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CHALLENGES WITH BUPRENORPHINE INDUCTIONS IN THE CONTEXT OF THE FENTANYL OVERDOSE CRISIS: A CASE SERIES

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Abstract

Introduction and Aims—North America is currently experiencing an epidemic of opioid overdose deaths, driven by the proliferation of fentanyl in the street drug market. Although buprenorphine/naloxone (BUP/NX) is an evidence-based, first-line opioid agonist for the management of opioid use disorder, a key challenge in its prescribing lies in the fact that it can precipitate opioid withdrawal during its initial induction process. At this time, there is minimal literature on the BUP/NX induction process in individuals who use illicit fentanyl regularly.

Design, Methods and Results—A case series from a Vancouver, Canada addiction medicine clinic of three fentanyl-exposed patients who experienced unexpected, precipitated withdrawal when initiating BUP/NX.

Discussion and Conclusion—These cases describe incidents of precipitated opioid withdrawal occurring after unusually long periods of fentanyl abstention. Although fentanyl is experienced as a short-acting opioid, the drug persists much longer in the body's peripheral tissues. Here, we highlight the new challenges fentanyl may pose to current BUP/NX induction strategies, and explore the possibility of a long-acting pharmacokinetic effect of fentanyl in the setting of repeated illicit use.

Keywords

addiction medicine; buprenorphine; fentanyl; opiate substitution treatment; precipitated withdrawal

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INTRODUCTION

North America is experiencing an epidemic of opioid-associated overdose deaths, driven by the proliferation of highly potent illicitly-manufactured fentanyl and its analogues [1, 2], and characterised by widespread adulteration of fentanyl in the street drug supply [3]. In British Columbia, Canada there was a rate of 27 fentanyl-associated deaths per 100 000 in 2018, with fentanyl detected in 86% of all illicit drug overdose deaths [4].

Buprenorphine/naloxone (BUP/NX) is a first-line option for the treatment of opioid use disorder (OUD) due to its milder side effect profile, relatively low overdose risk and proven benefit in both decreasing illicit opioid use and improving overall health outcomes [5, 6]. Typically administered via daily sublingual dosing, the medication has recently become available in a monthly subcutaneously injected formulation [7].

Despite the clear advantages of BUP/NX, a key limitation in its uptake with patients and providers alike lies in the oftentimes challenging induction process required when starting the medication [8–10]. Due to its pharmacological properties as a partial opioid agonist with a high binding affinity, buprenorphine has the potential to precipitate opioid withdrawal by displacing full opioid agonists at the mu-opioid receptors [11]. As such, the traditional regimen of BUP/NX induction requires that patients abstain from all opioids for a period of time prior to induction (typically 6–24 h for short-acting opioids), and initiate the induction process in a state of mild to moderate opioid withdrawal [11, 12].

Here, we report on three cases of unanticipated precipitated withdrawal during BUP/NX induction seen with individuals who use fentanyl daily, highlighting the challenges and additional considerations that must be made in the context of this emerging illicit drug.

METHODS

All three patient cases were identified and chosen from an outpatient addiction medicine clinic in Vancouver, Canada. They were not randomly selected. Written consent was received from all three patients; this study has received institutional ethics approval.

Case Reports

Case 1—A 49-year-old male with longstanding severe OUD presented for BUP/NX induction. He had been smoking 1 g/day of fentanyl exclusively for the past year. He had previously been trialled on methadone unsuccessfully. The patient was unemployed with stable housing. Aside from tobacco, he reported no other substance use and no significant medical conditions.

On the day of treatment initiation, the patient's reported last use of fentanyl, or any other opioids, was 36 h prior. During assessment, the patient was distressed, tearful and diaphoretic, endorsing mild nausea and diarrhoea, with a heart rate of 72 beats/min. He was determined to be in a moderate state of opioid withdrawal, with a clinical opioid withdrawal (COWS) score of 13. A urine drug test tested positive for fentanyl and negative for methadone, oxycodone and morphine. The patient was administered one 2 mg/0.5 mg BUP/NX tablet and instructed to remain in clinic for observation.

Within 30–40 min, the patient began exhibiting an increased severity of diaphoresis, lacrimation, rhinorrhea and diarrhoea. The patient was observed pacing and unable to sit, in a high state of agitation and with an observable tremor. It was concluded that the BUP/NX induction had precipitated an acute opioid withdrawal. The clinic induction was discontinued due to the degree of the patient's distress secondary to these symptoms.

