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Enhancing Patient Choice: Using Self-administered Intranasal Naloxone for Novel Rapid Buprenorphine Initiation

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Buprenorphine-naloxone (BUP-NX) is a lifesaving treatment for opioid use disorder. The increasing use of illicitly manufactured fentanyl, however, has made initiating BUP-NX more likely to precipitate withdrawal—an experience that deters treatment and causes return to use. If BUP-NX cannot be successfully started, it cannot work. We describe the case of a patient who was able to transition to a therapeutic dose of BUP-NX less than 3 hours after his last illicitly manufactured fentanyl use by choosing to self-administer intranasal naloxone. After the naloxone, the transition took 31 minutes, including 14 minutes of expected moderately severe withdrawal. He remains in care with BUP-NX and would recommend this transition approach to others.

Key Words: opioid use disorder, buprenorphine, retention in care, telehealth, transition to buprenorphine

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BACKGROUND

More than 100,000 overdose deaths were reported in 2021, largely driven by illicitly manufactured fentanyl (IMF).[1] Buprenorphine-naloxone (BUP-NX) is a first-line treatment for opioid use disorder (OUD) and, like methadone, reduces morbidity and mortality while increasing retention in care.[2] Unfortunately, initiating BUP-NX has become more complicated as IMF has largely replaced heroin in the US drug supply.

Buprenorphine, an opioid partial agonist, has high affinity and low intrinsic activation at the μ-opioid receptor. Because of these properties, buprenorphine can cause precipitated withdrawal if taken too soon or at a wrong dose after full agonist opioid.[3] Unfortunately, this precipitation risk increases with regular fentanyl use—likely because of fentanyl's lipophilicity, which leads to a large volume of distribution and slow dissipation when used chronically.[3] Patients have significant concerns about the severity of withdrawal needed to start buprenorphine as well as the risk of precipitated withdrawal; the possibility of a negative experience understandably fosters hesitance to begin treatment.[4–6]

Newer methods for BUP-NX initiation have been reported—generally categorized as very low- (or "microdosing"), low-, standard-, and high-dose (or "macrodose") protocols—each with potential benefits and risks (Table 1).[7,10] Less common methods use transdermal, buccal sublingual, and intravenous buprenorphine formulations not readily available for this outpatient purpose.[7] Additional effective, expedited approaches would empower patients, providing more choices regarding when and how quickly they can fully transition to lifesaving treatment.

We present a novel approach for rapid outpatient BUP-NX initiation where a patient chose self-administration of intranasal naloxone to induce withdrawal, followed shortly by 24–6 mg BUP-NX. The patient provided written informed consent for publication, including review of the article.

CASE REPORT

A 33-year-old man with 2 years of daily fentanyl use presented to our telehealth addiction medicine program. His daily use averaged 2, ranging up to 20, pressed fentanyl tablets, which he crushed and inhaled. He occasionally used cannabis but denied other substance use and any chronic medical or psychiatric conditions. His past OUD treatment included extended-release naltrexone injection for 1 month on 2 separate occasions. He had not yet tried BUP-NX or methadone treatment.

His goal was abstinence from IMF. He met the criteria for severe OUD and wanted to initiate BUP-NX maintenance treatment. Options for BUP-NX initiation were discussed in detail—including very low dose, low dose, and standard dose—as well as a rapid initiation based on prehospital protocols.[11] He opted for the rapid protocol, with his informed decision guided by preferences to stop IMF use immediately, start BUP-NX as soon as possible, and avoid protracted withdrawal.

His visit for BUP-NX initiation was performed via telehealth, with the patient and his wife at home and the clinician at a remote site. The patient preferred a clinician being present "just in case." The patient's last use of 2 pressed fentanyl tablets was 2 hours before the appointment (Table 2). A Clinical Opioid Withdrawal Scale (COWS) was used, and he scored 0 at the start of the appointment.[2] He empirically took 0.2 mg of oral clonidine

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TABLE 1. Methods for Transitioning From Full Agonists to Buprenorphine Using Readily Available Outpatient Formulations*

