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BRIEF RESEARCH REPORT

Toxicology

Microdosing and standard-dosing take-home buprenorphine from the emergency department: A feasibility study

Jessica Moe MD, MSc[1,2] | Katherin Badke PharmD, BScPharm[3] | Megan Pratt MSW, RSW[4] | Raymond Y Cho MD, BSc[5] | Pouya Azar MD[6,7] | Heather Flemming MD[1,2] | K. Anne Sutherland MD, MSc[1,2] | Barbara Harvey MScN, JD[2] | Lara Gurney MSN, RN[2] | Julie Lockington MN, RN[2] | Penny Brasher PhD[8] | Sam Gill RN, BScN[9] | Emma Garrod MSN, RN[10] | Misty Bath MScPH, BSN[11] | Andy Kestler MD, MScPH[1,12]

[1] Department of Emergency Medicine, University of British Columbia, Vancouver, British Columbia, Canada

[2] Department of Emergency Medicine, Vancouver General Hospital, Vancouver, British Columbia, Canada

[3] Department of Pharmaceutical Sciences, Vancouver General Hospital, Vancouver, British Columbia, Canada

[4] Social Work, Vancouver General Hospital, Vancouver, British Columbia, Canada

[5] Faculty of Medicine, University of British Columbia, Vancouver, British Columbia, Canada

[6] Department of Psychiatry, University of British Columbia, Vancouver, British Columbia, Canada

[7] Complex Pain and Addiction Services, Vancouver General Hospital, Vancouver, British Columbia, Canada

[8] Centre for Clinical Epidemiology and Evaluation, Vancouver, British Columbia, Canada

[9] Rapid Access Addiction Clinic, St. Paul's Hospital, Vancouver, British Columbia, Canada

[10] Urban Health Program, Providence Health Care, Vancouver, British Columbia, Canada

[11] Regional Prevention, Vancouver Coastal Health Authority, Vancouver, British Columbia, Canada

[12] Department of Emergency Medicine, St. Paul's Hospital, Vancouver, British Columbia, Canada

Correspondence
Jessica Moe, MD, MSc, Department of Emergency Medicine, Vancouver General Hospital, 920 West 10th Avenue, Vancouver, British Columbia, Canada V5Z 1M9.
Email: jessica.moe@ubc.ca

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Abstract

Objective: Emergency department (ED)–initiated buprenorphine may prevent overdose. Microdosing is a novel approach that does not require withdrawal, which can be a barrier to standard inductions. We aimed to evaluate the feasibility of an ED-initiated buprenorphine/naloxone program providing standard-dosing and microdosing take-home packages and of randomizing patients to either intervention.

Methods: We broadly screened patients ≥18 years old for opioid use disorder at a large, urban ED. In a first phase, we provided consecutive patients with 3-day standard-dosing packages, and then we provided a subsequent group with 6-day microdosing packages. In a second phase, we randomized patients to standard dosing or microdosing. We attempted 7-day telephone follow-ups and 30-day in-person community follow-ups. The primary feasibility outcome was number of patients enrolled and

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accepting randomization. Secondary outcomes were numbers screened, follow-up rates, and 30-day opioid agonist therapy retention.

Results: We screened 3954 ED patients and identified 94 with opioid use disorders. Of the patients, 26 (27.7%) declined participation: 10 identified a negative prior experience with buprenorphine/naloxone as the reason, 5 specifically cited precipitated withdrawal, and none cited randomization. We enrolled 68 patients. A total of 14 left the ED against medical advice, 8 were excluded post-enrollment, 21 received standard dosing, and 25 received microdosing. The 7-day and 30-day follow-up rates were 9/46 (19.6%) and 15/46 (32.6%), respectively. At least 5/21 (23.8%) provided standard dosing and 8/25 (32.0%) provided microdosing remained on opioid agonist therapy at 30 days.

Conclusions: ED-initiated take-home standard-dosing and microdosing buprenorphine/naloxone programs are feasible, and a randomized controlled trial would be acceptable to our target population.