In the immediate period afterwards, the patient's symptoms were challenging to bring under control with hydromorphone and clonidine. In the weeks that followed, the patient elected to not attempt another buprenorphine induction. He ultimately was initiated on slow-release oral morphine, an approved opioid agonist therapy in Canada that is considered third-line for patients who have not responded to methadone or BUP/NX [5].

Case 2—An otherwise healthy 41-year-old male with a history of severe OUD and stimulant use disorder presented for BUP/NX induction. He reported a 22-year history of opioid use, historically via injection but more recently via smoking. He had previously been on methadone for 15 years and noted one brief and unsuccessful trial of BUP/NX 3 years prior. He was unemployed and living in stable housing with his partner. In addition to opioids, he endorsed irregular methamphetamine, cannabis and nicotine use.

The patient had recently been prescribed slow-release oral morphine (maximum dose 900 mg/day), during which time he successfully decreased his concurrent illicit fentanyl use to 0.1 g/day. One week prior to the induction, he had stopped slow-release oral morphine due to challenges with finding a regular provider in his community and with the required daily witnessed ingestions.

At the time of BUP/NX induction, the patient reported that it had been over 24 h since his last use of opioids (0.05 g of fentanyl). He presented writhing and gagging uncomfortably in the waiting room, with a heart rate of 85. He was assessed to have a COWS of 19. A urine drug test from the previous day tested positive for fentanyl and amphetamines, and negative for methadone, oxycodone and morphine.

The patient was administered 2 mg/0.5 mg of BUP/NX and reassessed 1 hour later. At this time, his COWS had improved marginally to 15 and thus he was given another 2 mg/0.5 mg of BUP/NX. On reassessment after this second dose; however, the patient reported a sudden worsening of withdrawal symptoms, including akathisia, myalgias and diaphoresis. It was concluded that the additional BUP/NX administered had precipitated an acute opioid withdrawal. Due to concern about the risk of further precipitating withdrawal symptoms, the clinic induction was discontinued. The patient was instead provided with six tablets of BUP/NX to take home, and instructions to resume the induction later in the evening when his symptoms stabilised.

The patient returned to clinic the following day, reporting that his symptoms of opioid withdrawal had improved significantly after completing the full course of BUP/NX overnight. Unfortunately, the day thereafter he discontinued the medication, reporting an episode of vomiting after taking the tablets. He was lost to follow-up shortly afterwards.

Case 3—A 42-year-old male with a 7-month history of OUD presented as a new intake for BUP/NX induction. He reported first smoking fentanyl earlier that year, quickly escalating into regular use. He had never used any opioids prior to this and had never been trialled on an opioid agonist therapy. He endorsed smoking 0.25 g of fentanyl daily, primarily to manage his withdrawal symptoms. He reported smoking cannabis daily, smoking cocaine twice weekly and using alcohol intermittently. He was employed and living in stable housing with his partner and family.

The patient presented 22 h after his last reported opioid use (<0.1 g of fentanyl). Seen in clinic, he displayed tremors, lacrimation, anxiety, restlessness and a heart rate of 90; he was assessed to have a COWS score of 14. A urine drug test from the previous day was positive for fentanyl, opioids and cocaine, and negative for methadone and oxycodone.

The patient was administered 2 mg/0.5 mg of BUP/NX. One hour later, he reported mildly increased restlessness and anxiety and was given 600 mg of gabapentin (off-label use). At this time, he was noted to have a slightly increased COWS of 15. When reassessed 30 min later however, the patient reported that his restless and anxiety had continued to increase, becoming difficult to tolerate. He was observed at that time to be pacing the clinic hallway, unable to sit still. It was concluded that the BUP/NX induction had precipitated an acute opioid withdrawal, requiring a modification to the standard induction protocol.

The patient was given a large single dose of 16 mg/4 mg BUP/NX and 50 mg of quetiapine (off-label use), after which he reported a significant improvement in his symptoms over the following 3 h. He was given another two doses of 4 mg/1.0 mg BUP/NX in response to more mildly persistent symptoms and was ultimately determined to be stable enough to return home with three tablets of 2 mg/0.5 mg BUP/NX to take overnight.

The patient returned the following day, reporting that his symptoms had largely resolved. He was started on a prescription of 24 mg/6 mg BUP/NX daily, which he took regularly for 3 months until he was lost to follow-up.