Method†	Time After Last Use of Full Agonist Until the Initiation Phase‡ Can Begin	Duration of Initiation Phase	Withdrawal Severity§ Recommended at Start of Initiation Phase	Medication Taken During Initiation Phase	Expected Change in Withdrawal Symptoms during Initiation Phase	Continued Full Agonist Use During Transition period‖	Duration of Complete Transition Period
Very low dose[7]	None	Days to weeks	None	BUP-NX¶, initial dose <1 mg	N/A	Yes	Days to weeks
Low dose and standard dose[2,8]	1–2 d	Days	Moderately severe	BUP-NX, initial dose 1–4 mg	Improve	Patient dependent	Days
High-Dose[9#]	12 h	~2–3 h	COWS ≥8	BUP-NX, initial dose >8 mg	Improve	No	~15 h
Case study "Quick Start"	None	29 min	None	Intranasal naloxone, followed by 24 mg BUP-NX	Increased severity withdrawal (COWS 28) for short duration, then improve	No	<1 h

BUP-NX, buprenorphine-naloxone; COWS, Clinical Opioid Withdrawal Scale; N/A, not applicable.

*Readily available outpatient formulations: excluding Butrans patch, Belbuca buccal film, and intravenous buprenorphine.

†Method definitions (based on Weimer and Fiellin[10]): very low dose, also referred to as microdosing, initiation phase doses of buprenorphine begin with less than 1 mg, often starting at 0.5 mg; low dose: initiation phase dose of buprenorphine begins at 1 to 2 mg; standard dose, initiation phase dose of buprenorphine begins at 2 to 4 mg; high dose, also referred to as macrodosing, initiation phase dose of buprenorphine begins at ≥8 mg.

‡Initiation phase: portion of transition period starting with the first dose of an initiation medication (intranasal naloxone in case study, sublingual BUP-NX in all others) until a patient is on therapeutic dose of BUP-NX.

§Clinical Opiate Withdrawal Scale scoring[2]: 5–12, mild; 13–24, moderate; 25–36, moderately severe; more than 36, severe withdrawal.

‖Transition period: time from the patient's last use of a full agonist until they are on a therapeutic dose of BUP-NX. This period adds the time since last use to the initiation phase.

¶BUP-NX: dose in milligrams represents buprenorphine portion.

#Published studies occurred in emergency department or residential settings.

and 600 mg of gabapentin to mitigate the anticipated precipitated withdrawal from naloxone.

Thirty-five minutes later, with his COWS score remaining 0, he self-administered a full dose of 4 mg intranasal naloxone. Within 2 minutes, he developed withdrawal symptoms, and within 14 minutes, his COWS score was moderately severe at 28. He then self-administered 24–6 mg sublingual BUP-NX. Five minutes after the medication was fully absorbed, he felt well enough to request disconnection from the visit to take a nap. He was instructed to continue with sublingual 8–2 mg BUP-NX the following morning and follow-up.

At his follow-up visit the next day, the patient reported that he "took a nap for about an hour and woke up feeling normal. I was able to eat without any problem. No joint pains. Best detox I have had in my life." His advice to other individuals who choose to use this method of transition was as follows: "You will be sick for an hour and then you will be perfectly fine."

Four weeks later, the patient continues to attend telehealth appointments and is doing well on 16–4 mg BUP-NX daily.

DISCUSSION

To our knowledge, this is the first published case of a patient self-administering intranasal naloxone to induce withdrawal and expedite transition to sublingual BUP-NX. The patient began this process only 2 hours after his last use of fentanyl. Although he did anticipate—and experience—moderately severe withdrawal after naloxone, the symptoms were predictable and short-lived. In essence, he transitioned from fentanyl to a therapeutic dose of BUP-NX in less than 30 minutes without persistent withdrawal. The patient's comments reflect his brief, successful, and positive initiation experience.

This case highlights 2 different time frames that make transition to BUP-NX possible. The first is the time since last full agonist use and the related degree of withdrawal required by a method: *time since last use*. The second begins with the first dose

TABLE 2. Chronology of Transition From Fentanyl to Buprenorphine-naloxone

Event	Time Elapsed, min	Time Between Events, min	COWS*
Last use of fentanyl	120 min prior		0
Premedication with clonidine 0.2 mg and gabapentin 600 mg	0	120	0
4 mg (1 spray) intranasal naloxone	36	36	NS†
GI upset ("stomach not feeling right")	38	2	NS
COWS measured	42	4	9
Vomiting (2 episodes of vomitus, 3 episodes of dry heaving)	45	3	NS
24/6 mg sublingual buprenorphine-naloxone at once	50	5	28
Buprenorphine-naloxone fully dissolved.	60	10	NS
Subjective withdrawal symptoms 0–10; he states that he is at a 4. Feeling tired.			
Discontinued visit to sleep	65	5	NS

*Clinical Opioid Withdrawal Scale (COWS), excluding heart rate.

