Emergency department-initiated interventions for patients with opioid use disorder: a systematic review

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Short title: ED interventions for OUD

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JK, AO, KD, and AK obtained research funding and conceived the study and designed the search strategy. JK, AO, KD, RD, and AK selected studies for inclusion and JB performed data extraction. JB drafted the article and all authors contributed substantially to its revision. JK takes responsibility for the paper as a whole.

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Abstract

Objectives: The opioid crisis has risen dramatically in North America in the new millennium, due to both illegal and prescription opioid use. While emergency departments (EDs) represent a potentially strategic setting for interventions to reduce harm from opioid use disorder (OUD), the absence of a recent synthesis of literature limits implementation and scalability. To fill this gap, we conducted a systematic review of the literature on interventions targeting opioid use disorders initiated in emergency departments.

Methods: Using an explicit search strategy (PROSPERO), the MEDLINE, CINAHL Complete, EMBASE and EBM reviews databases were searched from 1980 to October 4, 2019. The grey literature was explored using Google Scholar. Study characteristics were abstracted independently. The methodological quality and risk of bias were assessed. **Results**: 12 of 2270 studies met the inclusion criteria (two of high quality). In addition to the heterogeneity of the outcome measures used (retention in treatment, opioid consumption, overdose), brief intervention and buprenorphine initiation (6 of 12 studies) were the most documented with mixed effects for the former and positive short-term and confined to single ED sites effects for the latter.

Conclusion: EDs can be an appropriate setting for initiating opioid agonist treatment (OAT), but in order to be sustained, it likely needs to be coupled with community-based follow-up and support to ensure longer-term retention. The scarcity of high-quality evidence on OUD interventions initiated in emergency settings highlights the need for future research.

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Introduction

Opioid use disorder (OUD) and opioid-related deaths have risen dramatically in North America in the new millennium and now reach epidemic proportions[1, 2]. In the U.S., opioid-related deaths increased by 345% from 9 489 to 42 245 between 2001 and 2016 (3.3 to 13.1 deaths per 100 000 population)[3]. This crisis has reduced overall life expectancy in British Columbia, the Canadian province where the highest death rates have occurred [4]. In the last 3 years, the opioid-related deaths in Canada have increased from 3 023 in 2016 to 4 588 in 2018 (8.4 to 12.3 deaths per 100 000 population)[5]. Over 14 700 Canadians lost their lives between January 2016 and June 2019 due to apparent opioid overdose [5]. Emergency department (ED) visits for opioid-related overdoses increased by 30% between July 2016 to September 2017 in the U.S[6]. In Canada, the age-adjusted rate of ED visits related to opioid poisoning has increased by 135% in Alberta and by 47% in Ontario from 2012-2013 to 2016-2017[7], respectively.

The growing use of EDs related to opioid poisoning and opioid use disorder offers both challenges and opportunities to screen for OUD and initiate interventions and referrals aiming to counter this crisis in a strategic location[1,8,9]. EDs have long been recognized as a primary access point to the health care system for many Americans and Canadians alike, particularly for sub-groups of the population that suffer disproportionately from OUD. It has been reported that 1 in 10 patients visiting EDs for OUD died due to complications related to opioids within the 12 months following their initial visit[10]. There are repeated opportunities to intervene as a large proportion of the opioid overdose patients will have a repeat overdose ED visit in the absence of outpatient treatment[6]. During the first 6 months of 2019, 12% of people who died from of apparent accidental poisoning related to fentanyl in Alberta had an ED visit in preceding 30 days and 2% had more than one ED visit [11]. However, the systematic identification of patients at risk and timely interventions in EDs remain constrained by a number of barriers at the patient, provider and health care system levels. Brief, evidence-based and scalable ED interventions could be a major step forward to address the opioid crisis[1,9].

The growing concern about the opioid crisis has stimulated research, cross-border knowledge sharing and health system-level initiatives[12,13]. Several literature reviews related to the opioid crisis have been recently completed to inform clinicians and decision makers on the effectiveness

of different strategies and to summarize the state of knowledge in this area[13-16]. Despite the potential role of EDs, a comprehensive evaluation of the literature related to OUD interventions initiated in EDs is still lacking.

Goals of this investigation

We conducted a systematic review of the literature addressing interventions targeting OUD initiated in EDs. Our primary question focused on the evaluation of ED-initiated interventions for people with OUD on a range of outcomes including engagement and retention in treatment, days of illicit or non-medical use, overdose risk, and cost. Our second question focused on comparing ED-initiated opioid agonist treatment (OAT) to other ED-initiated interventions for opioid use disorder such as Screening, Brief Intervention and Referral to Treatment (SBIRT) using similar outcome metrics.