DISCUSSION

Here, we present three cases highlighting the phenomenon of BUP/NX-induced precipitated withdrawal occurring in patients who use fentanyl regularly (either via direct smoking or inhalation of vapour). All patients reported adherence to an opioid abstention period within or greater than the 12–24 h recommended for short-acting opioids by BUP/NX induction guidelines [11–13]. Likewise, all began their induction in an objective state of opioid withdrawal that would be considered adequate for reducing the risk of precipitated withdrawal [11–13]. Despite this, in all three cases, a cautious 2 or 4 mg initial dose of buprenorphine was enough to precipitate withdrawal symptoms that ultimately required termination or modification of the induction process. Two of the patients described were never successfully started on BUP/NX. This is a reflection of the lower early treatment retention seen in patients that experience a precipitated withdrawal during induction [9], and the general challenge of sustaining patients with very high opioid needs on a partial agonist.

For the purposes of these cases, precipitated withdrawal is defined as an acute worsening of subjective and objective opioid withdrawal symptoms following BUP/NX administration, requiring termination or modification of the induction process due to patient distress. All three patients were unable to tolerate a standard induction regimen due to withdrawal symptoms. As otherwise healthy individuals without symptoms suggestive of alternative etiologies, in all three cases the patient's presenting symptoms were assessed by their providers to be instances of precipitated withdrawal. A limitation in the case data is a lack of documented COWS scores after BUP/NX administration. Although not recorded on a numerical scale, the symptom progression and degree of each patients' self-reported and observed distress is described in the vignettes.

Fentanyl is a highly lipophilic opioid that rapidly distributes into the body's tissues [14]; the drug's characteristic rapid and intense onset, and relatively short duration of action (1–2 h) [15] reflects this pharmacokinetic property in the central nervous system. While these characteristics would appear to support conceptualising fentanyl as a short-acting opioid, it is important to note that the drug persists in the body's peripheral tissues long after this initial effect. Fentanyl's short duration of action is primarily due to the drug's rapid redistribution into the peripheral tissues, rather than being eliminated or metabolised outright [16].

The rate-limiting step in the body's clearance of fentanyl lies in the release of the drug from adipose and other poorly perfused peripheral tissues back into the plasma [14, 17]. With a high affinity for fentanyl, these tissues appear to have the potential to act as physiological stores: accumulating and slowly releasing the drug back into the plasma long after the initial drug effect [18]. This mechanism is believed to be responsible for fentanyl's long terminal half-life, reported in anaesthesia studies to be between 2 and 7 h [14], and may also have important implications in the context of an opioid-tolerant individual self-administering fentanyl multiple times daily. Although there have been no studies that have explicitly investigated the pharmacokinetics of illicit fentanyl use, one animal model did show that multiple boluses of fentanyl, administered over spaced intervals, were shown to result in a progressively higher accumulation of the drug in the tissues, and a subsequently higher persistent plasma concentration [18]. This mechanism of peripheral tissue loading could, in theory, explain how fentanyl could produce a long-acting opioid effect that would need to be considered when initiating BUP/NX.

Although the assertion of a long-acting pharmacokinetic property to fentanyl lacks robust evidence, it is corroborated by recent observations in the literature. Antione et al. describes two cases of BUP/NX precipitated withdrawal occurring in regular fentanyl users who had abstained from fentanyl and all other opioids for over 20 h [19]. A recent qualitative study reported similar distressing occurrences of precipitated withdrawal occurring beyond the typical periods of opioid abstention [8]. A study in a closed residential treatment program showed a highly variable but consistently prolonged renal clearance of fentanyl in its patients, with most participants testing positive for fentanyl on urine screens beyond the 2–4 day window typically expected for short-acting opioids [20].

In response to their own clinical experiences with patients that use fentanyl, some providers have recommended changes to typical practice such as longer opioid abstention periods and more cautious starting doses of BUP/NX [21]. Recent years have seen the development of novel buprenorphine micro-induction regimens that do not require initiation in a state of significant opioid withdrawal and may reduce the risk of precipitated withdrawal [22–24]. The median starting doses of these published regimens is 0.5 mg, uptitrated over a median of 6 days; further research is necessary to determine effectiveness and optimal dosing [25].

CONCLUSION

Prescribers and individuals with OUD should be aware of the potential for BUP/NX to unexpectedly precipitate withdrawal in some patients who use fentanyl, despite adherence to traditionally adequate periods of opioid abstention. As fentanyl continues to adulterate the illicit drug supply in many communities, current induction regimens should be re-examined and adapted accordingly. BUP/NX inductions represent a vulnerable period for patients that use fentanyl; we must ensure that, wherever possible, we do not inadvertently act to turn them away from an effective and potentially life-changing therapy.

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