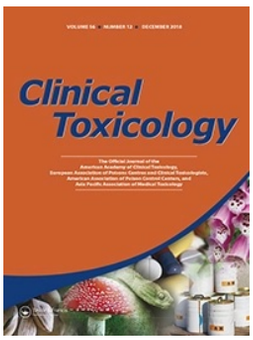

Clinical Toxicology

ISSN: 1556-3650 (Print) 1556-9519 (Online) Journal homepage: https://www.tandfonline.com/loi/ictx20

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To cite this article: Lauren R. Klein, Jon B. Cole, Brian E. Driver, James R. Miner, JoAn R. Laes, Erik Fagerstrom & Marc L. Martel (2019): An open-label randomized trial of intramuscular olanzapine versus oral clonidine for symptomatic treatment of opioid withdrawal in the emergency department*, Clinical Toxicology, DOI: 10.1080/15563650.2018.1547828

To link to this article: https://doi.org/10.1080/15563650.2018.1547828

Published online: 04 Feb 2019.

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2018.1547828

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CLINICAL RESEARCH

An open-label randomized trial of intramuscular olanzapine versus oral clonidine for symptomatic treatment of opioid withdrawal in the emergency department*

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ABSTRACT

Background: Patients with opioid withdrawal often present to the Emergency Department (ED), but many EDs do not have the infrastructure in place to initiate treatment with opioid agonists (methadone or buprenorphine). Therefore, ED management often entails symptomatic control. The purpose of this study was to compare olanzapine to clonidine for the treatment of opioid withdrawal symptoms.

Methods: This was a prospective, randomized clinical trial comparing 10 mg of IM olanzapine to 0.3 mg of oral clonidine for symptoms of opioid withdrawal. Adult (18 years and older) ED patients reporting a history of opioid use and symptoms consistent with withdrawal were eligible. Patients were excluded if they had already received treatment during the ED encounter, were pregnant, incarcerated, or unable to provide consent. Patients were randomized 1:1 to receive olanzapine or clonidine for their initial treatment. A baseline Clinical Opiate Withdrawal Scale (COWS) score was calculated. After 30 min, the patient could receive any additional treatment at the ED physician's discretion. The primary outcome was need for additional medication (rescue) within 1 h of study medication administration. Secondary outcomes included change in COWS score and adverse reactions.

Results: We enrolled 63 patients (33 olanzapine, 30 clonidine). Demographic characteristics were similar for both groups (median age 45, range 21–67, 54% male) as well as baseline COWS score (median score 11). The median time since last opiate use was 48 h for both groups (range 4–116). Rescue was given within 1 h for olanzapine for 9 (27%) patients and for clonidine in 19 (63%) patients (difference 36%, 95% CI 13–59%). Decrease in COWS score at 1 h was 8.3 for olanzapine and 5.1 for clonidine (difference 3.2, 95% CI 0.3–6). Adverse events were uncommon: akathisia (1, olanzapine), hypotension (2, clonidine), respiratory depression (0).

Conclusions: Treatment of opioid withdrawal symptoms with 10 mg of IM olanzapine results in a lower incidence of rescue medication administration and improved symptoms (COWS score) compared to 0.3 mg of oral clonidine.

ARTICLE HISTORY
Received 12 September 2018
Revised 18 October 2018
Accepted 1 November 2018
Published online 14 January 2019

KEYWORDS
Olanzapine; clonidine; opioid withdrawal

Introduction

Opioid use disorders are becoming increasingly common in the United States, and as a result, Emergency Departments (EDs) frequently see and treat patients presenting with symptoms of opioid withdrawal [1]. Opioid withdrawal symptoms can be severe and debilitating for the patient, often warranting intervention.

Treatment of opioid withdrawal in the non-ED setting (i.e. clinics, inpatient units, detoxification units) may involve use of opioid agonist therapies, namely buprenorphine and methadone [2–5]. Both buprenorphine and methadone have been shown to be safe and effective in treating opioid use disorders, and are considered standards of care in those settings. However, these treatments options have not been routinely incorporated into the ED management of patients with opioid withdrawal.

