Feasibility of Microdose Buprenorphine Starts with Methadone and Illicit Opioid Use

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Introduction

Buprenorphine is an effective treatment for opioid use disorder (OUD)[1,2]. However, a significant barrier to entering treatment is the risk of precipitated withdrawal, which manifests as immediate, severe opioid withdrawal symptoms that occur when buprenorphine is initiated while opioids are still present in the central nervous system[3]. To avoid precipitated withdrawal, induction protocols have relied on a period of abstinence and observed opioid withdrawal prior to buprenorphine initiation. However, this approach is less feasible in patients using opioids that have a prolonged half-life, such as methadone, extended-release opioids, and fentanyl. As both surreptitious and explicit fentanyl now predominates North American drug markets, this has become a pressing issue for outpatient buprenorphine treatment. “Microdosing” is an emerging strategy that allows for cross titration of buprenorphine with full-agonist opioids, which decreases the risk of precipitated withdrawal. However, research has been limited to date, particularly among patients using illicit opioids in unsupervised settings[4,5,6].

Methods

A cohort of patients was selected from two sites: CORE, a Narcotic Treatment Program (NTP) that offers methadone and buprenorphine, and an outpatient buprenorphine clinic within SANE, a syringe services program (SSP), both in Sacramento California. Every patient who was prescribed a microdosing protocol between March 2022 and December 2022 was selected for analysis.

CORE patients were administered microdose protocols ranging from 7 to 14 days, and were maintained on their baseline methadone maintenance throughout the protocol.

SANE patients received a uniform 10 day microdose protocol (Fig 3.) Both groups were instructed to stop full agonist opioids on the final day. These charts were thoroughly reviewed and relevant data was extracted based on predetermined variables. Proportions and simple statistics were performed using Microsoft Excel using intent to treat analysis.

This project was determined to be not human subjects research by the UC Davis IRB.

Figure 1.

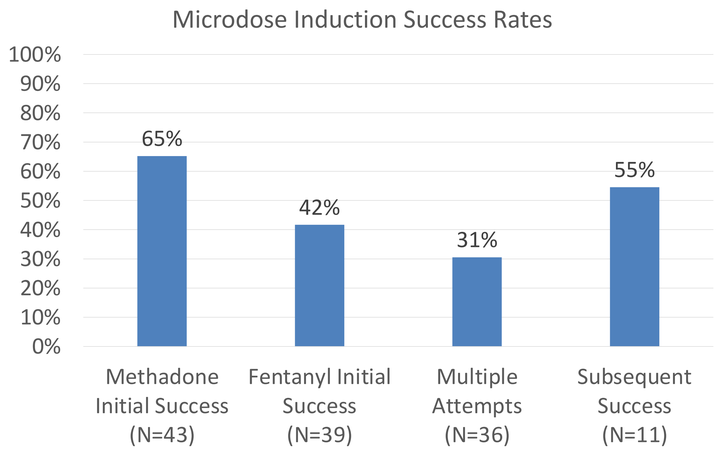

Figure 2.

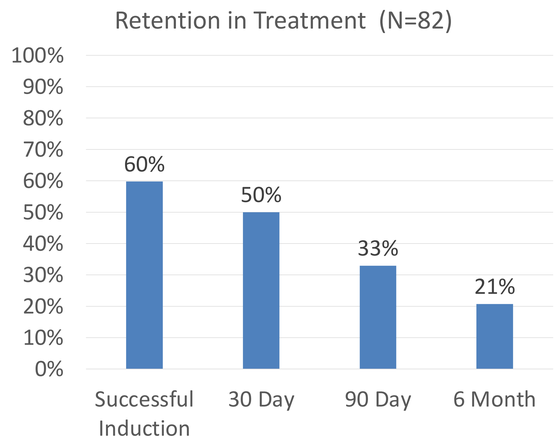

Table 1.

