Rapid review of the Emergency Department-Initiated Buprenorphine for Opioid Use Disorder.

Short Title: Review of ED Initiated Buprenorphine

Key words: Opioid Use Disorder, Emergency, Buprenorphine

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JH, MLJ, PD, AS, HS, KC conceived and designed the study. JH, HS performed the review. JH, HS, AS, RZ, KC, PD, PH, MLJ contributed to the manuscript preparation.
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Rapid Review of Emergency Department-Initiated Buprenorphine for Opioid Use Disorder.

ABSTRACT

Opioid related harms have been increasing in Australia over the last five years. People with opioid use disorder are over-represented in emergency department (ED) presentations. Opioid agonist treatment is the most effective community-based treatment. Buprenorphine is considered the safest of these treatments to use in the ED setting. This rapid review investigated the effectiveness of initiating Buprenorphine in the Emergency Department setting. Medline, Embase, Emcare, PSYCinfo, CINAHL and Cochrane Central Register of Controlled Trials databases were searched. Randomised and non-randomised studies published in peer reviewed journals that involved the initiation of buprenorphine in the ED setting were considered eligible. The search revealed 350 articles of which 11 were included in the review; three articles representing two randomised controlled trials and eight observational studies. Data were extracted from included papers and risk of bias assessed on the randomised controlled trials. Two randomised controlled trials showed that buprenorphine initiated in the ED does improve treatment engagement up to two months after an ED visit. Eight observational studies, one with a comparator group reported positive results for this intervention. There is strong evidence that clinicians should consider commencing buprenorphine in the ED for patients with opioid use disorder when combined with a direct and supported referral or “warm handover” to
community care. Further implementation studies and investigation of long-acting injectable buprenorphine treatment are required.

Key words: Opioid Use Disorder, Emergency, Buprenorphine

Introduction

Opioid use disorder (OUD), describes the chronic condition arising from opioid dependence and its associated harms (1). It carries a high individual, societal and economic burden (2). In Australia, between 2014 and 2019 there was a 40% increase in heroin-related harms and a significant increase in heroin-related emergency department (ED) attendances (3). It is critical for Australia to address the increasing incidence of opioid related deaths to prevent mirroring the “Opioid Epidemic” of North America (4, 5). Maintenance pharmacotherapy with opioid agonist treatment (OAT) has been shown to reduce withdrawal symptoms, cravings, non-medical opioid use, HIV infection rates and mortality (6, 7). In addition, OAT promotes patient satisfaction, psychological stability, social functioning and treatment engagement (2, 6, 7). One OAT that is considered appropriate for initiation in ED is buprenorphine/naloxone typically given sublingually (as Suboxone®) (8).

Some people with OUD have complex health needs, often feel marginalised from primary care and may have limited resources meaning that they often seek health care from the ED (9). Despite the high rates of overdose deaths post-ED discharge, this population is not routinely
granted access to treatment with buprenorphine, which is potentially life-saving and can alleviate the symptoms of withdrawal (10). The ED may offer an opportunity to engage people with OUD in treatment, link them in with longer term services, and promote strategies to reduce drug-related harms such as post-discharge overdose (11).

Buprenorphine is a partial opioid agonist which slowly dissociates from the µ-opioid receptor. It demonstrates a ceiling effect with regards to respiratory depression and euphoria, accounting for its increased safety in overdose (7, 12). Its long half-life provides the option of alternate-day dosing and patients report greater clarity of mind compared to other types of OAT such as methadone (2, 12). Induction is also safer than with methadone, and the maintenance dose can be reached within 2-3 days (2). Given its partial agonist action and strong affinity for the µ-opioid receptor, buprenorphine can precipitate withdrawal if given too soon after a full opioid agonist, such as heroin (2, 12). To prevent this, during induction the first dose should be delayed until the patient is experiencing moderate withdrawal symptoms (2). Buprenorphine is often combined with naloxone and delivered orally or sublingually in a combined film (as Suboxone®) (12). Naloxone, when delivered by this route, is not absorbed adequately to antagonize the buprenorphine but may do so if the buprenorphine/naloxone combination is injected; a potential deterrent (12). Compared to methadone, buprenorphine is safer in overdose, has fewer drug interactions, less dose variability between patients, is easier to titrate and is more difficult to divert (13). For these reasons, buprenorphine is typically considered the best choice of agent for initiation in the ED where close follow up in the days after discharge is often difficult.
The bulk of community-based OAT prescribing in Australia is carried out by a small number of specifically licenced private general practitioners (GPs) (10, 14, 15). Currently, these few prescribers cannot meet the needs of an increasing number of patients, and the current model for OAT is inadequate for those without a regular GP or a fixed address (3, 16). In 2019, long-acting injectable buprenorphine (LAIB) became available in Australia and may alleviate some of the difficulties of long-term treatment (17, 18). Injections given weekly or monthly, could reduce the demand on GPs and pharmacies and could improve quality of life by negating the need to attend a pharmacy frequently for supervised dosing of buprenorphine (17).