There is promising evidence emerging that opioid agonist therapies can be successfully and safely initiated in the ED [6–9], but several considerations prevent the universal implementation of this practice. First, although methadone can be administered in the ED per Title 21 Code of Federal Regulations Section 1306.07, ongoing methadone treatment necessitates federally regulated opioid treatment programs for future administrations [10]. Regarding buprenorphine, the Drug Addiction Treatment Act of 2000 imposes requirements and training for physicians who wish to obtain a waiver to prescribe it in their clinical practice. ED providers are able to administer buprenorphine without a waiver emergently

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*Presentations: 2018 Society for Academic Emergency Medicine Annual Meeting, Indianapolis, IN; 2017 North American Congress of Clinical Toxicology, Vancouver, British Columbia.

under the Federal Code of Regulations "three-day rule" [11], but its administration for more than these three days requires a licensed provider. Furthermore, there is evidence to suggest that withdrawal detoxification management with opioid agonist therapies without transition to timely addiction treatment may be associated with relapse, morbidity, and even death [12]. As such, many EDs are working towards developing the infrastructure to secure access to outpatient follow-up for patients who have started opioid agonist therapy in the ED, but until these resources are reliably available, many emergency physicians face barriers to starting opioid agonist treatments for opioid withdrawal.

If opioid agonist therapies are not administered in the ED for withdrawal, emergency providers often utilize symptom-based therapies. Clonidine, an alpha-2 agonist, is frequently used, as it is easily accessible in the ED and reasonably effective [13]. Providers may also utilize other treatments such as anti-emetics, non-narcotic pain medications (acetaminophen, ibuprofen), or benzodiazepines, but these treatments have not been well described in the ED.

Antipsychotic medications, such as olanzapine, offer another alternative for treatment of opioid withdrawal symptoms. Atypical antipsychotics and first-generation antipsychotics, particularly droperidol, have been shown to be useful in ED treatment of nausea, vomiting, anxiety, headaches, generalized pain, and agitation [14–19]. As many of these symptoms are hallmarks of opioid withdrawal, it is possible that olanzapine may be useful in treating this patient population.

This study compares olanzapine to clonidine for treatment of the symptoms of acute opiate withdrawal in the ED in a randomized clinical trial. We chose olanzapine because it has been shown to be well-tolerated and safe in the ED with a favorable side-effect profile [14,15]. We hypothesized that olanzapine would be superior to clonidine in treating the symptoms of opioid withdrawal in the ED. We specifically did not study opioid agonist therapies in this trial, as the purpose of this study was to compare symptom-based treatments, making this study generalizable to situations in which opioid agonist therapies are not available.

Methods

Study design and setting

This was a randomized, open-label, clinical trial of olanzapine versus clonidine for treatment of opioid withdrawal symptoms in the ED. Study enrollment occurred from October 2015 to June 2017. This trial was approved by the Institutional Review Board and registered at clinicaltrials.gov (NCT02643355).

This study took place at Hennepin County Medical Center in Minneapolis, Minnesota, an urban county ED with approximately 110,000 annual visits. None of the ED physicians had a waiver to prescribe buprenorphine at the time of the study, and there was no system in place to start opioid agonist therapies. Opioid detoxification facilities are present within the community, but none of them are directly affiliated with the study hospital. The study hospital has an Addiction Medicine inpatient consultation service, as well as an opioid treatment program and an office-based addiction clinic that provides opioid agonist therapies for outpatients.

Selection of participants

Screening and enrollment for this study was conducted by trained research associates (RAs), who staff the ED 24 h per day, 7 days per week. All RAs received individual in-person training by study investigators.

Adult (18 years of age and older) patients were eligible to be enrolled during their ED visit if they provided a history of recent opioid use, were experiencing symptomatic opioid withdrawal, and required medical treatment for their symptoms per the ED provider's discretion. We did not pre-specify a minimum elapsed interval from the time the patient last used opioids, given the variable pharmacokinetics of different opioids.

