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REVIEW

Initiation and Dosing of Extended-Release Buprenorphine: A Narrative Review of Emerging Approaches for Patients Who Use Fentanyl

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Abstract: Individuals with Opioid Use Disorder (OUD) who use fentanyl are at high risk of mortality due to opioid-related overdose. While buprenorphine extended-release (BUP-XR) may reduce this risk, there is a need to optimize clinical practice with BUP-XR to overcome barriers to treatment initiation and retention in patients who use fentanyl. Through a narrative review of evidence from peer-reviewed publications and conference abstracts, this article provides an overview of current novel initiation and dosing strategies for BUP-XR in patient populations with confirmed or presumed use of fentanyl. Evidence in this area is rapidly emerging with multiple studies describing BUP-XR initiation prior to 7-day stabilization on transmucosal buprenorphine (TM-BUP). Results from a randomized controlled study indicate that initiating BUP-XR following a single TM-BUP dose is noninferior to standard initiation in terms of treatment retention at injection 2, with similar rates of precipitated withdrawal and adverse events, and this protocol is now included in the approved prescribing information in the USA. While additional "macro/high-dose" or "micro/low-dose" and "direct dose" induction approaches have also been reported, evidence for these is limited to small uncontrolled studies or case reports. Consistent with evidence from studies of TM-BUP, which suggests individuals who use fentanyl may require higher maintenance doses in order to be retained in treatment, administrative and observational data suggests that use of the 300-mg maintenance dose, shortened intervals between doses, and supplemental TM-BUP may be feasible approaches to increase buprenorphine exposure in patients with ongoing symptoms and improve retention. Evidence in this area is rapidly evolving, and many of these strategies are increasingly being adopted clinically and incorporated into clinical guidelines. Further research should incorporate increased sample sizes, broader and more consistent outcome measurement, and increased duration of follow-up to facilitate more robust evaluation of efficacy and safety as well as increase comparability between studies.

Keywords: opioid use disorder, extended-release buprenorphine, long-acting buprenorphine, BUP-XR, fentanyl

Introduction

The opioid crisis continues to be a major cause of mortality across North America, with 81,806 individuals dying from related opioid overdose in the United States (US)[1] and 7792 in Canada[2] in 2022. A significant driver of this is the surge of high-potency synthetic opioids in the illicit opioid market, with over 80% of opioid-related deaths in both countries attributed to fentanyl.[1,2]

The majority of people who die from an opioid overdose have opioid use disorder (OUD), with only a subset receiving treatment prior to their death,[3] despite evidence for various treatments in reducing mortality in the fentanyl era.[4,5] Extended-release buprenorphine (BUP-XR, SUBLOCADE®) is a monthly subcutaneous buprenorphine injection available in both the USA and Canada, where fentanyl dominates the illicit drug supply. BUP-XR was developed to deliver sustained therapeutic levels of buprenorphine,[6,7] avoiding fluctuations from inconsistent daily dosing that could contribute to opioid withdrawal, craving, and relapse.[7] In a small open-label, cross over pharmacodynamic study using

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intravenous buprenorphine, sustained buprenorphine levels consistent with those delivered by BUP-XR were associated with reduced risk of respiratory depression from fentanyl,[8,9] and in clinical practice, BUP-XR treatment has also been associated with lower rates of nonfatal overdose compared to treatment with transmucosal buprenorphine (TM-BUP) or methadone (MET).[10]

The Phase 3 pivotal trial for BUP-XR[6] was conducted across the USA in 2015, just as fentanyl was emerging in northeastern states[11] and prior to widespread awareness of its unique clinical challenges. In addition to overdose risks associated with illicit fentanyl, clinical experience suggests that, compared with heroin use, fentanyl use may lead to more rapid onset, severe, or protracted withdrawal symptoms,[12] higher risk of precipitated opioid withdrawal (PW) during buprenorphine inductions,[13,14] and lower treatment retention.[15,16] These challenges have led to clinical guidelines and other consideration documents increasingly recommending a more flexible approach to treatment in patients who use fentanyl, including modifications to buprenorphine treatment initiation and maintenance dosing strategies.[17–21] Given the rapid evolution of clinical practice in this area, the objective of this narrative review is to describe the available literature on BUP-XR initiation and dosing strategies in the fentanyl era in order to better understand emerging clinical practice and inform future research needs.