KEYWORDS

Bernese method, buprenorphine, drug overdose, emergency service hospital, microdosing, microinduction, naloxone drug combination, opiate substitution therapy, opioid addiction, opioid-related disorders

1 | INTRODUCTION

1.1 | Background

The opioid overdose epidemic claimed >67,000 lives in the United States in 2018 and has caused North American life expectancy to decline.[1,2]

Public health data show that many individuals have emergency department (ED) contact before overdose.[3] ED visits are therefore critical opportunities to initiate preventive interventions. ED-initiated buprenorphine has been shown to increase 30-day retention in addiction care and reduce illicit opioid use.[4]

Buprenorphine (commonly available as buprenorphine/naloxone) is a first-line opioid agonist therapy in North America.[5] Because of partial opioid receptor agonism, it has a ceiling effect on opioid-mediated respiratory depression and carries a lower overdose risk compared with methadone and other full-agonist therapies. It therefore may be safely provided in take-home regimens.[6] Buprenorphine is a preferred opioid agonist therapy because of its favorable side effect profile[6–9] and evidence demonstrating a decreased risk of all-cause and overdose-related mortality compared with methadone.[10,11] However, retention remains a challenge: a systematic review revealed that retention on buprenorphine was similar to methadone at high but not low or flexible maintenance doses.[12]

As a result of high affinity, buprenorphine may cause precipitated withdrawal if it out-competes lower affinity opioids (eg, heroin, morphine) at opioid receptors. To avoid this effect, physicians or other prescribers counsel patients to wait 12 to 48 hours since last using opioids and to be in moderate withdrawal before initiating standard-dosed buprenorphine.[5] The need to experience withdrawal can be a major barrier and contributes to higher dropout rates for buprenorphine than methadone during treatment initiation.[13]

Microdosing, also known as the "Bernese method," is a novel approach that attempts to improve patient comfort by avoiding the need for opioid withdrawal during buprenorphine induction and minimizing risk of precipitated withdrawal.[14] Typical regimens use small initial doses that are titrated up over 5 to 7 days while patients continue their non-medical opioid use. Case reports indicate that patients may tolerate microdosing well with minimal opioid withdrawal symptoms and cravings.[15,16] The seminal "Bernese method" publications described initiating patients on buprenorphine doses of 0.2 mg (whereas standard dose inductions typically initiate doses ≥2 mg); however, no universally accepted regimen exists.[15] The theoretical basis of this approach is that small buprenorphine doses gradually accumulate at opioid receptors, replacing a patient's need for full agonists. Microdosing inductions can and have been used with a range of overlapping opioid agonists (eg, heroin, methadone, hydromorphine, fentanyl).[15–18] Where patients undertake a microdosing induction concurrently with non-medical opioid use, physicians or other prescribers counsel them that there is no set expectation to alter illicit drug use but that they may decrease their concurrent opioid use as per their symptoms.[15]

1.2 | Importance

Because of its favorable characteristics, microdosing is increasingly being used as a buprenorphine induction strategy[16,18]; however, a recent systematic review confirmed that published evidence to date is limited to case studies, and no rigorous studies have been conducted.[19]

Furthermore, microdosing has not been evaluated in the ED setting despite complexities that could conceivably make this approach favorable for many ED patients (eg, acute intoxication, painful conditions, time pressures, and ED resource limitations that make observed withdrawal difficult). There is an urgent need for clinical trials comparing effectiveness and safety of microdosing vis-à-vis standard inductions. As a preliminary step, studies assessing feasibility of ED-based standard-dosing and microdosing buprenorphine interventions are needed.

1.3 | Goals of this investigation

Our goal was to evaluate the feasibility of an ED-initiated buprenorphine/naloxone program providing standard-dosing and microdosing take-home packages. Once feasibility of ED-initiation was established, we evaluated acceptability of randomization.

The Bottom Line

Microdosing of buprenorphine is a novel approach for opioid use disorder treatment that does not require withdrawal. This pilot study found that randomization of emergency department patients to a take-home microdose or standard dose of buprenorphine was feasible.

2 | METHODS

2.1 | Study design and setting

This study was conducted at Vancouver General Hospital, an urban tertiary-care hospital with an annual ED census of 94,000 patients. The University of British Columbia Clinical Research Ethics Board approved this study (H19-00889).

2.2 | Participant selection

Trained research assistants screened patients ≥18 years old with 1 of 20 presenting complaints associated with overdose in public health data (Appendix A). Patients were asked about non-medical opioid use in the previous 30 days. If confirmed, they were administered the validated Rapid Opioid Dependence Screen for opioid use disorder (Appendix B).[20] Those screening positive were offered participation. Our initial inclusion criteria also included a positive urine toxicology screen for fentanyl or other opioids. Our institution uses test strips for fentanyl and opioid metabolites applied to a patient's urine sample when it is sent to a central laboratory. All women of reproductive age were also asked to produce a urine sample for a point-of-care urine pregnancy test, which was tested and resulted in the ED.