Patients were excluded if they were pregnant, incarcerated, suicidal, unable to provide written informed consent in English, hypotensive (systolic blood pressure $<$90 mmHg), had a known allergy to either study medication, or if they had already received any treatment for opioid withdrawal symptoms during their ED encounter (i.e. anti-emetics, analgesics). We did not exclude patients if they took their own medications prior to arrival to the ED. Full written consent was obtained for all enrolled subjects.

Interventions

Patients were randomized in a 1:1 ratio to receive either 10 mg of intramuscular (IM) olanzapine or 0.3 mg of oral clonidine. Dosing for olanzapine was chosen based on existing ED literature supporting the utility and safety of 10 mg IM [14,15], and dosing for clonidine was chosen as 0.3 mg is the upper limit of the range described in the opioid withdrawal literature [13]. Intramuscular olanzapine was chosen over oral disintegrating olanzapine, as the peak concentration for oral disintegrating olanzapine occurs 6 h after administration, and therefore would not be practical for this study.

Randomization was performed before the start of the trial with a computer-generated number sequence, and the intervention assignments were placed inside opaque envelopes. After enrollment, a research associate opened the next sequential envelope to reveal the treatment allocation.

The medication the patient was randomized to was given open-label by the patient's clinical nurse. After study medication administration, there was a mandatory 30-min interval in which the patient could receive no other additional interventions or treatments. The only exceptions to this was the placement of a peripheral IV and administration of normal saline. After 30 min, the provider could give the patient additional medication (rescue medication) if needed. The decision to administer rescue medication, and which rescue medication to administer (if needed) was not dictated by the study protocol, and was at the discretion of the treating physician. As such, patients could receive an additional dose of the study medication, cross-over to the other study medication, or receive another treatment.

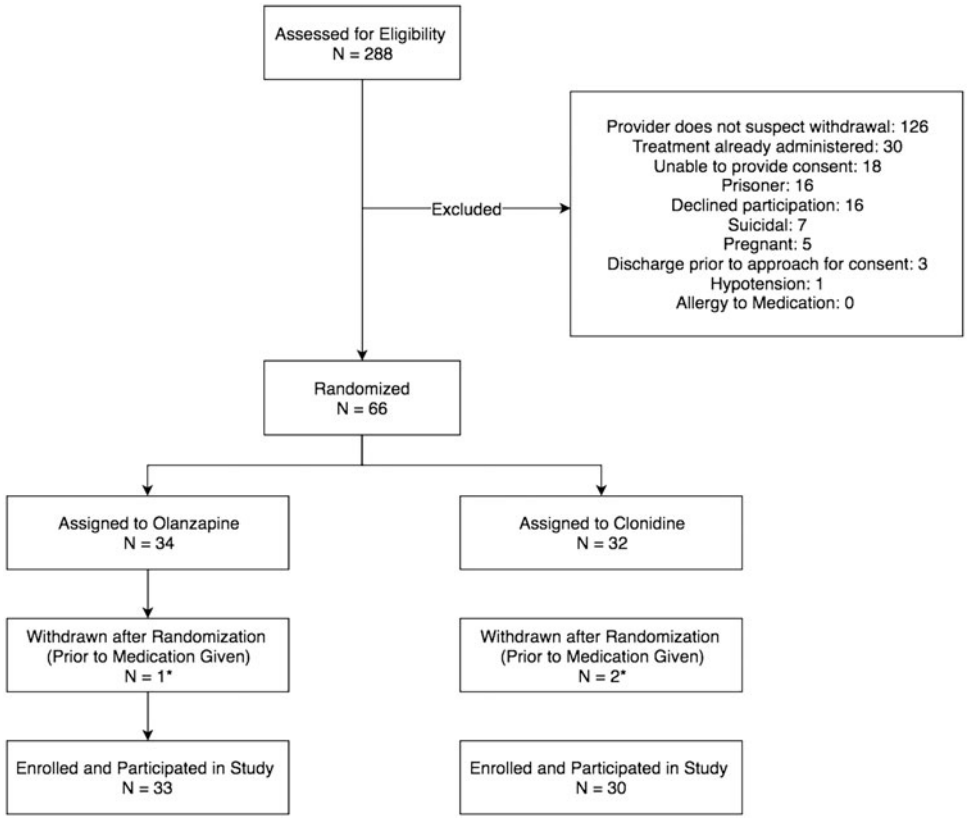

Figure 1. CONSORT Flow Diagram.
*For all three patients who were withdrawn after randomization, the patients eloped from the hospital prior to receiving medication.

