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Case Series: Rapid Induction Onto Long Acting Buprenorphine Injection for High Potency Synthetic Opioid Users

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Abstract

Background and Objectives: Highly potent synthetic opioids (HPSO) are increasingly responsible for opioid overdose deaths in the United States.

Methods: In an open-label, uncontrolled trial to test the feasibility of extended-release buprenorphine (BXR) injection treatment of heroin-using individuals with opioid use disorder testing positive for HPSO, participants were enrolled and began an induction with sublingual BXR ($n = 5$). During the induction, ancillary medications (clonidine, clonazepam, zolpidem, and prochlorperazine) were provided for breakthrough opioid withdrawal symptoms.

Results: Two participants received the BXR injection on the second day of the induction and three participants on the third day.

Discussion and Conclusion: All five participants were retained at least 1-month postinduction.

Scientific Significance: It may be feasible to provide BXR treatment to HPSO-positive heroin users rapidly to achieve clinical stabilization. (*Am J Addict* 2020;29:345–348)

INTRODUCTION

It is estimated that 2.4 million Americans meet criteria for an opioid use disorder (OUD).¹ The epidemic continues to evolve, with highly potent synthetic opioids (HPSO) driving recent increases in overdose death rates.² From 2014 to 2015, the overdose death rate due to HPSO increased 72.2%, from 2015 to 2016 the death rate increased 100%, and from 2016 to 2017 the death rate increased 45.2%.^{3,4} In 2017, approximately 68% (47 736) of the more

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Declaration of Interest

Drs Mariani, Naqvi, Iqbal, and Luo reported no biomedical financial interests or potential conflicts of interest. Also, Ms Mahony reported no biomedical financial interests or potential conflicts of interest. Dr Levin has acted as an unpaid consultant for Alkermes and US WorldMeds. The authors alone are responsible for the content and writing of this paper.

Clinical Trial Registration

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than 70 200 drug overdose deaths involved an opioid; HPSO accounted for 59.6% (28 466) of opioid overdose deaths, making HPSO the driving force in opioid overdose deaths.³ In New York City, from 2010 to 2017, unintentional overdose deaths increased from 8.2 per 100 000 residents to 21.2 per 100 000 residents. In 2017, 82% of all overdoses involved an opioid, and for the first time, the most common substance associated with overdose deaths were (57%) fentanyl analogues.⁵ Prior to 2015, fentanyl analogues never accounted for more than 3% of the overdose fatalities in New York City. The US opioid epidemic is evolving rapidly, and for our research group located in New York City, the changes have been dramatic.

HPSO are a class of full agonists at the μ -opioid receptor that include fentanyl, fentanyl analogues (eg, sufentanil, alfentanil, remifentanil, and carfentanil), and other novel synthetic opioids (AH-7921, U-47700, and MT-45). Fentanyl is a synthetic opioid approximately 50 to 100 times more potent than morphine, originally developed as a rapidly acting pain reliever.^{6,7} The estimates of potency for HPSO range up to 10 000 times that of morphine (eg, carfentanil).⁸ High lipophilicity,⁹ with rapid crossing of the blood-brain barrier, and high μ -opioid receptor affinity,¹⁰ are thought to be responsible for the clinical effects observed with HPSO, although definitive human studies are lacking.

Pharmacotherapy is a standard treatment recommendation for OUD and available treatments in the United States include methadone, buprenorphine (BXR), and extended-release naltrexone for injection. However, there are scant available data regarding the efficacy of these treatments for HPSO users. In 2018, the first extended-release BXR for injection (Sublocade; Indivior)¹¹ formulation became commercially available in the United States. As with other depot medication treatments, it is reasonable to expect that a depot injection formulation will offer advantages in compliance and treatment outcomes. This BXR formulation maintains a μ -opioid receptor occupancy of at least 70% for 2 weeks beyond the scheduled dose,¹² which theoretically provides an advantage in ensuring compliance. We hypothesized that the advantage that BXR offers, enhanced treatment compliance, would be a notable advantage for individuals with OUD positive for HPSO. In our New York City-based research clinic, approximately 90% of heroin users test positive for HPSO, and most are unaware of this status. As a test of the feasibility of BXR treatment for heroin-using OUD individuals positive for HPSO, we planned a small uncontrolled pilot study.