Materials and Methods

We completed a search of peer-reviewed literature (PubMed) and conference abstracts (ProQuest) up to Aug 29, 2024, and provided a narrative review of those which reported initiation and dosing of BUP-XR in populations exposed to fentanyl, with findings discussed in the context of recommended use established in the registrational trials for BUP-XR and included in the product labels.[22,23]

Multiple search terms were used to capture BUP-XRrelated terminology (eg, BUP-XR, long-acting buprenorphine, SUBLOCADE®), with studies and reports describing initiation and dosing of BUP-XR in patients with confirmed or presumed use of fentanyl included for narrative review. Given inconsistencies in identifying and reporting fentanyl use in earlier studies, based on drug seizure and overdose death reports, we presumed subjects using illicit opioids in the eastern, midwest, and southern USA after 2013[24] and in the western USA[25] and Canada after 2017[26] were exposed to fentanyl unless stated otherwise. Given the limited instances of fentanyl in the illicit drug supplies of Australia[27] and Europe,[28] publications from these regions were presumed not to include subjects exposed to fentanyl, unless this was specifically noted.

Studies describing alternate BUP-XR formulations not available in both Canada and the USA (eg, BUVIDAL®, BRIXADI®, PROPUBHINE®) were not reviewed, as these formulations would be subject to different initiation and dosing protocols.

Results

BUP-XR Initiation Protocols

In the initial registration trials for BUP-XR, participants were first inducted and stabilized with 8 to 24 mg TM-BUP daily for 7 to 14 days before initiating BUP-XR. [6] The purpose of this initiation period was to ensure tolerance and clinical response to buprenorphine (ie, reduction in withdrawal and cravings) prior to transitioning to a long-acting buprenorphine product. To complete TM-BUP induction, patients need to abstain from fentanyl or other opioids for a minimum period and be in at least moderate withdrawal prior to receipt of the first dose to reduce risk of PW, [29] a requirement which may limit the ability of many individuals to access this treatment. [30] Even after completing induction, patients who use fentanyl may experience further barriers with adhering to daily treatment for the required period prior to transitioning to BUP-XR. [31–33] Given these issues, the necessity of undergoing a standard TM-BUP induction and completing the recommended 7 days of treatment has been challenged by several clinical guidelines, [17–21] and multiple publications suggest that alternate induction protocols and/or a less than 7-day stabilization may be feasible when clinically indicated. [31–50]

While there is significant variation in the approaches reported across different studies, in general alternate BUP-XR initiation strategies may be categorized as rapid/test, macro/high-dose, micro/low-dose, or direct dose protocols (Table 1).

Table 1 BUP-XR Initiation Protocols with <7-Day TM-BUP Stabilization Periods Described in Patients Using Fentanyl