Outcome measures

For all enrolled patients, baseline data were obtained including demographics and opioid use history. Baseline severity of symptoms was scored using the Clinical Opiate Withdrawal Scale (COWS). Baseline level of alertness was scored using the Observer's Assessment of Alertness/Sedation Scale (OAA/S). Additional assessments occurred at 60 min post-medication administration, 120 min post-medication administration, and at the time of disposition. These assessments were conducted by the RAs, and included calculation of the COWS score, calculation of the OAA/S score, and recording of any medications given during the previous interval.

At the end of the patient encounter, the treating provider completed a standardized data collection form to record the following: patient disposition, time in department, and whether or not adverse events occurred including dystonia, akathisia, allergic reaction (rash/hives/wheezing), or hypotension (systolic blood pressure $<$90 mmHg). They also indicated if any respiratory events occurred including the need for oxygen supplementation (by nasal cannula or face mask) not present at baseline, nasal/oral airway placement, use of bag valve mask, jaw thrust, or endotracheal intubation.

Primary outcome

The primary outcome for this study was need for rescue medication 60 min after study drug administration (i.e. rescue doses of medication given 30–60 min after initial treatment). Rescue medication was defined as the administration of an additional treatment for the patient's symptoms. Medications considered rescue included doses of olanzapine, clonidine, ondansetron, metoclopramide, prochlorperazine, diphenhydramine, acetaminophen, ibuprofen, haloperidol, ketamine, or benzodiazepines.

Data analysis

Sample size calculations were performed using estimates from a previous study looking at patients who received olanzapine in the ED for all indications [14]; a subset of these patients received the olanzapine for opioid withdrawal and approximately 40% of those patients received rescue medications. We estimated that olanzapine would result in a relative reduction of rescue medication administration of 50% compared to clonidine. We would therefore need 56 patients total to achieve 80% power, with a two-sided alpha of 0.05.

All data were analyzed and presented descriptively, including counts, proportions, means, and medians when appropriate. Demographic variables were compared between groups with a Chi-square test or Mann–-Whitney U-test as appropriate (with a two-sided alpha of 0.05). Comparisons of outcomes were conducted using differences in proportions or means with associated 95% confidence intervals (CIs) of the difference. Data analysis was performed in Stata (Version 15, College Station, TX).

Results

During the study period, we screened 288 patients and 63 were enrolled. Details of screening and enrollment are

depicted in Figure 1. Table 1 includes baseline demographic data and opioid use history data. Demographics were similar between the two groups (*p*-values for all comparisons were greater than .05).

Regarding the primary outcome of the study, a total of 28 patients out of 63 (44%) received rescue medications within 1 h, 9 (27%) in the olanzapine group, and 19 (63%) in the clonidine group, with a difference of −36% (95% CI of the difference −59 to −13%). Additional outcome results are displayed in Table 2.

Adverse events in this study were uncommon. Only one case of akathisia was reported for olanzapine and two incidences of hypotension were reported for clonidine (Table 3).

Table 1. Baseline characteristics and opioid use history.