Demographics

	N	n	Percentage
Female Identifying	39	21	54%
White Identifying	38	27	71%
Methadone use	82	46	56%
Fentanyl use	35	25	71%
Polysubstance use	59	34	58%
Unstably Housed	59	18	31%
Psychiatric Diagnoses	59	35	59%
Overdose History	38	22	58%
SANE (SSP) patient	82	39	48%
CORE (NTP) patient	82	43	52%
	N	**Average**	**Range**
Microdose Duration (days)	80	9.6	7-14
Terminal Bup Dose (mg)	37	21.3	6-32

Figure 3.

Example Buprenorphine Microdose Schedule

	Strength	AM	PM	Opioid Dosing
Day 1	2/0.5mg Film	1/4 film (0.5mg)	1/4 film (0.5mg)	Continue Full Agonist Opioids Consistently
Day 2	2/0.5mg Film	1/4 film (0.5mg)	1/4 film (0.5mg)	
Day 3	2/0.5mg Film	1/2 film (1mg)	1/2 film (1mg)	
Day 4	2/0.5mg Film	1/2 film (1mg)	1/2 film (1mg)	
Day 5	2/0.5mg Film	1 film (2mg)	1 film (2mg)	
Day 6	2/0.5mg Film	1 film (2mg)	1 film (2mg)	
Day 7	2/0.5mg Film	1 film (2mg)	2 film (4mg)	
Day 8	8/2mg Film	1/2 film (4mg)	1/2 film (4mg)	
Day 9	8/2mg Film	1/2 film (4mg)	1 film (8mg)	
Day 10	8/2mg Tab	1 film (8mg)	1 film (8mg)	Stop other opioids
Day 11	8/2mg Tab	Up to 2 film (16mg)	Up to 2 film (16mg)	

Results

A total of 82 patient charts were included for analysis, N=43 from CORE (NTP) and N=39 from SANE (SSP). 46% (n=36) were actively using fentanyl, 56% (n=46) were on methadone maintenance, and 58% (n=34) reported polysubstance use (N=59). 31% (n=18) reported lack of stable housing, 59% (n=35) reported psychiatric diagnoses, and 58% (n=22) had history of overdose.

Ultimately 60% (n=49) were successful started using microdose. Retention at 30, 90, and 180 days was 50%, 33%, 21%, respectively.

On the initial attempt, 65% (n=30) of those on methadone and 42% (n=15) of those using illicit opioids were successful. Among those not successful on the first attempt, 25% (n=11) participated in multiple attempts, and 55% (n=6) of these were ultimately successful started. The average microdose duration was 9.6 days, ranging from 7-14 days, and the average terminal buprenorphine dose was 21.3mg daily. 53% (n=25) of patient experienced some withdrawal during the protocol.

Conclusions

These cohorts experienced numerous barriers to initiating buprenorphine treatment, due primarily to methadone and fentanyl use, in addition to homelessness, poly-substance use, and co-occurring psychiatric disease. Utilizing a microdose initiation protocol, a substantial proportion were successfully started on buprenorphine and retained in treatment.

Patients on methadone demonstrate slightly higher rate of initial success, likely attributable to consistent dosing and supportive structures, compared to those using fentanyl in less predictable quantities, frequencies, and circumstances. Among those who were not successful on the first try, some participated in multiple attempts, and had a high rate of subsequent success. There are myriad reasons for not completing the initiation, including inconsistent opioid or buprenorphine dose, withdrawal symptoms, or circumstantial challenges. Multiple attempts should be encouraged. Further qualitative research should explore these experiences and challenges in order to optimize dosing schedules, patient education, and supports offered to overcome common pitfalls.

Buprenorphine microdose starts are feasible, even in traditionally challenging populations with notable pharmacological and structural obstacles. The aversion to opioid withdrawal—particularly the risk of precipitated withdrawal–is a strong motivating factor and can pose a significant barrier to treatment. Fentanyl presents new challenges, given its potency, high lipophilicity, and prolonged half-life in chronic use. Novel approaches are required to provide equitable, patient-centered access to care for these patients. By limiting exposure to withdrawal symptoms during buprenorphine initiation, microdose initiation provides a promising tool for increasing treatment initiation.

Additional research should utilize randomized controlled trials to evaluate various microdose protocols to determine the most reliable protocol that can achieve buprenorphine induction in the shortest period of time, while minimizing the incidence of precipitated withdrawal..

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Disclosures:
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