Citation	Location	Study Description	Day 1	Day 2	Day 3	Day 4	Day 5
BUP-XR initiated without any immediate prior TM-BUP dose, in patients with previous exposure to TM-BUP							
Wethern, 2023[29]	Denver, Colorado, USA	Case study (n=2)	300 mg BUP-XR				
Mooney 2024[48]	Portland, Oregan, USA	Case study (n=2)	300 mg BUP-XR				
BUP-XR initiated after single TM-BUP dose							
Hassman 2023[37]	Berlin, NJ, USA	Open label, uncontrolled (n=26)	4 mg TM-BUP 300 mg BUP-XR				
Ochalek, 2023[39]	Richmond, VA, USA	Open label, uncontrolled (n=19)	4 mg TM-BUP 300 mg BUP-XR				
Shiwach 2024[14]	Multiple Sites, Canada/ USA	Randomized controlled trial (n=489)	4 mg TM-BUP 300 mg BUP-XR				
BUP-XR initiated after macro/high-dose TM-BUP induction							
Mariani, 2021[41]	New York, NY, USA	Open label, uncontrolled (n=5)	24 mg TM-BUP (divided) 300 mg BUP-XR				
Taylor 2024[30]	Boston, MA, USA	Case study (n=1)	12mg IN-NAL 16mg TM-BUP 300 mg BUP-XR				
Kahan, 2023[32]	Timmins, ON, Canada	Case study (n=2)	28–32 mg TM-BUP (divided)	32 mg TM-BUP 300 mg BUP-XR			
LeSaint 2024[42]	San Francisco, CA, USA	Case study (n=1)	32mg TM-BUP (divided)	32 mg TM-BUP 300 mg BUP-XR			
Mariani, 2020[40]	New York, NY, USA	Open label, uncontrolled (n=5)	10–24 mg TM-BUP (divided)	16–24mg TM-BUP (divided) 300 mg BUP-XR			
				8–24mg TM-BUP (divided)	16 mg TM-BUP (divided) 300 mg BUP-XR		
BUP-XR initiated after micro/low-dose TM-BUP induction							
Azar 2024[46]	Vancouver BC, Canada	Case study (n=2)	6 x 20 ug/h BUP TD patches	Additional 6 x 20 ug/h BUP TD patches	BUP-TD patches removed 4mg TM-BUP 300 mg BUP-XR		
Azar, 2023[45]	Vancouver, BC, Canada	Case study (n=1)	6 x 20 ug/h BUP TD patches	Additional 6 x 20 ug/h BUP TD patches	BUP-TD patches removed 300 mg BUP-XR		
Azar, 2020[44]	Vancouver, BC, Canada	Case study (n=1)	3 mg TM-BUP (divided)	7 mg TM-BUP (divided)	8 mg TM-BUP	300 mg BUP-XR	
Gorham 2024[47]	Kansas City, KS, USA	Case study (n=1)	1x10 ug/h BUP TD patch1mg TM-BUP bid	1x10 ug/h BUP TD patch1mg TM-BUP qid	1x10 ug/h BUP TD patch1mg TM-BUP 8x/d	1x10 ug/h BUP TD patch8mg TM-BUP	300mg BUP-XR

Abbreviations: BUP-XR, extended-release buprenorphine; IN, intranasal; BUP-TD, transdermal buprenorphine; TM-BUP, transmucosal buprenorphine.

There was considerable variability across studies in outcomes reported, including rate of initiation completion, incidence of PW, severity of withdrawal symptoms, retention in treatment, opioid abstinence, health service utilization, and/ or adverse events.

Rapid/Test Dose Induction

The largest volume of evidence for alternate BUP-XR initiation protocols is with rapid/test dose protocols that provide the first 300-mg BUP-XR injection 1 hour after a single 4-mg TM-BUP test dose. With this protocol, patients were required to have a Clinical Opioid Withdrawal Scale (COWS) score ≥8 prior to receiving TM-BUP. While initial pilot studies provided support for the feasibility of this approach for patients who use fentanyl in outpatient[39,40] and emergency department[41] settings, a recently completed randomized controlled trial (n=723; 77% fentanyl positive at baseline) has compared outcomes between this approach and the traditional TM-BUP induction and stabilization period.[14] In this study, rapid/test dose initiation was found to be noninferior to standard initiation in terms of treatment retention at injection 2 (62.8% vs 47.9% for fentanyl-positive subjects), with comparable rates of PW and other safety events between the two methods. While this protocol has been included in the updated prescribing information in the USA,[22] the Canadian product monograph still requires patients to undergo a standard induction and are stabilized for a minimum of 7 days on TM-BUP.[23]

Macro/High-Dose Induction

Five reports examined the feasibility of BUP-XR initiation after a "macro" or "high" dose TM-BUP induction in a total of 14 patients, with no comparison of outcomes with standard approaches.[32,34,42–44] In the first case series, n=5 patients with heroin/fentanyl use and baseline COWS scores >6 (range 10–16) received up to 24-mg TM-BUP in divided doses on Day 1 of induction, with the first 300-mg BUP-XR injection given on Day 2 (n=2) or Day 3 (n=3).[42] All participants completed initiation with no PW attributed to BUP-XR, although 2 participants were not able to attend the clinic on the second day of TM-BUP initiation due to severe withdrawal symptoms. In order to address this, a follow-up study was conducted where the BUP-XR injection was provided the same day as the initial TM-BUP induction. This open-label study included 5 heroin/fentanyl using participants with COWS score >6 (range 8–18) given 24-mg TM-BUP in 4 divided hourly doses, followed by a 300-mg BUP-XR injection that same day.[43] All patients completed initiation (ie, received the 300-mg injection) with no incidence of protracted PW. All 5 participants were retained for 3 months and received all 3 scheduled BUP-XR injections.