Variable	Olanzapine ($n = 33$)	Clonidine ($n = 30$)
Age (median, range)	35 (22–60)	34 (21–67)
Gender (male)	21 (63%)	15 (50%)
Ethnicity		
Caucasian	13 (40%)	13 (43%)
African-American	13 (40%)	7 (23%)
Native American	4 (12%)	5 (17%)
Other	3 (9%)	5 (16%)
Comorbidities		
Schizophrenia	0	1 (3%)
Bipolar disorder	5 (15%)	5 (17%)
Anxiety	7 (21%)	3 (10%)
Depression	6 (18%)	8 (27%)
Home antipsychotic use	6 (18%)	5 (17%)
Chronicity of opioid use		
Less than 6 months	4 (12%)	4 (13%)
Between 6 months and 1 year	3 (9%)	6 (20%)
Between 1 year and 5 years	12 (36%)	10 (33%)
Greater than 5 years	14 (42%)	10 (44%)
Previously received naloxone	8 (24%)	5 (17%)
Previous opioid-related ED encounter	14 (42%)	9 (30%)
Previous treatment/Detoxification Program	13 (39%)	8 (27%)
Opiates used within last 7 days		
Heroin	19 (58%)	10 (33%)
Methadone	8 (24%)	9 (30%)
Oxycodone/Hydrocodone	5 (18%)	4 (22%)
OxyContin®	3 (9%)	2 (7%)
Buprenorphine	1 (4%)	1 (6%)
Hours elapsed since last use (median, range)	48 (4–108)	48 (4–116)
Baseline COWS score (median, range)	11 (4–23)	11 (4–22)

COWS: Clinical Opiate Withdrawal Scale.
All between group comparisons were nonsignificant ($p > .05$).

Discussion

This was a randomized clinical trial of olanzapine versus clonidine for the treatment of symptoms of opioid withdrawal in the ED. Although not classically considered for this indication, we hypothesized that olanzapine would be useful in treating opioid withdrawal symptoms. Our hypothesis was based on the known mechanism of action and pharmacokinetics of olanzapine; olanzapine has a fairly rapid peak plasma concentration (15–45 min) and has a complex pharmacological profile including agonist activity at alpha-2 adrenergic receptors, as well as antagonism at muscarinic, serotonergic, dopaminergic, and histaminergic receptors. Antipsychotics with these properties have been shown to be effective in treating components of opioid withdrawal, such as nausea, vomiting, pain, anxiety, among others [14–20]. As such, the results of this clinical trial suggest that the utilization of olanzapine to treat opioid withdrawal symptoms was more effective than clonidine in regards to the need for rescue medications.

The primary outcome in this study was the need for rescue medication, defined as the administration of additional medications to treat the patients' symptoms during the encounter. While there are other outcomes that would have been reasonable to assess the patients' symptomatic improvement, such as the COWS score [21] or the Clinical Institute Narcotic Assessment (CINA) score [22], we elected to use rescue medication administration, as many emergency providers may find this to be a practical, and clinically relevant outcome. Though there is value in knowing the difference in COWS score over time as a result of treatment, in the ED, there is an advantage to treating conditions with single doses of medication. Monotherapy should result in fewer side effects, and generally provides patients with the most rapid relief of the symptoms they came to the ED for (which may also improve patient satisfaction). Monotherapy may even result in a decreased length of stay since there are fewer interventions involved; though this study was not designed to detect differences in length of stay, the estimate for the olanzapine group was shorter for the clonidine group.

Table 2. Primary and secondary outcome data.

	Olanzapine	Clonidine	Difference (95% CI)
Primary outcome			
Rescue medications administered within 1 h	9 (27%)	19 (63%)	−36% (−59 to −15%)
Clonidine	5 (15%)	1 (3%)	12% (−2 to 25%)
Olanzapine	4 (12%)	7 (23%)	−11% (−30 to 8%)
Ondansetron	4 (12%)	11 (37%)	−25% (−46 to −4%)
Ibuprofen/Acetaminophen	2 (6%)	2 (7%)	−1% (−13 to 11%)
Diphenhydramine	1 (3%)	4 (13%)	−10% (−23 to 33%)
Benzodiazepines	2 (6%)	4 (13%)	−7% (−21 to 8%)
Secondary outcomes			
Rescue medication, within 2 h	12 (36%)	24 (80%)	−44% (−66 to −22%)
Rescue medication, entire encounter	14 (46%)	25 (83%)	−37% (−59% to −15%)
Change in COWS score, 1 h (mean)	8.3	5.1	3.2 (0.3 to 6.0)
Change in COWs score, final (mean)	9.9	7.8	2.1 (−1 to 5.1)
Time in department (mean minutes)	242	256	−14 (−76 to 49)
Return visit within 7 days for withdrawal	1 (3%)	0	3% (−3 to 9%)
Return visit within 7 days for any reason	1 (3%)	3 (10%)	−7% (−20 to 5%)

COWS = Clinical Opiate Withdrawal Scale.
A 95% CI that does not cross zero is statistically significant.