Materials and methods

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses[17], we conducted a systematic literature search (Figure 1: Flow Chart of Study Selection) using PubMed/MEDLINE, CINAHL Complete, EMBASE/Ovid SP and EBM reviews from January 1, 1980 to April 6, 2018 using keywords related to opioid drug disorders and interventions initiated in EDs, and limited to studies published in English or French. The search was updated with the same search terms on October 4, 2019. The grey literature was explored using Google Scholar. In addition, we scanned reference lists of identified articles and related reviews. The protocol for this review is registered with PROSPERO (ID= CRD42018095538).

Inclusion criteria were as follows: (1) OAT or another addiction treatment was initiated in the ED or after discharge following an intervention initiated in the ED, or (2) an opioid agonist was used in the ED to treat withdrawal symptoms with immediate linkage to OAT or other addiction treatment/follow-up, or (3) other interventions for people with OUD that were initiated in the ED. In terms of study design, we included randomized controlled trials (RCTs), cohort studies, and studies in which a comparator was available. The outcomes of interest included conventional metrics used in the addiction research such as rates of screening and referral to treatment,

engagement and retention in treatment, relapse, days of illicit or non-medical use, and overdose risk.

Studies were excluded if the title was related to pain, cancer, surgery, acetaminophen/paracetamol, hepatitis C or any neurologic topic. Studies about the frequency of ED visits by people on OAT, or studies about service utilization or health care utilization were also excluded. Studies about OUD diagnosis in the ED, guidelines or protocols about opioid prescriptions for pain in the ED, or buprenorphine treatment in general (i.e., efficacy, safety, comparisons with other agonists) were also excluded. Studies in other settings without ED involvement or related to interventions in the ED for patients without OUD (e.g, primary addiction to other substances) were also excluded. We also excluded studies that were based on the same sample as the included studies and duplicate references.

All authors were involved in determining eligibility of identified studies. The search results were first scanned by title alone and irrelevant studies were excluded based on exclusion criteria. On the second pass, 2 pairs of independent reviewers assessed eligibility of remaining studies by reading the abstract. The eligibility was ultimately determined after a full text review by two pairs of independent reviewers. Articles with unclear eligibility were obtained in full and discussed until consensus was reached.

The methodological quality and risk of bias were assessed using the Cochrane Review Group's tools for randomized control trials and for non-randomized studies [18,19]. All study screening and risk of bias assessment was conducted by two reviewers independently and discrepancies resolved by consensus of the lead investigators (AO, JK).

From all retained articles, we extracted the first author's name, year of publication, country, calendar year(s) the study was conducted, setting of the study, age of participants, sex of participants, type of interventions, and key outcomes. In order to facilitate comparability based on study design, we grouped separately results of the studies using randomized controlled trial (RCT) design and non-RCT studies. Furthermore, within these groupings we synthesized the results separately for OAT and non-opioid agonist treatment interventions.

Insert Figure 1 here

Results

Among 2270 studies identified by the initial search strategy, 12 met our eligibility criteria (Figure1). The reasons for exclusions after reading the abstracts were as follows: abstract only (n=5), out of scope (n=9) and duplicate data (n=4). Because of the heterogeneity in study outcomes and designs, meta-analysis was not possible. The key characteristics of RCT studies (n=7) are shown in Table 1a. Three studies evaluated the effect of OAT while four studies were related to other interventions (non-OAT). In terms of methodological quality, there were two high-quality studies, two fair-quality studies, and three low-quality studies. The majority of the studies were recent and conducted in the U.S. The characteristics of non-RCT studies are presented in Table 1b (n=5) with two fair-quality studies evaluating the effect of OAT and three low-quality studies on the effect of non-OAT interventions.

Insert Table 1a here Insert Table 1b here

Appendix 1 presents the results of RCT studies. Among non-OAT studies, SBIRT was the most frequently evaluated intervention using the RCT design (3 studies). One intervention evaluated SBIRT and take-home naloxone kit, one tested the effect of case management, and one evaluated motivational interviewing. Interventions aiming to reduce overdoses were assessed by two studies (2/4). Among the OAT interventions, two studies were on initiation of buprenorphine and one focused on the effect of distributing vouchers for OAT with methadone.

