Editor's key points

- This pilot study established a simple protocol for treating opioid withdrawal in the emergency department (ED) that was well received by both ED staff and patients.
- There was a trend of patients who were offered buprenorphine in the ED following up in the rapid access clinic within a few days.
- Participants receiving the buprenorphine protocol had statistically significantly improved opioid agonist treatment retention at 1 month.

Buprenorphine in the emergency department

Randomized clinical controlled trial of clonidine versus buprenorphine for the treatment of opioid withdrawal

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Abstract

Objective To compare buprenorphine to clonidine for the treatment of opioid withdrawal in the emergency department (ED) and to study the effect assigned treatment medication had on longer-term addiction treatment outcomes.

Design Randomized controlled trial.

Setting Toronto, Ont.

Participants Twenty-six patients presenting to the ED while in opioid withdrawal or soon to be in opioid withdrawal.

Main outcome measures Patients were randomized to receive either clonidine or buprenorphine treatment. Both groups also received a corresponding discharge prescription and information on how to follow up in the addictions rapid access clinic (RAC) within a few days. Participants were followed for 1 month with respect to attendance at the RAC and to opioid agonist treatment status. Outcome measures included attendance at the RAC within 5 days of the initial ED visit and opioid agonist treatment status at 1 month (as determined by clinic attendance or self-report during a follow-up telephone interview).

Results Participants who received buprenorphine in the ED were more likely to be receiving opioid agonist treatment at the 1-month mark compared with those participants who received clonidine to treat their withdrawal ($P = .011$).

Conclusion When opioid withdrawal is treated with buprenorphine in the ED, patients are more likely to be receiving opioid agonist treatment and connected with addiction treatment 1 month later.

Trial registration number NCT03174067 (ClinicalTrials.gov).

La buprénorphine au service des urgences

Essai clinique randomisé contrôlé sur la clonidine par rapport à la buprénorphine pour le traitement du sevrage des opioïdes

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Résumé

Objectif Comparer la buprénorphine à la clonidine dans le traitement du sevrage des opioïdes au service des urgences, et étudier les effets de la médication thérapeutique assignée sur les résultats du traitement de la dépendance à plus long terme.

Type d'étude Essai randomisé contrôlé.

Contexte Toronto (Ontario).

Participants Vingt-six patients qui se sont présentés aux urgences alors qu'ils étaient en état de sevrage des opioïdes ou sur le point de l'être.

Principaux paramètres à l'étude Les patients ont été choisis aléatoirement pour recevoir un traitement soit à la clonidine ou à la buprénorphine. Les 2 groupes ont aussi reçu, à leur congé, une ordonnance correspondante, de même que des renseignements concernant le suivi quelques jours plus tard à la clinique d'accès rapide (CAR) pour dépendances. Les patients ont été suivis pendant 1 mois relativement à leur participation à la CAR et à l'état du traitement par agonistes opioïdes. Au nombre des paramètres mesurés figuraient leur présence à la CAR dans les 5 jours suivant leur visite initiale aux urgences et l'état de leur traitement par agonistes opioïdes au bout d'un mois (tels que déterminés par leur présence à la clinique ou par leur auto-évaluation lors d'une entrevue téléphonique de suivi).

Résultats Les participants ayant reçu de la buprénorphine aux urgences étaient plus susceptibles de suivre un traitement par agonistes opioïdes au bout d'un mois que ceux qui avaient reçu de la clonidine pour traiter leur sevrage (p = ,011).

Conclusion Lorsque le sevrage des opioïdes est traité à l'urgence avec de la buprénorphine, il est plus probable que les patients suivent un traitement par agonistes opioïdes et maintiennent la thérapie contre la dépendance 1 mois plus tard.

Numéro d'enregistrement de l'essai NCT03174067 (ClinicalTrials.gov).