Emergency physicians or nurses clinically assessed all patients and determined whether they were experiencing active opioid withdrawal. Where withdrawal was clinically suspected, the patient was assessed using the standardized Clinical Opiate Withdrawal Scale.[21] If patients were experiencing moderate to severe withdrawal (Clinical Opiate Withdrawal Scale >12), they were offered standard-dosed buprenorphine/naloxone in the ED using an in-ED clinical protocol and were not eligible for the take-home buprenorphine/naloxone interventions offered by the current study.

Patients were excluded if they had filled an opioid agonist therapy prescription within 5 days, were non-English speaking, non-communicative, taking opioids for cancer/palliation, admitted, or discharged in police custody. Pregnancy was an exclusion criteria for our ED-initiated take-home study interventions and mandated expert consultation with our addictions service to arrange for admission or close specialist follow-up.

2.3 | Interventions

Our multidisciplinary team collaboratively developed our buprenorphine/naloxone interventions.

2.3.1 | Phase 1

In phase 1, our focus was on the logistics of identifying eligible patients and initiating intervention in the ED. We implemented the 2 interventions sequentially (aiming for 15 patients in each block). In the first block, each patient received a 3-day take-home buprenorphine/naloxone standard-dosing package. The initial dose was 2/0.5 mg, which could be repeated hourly to a maximum of 12/3 mg in 24 hours. Patients were counseled to start after their ED visit once they were experiencing moderate opioid withdrawal and to avoid opioid use during induction. For days 2 and 3, patients took the total dose achieved on day 1 (target 12/3 mg). After enrolling the 15th patient for the standard-dosing regimen, we switched to enrolling for microdosing.

Subsequently, each patient received a 6-day take-home buprenorphine/naloxone microdosing package with an initial dose of 0.5/0.125 mg (Table 1). Patients were counseled that they could initiate the first dose at any time that was convenient for them (including in the ED, if preferred) and to continue concurrent illicit opioid use during induction, without requiring opioid withdrawal.

Patients were informed before enrollment whether they would receive standard dosing or microdosing.

2.3.2 | Phase 2

With feasibility of ED initiation established and before launching a definitive trial, we wanted to evaluate if patients would accept random

TABLE 1 Outpatient microdosing regimen

Day	Dose	Number of tablets per dose (buprenorphine-naloxone 2 mg–0.5 mg tablet)
1	Buprenorphine 0.5 mg–naloxone 0.125 mg SL BID	One-quarter tablet
2	Buprenorphine 1 mg–naloxone 0.25 mg SL BID	One-half tablet
3	Buprenorphine 2 mg–naloxone 0.5 mg SL BID	1 tablet
4	Buprenorphine 3 mg–naloxone 0.75 mg SL BID	One and a half tablet
5	Buprenorphine 4 mg–naloxone 1 mg SL BID	2 tablets
6	Buprenorphine 12 mg–naloxone 3 mg SL BID	6 tablets

BID, twice daily; SL, sublingual.

allocation. Thus, in a second phase, patients were randomized (1:1) to either standard dosing or microdosing.

2.4 | Cointerventions

Clinical pharmacists or emergency physicians counseled all patients regarding buprenorphine/naloxone use, benefits, and risks. All patients were offered symptomatic treatments as outlined within a standardized clinical protocol signed by the physician to order the standard-dosing or microdosing buprenorphine/naloxone package (ondansetron, ibuprofen, acetaminophen, and quetiapine on an as-needed basis). ED social workers assisted with psychosocial needs. All patients were referred to a low-barrier rapid access addictions clinic and were given an information pamphlet with the clinic's location and hours, where they could walk in 7 days per week with no required appointment and no cost. All patients were counseled to followup with an addictions physician either at our partner clinic or at another clinic of their own choosing (within 3 days for standard dosing and within 6 days for microdosing) who would provide an ongoing buprenorphine/naloxone prescription tailored to patients' needs beyond the induction period.