The application of a macro/high-dose protocol in emergency department (ED) settings has also been reported in 4 cases. In two reports,[32,44] 3 individuals with fentanyl use who presented to the ED in withdrawal received BUP-XR after stabilization with high-dose TM-BUP (28–32 mg in divided doses). An additional 32-mg TM-BUP was provided the following day, followed by a 300-mg BUP-XR injection. Both patients received their second BUP-XR injection in the community. In another report from an ED setting, a patient in spontaneous opioid withdrawal received 32-mg TM-BUP in divided doses, returned the next day for an additional 32-mg TM-BUP and a 300-mg BUP-XR injection.[42] In the fourth case, the patient underwent a macro/high-dose protocol after being in severe opioid withdrawal following overdose reversal by 12-mg intranasal naloxone. In this case, 16-mg TM-BUP was provided followed by 300-mg BUP-XR, although intervals between doses were not reported.[32]

Micro/Low-Dose Induction

Five case reports of BUP-XR initiation in a total of six patients using fentanyl following 3 different "micro" or "low" buprenorphine dosing induction protocols were identified.[45–49] In the first case study, an individual using illicit fentanyl started a TM-BUP microdosing protocol in the community, receiving ascending twice daily doses with continued fentanyl use, starting with 0.5 mg administered as 0.25 mg twice daily on Day 1 and reaching a single 12-mg dose on Day 7; COWS scores were not reported.[45] Following the 12-mg dose, the patient experienced severe PW (COWS=18) that required management with additional TM-BUP and ketamine. The patient continued the induction, receiving 24-mg TM-BUP on Day 10 followed by BUP-XR.

In another case report, an adolescent with severe OUD and multiple recent overdoses underwent a more rapid micro-induction protocol.[46] TM-BUP was administered in an inpatient setting every 3 hours for 3 days (a total of 3 mg on Day

1, 7 mg on Day 2, and 8 mg on Day 3), and 300-mg BUP-XR was administered on Day 4. Hydromorphone was administered orally on Days 1 and 2 (15 mg and 5 mg, respectively). This approach was well tolerated with minimal withdrawal symptoms and no signs of PW, though the patient did not return for a subsequent dose. In two additional reports by the same group,[47,48] BUP transdermal patches (BUP-TD) were used instead of TM-BUP, with 6, 20-ug/h patches added on Day 1, and an additional 6 on Day 2, with the patches removed and 300-mg BUP-XR given on Day 3, with or without an additional TM-BUP. To maintain low levels of withdrawal symptoms and cravings and prevent the patient from leaving the hospital to use illicit fentanyl, full agonists were provided during the induction. After receipt of BUP-XR, full agonists were discontinued and the patient received additional 2–4 mg TM-BUP as needed, up to a maximum of 32 mg for 1 day before being discharged. An additional case of BUP-TD micro/low-dose initiation to BUP-XR has also been reported applying a lower dose (1x10 ug/h) combined with TM-BUP in escalating doses.[49]

Direct Dose Induction

In two conference abstracts, clinicians bypassed the use of TM-BUP prior to BUP-XR to overcome challenges with medication adherence.[31,50] In the first report, 2 youths received a BUP-XR injection ≤1 day after discontinuing fentanyl.[31] Neither case reported PW. Further details, including pre/post-treatment COWS scores and subsequent outcomes, were not reported. In the second, 2 individuals with prior unsuccessful TM-BUP initiation attempts received a BUP-XR injection within 1–4 hours of most recent fentanyl use.[50] While not quantified, withdrawal symptoms reportedly worsened approximately 2h after the injection, continued throughout the first 24–48h, and resolved within 72h. Both patients continued to use illicit fentanyl for the first 48–72h of induction, and one also received additional TM-BUP (up to 40 mg/day).