Points de repère du rédacteur

- Cette étude expérimentale établissait un protocole simple pour traiter le sevrage des opioïdes au service des urgences, qui a été bien accueilli autant par le personnel des urgences que par les patients.
- Un groupe de patients à qui on a offert de la buprénorphine aux urgences a davantage eu tendance à procéder à un suivi à la clinique d'accès rapide quelques jours après.
- On a observé une amélioration statistiquement significative chez les participants qui ont suivi le protocole à la buprénorphine dans le maintien du traitement par agonistes opioïdes à 1 mois.

There has been a substantial increase in opioid-related morbidity and mortality across Canada in the past several years and opioid deaths are now at an all-time high. In 2017 there were about 4000 opioid-related deaths in Canada (11.1 deaths per 100000 population),[1] confirming that we are in the midst of an opioid crisis.

Many patients with opioid use disorder have substantial contact with the health care system. Beyond ambulatory clinics, many patients present to emergency departments (EDs) with withdrawal, overdoses, abscesses, infective endocarditis, and other illnesses related to opioid use disorder. More than 30% of ED visits involving nonmedical use of pharmaceuticals in 2011 in the United States involved opioids.[2] Of importance, more than one-third (38%) of patients with opioid use disorder in one study stated that their first point of contact with the health care system was the ED.[3]

Given that many of these patients are presenting to the ED in withdrawal (in one study, 53% of patients with opioid addiction presenting to the ED were in withdrawal[4]) or are soon to be in withdrawal, and are seeking opioids or treatment after an opioid overdose, this represents an ideal time to initiate opioid agonist treatment with medications such as buprenorphine or methadone.

Typically, patients are treated in the ED with either clonidine, which is less effective than an opioid agonist in relieving withdrawal symptoms,[5] or with a short-term opioid prescription, which puts them at increased risk of future overdose, as overdose-related deaths are often preceded by a physician's prescription for opioids.[6]

Buprenorphine-naloxone, a partial μ-opioid agonist used in the long-term maintenance treatment of opioid addiction, has been shown to be more effective than clonidine in the treatment of opioid withdrawal[7,8] and might be a good option to both treat opioid withdrawal in the ED and to transition patients to maintenance buprenorphine treatment. Buprenorphine's pharmacologic properties allow quick dose titration with low risk of overdose and quick, yet long-lasting, relief of opioid withdrawal symptoms. Indeed, one trial, published after we started enrolling patients, found that patients starting buprenorphine in the ED were more likely to be enrolled in a formal addiction treatment program than those receiving screening and referral to treatment.[9] Another study starting inpatients on buprenorphine found that it was more successful at transitioning patients into a longer-term outpatient abstinence program than tramadol initiation was.[10] Thus, there might be a role for using buprenorphine in the ED as a means to both relieve withdrawal and facilitate transfer to a rapid access clinic (RAC) and a longer-term treatment program.

Referral from the ED to an addiction clinic remains highly variable, as many communities do not have addiction clinics or have treatment entry barriers such as long wait times, complex intake procedures, and exclusive clinical criteria. In one study, the strongest predictor of patients with addiction not attending an intake appointment for treatment was appointment delay, with delay within the first 24 hours being the most important: the longer the delay between initial contact and an intake appointment, the less likely the patient was to follow up.[11]

Our study of patients in withdrawal management facilities who received rapid addiction treatment consultation found that they were significantly more likely to attend and to be retained in treatment (A. Srivastava, M. Kahan, unpublished data, 2017).

We hypothesize that if a patient's opioid withdrawal is adequately treated in the ED with an opioid agonist like buprenorphine and he or she is given an interim prescription until he or she can be seen in an addiction clinic to continue long-term opioid agonist treatment, then the chances that the patient is "lost to follow-up" are likely to diminish significantly.

Until 2010, the standard treatment of opioid withdrawal in the ED at our institution was clonidine. However, we began to lay the groundwork for this pilot study in 2010 by meeting with ED staff and the hospital pharmacy to make buprenorphine available on the hospital formulary. We developed a standardized "buprenorphine order set" to treat opioid withdrawal that was readily available in the ED. Later, we developed this pilot randomized, open-label, controlled trial using buprenorphine to treat opioid withdrawal in our ED and evaluated its effect on follow-up rates at our on-site RAC and on treatment status at 1 month.