†COWS not scored.

of an initiation medication (intranasal naloxone in case study, sublingual BUP-NX in other methods) until reaching a therapeutic dose of BUP-NX: the *initiation phase*. Time since last use plus the initiation phase represent the total time needed, which we refer to as the *transition period*. There are likely more fluent ways of describing these durations. The utility of this model is how it reveals the need for strategies to shorten either (or both) of the 2 periods to expedite a safe transition to BUP-NX.

This case builds on EMS experience starting buprenorphine directly after naloxone reversal of opioid overdose.[11] There is also an emergency department report of a patient choosing intravenous naloxone, followed by initiation of sublingual buprenorphine, to begin treatment while monitored.[12] Although our case differs in a number of key ways, these reports support further study of voluntary naloxone use to expedite BUP-NX initiation. Our case also lends support for a higher first dose of BUP-NX when patients are transitioning from fentanyl. As with other approaches, rapid initiation has risks, but none that compare with ongoing use of lethal opioids.

Standard buprenorphine initiations require patients to wait after their last full agonist use and experience significant withdrawal symptoms. Very low-dose buprenorphine transitions intentionally minimize withdrawal, but patients usually continue illicit opioid use while gradually increasing their daily buprenorphine dose over several days to weeks; a recent review found this transition to take a median of 8 days (range, 3–120 days).[7] Although very low-dose and low-dose transitions aim to avoid precipitated withdrawal, it can still occur.[5] High-dose (defined as total dosing up to 32 mg) initiation has been done in emergency departments, but these protocols also require patients to wait at least 12 hours since their last use before taking a first buprenorphine dose.[9] Outpatient use of the high-dose method has not yet been described.

Case reports are limited in extrapolating from a single patient's experience, even as they identify potential practice improvements.[13] Our report has additional limitations. The method we describe, including its predictable withdrawal, will not appeal to everyone. Because current transition methods each have virtues and drawbacks, shared decision making among available options is likely the most appropriate framework for patients.[14] Another limitation concerns the optimal dose of buprenorphine. We used a 24-mg dose to occupy the most μ-opioid receptors possible after naloxone's rapid displacement of full agonist, but this was an empiric choice.

Naloxone is not indicated for nonoverdose use, which may present a clinical obstacle. Other pharmaceuticals commonly prescribed in addiction medicine, however, are also not approved as used and are unlikely to be submitted for a new indication.[15] The overriding clinical decision making depends on relative risk and benefit. In the case of OUD, ongoing use is associated with morbidity and mortality. Successful, safe conversion to buprenorphine is paramount for many people's survival and, as in our case report, can be facilitated by naloxone. Further investigations could examine efficacy with full agonists other than fentanyl, a lower dose of naloxone to minimize withdrawal, and the utility of medications to mitigate symptoms.

The described approach has potential for home or outpatient settings. It allows flexible timing as to a person's last use of fentanyl, provides more autonomy in starting BUP-NX, makes use of intranasal naloxone availability, and better aligns with the short time when beginning treatment is especially salient—paralleling "Quick Start" methods for contraception initiation.[4,16] In addition, the expedited timeline may appeal to patients with work, family, or other obligations. Depending on their preferences, patients could make this transition on their own, with a peer recovery specialist or other trusted person, or with a clinician. This specific case also demonstrates the utility of telehealth in supporting patients during BUP-NX initiation.[17]

In times of crisis—wounds in World Wars, burns in mass casualties, and the HIV/AIDS epidemic—medical practice has had to respond in seemingly unconventional ways to save lives.[18–20] People suffering from OUD are pleading for the same intrepid focus to help them begin BUP-NX.[6] We welcome further study—in a larger cohort of patients—of the unconventional but effective approach described in this case report.

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