BUP-XR Dosing

Maintenance Dose

After induction and stabilization on TM-BUP, participants in the registrational trials were transitioned to BUP-XR with two 300-mg starting doses, followed by 300-mg or 100-mg BUP-XR maintenance doses.[6] These 2 maintenance doses were selected in order to either maintain buprenorphine exposure levels from the initial doses (100-mg maintenance dose) or provide higher concentrations (300-mg maintenance dose) hypothesized to be necessary for some participants, based on their drug use history and clinical condition.[6] This hypothesis was supported by a subsequent secondary subgroup analysis, which found that while the 100-mg maintenance dose was equally effective in non-injecting participants, in participants with a history of injecting illicit opioids, the 300-mg maintenance dose was associated with higher rates of treatment retention and opioid abstinence.[51] While the recommended maintenance dose for BUP-XR in both the USA[22] and Canada[23] is 100 mg monthly, it may be increased to 300 mg monthly based on clinical need.

Administrative data shows that rates of utilization of the 300-mg maintenance dose in patients with presumed exposure to fentanyl ranged from 19% in a commercially insured USA cohort in 2018[52] to 47.4% in a Canadian cohort from 2020 to 2022.[36] Consistent with this, individual programs reported rates of 300-mg maintenance dose from ≥24%–71%,[35,53–59] and 90% of patients in a correctional facility received the 300-mg maintenance dose (Table 2).[60] The clinical rational for the 300-mg dose selection was discussed as being in relation to ongoing withdrawal or cravings.[57,59,60] Only one study maintained that all patients on the 100-mg maintenance dose; however, in this sample, only 7% of subjects reported that fentanyl was their opioid of choice, versus >50% prescription opioids.[53]

Currently, there is only one study available comparing outcomes between patients who receive the 100-mg versus 300-mg maintenance dose.[55] In this study, patients at a low-barrier rapid access addiction clinic who were naturalistically treated with the 300-mg maintenance dose at month three had greater retention than those who received the 100-mg dose, over the 23-month study period. Active fentanyl use was noted in 65.5% who received the 100-mg as the third dose and in 72.2% who received 300-mg. A randomized trial comparing outcomes between the 100-mg and 300-mg maintenance dose in high-risk individuals with OUD, including those who use fentanyl, is currently underway.[61]

Table 2 Proportion of Subjects Receiving 300-mg Maintenance Dose

Citation	Location	Setting	N	% Exposed to Fentanyl	% Receiving 300-mg Dose	Treatment Month
Griffith 2022[53]	Little Rock, AR, USA	Veterans Affairs Addiction Clinic	15	Not stated. 7% reported fentanyl as opioid of choice; 7% hydrocode, 20% oxycodone, 20% heroin	0[a]	Up to 12[b]
Morgan 2021[52]	National Sample, USA	Commercially Insured Cohort	204	Not stated.	26	3
					19	4
					19	5
Lee 2021[54]	London, ON, Canada	Rapid Access Clinic	75	44% reported fentanyl as opioid of choice, 4% heroin, 61% other	24.2	Not stated
Lee 2023[10]	BC and ON, Canada	Addiction Clinics	128	Approximately 20% had UDS positive for fentanyl at month 1	31	6
Deng 2023[55]	Vancouver, BC, Canada	Low-threshold Addiction Clinic	47	68.1% reported fentanyl as opioid of choice.	38.3	3
Peckham 2021[35]	Boston, MA, USA	Low-threshold Addiction Clinic	40	97.5% self-reported heroin/ fentanyl use; 2.5% prescription opioid use	53.8	3
					38.5	4
Galati 2023[56]	St Louis, MO, USA	Women's Health Clinic	15	26.7% UDS positive for fentanyl during BUP-XR treatment	50.0	4–22
Heil 2023[37]	Camden, NJ, USA	Addiction Clinic	108	88.8% self-reported history of heroin/ fentanyl use	70.8	3–6[b]
Hanley 2023[58]	Boston, MA, USA	Outpatient Clinic	208	Not stated	70.8	At least 3
Cotton 2022[57]	Seattle, WA, USA	Veterans Affairs Addiction Clinic	26	Not stated. Clinically and medically complex.	77	Up to 10[b]
Martin 2022[60]	Rhode Island, USA	Correctional Facility	54	Not stated	90	At least 2

Notes: [a]Methods state 100-mg maintenance dose protocol used for all. [b]Breakdown not given.
Abbreviations: BUP-XR, extended-release buprenorphine; MET, methadone; TM-BUP, transmucosal buprenorphine/naloxone; UDS, urine drug screen.