Methods

Patients with a minimum age of 16 years presenting in opioid withdrawal or soon to be in opioid withdrawal, as identified by the ED physicians, were offered the option of registering in this clinical trial. The trial was approved by the Research Ethics Board of St Joseph's Health Centre in Toronto, Ont. Patients who were actively involved in a methadone or buprenorphine treatment program, were pregnant, were taking large amounts of benzodiazepines, or had active liver disease were excluded. We did not exclude patients with alcohol or other substance use disorders and, in an attempt to make this protocol practical for front-line, busy ED physicians, left it to the clinical judgment of the ED physicians to interpret the product monograph and to determine what would constitute active liver disease or impairment from benzodiazepines that would contraindicate the short-term administration of buprenorphine.

Emergency department physicians and nurses received separate, brief, 10-minute, informal "question-and-answer" information sessions on the study, and a brief explanation of the Clinical Opiate Withdrawal Scale (COWS) scoring system and the basics of prescribing buprenorphine. The information sessions were

optional, as was the explanation of COWS and prescribing. Preprinted order sets for the administration of buprenorphine were developed and made available in the ED.

Emergency department physicians were asked to identify patients in opioid withdrawal and to use a random number generator application on their cell phones to randomize participants to receive either clonidine or buprenorphine. The physicians received packages with preprinted order sheets for either buprenorphine or clonidine, COWS scoring sheets, and patient take-home information sheets. The pages were colour coded and had a printed algorithm to minimize the time requirements for ED physicians. The ED physicians were instructed to use the COWS scoring sheets for both treatment groups only if they found it helpful as a tool in their clinical assessment, but it was not required.

The ED physicians were instructed to treat the clonidine group using a set of preprinted orders and were asked to give the patients a preprinted 5-day discharge prescription for clonidine and a 1-page flyer with details on and a map to the RAC, along with advice to follow up at the next available RAC appointment. The RAC is open for walk-in appointments twice a week and is on-site in the hospital, close to the ED.

To treat the buprenorphine group, physicians also had the optional COWS scoring sheet in their package, as well as preprinted order sets for prescribing buprenorphine. The preprinted order sets allowed ED nurses to administer up to 12 mg of buprenorphine. On discharge from the ED, participants were given preprinted take-home prescriptions for a 5-day supply of buprenorphine (8 mg/day in 5 tablets) to be dispensed at one time. The prescription included a map to the nearest outpatient pharmacy (within walking distance, open 7 days a week) where buprenorphine was readily available, and printed information and a map for the hours and location of the RAC. We used 8-mg tablets instead of 2-mg tablets because at the time the study started (2013) the Ontario Drug Benefit program did not cover the 2-mg tablets. Participants could adjust their own daily dose to last until they reached the RAC (open twice a week). We did not track patients to assess if they filled their buprenorphine or clonidine prescriptions at an outpatient pharmacy.

In the RAC follow-up appointment, patients were screened more formally for opioid use disorder and received more in-depth counseling about treatment options. The treating primary care or addiction physician was unaware of the patient's participation in the study.

Outcome measures included attendance at the RAC within 5 days of the initial ED visit and opioid agonist treatment status at 1 month (as determined by clinic attendance or self-report during a follow-up telephone interview). Participants were offered a $10 coffee gift card for completing the 1-month follow-up.

Statistical analysis

Associations between categorical variables were tested using the Fisher exact test. We tested for equality of a continuous distribution across a binary indicator using the Wilcoxon rank sum test; and across a general k-level ($k>2$) categorical variable using the Kruskal-Wallis test. Summary measures of categorical variables are presented as counts and percentages and those of continuous variables are presented as means.

Results

Twenty-six participants were prospectively randomized to buprenorphine or clonidine treatment. There were 13 patients in each arm. **Figure 1** shows outcomes by treatment arm. Participants in both groups were similar in baseline demographic characteristics with respect to age, sex, and intravenous drug use. The patients in the buprenorphine group were more likely to have had a history of opioid agonist treatment (**Table 1**).