2.5 | Follow-up

We obtained comprehensive contact information from patients at enrollment, including phone numbers, alternative contacts, emails, and pharmacy, housing, and/or shelter information. Research assistants attempted telephone follow-up at 7 days. At 30 days, our team social worker (phase 1) or outreach worker (phase 2) used a range of modalities to reach patients, including active community tracing using provided contact information and/or leaving messages at their residences or social gathering places, and arranged interviews at public locations. We provided patients with $10 and $20 honoraria for participating in 7-day and 30-day follow-up interviews, respectively. Furthermore, we held case discussions with our partnering rapid access addictions clinic to determine patients' clinical course.

2.6 | Measurements

Patients who declined participation were asked to provide their reasons. Research assistants collected demographic, socioeconomic, and opioid use information from enrolled patients. At 7 and 30 days, patients were asked about their experiences with buprenorphine/naloxone and whether they continued to take buprenorphine/naloxone or another opioid agonist therapy. We collected times associated with each enrollment step to inform process improvement.

2.7 | Outcomes

The primary feasibility outcomes were number of patients enrolled and acceptability of randomization. Secondary feasibility outcomes were numbers screened, contacted at follow-up, and 30-day opioid agonist therapy retention.

2.8 | Analysis

We summarized patient characteristics and feasibility outcomes using descriptive statistics.

3 | RESULTS

3.1 | Screening

From July 2019 to March 2020, we screened 3954 ED patients. We identified 135 patients who endorsed non-medical use and 94 who screened positive for opioid use disorder (Figure 1).

3.2 | Enrollment and reasons for declining

Of 94 eligible patients, 26 (27.7%) declined. A total of 10 declined in phase 1 (n = 7 offered standard dosing, and n = 3 offered microdosing), and 16 in phase 2. Of the patients, 10 cited negative prior experiences with buprenorphine/naloxone as the reason for declining, of whom 5 specifically mentioned a fear of precipitated withdrawal. Other reasons included the following: currently uninterested (n = 9), not wanting/needing help (n = 4), preference for sustained-release morphine (n = 2), and preference to choose the dosing strategy rather than be assigned by any other means (n = 1).

We consented and enrolled 68 (72.3%) of 94 eligible patients in the study. Among these 68 enrolled patients, substance misuse/intoxication, overdose, or substance withdrawal comprised only 27.9% (19/68) of all presenting complaints. Of 6 patients who had