Alternate Dosing Intervals

Accelerated Dosing

In the registrational trials, BUP-XR was administered monthly with 26–30 days between subsequent doses.[6] In the commercially insured USA cohort, which includes patients with presumed exposure to fentanyl, a subset of participants received more frequent, off-label, dosing: 14% of BUP-XR doses (n=44) were provided <26 days since the prior administration (for those, median 23 days, range 14–25 days), though rationale for this, or timing during BUP-XR treatment was not reported.[52] Likewise, the analysis of Ontario administrative data shows a median dosing interval of 28 days, with 15.9% of injections being <26 days apart (n=2141), including 2.2% <14 days (n = 295).[36] While the safety and tolerability of providing the second 300-mg dose a week after the first has been supported by a post-marketing registrational study;[14] there are no studies comparing outcomes between subjects who receive an accelerated versus standard dosing schedule. The approved use for BUP-XR for both USA[22] and Canada[23] outlines monthly dosing, with a minimum 26 days between doses; however, the updated prescribing information in the USA does allow for the second 300-mg dose to be provided one week after the first injection.

Delayed Dosing

In the registrational trials, delays of dosing of up to 2 weeks (ie, 6 weeks between injections) were permitted, with participants discontinued from the study if presenting beyond this period for a follow-up injection.[6] Similarly, the BUP-XR product labels in the USA[22] and Canada[23] outline that unavoidable occasional delays in dosing up to 2 weeks are not

expected to have a clinically significant impact on treatment effect. In the USA commercially insured cohort with presumed fentanyl use, 12% of BUP-XR injections (n=37) occurred beyond the approved 6-week time frame (median 83 days, range 47−128 days).[52] In a claims level analysis, Ontario data showed that 4.1% of doses (n=549) were dispensed >44 days after the previous injection, and when defining treatment discontinuation as >56 days between doses, found that 32.3% who discontinued BUP-XR were subsequently re-initiated. In 50% of instances, re-initiation occurred 29–56 days after the initial discontinuation (ie, 3–5 months after their last injection).[36] A retrospective study of 26 veterans reported 70% of subjects received at least one delayed dose,[57] consistent with data from a rapid access clinic where only 40% of long-term patients received their injection on time.[54] In this setting, participants who presented longer than 8 weeks between injections were re-initiated on TM-BUP (minimum 8 mg) for 1 week prior to restarting BUP-XR, as part of a flexible re-entry program. Similarly, a pilot program of 108 participants in the correctional setting also permitted participants to restart BUP-XR, though specific protocols were not discussed.[62] There are no data comparing clinical profile or outcomes between subjects who receive their doses within the recommended dosing interval and those who receive a delayed dose.

Adjunctive TM-BUP

Supplemental TM-BUP was not permitted during the registrational trials[6] and is not included in the approved USA[22] or Canadian[23] labelling for BUP-XR. Administrative data from Ontario suggest this off-label practice is commonly used: 52.0% of patients treated with BUP-XR received supplemental TM-BUP, including 34.9% more than 14 days following their first injection.[36] Several studies likewise provided supplemental TM-BUP dosing after initiating BUP-XR,[35,37,55,59,63] typically to control withdrawal or cravings. Dose, duration, and frequency of use is variable—ranging from 2 to 4 mg daily in the first few months only in more stable populations with low rates of illicit opioid use who are transitioning from long-term treatment with TM-BUP[59] to higher doses and longer durations in lower threshold or specialty settings.[35,37,55] In two retrospective studies from programs where patients had high rates of fentanyl use,[35,55] over half of patients were provided supplemental TM-BUP. In the first, 4–24 mg supplemental TM-BUP was given to 55% of patients (daily/as needed).[35] Supplemental dosing was more frequent in patients with <7-day TM-BUP initiation than those with standard ≥7-day stabilization (90% vs 30.4%). In a Canadian rapid access clinic, 53.2% of patients (68.1% reported their opioid of choice was fentanyl) required supplemental TM-BUP in the first three months of treatment, though information on dose or use beyond this time frame was not provided.[54] There are no studies comparing outcomes between participants who receive supplemental TM-BUP and those who do not.