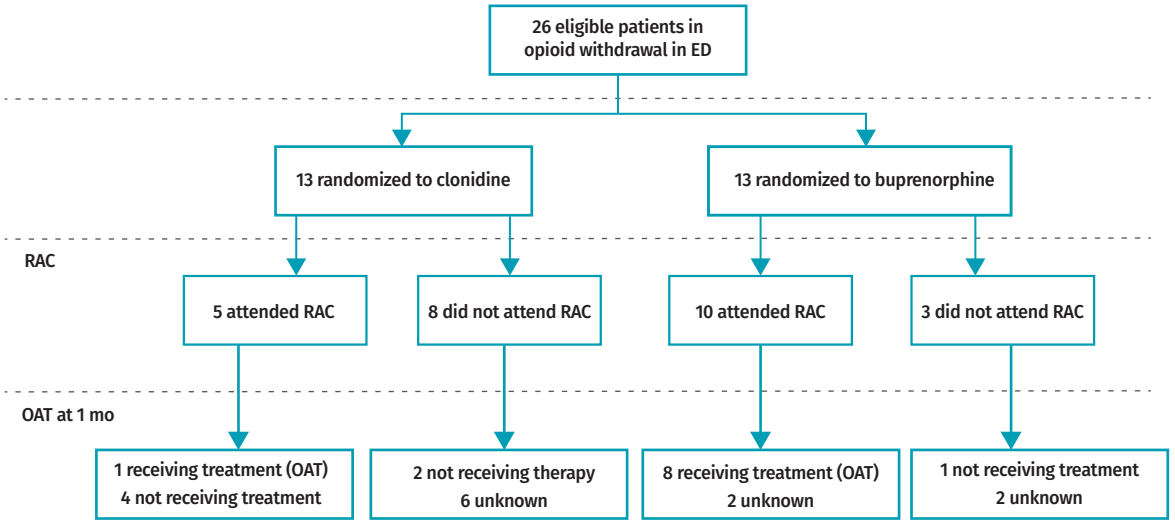
Significantly, patients in the buprenorphine arm were more likely to be receiving opioid agonist treatment at 1 month (n=8, 62%) than those in the clonidine arm were (n=1, 8%; $P=.011$) (**Table 2**). In the clonidine group, only 5 of 13 (38%) patients came for follow-up in the RAC whereas 10 of 13 (77%) patients came for follow-up in the RAC in the buprenorphine group. While this was not statistically significant, it shows a trend toward participants who received buprenorphine in the ED being more likely to attend the RAC.

Those patients who presented to the RAC were more likely to be receiving opioid agonist treatment at 1 month than those who did not present ($P=.004$) (**Table 3**), although this likely just reflects the patients who received buprenorphine and presented to the RAC.

There was no significant difference in RAC attendance rate for those who lived in the greater Toronto area versus those who did not (**Table 2**). In fact, patients with no fixed address followed up at the clinic. This might reflect the fact that they were likely transferred by the ED to our adjacent withdrawal management ("detox") facility and a social worker might have facilitated their transfer to the clinic.

At our follow-up with participants, which ranged from 3 to 5 days after their ED presentation, we asked them to rate their addiction treatment in the ED on a Likert scale from 1 to 5, with 1 being "terrible" and 5 being "excellent." There were 15 responses at the 1-month mark, with 5 patients saying their experience was "excellent," 8 patients saying their experience was "good," and only 2 answering "just OK." Not surprisingly, most of these answers (11 of 15) came from patients in the buprenorphine group, as this was the group that was more likely to follow up and to be in treatment at 1 month. Many of the patients who followed up in the RAC told us that receiving buprenorphine in the ED was a positive and

Figure 1. Flowchart of patient treatment outcomes by randomization group



ED—emergency department, OAT—opioid agonist treatment, RAC—rapid access clinic.