RCT design with non-opioid agonist treatment

The evidence for the effectiveness of non-OAT interventions was inconsistent. The Merchant et al study showed no statistically significant effect of SBIRT on drug treatment utilization compared to the control group. However, the same study showed that the more intensive intervention led to a higher utilization of drug treatment compared to the control and SBIRT groups[20]. While one study supported that SBIRT had a statistically significant effect after 30 days on the self-reported illicit opioid use in the past 7 days[21], another study reported no statistically significant impact on substance use[22].

In terms of interventions to reduce overdose risk, Banta-Green et al showed that SBIRT combined with a take-home naloxone kit and overdose response training did not reduce the risk of overdose events compared to the group without treatment[23]. Compared to baseline and usual care, the relative risk of non-medical opioid use and overdose risk behavior decreased significantly after six months among the motivational interview intervention group[24].

RCT design with opioid agonist treatment

Both RCTs on buprenorphine initiation found a statistically significant effect on engagement in treatment after 30 days[20,24]. Srivastava et al reported that more patients receiving buprenorphine for opioid withdrawal were taking OAT one month after their ED visit, compared to those who had received clonidine [25]. D'Onofrio et al reported that buprenorphine significantly increased engagement in addiction treatment compared to referral alone and SBIRT groups [21]. The latter study also showed a greater reduction in drug use compared to referral and brief intervention groups.

A study by Barnett et al compared the usual care with case management and with a voucher for methadone treatment with respect to engagement in treatment [26]. The voucher group consisted of distributing vouchers for the first 3 months of an individualized methadone dose and then tapering it off during the subsequent 3 months. The vouchers for methadone group had a higher rate of methadone treatment than usual care and case management during first 6 months following randomization [26]. The voucher group also reported less heroin use than the usual care and case management groups at 3 months after randomization, but not at 6 months. The cost of the voucher intervention was significantly higher than usual care.

Non-RCTs design

Among the non-OAT interventions, one study was on collaborative care (Whiteside et al)[27], one on positive feedback (Suffoletto et al)[28], and one on take-home naloxone kits (Kestler et al)[29]. There were two studies using a non-RCT design with buprenorphine (Berg et al and Hu et al)[30,31]. Results of these studies are summarized in Appendix 1.

Non-RCT design with non-opioid agonist treatment

There was some evidence that non-OAT interventions were effective in patients with OUD based on low-quality studies. Whiteside et al evaluated the effect of collaborative care that included a brief behavioural intervention, team-based care for care coordination, evidence-based pharmacotherapy guideline application and care management with coordinated longitudinal health care on prescription opioid misuse[27]. Although the relative risk of prescription opioid misuse was higher after one month and lower after six months, the treatment effect itself was not statistically significant. A study by Suffoletto et al evaluated the effect of a positive feedback by text messages on engagement and drug use among individuals with OUD and concluded that the effect was weak[28]. Finally, Kestler et al study showed that a majority of patients at high risk of opioid overdose accepted a take-home naloxone kit [29].

> Insert Table 2a here Insert Table 2b here

Non-RCTs design with OAT

Hu et al found that 35% of the patients who received buprenorphine continued treatment after six months but there was no comparison group with baseline data[31]. Buprenorphine treatment decreased relapse rate compared to those who stopped the treatment or had no treatment. A study by Berg et al reported a non-significant difference between the buprenorphine and symptomatic treatment groups regarding the number of withdrawal symptoms. However, the buprenorphine group reported significantly less nausea, vomiting, abdominal cramping and diarrhea than the symptomatic treatment group [30]. The methodological quality and risk of bias assessments for both randomized control trials and for non-randomized studies are displayed in Tables 2a and 2b.

Discussion

The aim of this systematic review was to summarize the evidence for ED-based interventions for people with OUD. Two major conclusions emerge from our review. First, there is a paucity of strong empirical evidence about the effectiveness of any ED initiated intervention designed to reduce harm from OUD. Only 12 studies met our broad eligibility criteria and only two were of high methodological quality. Moreover, only two studies evaluated the effect of ED-based intervention on overdose risk. That said, there is good evidence on the efficacy of OAT treatment

in the ED, but more studies establishing its effectiveness across different settings and populations are needed. The multitude of interventions studied, the use of heterogeneous outcomes, and, at times conflicting results limit the ability to draw consistent conclusions about which components of interventions contribute most to their efficacy. Studies with standardized interventions and consistent outcome measures are needed to overcome these limitations, yet their absence to date should not deter program implementation in an ongoing epidemic of opioid deaths with a paucity of effective treatments. Provided they are established with appropriate evaluation frameworks, it is precisely the further implementation of ED OAT programs that will fill evidence gaps, while providing much needed service. Furthermore, given the general paucity of evidence for any ED-based intervention for OUD, our findings also support the observation and interpretation that OAT is the single ED-based intervention for which there is the highest quality data.