Table 3. Adverse events.

	Olanzapine	Clonidine
Akathisia	1 (3%)	0
Dystonia	0	0
Hypotension (SBP <90)	0	2 (7%)[a]
Allergic reaction	0	0
Respiratory depression	0	0

[a]One patient had a nadir SBP of 88 that improved without intervention; the other patient had a nadir SBP of 82 that improved after 1 L of normal saline.

As a result of their complex pharmacology, olanzapine and other antipsychotics can be used in a versatile manner in the ED [14–17]. Even though there are several opioid withdrawal symptoms that olanzapine may not treat (piloerection, sweating, rhinorrhea, among others), there are many that olanzapine have been shown to be useful in treating. Olanzapine use in the ED is most commonly described when treating agitation; though generally not overtly violent, individuals experiencing opioid withdrawal may exhibit mild agitation and anxiety [14,15,23,24]. Olanzapine, as well as other antipsychotics, have also been shown to be useful in treating pain, perhaps due to its alpha 2 adrenergic stimulation [19,25,26]. There is also data to support the use of olanzapine in patients with nausea, vomiting, abdominal pain, and headaches, all consistent with its known properties of antagonizing muscarinic, serotonergic, dopaminergic, and histaminergic receptors [14,15,17]. Again, though not a comprehensive list of opioid withdrawal symptoms, these represent several of the more uncomfortable and debilitating symptoms patients present with, and is likely why olanzapine was found to be effective in this trial. This notion is also further supported by a recent case report describing the use of daily olanzapine for treating opioid cravings in a palliative care patient [27].

This trial used symptom-based therapies, rather than opioid agonist therapies. We acknowledge the emerging evidence that positively supports the use of opioid agonist therapies in the ED, and that these should become standard of care given the robust evidence that these medications are safe and effective [2–5]. D'Onofrio and colleagues recently conducted a randomized trial of referral to opioid treatment versus referral plus brief intervention versus referral, brief intervention plus ED initiation of buprenorphine [6]. The authors concluded that initiation of buprenorphine increased engagement in addiction treatment and reduced self-reported opioid use. This trial, however, did not study the effect of buprenorphine on the patients' withdrawal symptoms while in the ED. The authors also comment in their discussion that all of their ED providers were trained to prescribe buprenorphine, and they had high-quality outpatient follow-up arranged as a result of this study. As such, their findings, although encouraging, may not be generalizable unless this infrastructure is available. Another recent study discusses the feasibility and effectiveness of utilizing 10 mg of intramuscular methadone to treat acute opioid withdrawal symptoms [9]. They report that a one-time dose of intramuscular methadone was effective (decreased COWS score by a mean of 7.6) and safe (no respiratory events, no excessive sedation). These findings appear similar to olanzapine in our study; we identified a decrease in COWS score of 9.8 at discharge and had no respiratory or over-sedation events either. Also similar to our study, this single dosing regimen did not address long-term opioid withdrawal needs.

In this study, we did not robustly address outcomes for the post-ED encounter period. We collected information on whether a patient had a return ED visit within seven days, but could not assess the extent to which these visits may or may not have been related to withdrawal. In clinical practice, treating opioid addiction will not be limited to a single ED encounter and patients could potentially have multiple visits to the ED during their detoxification period. In this study, we did not specify if providers should provide any discharge prescriptions, which could influence the follow-up rate. Ultimately, treatment of opioid withdrawal and opioid use disorders requires long-term care coordination between primary care, and Addiction Medicine services if available.