Table 1. Demographic characteristics

VARIABLE	BUPRENORPHINE ARM (N = 13)	CLONIDINE ARM (N = 13)	*P* VALUE
Mean age, y	38.85	38.38	.925
Sex, n (%)			
• Women	9 (69)	6 (46)	
• Men	4 (31)	7 (54)	.43
History of OAT, n (%)	8 (62)	2 (15)	.041
Location, n (%)			
• Lives in GTA	6 (46)	9 (69)	.428
• NFA	3 (23)	1 (8)	
IVDU, n (%)			
• Past year*	6 (46)	4 (31)	.78
• Lifetime	8 (62)	5 (38)	.353

*Missing data—not reported by some patients.
GTA—greater Toronto area, IVDU—intravenous drug use, NFA—no fixed address, OAT—opioid agonist treatment.

Table 2. Results and follow-up or treatment status by treatment arm

OUTCOME MEASURE	BUPRENORPHINE ARM (N = 13), N (%)	CLONIDINE ARM (N = 13)	*P* VALUE
Attended RAC	10 (77)	5 (38)	.111
Available for 1-mo follow-up	10 (77)	7 (54)	.509
Receiving OAT at 1 mo*	8 (62)	1 (8)	.011

*Missing data—not reported by some patients.
OAT—opioid agonist treatment, RAC—rapid access clinic.

Table 3. Association between clinical or demographic factors and RAC follow-up

FACTOR	FOLLOWED UP IN RAC (N = 15)	DID NOT FOLLOW UP IN RAC (N = 11)	*P* VALUE
Mean age, y	41.00	35.36	.247
Sex, n (%)			
• Female	8 (53)	7 (64)	.7
• Male	7 (47)	4 (36)	
Location, n (%)			
• Lives in GTA	7 (47)	8 (73)	.470
• Lives outside GTA	5 (33)	2 (18)	
• NFA	3 (20)	1 (9)	
History of IVDU in the past y,* n (%)	7 (47)	3 (27)	.26
History of OAT, n (%)	8 (53)	2* (18)	.109
Receiving OAT at 1 mo,* n (%)	9 (60)	0 (0)	.004

*Missing data—not reported by some patients.
GTA—greater Toronto area, IVDU—intravenous drug use, NFA—no fixed address, OAT—opioid agonist treatment, RAC—rapid access clinic.

helpful experience for them. This is consistent with the feedback we received from other patients who did not participate in the study but received buprenorphine in the ED and attributed facilitating their follow-up at our clinic to that intervention.

Discussion

While this was a pilot study with a small number of patients enrolled, it established a simple protocol in our ED for treating opioid withdrawal that was well received by both ED staff and patients and that resulted in statistically significant improvement in opioid agonist treatment retention at 1 month. It has now become the standard of care in our ED.

We did not perform health care provider satisfaction surveys but informal discussions with ED nurses and physicians were consistently positive and enthusiastic. At an interim informational session, many physicians stated they found the preprinted buprenorphine treatment protocol useful. They also finally felt like they had something therapeutic to give patients in opioid withdrawal rather than just writing another prescription for opioids or giving clonidine, which they did not believe was of long-term benefit.

The demographic characteristics of both treatment arms were very similar but the buprenorphine group was more likely to have been previously exposed to opioid agonist treatment, with 8 patients saying they had received opioid agonist treatment in the past. However, only 5 of these 8 patients ended up receiving opioid agonist treatment at 1 month, suggesting that previous exposure might have been important but not the only factor in treatment status at 1 month.

