A Plea From People Who Use Drugs to Clinicians: New Ways to Initiate Buprenorphine Are Urgently Needed in the Fentanyl Era

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With the worst opioid overdose death crisis in the United States history, urgent new approaches to assist people who use drugs onto medication for opioid use disorder are necessary. In this commentary, addiction medicine clinicians and drug user union representatives align to argue that conventional ways of buprenorphine initiation that require periods of withdrawal must be augmented with additional novel approaches to initiation. In the fentanyl era, members of the New England Users Union and Portland Users Union report encountering precipitated withdrawal, being unable to stop using full agonist opioids for a required period of time, and difficulty initiating this medication that could offer them some stability and life-saving treatment. People who use drugs should be involved at all levels with ongoing research, clinical and policy efforts to improve buprenorphine initiation as their lives and their suffering are at stake.

Key Words: Bernese method, buprenorphine, low dose initiation, microdose

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It is an imperative of both clinical and public health significance to help people who have opioid use disorder initiate medication for opioid use disorders (MOUD) as quickly and easily as possible, given the widespread prevalence of fentanyl in the United States' unregulated drug supply. As the opioid overdose death rate was recently revised to greater than 96,000 in the past year,[1] with death rates only climbing, clinicians must work assiduously with people with opioid use disorder to start evidence-based treatment as easily as possible.

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With a shift in the unregulated drug supply from heroin to predominantly illicitly manufactured fentanyl, there are concerns that fentanyl's lipophilicity potentially increases the risk of precipitated withdrawal even after waiting for symptoms of withdrawal to start, theoretically making initiations harder than with other opioids such as heroin.[2,3] Yet, buprenorphine initiations have remained largely unchanged. Buprenorphine initiation is conventionally taught as a multistep process to minimize risk of precipitated withdrawal: primarily by waiting for withdrawal symptoms requiring no use of opioids for between 12 and 72 hours depending on the opioid used, starting with 2–4mg doses of buprenorphine and repeating to a max of 8–16mg in the first day.[4]

In the fentanyl era, we should be considering other means of initiation. An alternate approach to starting buprenorphine gaining popularity is low dose initiation of buprenorphine, often termed "microdosing'' or the Bernese method.[5–7] In this method, primarily described in case reports in both outpatient and inpatient settings,[8–10] buprenorphine is started at doses as low as 0.5 mg and uptitrated over days to a therapeutic dose while continuing full opioid agonists throughout the process. With each buprenorphine dose and dose increase, only small amounts of the full agonist are displaced from the opioid receptor minimizing risk of precipitated withdrawal. As full opioid agonists, prescribed or not, are continued throughout the process, theoretically there is no need for withdrawal in order to start the process. In fact, the goal of this method is to avoid it.

This approach of overlapping full agonists while initiating buprenorphine also presents opportunities for transitions to buprenorphine for people it may otherwise be difficult for, such as those on methadone who previously had to dose reduce down to 30 mg and/or face increased risk of recurrence of use during the transition, people on long term opioid therapy for chronic pain, and for others with medical frailty in which withdrawal is not tolerable.

High dose initiation, or "macro-dosing," is another novel approach but currently lacks a uniform approach and has a more limited literature of its use. Generally, it relies on waiting on withdrawal symptoms and then utilizing higher doses of buprenorphine (up to 32 mg) to both displace the full agonist and fully bind to any unoccupied opioid receptors. The largest study to date, a retrospective chart review of 579 emergency department visits in Oakland, California, showed

it was well tolerated but was limited only to the emergency department and did not report fentanyl use.[11]

Reports of these initiation methods have been reaching people who use drugs, some of whom were previously unwilling to consider buprenorphine an accessible tool for their future. Across the country, organizations of people who use drugs known as drug user unions, a term coined by people who use drugs, have formed, defining themselves as "citizen advocacy groups of people with current and former experiences using drugs who have been affected by drug policy and the criminalization of substance use and seek to advance a health and human rights approach to their care." They mention searching for clinicians who already knew about or were willing to be educated about low dose initiation. Unfortunately, some people reported being dismissed, questioned, or admonished for asking about this method.