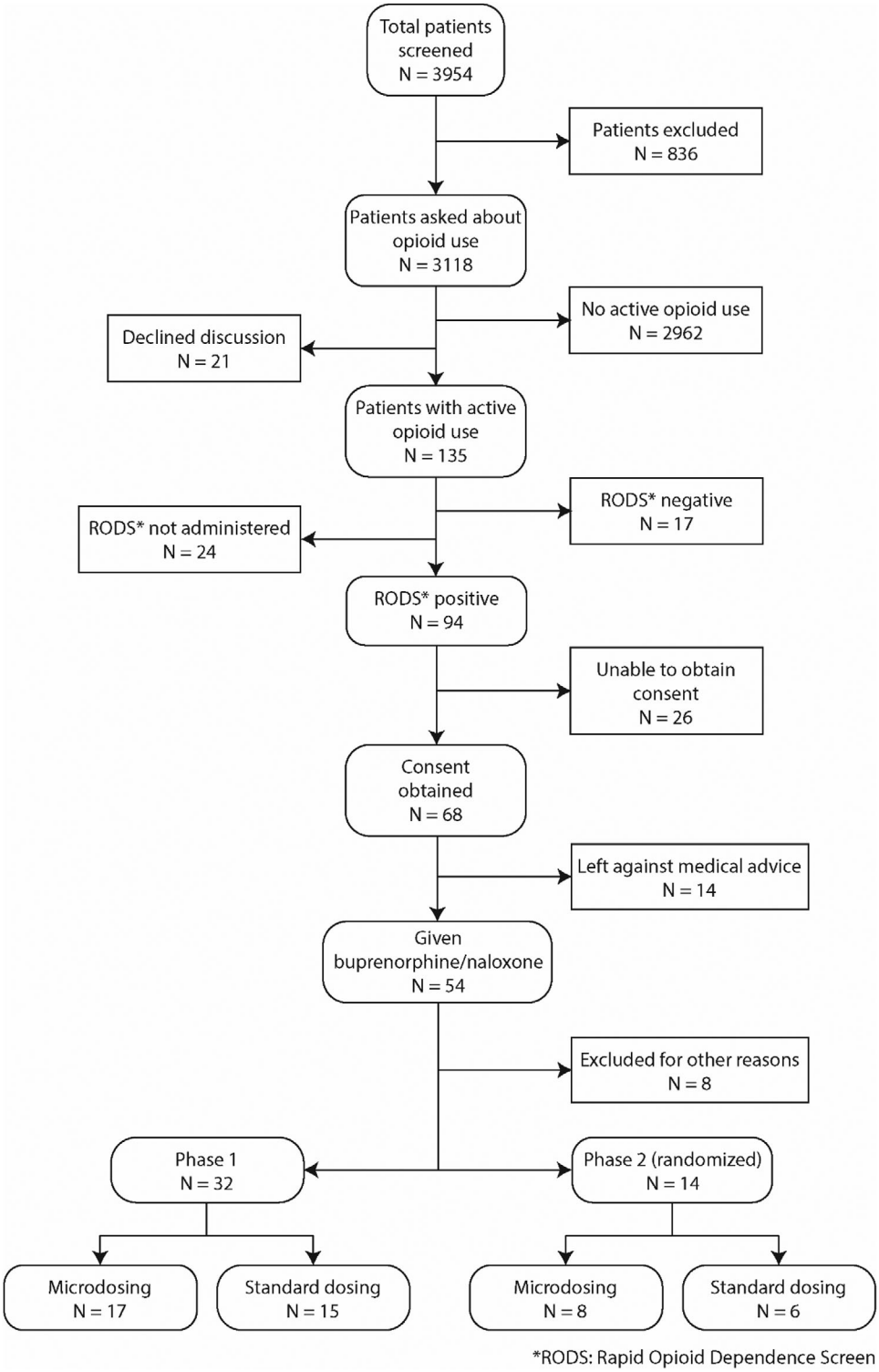

FIGURE 1 Study flow diagram

presented with substance withdrawal symptoms, all reported having used opioids and 4 endorsed exposure to a mixture of substances, including cannabis, amphetamines, and cocaine in addition to opioids. None of the included patients who had presented with withdrawal symptoms were clinically assessed to be in moderate to severe withdrawal (Clinical Opiate Withdrawal Scale >12), and therefore these patients remained eligible for our take-home buprenorphine/naloxone standard-dosing and microdosing interventions.

After enrollment, 14 patients left the ED against medical advice before receiving their buprenorphine/naloxone package. A total of 8 patients were excluded after enrollment as a result of newly developed exclusion criteria (n = 5 admitted, n = 2 had received an

opioid agonist therapy within 5 days, n = 1 discharged in police custody). During both phases we provided 21 patients with standard dosing and 25 with microdosing (Figure 1).

3.3 | Patients leaving against medical advice

In phase 1, 14/52 (26.9%) patients consenting to participation left against medical advice before receiving their buprenorphine/naloxone package. Uniformly, these patients experienced longer times to complete enrollment processes and longer ED lengths of stay (Appendix C). Urine toxicology testing to confirm opioid use was commonly a rate-limiting step, and results rarely changed management. For instance, false negatives occurred in patients with strong clinical evidence of opioid use who had used synthetic opioids not detected by our test. In phase 2, we eliminated the need for a confirmatory urine test before enrollment. After this amendment, no patients left against medical advice. Importantly, however, during phase 2, 78.5% (11/14) of patients were enrolled in a concurrent study providing cash honoraria for completing surveys in the ED, which likely contributed to the decline in patients leaving prematurely.

3.4 | Allocation

During phase 1, we enrolled 15 patients in the standard-dosing group and then 17 patients in the microdosing group. During phase 2, we randomized 14 patients: 6 to standard dosing and 8 to microdosing.

3.5 | Characteristics of study participants

Characteristics of enrolled patients are shown in Table 2. Most were in their 30s and 40s, men, and White. Patients commonly reported unstable housing, unsteady employment, and lack of a regular family physician.

Most patients endorsed using heroin or fentanyl and having last used within 24 hours of ED presentation. Of the patients, 4 (2 who received standard dosing and 2 who received microdosing) reported last having used opioids 7 or 8 days before ED presentation. For these complex cases, we consulted our partnering addictions specialists. As there was clinical ambiguity regarding exact timing of last opioid exposure based on patients' clinical symptoms and the accuracy of their recall, we collaboratively determined that these patients remained candidates for buprenorphine/naloxone induction.

