine treatment (n = 34; 77%). All individuals who returned to sublingual buprenorphine did so within 45 days of their last injection. Seven persons left buprenorphine treatment altogether and three did not complete 3+ injections because they lost insurance coverage. No severe adverse events occurred in this study, and no one discontinued because of an adverse event.

4. Discussion

Treatment programs need new approaches to address the opioid overdose epidemic, as retention on MOUD continues to be a major barrier to OUD treatment efficacy. In this observational cohort study of persons with OUD who had been using daily sublingual buprenorphine and then sought monthly injectable buprenorphine treatment, nearly half (47.8%) received fewer than three additional monthly injections following their initial injection in a primary care–based buprenorphine treatment program.

In studies of BUP-XR as the initial OUD treatment—rather than transition from prolonged use of a sublingual formulation as we describe here—Morgan et al. reported that three months after initiation 50% (95% confidence interval [CI] 40%–60%) of patients on extended-release buprenorphine had discontinued BUP-XR in a commercially insured population. While this high rate of discontinuation is notable, Morgan et al.’s comparison with other MOUDs—64% (95% CI 61%–69%) of extended-release naltrexone, 34% (95% CI 33%–35%) of mupasant buprenorphine/naloxone, and 58% (95% CI 54%–62%) of methadone initiators—suggests the problem of treatment retention is formidable regardless of medication type.

Here, we found that heroin use in the three months prior to transition of BUP-XR was a negative predictor of retention in BUP-XR treatment. This finding is consistent with earlier data regarding sublingual buprenorphine (Fiellin et al., 2008; Stein, Cioe, & Friedmann, 2005). Recent heroin use suggests uncontrolled cravings and may contribute to or portend relapse following MOUD treatment termination. Persons with a chronic pain diagnoses remained in BUP-XR treatment longer. Chronic pain is common among persons with OUD and is a relapse risk (Stein et al., 2015). Shulman et al. (2020) showed in a large cohort that after initiating buprenorphine or XR naltrexone, pain was associated with relapse to opioid use. Persons with chronic pain may have greater pain relief on BUP-XR than with sublingual buprenorphine due to the higher steady state medication level, and this analgesia may prompt persons to remain in BUP-XR treatment. Those with chronic pain may also be more connected with general medical care at the clinic, helping them to engage in buprenorphine care. Providers could augment BUP-XR with as-needed sublingual buprenorphine in this program, and this arrangement may have been helpful, although we lack systematic data on how often such augmentations occurred. We do not know whether any additional doses were used for pain episodes or to reduce opioid urges.

Our finding that duration of prior sublingual therapy was associated with remaining on BUP-XR is consistent with the notion that longer treatment may indicate greater life stability and commitment to remaining opioid free. Alternately, persons receiving buprenorphine longer may be more stable in their home and emotional life and therefore willing and able to tolerate whatever physical or psychological changes transitioning successfully to a “new” injectable medication requires, where one necessarily gives up daily control of medication use, such as dosing at a preferred time of day.

Having a documented psychiatric diagnosis was not statistically associated with treatment discontinuation (p = .14), but the documented effect size suggests directionally that psychiatric diagnosis may play a role in long-term care. Research has found lifetime diagnosis of depression to be associated with decreased opioid use in persons receiving buprenorphine (Dreifuss et al., 2013); other work has also noted increased odds of achieving opioid abstinence in persons with any psychiatric diagnosis (Griffin et al., 2014). Buprenorphine may have some antidepressant effects (Dreifuss et al., 2013), but also patients with psychiatric co-morbidities may be more highly motivated to continue medical treatment generally (Griffin et al., 2014; Saunders et al., 2015).

Our study had limitations. The study recruited the relatively small sample from a single treatment program. Second, health insurance coverage is nearly universal in Massachusetts, and was not a barrier to initiation, which may be a structural impediment in other states, although as described here lapses in insurance may interfere with treatment at times. Third, the study did not assess reasons for the transition to BUP-XR. Anecdotally, we know that such transition could have been clinician-directed—for those persons known to be diverting medication, who were demonstrating ongoing illicit opioid use, or who were having difficulty attending clinic appointments—or patient-directed, due to adverse reactions to the sublingual formulation (strong aversion to the taste, lengthy dissolution times), or due to preference for the convenience of BUP-XR. Fourth, we did not collect data about ongoing use of opioids or other substances during the entire study period so we do not know abstinence rates or if compensatory use of other drugs occurred during BUP-XR treatment. Fifth, we do not know the reasons for BUP-XR discontinuation, which could have included the pain of injections, or perhaps the long duration of BUP-XR’s effect whereby patient do not feel the need for a monthly dose. Sixth, for those 77% who returned to sublingual buprenorphine after XR-discontinuation, we do not know if any gap in medication coverage produced a lapse of consequence. Finally, we were not able to assess additional predictive psychosocial factors that might have been collected with an in-person interview. Certainly, data from large, prospective studies of BUP-XR transitions would be of interest.

In conclusion, retention in BUP-XR remains problematic, and treatment programs need novel behavioral retention interventions. Long-acting depot formulations of MOUD offer novel treatment options, but they are not a panacea, and shared-decision making around treatment remains critical. Still, these real-world data begin to build the evidence base to inform treatment decisions that patients, clinicians, payers, and policy-makers face.

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CRediT authorship contribution statement

Stein - conceptualization, methodology, writing original draft,
supervision.
Bailey - resources, writing review and edit, supervision.
Herman - writing review and edit, project administration, supervision.
Anderson - formal analysis, writing review and edit.
Vannoppen - investigation, data curation, writing review and edit.

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