Discussion

Fentanyl's dominance in the illicit drug supply has increased the urgency for appropriate clinical management of OUD. Due to its potency, individuals who use fentanyl are at high risk of mortality from respiratory depression and overdose.[8,9] Individual bolus doses have a rapid, intense onset and short half-life,[64] which contributes to patients using multiple times a day.[65] In addition to increasing opioid tolerance, frequent fentanyl use is believed to lead to accumulation in adipose tissue.[64] While the clinical implications of this have not been established, it has been hypothesized to contribute to prolonged positive urine drug screens, as well as more severe or nonlinear withdrawal presentations[64] and increased risk of PW during buprenorphine initiations.[14,66] Furthermore, many patients who use fentanyl are clinically unstable and socioeconomically marginalized, preventing them from effectively managing treatment for this disorder.[35] Current clinical guidelines for OUD outline that when initiating patients with OUD who use fentanyl with buprenorphine, it is important to achieve therapeutic doses as quickly as possible while also mitigating PW risk.[20] These guidelines indicate that doses must be both achieved and maintained to sufficiently address withdrawal symptoms and cravings, reduce the risk of overdose from subsequent fentanyl use, and support treatment engagement and retention.[20] For many patients, buprenorphine doses higher than those included in the approved product information may be needed.[20,21]

Several strategies to optimize BUP-XR initiation and dosing in patients who use fentanyl have been reported, although these practices are outside the approved use of BUP-XR in the USA and Canada and the level of evidence in support is variable. A large randomized controlled study supports the non-inferior efficacy and comparable safety of BUP-XR initiation following a single 4-mg TM-BUP test dose versus the standard initiation protocol[14] with case reports,

and small, open-label, uncontrolled trials provide preliminary data regarding other methods.[31,32,34,42–50] The large randomized controlled trial of rapid/test dose initiation[15] confirmed prior observations that PW is elevated in patients who use fentanyl when compared to non-fentanyl-using populations.[16] While in this study, there was no difference in rates of PW between rapid and standard initiation, it has been hypothesized that both micro/low-dose and macro/high-dose initiation protocols may reduce the risk of this outcome,[67] although there are currently no studies available to investigate this. Given that in the randomized controlled trial individuals who experienced PW with rapid/test dose initiation had high rates of continuation on BUP-XR,[14] further research is needed to understand how appropriate preparation and management of PW may mitigate the impact of this event on treatment retention and other outcomes.

In addition to modifications in induction protocols, clinical guidelines, consideration documents,[20,21] and emerging literature[68,69] suggest that individuals who use fentanyl may require higher buprenorphine maintenance doses to achieve clinical stability. Exposure-response analysis examining the relationship between buprenorphine plasma concentrations and outcomes in the registrational trials for BUP-XR suggests that individuals who inject drugs may require buprenorphine plasma concentrations of 5–6 ng/mL to maximize abstinence compared to 2–3 ng/mL for individuals who do not inject.[51] This corresponds to improved abstinence in those who inject who were randomized to the 300-mg versus 100-mg maintenance dose observed during the phase 3 trial,[51] though this has yet to be replicated in individuals who use fentanyl, including those using intranasally or via inhalation. A need for higher buprenorphine levels to stabilize patients using fentanyl may explain the rates of 300-mg maintenance dose use in studies from North America. In contrast, use of the 300-mg maintenance dose appears to be lower in studies from countries such as the UK and Australia,[70–73] where illicit fentanyl has lower prevalence.