Few patients reported having a current opioid prescriber (2/46; 4.3%) or having been initially prescribed opioids as a precursor to their opioid use disorder (9/46; 19.6%). A majority (37/46; 80.4%) had previously attempted opioid agonist therapy, 17/46 (37.0%) had made >1 previous attempt, and 27/46 (58.9%) had attempted buprenorphine/naloxone specifically. Where obtained, urine toxicology testing indicated that most patients (28/34; 82.3%) were exposed to multiple substances.

3.6 | Follow-up

In phase 1, we experienced a 7-day follow-up rate of 12.5% (4/32) by telephone. During phase 2, we attempted initial contact by anonymized text message. After this protocol change, we increased our follow-up rate to 35.7% (5/14).

We experienced 30-day follow-up rates of 31.3% (10/32) and 35.7% (5/14) in phases 1 and 2, respectively.

3.7 | Retention

Our estimation of opioid agonist therapy retention is inferred from the patients with whom we were able to followup. Based on 30-day interviews and discussions with our partnering addictions clinic, we identified that at least 23.8% (5/21) of patients provided standard dosing, and 32% (8/25) of patients provided microdosing remained on opioid agonist therapy 30 days after their ED visit. Of patients receiving opioid agonist therapy at follow-up, 60% (3/5) of those initially provided standard dosing, and 37.5% (3/8) of those provided microdosing had been transitioned to another form of opioid agonist therapy (methadone, methadose, or sustained-release morphine).

3.8 | Limitations

A study limitation is high loss to follow-up, which would be a barrier to determining effectiveness of dosing strategies in future larger trials. At 7 days, we found that many of the telephone numbers provided did not work when called. Our successful 7-day follow-up rates improved after our transition to texting. Our 30-day in-person contact rates were more successful but remained low. Community follow-up proved a time-intensive and resource-intensive practice that would unlikely be feasible in a larger trial. Given low follow-up rates, we cannot accurately discern retention in opioid agonist therapy among our enrolled patients. Furthermore, our reliance on self-reports to determine compliance with the induction regimens and retention in treatment may have limited the accuracy of our outcome ascertainment.

There is a potential that our study sample is not representative of the target population. Our study relied on research assistant availability (weekdays from 8:00 AM to 11:00 PM and weekends from 1:00 PM to 9:00 PM). As a result of resource limitations, we were unable to enroll patients overnight. However, our enrollment hours included late evenings, and therefore we believe the sample is likely representative.

4 | DISCUSSION

Our study, which provided 21 patients with standard-dosing packages and 25 patients with microdosing packages, demonstrates that ED-initiated standard-dosing and microdosing take-home buprenorphine/naloxone programs are feasible. Patients were generally

TABLE 2 Characteristics of enrolled patients

	Standard dosing, phase 1	Microdosing, phase 1	Standard dosing, phase 2 (randomized)	Microdosing, phase 2 (randomized)
Total patient, n	15	17	6	8
Mean age (SD)	40.9 (8.7)	35.4 (8.7)	31.8 (4.3)	33.1 (11.7)
Male	11	13	4	4
Housing status				
Homeless	4	7	2	2
Shelter	6	2	1	1
Family	1	2	0	0
Modular housing	0	2	1	3
Fixed address	2	1	2	2
N/A or prefer not to answer	2	3	0	0
Employment status				
Unemployed	13	13	3	7
Disability	0	1	0	0
Temporary/part-time	1	2	0	0
Full-time	1	1	2	1
N/A or prefer not to answer	0	0	1	0
Ethnicity				
White	7	9	2	6
First Nations	5	3	1	1
Hispanic	1	0	0	0
African American	0	1	0	0
Asian	0	0	0	0
N/A or prefer not to answer	2	4	3	1
Regular pharmacy	11	5	3	2
Primary care				
No family physician	12	11	4	8
Walk in	0	0	0	0
Community	1	2	2	0
Family physician	2	4	0	0
Presenting complaints				
Substance misuse/intoxication	2	2	1	0
Localized swelling/redness	1	7	1	3
Overdose ingestion	2	0	0	2
Back pain	0	0	0	0
Substance withdrawal	3	1	1	1
Cellulitis	2	0	0	0
Altered level of consciousness	1	0	0	0
Head injury	1	1	0	0
General weakness	1	0	0	0
Infection, rule out bug bite	1	0	0	0
Nausea, vomiting, looks unwell	1	0	0	0
Medication request	0	1	0	0
Cough	0	2	0	0