Surprisingly, 3 of the 4 patients with no fixed address in our study followed up at our RAC. This was most likely because after their ED visit they were transferred to an on-site residential withdrawal management service affiliated with our hospital and likely were accompanied by the counselors to the RAC. This is consistent with another study that found that being homeless was associated with addiction treatment access.[12]

In the clonidine arm, only 5 patients of 13 presented to the RAC compared with 10 of 13 patients in the buprenorphine arm. While this was not a statistically significant difference, it does demonstrate a trend toward patients who were offered buprenorphine in the ED following up in our RAC within a few days. Of the 5 patients who received clonidine in the ED and still followed up at the RAC, only 1 was prescribed long-term buprenorphine on the first visit in the RAC and continued to take it at 1 month. Three others in the clonidine group who followed up at the RAC declined buprenorphine. In one case the patient wanted buprenorphine but was not eligible for the provincial drug plan's "limited use" criteria at that point (since eliminated, with open access for all eligible patients). The patient agreed to start methadone instead but did not return to the clinic to start it. One of the 3 patients who declined buprenorphine returned to the clinic 6 months later and was started on methadone, suggesting that initial attendance at the RAC might have been helpful by exposing the patient to treatment options.

Our finding that giving buprenorphine in the ED leads to improved treatment retention at 1 month is consistent with previous studies that have shown that even small improvements in process lead to statistically significant reductions in days to treatment initiation and retention.[13] It is also consistent with a trial by D'Onofrio et al that demonstrated that patients who were taking buprenorphine in the ED were statistically significantly

more likely to be in formal treatment 1 month later.[9] Our study was different in that our protocol did not have any special training for doctors or nurses or any extra resources or staff. Our protocol only allowed for the administration of buprenorphine to patients in opioid withdrawal, with a subsequent 5-day prescription. We did not give take-home buprenorphine prescriptions to patients who were not yet in withdrawal so that they could initiate their first buprenorphine dose at home. All first doses of buprenorphine were witnessed in the ED. While this might have contributed to some patients with opioid use disorder not receiving buprenorphine, it also meant that ED physicians did not have to spend as much time screening patients for opioid use disorder that was less readily apparent. Moreover, our understanding from the ED physicians is that this was not an issue, as most patients had an average length of stay of several hours in our ED and were in withdrawal by the time they saw the ED physician.

The simplicity of our protocol, which involved minimal training and no extra staff or resources, makes it easy to adapt it to community settings with limited resources. Through another project,[14] we have started rolling out this protocol to EDs in community and teaching hospitals across Ontario to help stem the opioid crisis.

Limitations

One of the limitations of our study, other than the small sample size, is that we did not keep a record of how many patients were approached for the study and how many declined to participate. We did not have a research assistant in the ED and relied on ED physicians remembering to enrol patients. We established the protocol for using buprenorphine in our ED in 2010 to assess its feasibility and acceptability, but its uptake was minimal and we did not officially start this pilot study until 2013. This trial encouraged more physicians to join in this practice and protocol, and gradually many patients became aware that our ED was the only one in the city where this treatment was available. We do not know how this might have affected patient recruitment for the study.

Conclusion

With a simple set of preprinted orders and minimal resources we were able to establish a protocol for treating opioid withdrawal in our ED and for increasing the likelihood that patients would continue taking opioid agonist treatment. Future areas of research would include monitoring subsequent ED use and a larger-scale trial that implements a protocol that includes giving all patients with suspected opioid use disorder a buprenorphine prescription or a supply of a few initial doses of buprenorphine, regardless of their withdrawal status, and an overdose prevention naloxone kit. This is particularly important, as increasing numbers of patients are presenting with overdose, are treated with naloxone, and then are leaving before they are in withdrawal. Giving all patients with a potential opioid use disorder, regardless of withdrawal status, and without time-consuming formal screening, a prescription or short-term supply of buprenorphine with information on home induction might be the simplest and least resource-intensive solution to starting to address opioid use disorders in EDs. Such a protocol would save nurses and physicians the time associated with formal opioid use disorder screening in the ED and the time associated with dispensing buprenorphine in the ED, and could potentially capture those patients who present with an opioid overdose and who are at highest risk of a subsequent opioid overdose.

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Contributors

All authors contributed to the concept and design of the study; data gathering, analysis, and interpretation; and preparing the manuscript for submission.

Competing interests

This research received support from an unrestricted grant from Merck-Frosst Canada, which no longer exists as an entity and does not manufacture the medication studied.

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