Given the scale of the opioid crisis and the need for interventions across the healthcare landscape, larger, multi-centered and pragmatic studies demonstrating the impact of interventions suited to system-wide scale-up are urgently needed. The broad implementation of interventions in the absence of strong evidence may serve to further marginalize and underserve an already stigmatized population of people who use drugs. This, however, must be balanced against the risk of escalating morbidity and mortality while more research is conducted.

Second, although initiation of OAT in ED offered the most consistent and promising results (6 among 12 studies) compared to non-opioid agonist treatment, the evidence was based largely on fair- or low-quality studies. Furthermore, the positive effects were mainly short term and confined to single ED sites. While initiation of buprenorphine in the ED appears to be one promising measure to address the opioid crisis [14,32], interventions must be tailored to local context and need to address patients across a broad spectrum of opioid use disorder severity. A study by D'Onofrio et al.[33], based on the same population as the 2015 study included in the present review, showed that engagement in formal treatment was lower than referral after 6 months and lower than brief intervention after 12 months. In other words, the longer-term effectiveness remains unclear. Our review showed that ED can be a successful vehicle for initiating OAT, but in order to be sustained, it likely needs to be coupled with community-based follow-up and support to ensure longer-term retention.

While further research is needed, EDs are an appropriate setting for OAT initiation and a key entry point into life-saving treatment for substance use disorders. In order for ED OAT interventions to be scaled-up and sustained, a number of barriers ranging from physician readiness, lack of formal training, time constraints, absence of community-based referal networks to ensure longer-term retention need to be successfully addressed [34].

This review has several limitations. As indicated elsewhere, because of the heterogeneity in study outcomes and designs, meta-analysis was not possible. Furthermore, the determination of meaningful effect for each study outcome was based on statistical significance, which does not necessarily represent clinical or population-level significance.

Our review of the literature addressing interventions targeting OUD initiated in EDs highlights the scarcity of high-quality evidence and the need for future research. As more ED sites in North America plan to implement interventions for OUD, given the high mortality/morbidity associated with OUD, it is imperative that research and program evaluation are a core component given the current state of evidence.

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Source	Location	Population	N	Intervention	Follow- up	Retention	Outcome	Quality
Non-opioid ag	gonist treatme	nt			· ·	·		
Banta-Green (2018)	Two EDs in Seattle	Adults at elevated risk for opioid overdose involving heroin or pharmaceutical opioids Mean age: 40.2 (11.5) 28% female 53% white 53% homeless Mean number of days opioids used in the past 30 days: 24.7 (8.6) 19% have overdosed past 3 months	256	(I)Overdose education (8 min video and flier) with a brief behavioural intervention and take- home naloxone. (C)Usual care.	1064 days	94.1%	(1) Opioid overdose event. (2) Time for first overdose	High
Bohnert (2016)	ED in Michigan	Patients who reported prescription opioid misuse Mean age: 36.8 (11.1), 64% female 75% Caucasian 75% prior overdose 8% any prior opioid agonist therapy	204	(I)30-minute motivational interviewing-based session. (C) Educational enhanced usual care	6 months	86.4%	(1) Overdose risk behavior (2) Non-medical opioid use	High
Bogenschutz (2014)	Six urban academic hospital EDs in US	Adult patients using substances Scoring ≥ 3 on the 10-item Drug Abuse Screening Test and using drugs. Mean age: 36 (12) 70 % male 50 % white 60% never married 42 % unemployed in past 30 days 44 % cannabis (primary substance) days of primary drug: 16.2 (11.6)	1285	(BI) Brief intervention with telephone boosters. (RT) Referral to addiction treatment if indicated. (C) An informational pamphlet	12 months	81.2%	 Number of days abstinent from all drugs at 3, 6, and 12 months. Objective evidence of drug use based on analysis of hair samples 	Fair
Merchant (2015)	Two urban ED in Providence	Patients	1057	(I) Brief intervention or more intensive intervention and booster sessions at 2 to 4 weeks after ED enrollment. (C) Study questionnaire only	3 months	61.5%	(1) Total drug use/misuse frequency.	Low