METHODS

This study was approved by the New York State Psychiatric Institute Institutional Review Board and eligible participants signed consent. The study presented in this report is the first phase of an ongoing research project. Participants were 18 years of age or older, were voluntarily seeking treatment for heroin use, met DSM-5 criteria for OUD as a primary diagnosis, and tested positive for HPSO use. All participants were daily heroin users physically dependent on opioids. Potential participants were excluded for: a substance use disorder other than opioid as the primary diagnosis, having a psychiatric diagnosis that might interfere study participation, methadone or BXR maintenance treatment, having an allergy to BXR, pregnancy or lactation, unstable medical conditions, or being physiologically dependent on alcohol or sedative-hypnotics.

Sublingual (SL) BXR treatment is required prior to administering BXR to confirm that the participant has an adequate opioid tolerance. The prescribing instructions for this BXR formulation require that patients receive at least 8 mg of SL BXR for at least 7 days prior to receiving the first injection. We were interested in testing the feasibility of a more rapid administration schedule BXR to HPSO-positive participants. Our initial plan was to administer BXR on the fourth day of SL BXR administration. As clinical trial operations progressed, we quickly surmised that any delay after determining the patient had an adequate opioid tolerance to receive BXR 300 mg would put the participant at risk for a failed induction. Our concern was that each day that the injection was delayed there was a risk of relapse to heroin-HPSO use. Therefore if there was no clinical advantage in waiting after tolerance to BXR was established, advancing the injection schedule sooner, could establish more rapid clinical stability, as once the participant received the injection the effects of heroin-HPSO would be mostly blocked. We modified the protocol to immediately proceed to the BXR 300 mg injection after a participant received and tolerated at least 16 mg of BXR on two consecutive days.

The SL BXR induction was initiated once participants achieved a clinical opioid withdrawal scale (COWS) score greater than 6. This is a COWS threshold for starting BXR that we have used successfully in prior research studies. SL BXR (up to 24 mg per day) was discontinued after the BXR injection was administered. During the induction, ancillary medications (clonidine, 0.1 mg up to six times daily; clonazepam, 0.5 mg up to three times daily; zolpidem, 10 mg; prochlorperazine, 10 mg) were provided for breakthrough opioid withdrawal symptoms during the induction and for 2 days after the BXR injection.

RESULTS

The participant outcomes are outlined in Table 1. All five participants who started the SL BXR induction received the BXR injection and continued in the trial for at least 4 weeks. One additional participant signed consent, was not in adequate withdrawal to begin the induction, received instructions to return to the clinic in withdrawal the next day, but was lost to follow up.

DISCUSSION

The presence of HPSO in the heroin supply is a recent phenomenon and there are minimal empiric data on how to treat these patients available. We conducted an open-label investigation of the use of BXR for HPSO-positive individuals to determine the optimal dosing strategy. We are unaware of any published reports of the use of BXR to specifically target HPSO-positive individuals.

We initially planned to administer BXR after participants received at least 8 mg of SL BXR for 3 days (3-day SL BXR induction, day 4 BXR injection), which was a more rapid injection schedule than provided in this BXR formulations prescribing instructions. We planned this more rapid schedule based on the following considerations: (a) patients testing positive for HPSO have inherently a high opioid tolerance and therefore a low risk of BXR overdose; (b) 3 days of 8 mg SL BXR would demonstrate adequate tolerance to BXR; and

(c) the primary advantage of BXR is the depot administration and assurance of compliance and providing this definitive treatment earlier in the induction process would decrease the risk of a failed induction.

As we clinical trial operations began, we quickly came to the conclusion that once adequate tolerance to BXR was established, further delay to administering the BXR injection would put the participant at risk for a failed induction. We modified the protocol to permit more rapid progression to BXR injection and the demonstration of the feasibility of this approach is the main value of this case series.

Observations from these five participants suggest that opioid withdrawal symptoms in HPSO-positive heroin users can develop rapid and severe withdrawal symptoms despite treatment with up to 24 mg of SL BXR. We observed that once HPSO withdrawal begins, symptoms can escalate rapidly despite administering what are usually clinically effective doses of BXR (16–24 mg). Participants who received an average of 16 mg a day for either 2 or 3 days had no difficulty tolerating the BXR 300 mg injection. Within 24 hours after BXR administration, withdrawal symptoms were well controlled. This pattern is consistent with the known pharmacokinetics of this BXR formulation, which is that there is a serum blood level spike approximately 24 hours after administration.¹³

One question is whether BXR-precipitated withdrawal accounted for any of the clinical presentation. BXR-precipitated withdrawal is a clinical phenomenon due to the partial agonist and strong μ -opioid receptor binding properties of BXR. When BXR out-competes full agonists for μ -opioid receptor occupancy, the net level of opioid agonism rapidly drops and withdrawal symptoms occur. The main strategy to avoid BXR-precipitated withdrawal is to delay the first dose of BXR until adequate withdrawal symptoms have developed. We set a COWS threshold of greater than 6 to receive the first BXR dose and started with a 2 mg test dose. In none of the five participants did the COWS score rise immediately after the first BXR dose, as would be expected in BXR-precipitated withdrawal. The pattern we observed was that as the SL BXR induction progressed, opioid withdrawal symptoms initially improved, then worsened over time despite aggressive SL BXR dosing.