Several members of the New England and Portland Users Unions report that the root cause of poor treatment often lies in entrenched stigma. Medicine still tends to harbor holdovers from a dehumanizing and punitive culture, in which substance use is viewed as a moral failing, and as a corollary, acute suffering (withdrawal) is seen as necessary in order to achieve successful behavioral change. This approach is at odds with whole person-centered care that use evidence-based approaches to treat substance use disorders compassionately.[12]

Other union members had not heard of low dose initiation but lamented that it may have given them a chance to access life-saving MOUD. Some people put forward anecdotes of friends or family who fatally overdosed shortly after unsuccessful and agonizing attempts to initiate with the traditional method in which precipitated withdrawal took place.

These anecdotal accounts from people actively using drugs included other over-arching themes such as a lack of peer support, difficulty getting in touch with clinicians throughout the process, and being unheard regarding experiences of precipitated withdrawal. One activist said they were told that the acute physical symptoms they experienced while initiating buprenorphine were "psychosomatic." Another said that they were given further punitive restrictions, which complicated an already grueling initiation process, because one urinalysis came back positive for a nonprescribed agonist: "I was violently ill, terrified, and couldn't get anyone on the phone. . . I just wanted it to stop. . . of course I tried to use."

Many of the clinicians involved in these stories likely did their best with their current knowledge and training. But these ancedotes are a reminder of the need for addiction medicine practitioners to reframe the approach toward withdrawal, especially in the context of fentanyl, and for strategies such as low dose buprenorphine initiation to be offered in continuing medical education. While many clinicians have been taught that opioid withdrawal is painful but not deadly, many people who use drugs in the fentanyl era feel that the threat of withdrawal forces them to continue to use a lethal supply of street opioids. In fact, having complicated withdrawal during initiation has been associated with lower buprenorphine retention rates.[13] These reports from Users Unions members demonstrate that there should also be a renewed focus on how to support people who use drugs during the withdrawal process via any of these initiation attempts.

We have several recommendations for policymakers and clinicians. First, whether attempting novel or conventional initiations with buprenorphine, patient autonomy and patient input are critical to successful initiations and ongoing collaborations. Clinicians and patients should approach and be open to clinical encounters rooted in mutual respect of the expertise in the other. More strategies for addiction medicine doctors are urgently needed to make evidence-based medications as accessible as possible and to promote treatment retention while state and federal policies around buprenorphine and methadone access are also being addressed.

We recommend considering this method for patients that have previous adverse experiences with traditional initiation, for patients who would like to transition from methadone to buprenorphine, or for patients who are interested in initiating buprenorphine via low dose initiation. In addition, it could engage patients who might not have considered MOUD who might be open to trying buprenorphine if they knew this method existed. Ongoing clinician and patient education as well as continued support and troubleshooting via mechanisms like PCSS regarding these novel initiation methods is critical.

Second, more research, including both quantitative and qualitative studies with a focus on patient preference and ease of initiation comparing these alternative methods to traditional methods, is urgently needed. More specifically, it is important to understand which patient populations these initiation methods may benefit that might vary based on macro-level factors, such as location and available unregulated drug supply, as well as individual characteristics, such as age, gender, substances used, as well as other mental health and medical conditions.

Finally, people with lived and living experience of using drugs must be seen as vital partners in both research and clinical practice.[14] On a research level, people who use drugs must be involved in informing the research design, process, metrics/outcomes and execution of these studies. At all levels, from clinic guidelines to the statehouse, people who use drugs should be part of ongoing advisory groups that affect their care.

In our current fentanyl era, patients and people who use drugs are pleading with clinicians to be open to education on and willingness to attempt these novel initiation methods as we await larger trial results.[15] While it may seem contradictory to encourage clinicians to attempt this novel buprenorphine initiation method with a smaller evidence base than traditional methods, the Users Union leaders feel urgency akin to the human immunodeficiency virus/acquired immunodeficiency syndrome era, where affected patient-advocates from groups like AIDS Coalition To Unleash Power (ACT UP) pushed for access to any and all potentially life-saving treatments as they were being developed. In both contexts, directly impacted people were curious, educated and open to enrollment in trials to better understand treatments.We as clinicians and researchers must simultaneously ensure that these methods are evaluated rigorously and are supportive of ongoing randomized controlled trials while simultaneously being open

to using them now to save lives. The lives of people who use drugs depend on our future ability to collaborate and work with our patients on individual and community levels to successfully initiate, maintain and expand access to MOUD.

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