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Barnett (2006)	Large urban ED in San Francisco	Patients with opioid dependence Age: 18 to 65 range	126	(VO)Vouchers for methadone treatment. (CM) Case management. (BO) Both these interventions. (C) Usual care	6 months	100%	(1) Cost. (2) Self- report of heroin use	Low	
D'Onofrio (2015)	Large urban academic hospital ED in US	Patients with opioid dependence Mean age: 31.4 (10.6) 76.3% men 75.4% white 41.3% high school graduate or equivalent 66% identified via screening and 34 % seeking treatment for opioid dependence	329	(BU) Buprenorphine. (BI) Brief intervention. (C) Referral	30 days	74.2%	(1) Engagement in addiction treatment. (2) Number of days of illicit opioid use per week	Fair	
Srivastava (2019)	ED in Toronto (Canada)	Patients in withdrawal. Mean age (I=38.85) (C=38.38); % female (I=69%) (C=46%); History of opioid agonist treatment (I=62%) (C=15%)	26	(I) Buprenorphine. (C) Clonidine	1 month	65.4%	(1) Attend to an addiction rapid access clinic. (2) Opioid agonist treatment status at 1 month	Low	

Table 1b. Description of non-randomized studies

Source	Location	Population	N	Study design	Follow- up	Intervention	Outcome	Quality
Non-onioid	l agonist troatm	ont	•	·	•		·	
Kestler (2016)	Urban ED, Canada	Patients at risk of opioid overdose. Age: 54.2% ≥ 40 years old; 75 % of respondents used injection drugs, 37% female; 26% identified as "Indigenous; 65% Caucasian.	201	Cross-sectional	N/A	Take-home naloxone	Acceptance of take-home naloxone	Low
Suffoletto (2017)	Urban ED	Adults seeking care in an urban ED for opioid use disorder. Mean age: 22 (1.8); 55 % female; 7 5 % white; 90 % undergone some opioid use disorder treatment in the past; 80 % undergone treatment more than 1.	20	Mixed	28 days	A morning "push" message focused on positive thinking, adaptive coping feedback tailored to twice-daily assessments of craving severity and contextual correlates of craving, and end- of-day feedback on daily opioid use and goal commitment.	(1) PIER1 Engagement (2) Response Rates (3) Craving Severity (4) Opioid Use	Low
Whiteside (2017)	Large urban, academic Level 1 trauma center in Seattle	Adult patients. Mean age: 44.6 (13.5); 33% female; 27% homeless or temporarily housed; 60 % white	30	Pilot cohort study	6 months	ED-LINC intervention: active care coordination and linkage; medication safety and utilization of opioid guidelines; longitudinal care management for 4 months after enrollment; utilization of EMR innovations and the prescription monitoring program (PMP) information for assessment and follow-up.	Prescription drug misuse	Low

Opioid ago	onist treatment							
Berg (2007)	Urban ED within a large academic teaching hospital, US	Adult patients. Age (%): 18-24 years (6); 25-34 y (23); 35-44 y (35); 45- 60 y(25). 64 % male; 24 % white; 76% African American; 64 % uninsured	158	Retrospective chart review	10 weeks	(1) Buprenorphine (with or without symptomatic treatment); (2) symptomatic treatment(s) only; or (3) no pharmacologic treatment	(1) Number and presence of opioid withdrawal symptoms. (2) Drug- related ED visits	Fair
Hu (2019)	Four acute care community hospitals with EDs (Bowmanville, Oshawa, Port Perry, and Ajax/Pickering) in Ontario, Canada.	Patients in opioid withdrawal. Mean age: 31.5 (10.0) 75.9% male 75.5% Caucasian	43	Retrospective chart review	6 months	Buprenorphine	Treatment retention	Fair

Reference	Random	Allocation	Blinding of	Blinding of	Incomplete	Selective
	sequence	concealment	participants	outcome	outcome	outcome
			and personnel	assessment	data	reporting
Banta-Green	low	low	low	low	low	low
(2018)						
Barnett	low	high	unclear	unclear	unclear	low
(2006)						
Bohnert	low	low	unclear	low	low	low
(2016)						
Bogenschutz	low	low	high	low	low	low
(2014)						
D'Onofrio	low	low	high	low	low	low
(2015)						
Merchant	low	low	low	high	high	low
(2015)						
Srivastava	low	low	low	high	high	low
(2019)						

Table 2a. Assessment of risk of bias: randomized studies[17]

Table 2b. Assessme	nt of risk of bias:	non-randomized studies[18]
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Reference	Confounding	Selection of participants	Measurement of interventions	Departures from intended interventions	Missing data	Measurement of outcomes	Selection of the reported result
Kestler (2016)	low	high	low	low	low	high	low
Berg (2007)	N/A	low	high	low	low	low	low
Suffoletto (2017)	low	high	low	high	high	low	low
Whiteside (2017)	high	high	low	low	low	high	low
Hu (2019)	high	high	low	low	low	high	low