We would offer the following conclusions based on our limited experience with using BXR for HPSO-positive outpatients with OUD. Once an adequate tolerance to opioids is demonstrated by tolerating a typical clinical dose of SL BXR (16 mg on 2 consecutive days), there is no clinical advantage to delaying receiving the BXR injection. Administration of BXR reduces withdrawal symptoms within 24 hours of administration; the effects do not appear to be immediate. The fact that we were able to successfully induct onto BXR all five HPSO-positive participants who began the induction is promising. Our clinical observation is that relatively rapid stabilization of HPSO-positive patients can be achieved using BXR.

For future research, we would recommend advancing the BXR injection to the first day of the BXR injection for participants who can tolerate clinical doses of BXR SL (eg, 16–24 mg), to reduce the risk of development of severe withdrawal symptoms and a failed induction. The main clinical challenge of outpatient SL BXR induction is that persistent withdrawal symptoms may lead to BXR non-compliance, relapse, and a failed induction.

This challenge may be heightened with HPSO, where the degree of physical dependence may be greater than with prescription pain medication or heroin. Controlled trials comparing this formulation of BXR and SL BXR for the treatment of OUD positive for HPSO are needed.

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TABLE 1.

Clinical outcomes for participants

Subject	Day 1	Day 2	Day 3	Day 4	Current status
001 28 y/o Male Hispanic	COWS = 10 at start of induction Total BUP-SL = 24 mg (22 mg in clinic; 2 mg take-home at night)	BUP-SL 8 mg at home in morning COWS =11 arrival at clinic BUP-SL 8 mg in clinic COWS = 2 BXR 300 mg injection CsOWS = 0	COWS = 7	COWS =4	Received 3rd BXR injection Retained in trial >8 weeks and continuing to attend study visits No opioid use since day prior to start of induction
003 46 y/o Male Black	COWS = 10 at start of induction Total BUP-SL = 10 mg (8 mg in clinic; 2 mg at home)	BUP-SL 8 mg at home COWS = 4 arrival at clinic BUP-SL 8 mg in clinic BUP-SL 8 mg at home Total BUP-SL = 24 mg	BUP-SL 8 mg at home COWS =11 arrival at clinic BUP-SL 8 mg in clinic BXR 300 mg injection COWS = 0	COWS = 0	Received 2nd BXR injection Retained in trial >8 weeks and continuing to attend study visits No opioid use since day prior to start of induction
004 33 y/o Male Other race	COWS = 16 at start of induction Total BUP-SL = 24 mg (16 mg in clinic; 8 mg take-home at night)	BUP-SL 8 mg at home COWS = 1 arrival at clinic BUP-SL 8 mg in clinic BXR 300 mg injection	COWS = 0	COWS = 0	Due to receive 2nd Sublocade injection Retained in trial >4 weeks and continuing to attend study visits Used heroin once per week since induction
005 43 y/o Male Other race	COWS = 12 at start of induction Total BUP-SL = 24 mg all in clinic	BUP-SL 8 mg at home Patient unable to attend clinic due to severe withdrawal symptoms	COWS =11 arrival at clinic BUP-SL 8 mg COWS = 3 BUP-SL 8 mg BXR 300 mg injection COWS = 1	COWS = 2	Due to receive 2nd Sublocade injection Retained in trial >4 weeks and continuing to attend study visits No opioid use since day prior to start of induction
006 55 y/o Male Black	COWS = 10 at start of induction Total BUP-SL = 24 mg (16 mg in clinic; 8 mg take-home at night)	BUP-SL 8 mg taken very early morning Severe withdrawal symptoms; unable to come to clinic Used 2 bags heroin	COWS =10 arrival at clinic BUP-SL 8 mg COWS = 2 BUP-SL 8 mg BXR 300 mg injection COWS = 0	COWS = 0	Due to receive 2nd Sublocade injection Retained in trial >3 weeks and continuing to attend study visits Used heroin twice first week after induction

Abbreviations: BXR = buprenorphine; COWS = clinical opioid withdrawal scale; SL = sublingual.