The main limitation of this study is its lack of blinding. Lack of blinding may have increased the chance for bias in the treating providers' decision to administer rescue medication. Both medications, however, are used very commonly in our ED and are generally both considered for use in this clinical scenario. This is evidenced by the fact that patients frequently were given the medication they were *not* randomized to for rescue.

Our lack of blinding and use of medications given via different routes (oral versus intramuscular) may also have introduced bias for the patient [28,29]. It is possible that some patients "expect" parenteral medications to be more effective. Such bias, however, would also be present in clinical care external to the study.

An additional limitation is the different time to onset and peak effect of the medications. It is possible that olanzapine was superior in regard to our primary outcome because of the time to peak plasma concentration, which is 15–45 min for olanzapine and between 60 and 180 min for clonidine [30,31]. We attempted to mitigate this by collecting data at 120 min and at the time of disposition; in all of these secondary comparisons, olanzapine was still superior. This notion also highlights the fact that clonidine's long time to peak effect renders it a potentially poor option for physicians treating opioid withdrawal in the ED.

Finally, bias may have been introduced as we did not specify a time since last opioid use to be enrolled in the study. Individuals who used opioids more recently would likely have less severe symptoms, which could have altered our results. Bias may have also been introduced by medications taken by patients prior to arrival, as we could not control that. The randomized nature of this study, however, was intended to mitigate these concern.

In summary, 10 mg of intramuscular olanzapine given for opioid withdrawal symptoms resulted in the administration of less rescue medication compared to 0.3 mg of oral clonidine. Olanzapine can be considered for use in treating opioid withdrawal symptoms in ED patients, if those EDs do not have programs available to administer opioid agonist treatments.

Disclosure statement

No potential conflict of interest was reported by the authors.

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References

[1] Rudd RA, Seth P, David F, et al. Increases in drug and opioid-involved overdose deaths – United States, 2010-2015. MMWR Morb Mortal Wkly Rep. 2016;65:1445–1452.

[2] Gowing L, Ali R, White JM, et al. Buprenorphine for managing opioid withdrawal. Cochrane Database Syst Rev. 2017;2: CD002025.

[3] Nielsen S, Larance B, Degenhardt L, et al. Opioid agonist treatment for pharmaceutical opioid dependent people. Cochrane Database Syst Rev. 2016;5:CD011117.

[4] Mattick RP, Breen C, Kimber J, et al. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014;2:CD002207.

[5] Amato L, Davoli M, Minozzi S, et al. Methadone at tapered doses for the management of opioid withdrawal. Cochrane Database Syst Rev. 2013;2:CD003409.

[6] D'Onofrio G, O'Connor PG, Pantalon MV, et al. Emergency department-initiated buprenorphine/naloxone treatment for opioid dependence: a randomized clinical trial. JAMA. 2015;313: 1636–1644.

[7] Busch SH, Fiellin DA, Chawarski MC, et al. Cost-effectiveness of emergency department-initiated treatment for opioid dependence. Addiction. 2017;112:2002–2010.

[8] Berg ML, Idrees U, Ding R, et al. Evaluation of the use of buprenorphine for opioid withdrawal in an emergency department. Drug Alcohol Depend. 2007;86:239–244.

[9] Su MK, Lopez JH, Crossa A, et al. Low dose intramuscular methadone for acute mild to moderate opioid withdrawal syndrome. Am J Emerg Med. 2018;11:1951-1956. doi:10.1016/j.ajem.2018.02.019.

[10] Title 21 Code of Federal Regulations PART 1306. Diversion Control Division n.d. https://www.deadiversion.usdoj.gov/21cfr/cfr/1306/1306_07.htm (accessed May 2018).

[11] Emergency Narcotic Addiction Treatment. US Department of Justice Diversion Control Divison n.d. https://www.deadiversion.usdoj.gov/pubs/advisories/emerg_treat.htm (accessed May 2018).

[12] Bruneau J, Ahamad K, Goyer MÈ, et al. Management of opioid use disorders: a national clinical practice guideline. CMAJ. 2018; 190:E247–E257.