(Continues)

TABLE 2 (Continued)

	Standard dosing, phase 1	Microdosing, phase 1	Standard dosing, phase 2 (randomized)	Microdosing, phase 2 (randomized)
Suicidal ideation	0	1	0	0
Respiratory distress	0	1	0	0
Wound check	0	1	0	0
Chest trauma	0	0	1	0
Dysuria/possible UTI	0	0	1	0
Headache	0	0	1	0
Chest pain/respiratory symptoms	0	0	0	1
Abdominal pain, moderate pain	0	0	0	1
Substances present in urine[a]				
Benzodiazepines	2/15	2/16	1/1	0/2
Cannabinoids	5/15	2/16	0/1	0/2
Cocaine	5/15	5/16	1/1	0/2
Opiates	5/15	12/16	0/1	1/2
Amphetamine/methamphetamine	8/15	13/16	1/1	2/2
Fentanyl	10/15	16/16	1/1	2/2
Number of substances present in urine				
0	1/15	0/16	0/1	0/2
1	4/15	1/16	0/1	0/2
2	5/15	4/16	0/1	1/2
3	1/15	5/16	0/1	1/2
4	2/15	4/16	1/1	0/2
5	2/15	2/16	0/1	0/2
6	0/15	0/16	0/1	0/2
Reported types of opioid use				
Heroin	11	9	3	5
Fentanyl	10	8	4	7
Oxycodone	3	2	0	0
Buprenorphine	1	1	0	0
Number of opioid types used				
1	3	12	5	4
2	4	3	1	4
3	4	1	0	0
N/A	4	1	0	0
Patient-reported time of last opioid use (days)				
0	8	11	2	3
1	1	4	3	4
2	1	1	0	0
3	2	0	0	0
4	0	0	0	0
5	0	0	0	0
6	0	0	0	1
7	0	1	0	0
8+	2	0	0	0
N/A	1	0	1	0

(Continues)

TABLE 2 (Continued)

	Standard dosing, phase 1	Microdosing, phase 1	Standard dosing, phase 2 (randomized)	Microdosing, phase 2 (randomized)
Opioid type last used				
Heroin	1	7	3	3
Fentanyl	10	9	3	4
Oxycodone	1	0	0	0
N/A or prefer not to answer	3	1	0	1
Current opioid source				
Prescriber	2	0	0	0
Street	12	14	4	7
N/A or prefer not to answer	1	3	2	1
Was initially prescribed opioids				
Yes	4	1	3	1
No	10	15	2	7
N/A or prefer not to answer	1	1	1	0
Previously on OAT				
Yes	11	15	5	6
No	3	2	1	2
N/A or prefer not to answer	1	0	0	0
Types of OAT used				
Buprenorphine/naloxone (Suboxone, Indivior Inc, North Chesterfield, VA)	7	12	5	3
Methadone	8	5	2	6
Methadose	0	0	0	1
Slow-release morphine (Kadian, Allergan USA Inc, Madison, NJ)	2	3	1	1
Number of types of OAT attempted				
0	4	2	1	2
1	5	11	2	2
2	6	2	3	3
3	0	2	0	1

N/A, Not applicable; OAT, opioid agonist therapy; UTI, urinary tract infection.

[a]Note: n = 1 missing urine toxicology result among phase 1 microdosing patients. Urine toxicology testing was not mandatory in phase 2; sent at physician or nurse discretion.

amenable to both and open to enrollment in a study examining these interventions. Furthermore, patients were willing to be randomized; none specifically cited randomization as a reason for declining, although one identified wanting to choose rather than to be assigned the intervention (whether by randomization, consecutive assignment, clinician discretion, or by any other means of allocation).

Interpreting our results in light of potential benefits of microdosing vis-à-vis standard dosing supported by case reports (eg, increased patient comfort because of avoidance of withdrawal, successful inductions in patients who had previously failed standard dosing)[15,16,19] and also considering potential complexities of a longer induction regimen (eg, a more complicated protocol to follow, ongoing overdose risk while patients continue to use illicit opioids), our results support clinical equipoise regarding the comparative effectiveness of microdosing versus standard dosing in successfully inducing patients to opioid agonist therapy. A definitive trial comparing microdosing and standard-dosing buprenorphine/naloxone inductions is urgently needed. In the context of evidence that ED provision of buprenorphine/naloxone effectively engages patients in ongoing addictions care,[4] ED visits are crucial opportunities to identify patients at risk for overdose and to trial the effectiveness of buprenorphine/naloxone microdosing regimens.