Other strategies have been described to achieve elevated buprenorphine levels, such as using supplemental TM-BUP,[35–37,55,59,63] and accelerating the dosing interval.[14,36,52] Uncontrolled data on the use of supplemental dosing in individuals who received <7-day TM-BUP stabilization[35] and acceleration of the second monthly dose in subjects initiated rapidly following a nonfatal overdose[41] suggest the potential that individuals with lower levels of stability prior to their first BUP-XR injection may benefit from these strategies; however, randomized controlled studies are needed to establish this. Despite this absence of data, several clinical guidelines support the use of supplemental dosing,[17–21] with more limited inclusion of recommendations regarding shorter dosing intervals.[19] This is reflected in the identified publications, with reports of supplemental dosing appearing in high proportion of patients in multiple publications, compared to accelerated dosing, which was noted in a low number of publications and a small subset of patients. This is a rapidly evolving area of practice, however, and emerging data on the safety and efficacy of rapid initiation along with accelerated initial dosing intervals[14] suggests opportunities for improving retention in patients at high risk due to frequent fentanyl use. These approaches may not be unique to individuals who use fentanyl, as studies from the UK and Australia have likewise reported supplemental dosing[70,73] and accelerated loading dose intervals;[73] as such, further research is needed to identify other clinical factors that may predict the need for higher buprenorphine exposure during the initial stages of treatment.

Limited data also suggest the need for flexibility to adapt to missed doses to avoid treatment discontinuation. Individuals with OUD often experience socioeconomic marginalization, have medical and psychiatric comorbidities, and/or experience relapse of illicit opioid use that contribute to challenges attending medical appointments, all of which may be further exacerbated in individuals who use fentanyl.[35] Alternately, it may be hypothesized that as patients stabilize on treatment, the long half-life of BUP-XR and delayed withdrawal symptoms from missed doses may lead patients to deprioritize monthly injections.

Our findings are limited by the narrative, nonsystematic review strategy, which, while allowing for more flexible investigation of a rapidly evolving clinical area (such as through inclusion of preliminary findings from conference abstracts), may have inadvertently excluded discussion of publications that would address the noted research gaps. Importantly, protocols described are largely supported by small, uncontrolled open-label studies and case reports in specialized settings with small samples sizes and limited duration of follow-up, making conclusions regarding their safety and efficacy across clinical practice premature. Furthermore, while we have hypothesized that use of these protocols is due specifically to the needs of individuals who use fentanyl, in many reports, fentanyl use was presumed based on geography and year, and/or no specific comparisons were done between subjects who were positive versus negative for

fentanyl use. Given the likely variability between individuals in the level of fentanyl exposure, even within a specific geographical area, further research is needed to confirm the association between fentanyl use and need for novel treatment approaches.

Conclusion

Through a narrative review of evidence from peer-reviewed publications and conference abstracts, this article provides an overview of novel initiation and dosing strategies for BUP-XR in patient populations with confirmed or presumed use of fentanyl. Results from a randomized controlled study indicate that initiating BUP-XR following a single TM-BUP dose is noninferior to standard initiation in terms of treatment retention at injection 2, with similar rates of precipitated withdrawal and adverse events, with prescribing information in the USA updated to include this use. Additionally, "macro/high-dose" or "micro/low-dose" and "direct dose" induction approaches have also been reported, although current evidence is limited to small, uncontrolled studies or case reports. Consistent with evidence from studies of TM-BUP, which suggest individuals who use fentanyl may require higher maintenance doses in order to be retained in treatment, administrative and observational data suggests that use of the 300-mg maintenance dose, shortened intervals between doses, and supplemental TM-BUP may be feasible approaches to increase buprenorphine exposure in patients with ongoing symptoms and may improve retention.

While adoption of these strategies into clinical practice and guidelines is growing, research is still needed to understand how these strategies may best be employed. Other opioid agonist treatment strategies, as well as alternate long-acting buprenorphine formulations, which have their own unique initiation and dosing protocols, were also not discussed. Indeed, innovations in practice for BUP-XR should not be viewed in isolation, rather all OUD treatment approaches, including other medications as well as nonpharmacological approaches, must all adapt to better address the ongoing opioid crisis. As the illicit drug supply continues to increase in potency and complexity and clinical cases are further complicated by stimulant and benzodiazepine co-use, continued research is urgently needed to evaluate the rapid evolution of clinical management of OUD.

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