[13] Gowing L, Farrell M, Ali R, et al. Alpha$_2$-adrenergic agonists for the management of opioid withdrawal. Cochrane Database Syst Rev. 2016;5:CD002024.

[14] Martel ML, Klein LR, Rivard RL, et al. A large retrospective cohort of patients receiving intravenous olanzapine in the emergency department. Acad Emerg Med. 2016;23:29–35.

[15] Cole JB, Moore JC, Dolan BJ, et al. A prospective observational study of patients receiving intravenous and intramuscular olanzapine in the emergency department. Ann Emerg Med..2017; 69:327.e2–336.e2.

[16] Navari RM, Qin R, Ruddy KJ, et al. Olanzapine for the prevention of chemotherapy-induced nausea and vomiting. N Engl J Med. 2016;375:134–142.

[17] Hill CH, Miner JR, Martel ML. Olanzapine versus droperidol for the treatment of primary headache in the emergency department. Acad Emerg Med. 2008;15:806–811.

[18] Yildiz A, Sachs GS, Turgay A. Pharmacological management of agitation in emergency settings. Emerg Med J. 2003;20:339–346.

[19] Richards JR, Richards IN, Ozery G, et al. Droperidol analgesia for opioid-tolerant patients. J Emerg Med. 2011;41:389–396.

[20] Chase PB, Biros MH. A retrospective review of the use and safety of droperidol in a large, high-risk, inner-city emergency department patient population. Acad Emerg Med. 2002;9:1402–1410.

[21] Wesson DR, Ling W. The Clinical Opiate Withdrawal Scale (COWS). J Psychoactive Drugs. 2003;35:253–259.

[22] Tompkins DA, Bigelow GE, Harrison JA, et al. Concurrent validation of the Clinical Opiate Withdrawal Scale (COWS) and single-item indices against the Clinical Institute Narcotic Assessment (CINA) opioid withdrawal instrument. Drug Alcohol Depend. 2009;105:154–159.

[23] Chan EW, Taylor DM, Knott JC, et al. Intravenous droperidol or olanzapine as an adjunct to midazolam for the acutely agitated patient: a multicenter, randomized, double-blind, placebo-controlled clinical trial. Ann Emerg Med. 2013;61:72–81.

[24] Taylor DM, Yap CYL, Knott JC, et al. Midazolam-droperidol, droperidol, or olanzapine for acute agitation: a randomized clinical trial. Ann Emerg Med. 2017;69:318.e1–326.e1.

[25] Schreiber S, Getslev V, Backer MM, et al. The atypical neuroleptics clozapine and olanzapine differ regarding their antinociceptive mechanisms and potency. Pharmacol Biochem Behav. 1999;64: 75–80.

[26] Torigoe K, Nakahara K, Rahmadi M, et al. Usefulness of olanzapine as an adjunct to opioid treatment and for the treatment of neuropathic pain. Anesthesiology. 2012;116:159–169.

[27] Go SI, Song HN, Lee SJ, et al. Craving behavior from opioid addiction controlled with olanzapine in an advanced cancer patient: a case report. J Palliat Med. 2018;21:1367–1370.

[28] Schwartz NA, Turturro MA, Istvan DJ, et al. Patients' perceptions of route of nonsteroidal anti-inflammatory drug administration and its effect on analgesia . Acad Emerg Med. 2000;7:857–861.

[29] Peerdeman KJ, Tekampe J, van Laarhoven AIM, et al. Expectations about the effectiveness of pain- and itch-relieving medication administered via different routes. Eur J Pain. 2018;22:774–783.

[30] Catapres (clonidine hydrochloride) Label - FDA n.d. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/017407s034lbl.pdf (accessed June 2018).

[31] Cole JB, Klein LR, Martel ML. Parenteral antipsychotic choice and its association with ED length of stay for acute agitation secondary to alcohol intoxication. Acad Emerg Med. 2018; doi:10.1111/acem.13486. [Epub ahead of print]