This study demonstrates the importance of streamlining ED care to prevent patients with opioid use disorder from leaving against medical advice. Although we recognize the utility of urine toxicology testing in identifying nuances that could influence induction timing or rate of dose escalation (eg, exposure to fentanyl or synthetic

derivatives or baseline exposure to buprenorphine) and in ongoing monitoring, learning from our experience, other sites should consider eliminating urine toxicology testing as a prerequisite for buprenorphine/naloxone eligibility to minimize barriers to treatment initiation. This adaptation allowed us to decrease the number of patients who left prematurely.

Our challenges with follow-up indicate a need to engage patients to optimize follow-up processes. Future studies could also consider more effective methods of ascertaining patient outcomes (eg, pharmacy or administrative health records). Future studies should elucidate feasibility and barriers to patients completing microdosing regimens as directed and following up with outpatient clinics as planned; should assess how the occurrence of precipitated withdrawal compares with standard dosing; should explore the optimal dosing regimen for microdosing, which has yet to be determined; and should consider other adjuncts that could facilitate compliance during induction.

Our study provides an interesting characterization of ED patients with opioid use disorder. Most had presented for reasons unrelated to substance use, indicating a need for broader screening criteria to identify patients who could benefit from ED-initiated buprenorphine/naloxone. This finding aligns with previously published work in other ED settings indicating that eligible patients for buprenorphine/naloxone and take-home naloxone kits present with a wide range of medical issues.[4,22] Most of our enrolled patients lacked a family physician, suggesting that improving low-barrier access to primary care is a potential unmet need. In addition, most had previously attempted opioid agonist therapy, and most had multiple substances present on urine toxicology, where obtained. These findings highlight the importance of understanding distinct needs of patients who are not naïve to opioid agonist therapy (eg, addressing fears associated with previous failed attempts) and unique risks associated with polysubstance use (eg, methamphetamine-associated psychosis) in our target ED population with opioid use disorder. In phase 1, urine toxicology results may suggest slight differences in proportions of standard-dosing and microdosing patients who were exposed to fentanyl and amphetamines. Discrepancies are to be expected given fluctuations in the presence of fentanyl, synthetic opioid derivatives, and contaminants in the illicit drug supply over time. Although we recognize that patients' experiences with induction may vary based on the substances to which they have been exposed, given that the observed discrepancies did not arise from a systematic difference in patient allocation to the study interventions, they are unlikely to have a bearing on our main objectives, which were to determine feasibility of enrollment and randomization.

In summary, our study demonstrates that an ED-initiated take-home buprenorphine/naloxone standard-dosing and microdosing program is feasible and that randomization is not a deterrent to our target population in a study context. We conclude that enrollment into a randomized controlled trial comparing standard-dosing and microdosing buprenorphine/naloxone interventions would be feasible in the ED setting.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Jessica Moe conceived the study, co-led implementation, supervised study staff, obtained research funding, analyzed the data, interpreted results, and provided overall study oversight. Katherin Badke conceived the study, co-led implementation, supervised study staff, obtained research funding, analyzed the data and interpreted results. Raymond Y. Cho assisted with data analysis and results interpretation. Megan Pratt, Pouya Azar, Heather Flemming, K. Anne Sutherland, Barbara Harvey, Lara Gurney, and Julie Lockington assisted with study conception, implementation, and results interpretation. Penny Brasher provided feedback on study design, data analysis, and results interpretation. Sam Gill, Emma Gurney, and Misty Bath supported study implementation. Megan Pratt and Sam Gill assisted with patient follow-ups. Andy Kestler assisted with study conception, implementation, data analysis, and results interpretation. Jessica Moe drafted the article and all authors contributed substantially to its revision. Jessica Moe takes responsibility for the article as a whole.

ORCID

Jessica Moe MD, MSc https://orcid.org/0000-0001-9557-1671

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AUTHOR BIOGRAPHY

Jessica Moe, MD, MSc, currently practices as an emergency physician at Vancouver General Hospital and British Columbia Children's Hospital.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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