Opioid withdrawal has historically been neglected in EDs (19). The recommended treatments simple analgesia, antiemetics, anti-diarrhoeal agents, benzodiazepines, antipsychotics and alpha-2 adrenergic agonists clonidine that target individual symptoms are often insufficient and may have unwanted side-effects (19). Untreated opioid withdrawal has been shown to result in high risk illicit opioid use and increased mortality after discharge (20). When people in acute withdrawal are not offered effective treatment, they often choose to leave against medical advice, even in circumstances where medical treatment is essential (21).

Buprenorphine can rapidly relieve these symptoms in the ED. In this review we examine the effectiveness of ED-initiated buprenorphine for reducing withdrawal symptoms, increasing addiction treatment engagement and reducing harms in the months after index visit.
Methods

A literature search was conducted using Ovid Medline(1946-present), Embase(1974-present), Emcare(1995-present), PSYCinfo(1809-present), CINAHL and Cochrane Central Register of Controlled Trials databases.

Medical subject heading search terms, text and keywords associated with emergency department-initiated buprenorphine were used (Appendix 1). Bibliographies of included articles were also inspected for additional references. There were no limits imposed. Randomised and non-randomised studies published in peer reviewed journals that involved the initiation of buprenorphine in the ED setting were considered eligible.

Results

The search yielded eleven studies that investigated buprenorphine initiation in the ED for OUD (Figure 1.). The RCT conducted by D’Onofrio et al. in 2015 was identified as the landmark study (8). In 2017, the same authors published a subsequent paper on the longer-term outcomes of this RCT (11). These constitute level I evidence (22). The other RCT identified was conducted by Srivastava et al (23). These studies are detailed in Table 1.

RCTs

In the study conducted by D’Onofrio et al. the patients included were seeking treatment for OUD, or post-opioid overdose or identified on screening as having OUD. Opioid dependence
was confirmed with DSM4 criteria and an opioid-positive urine screen. Participants were randomly assigned to: a) referral to community-based treatment (Referral), b) brief intervention and facilitated referral to community-based treatment (BI) or c) brief intervention and ED-initiated buprenorphine and referral to primary care for 10 weeks of ongoing buprenorphine (Buprenorphine). The primary outcome was enrolment in addiction treatment at 30 days. Secondary outcomes were self-reported 7 days of illicit opioid use, urine toxicology for illicit opioids, HIV risk behaviour and use of addiction treatment services.

A maximum of 8mg of buprenorphine was initiated in the treatment arm if participants displayed withdrawal symptoms (49, 43%), otherwise they underwent unsupervised home induction (65, 57%). The participants were given take-home doses to bridge them until an appointment in primary care within 72 hours. They were then prescribed buprenorphine from a primary care service for 10 weeks.

The participants had similar characteristics to individuals in Australia who inject drugs and present to EDs (9) (Table 1). However, Australians rarely present to the ED purely for assistance with withdrawal (9).

Non-English speakers and those with insufficient contact information were excluded. In Australia, OUD has greatly affected the homeless population, many of whom may not have a mobile phone (24). This vulnerable population has traditionally not engaged in addiction
treatment services and would likely benefit from EDIB (24). In addition, this study did not include patients who were admitted to hospital.

Those allocated to the Buprenorphine group significantly increased engagement in treatment at 30 days compared to BI or Referral groups. It also significantly reduced self-reported 7-day illicit opioid use for both time and intervention effects and decreased use of inpatient addiction services. However, there was no difference across all three groups in the rate of positive urine samples or self-reported HIV risk-taking behaviour at 30 days.

Using treatment engagement at 30 days as the primary outcome has been criticised for being misleading and vague (25). Critics have argued that improvement in the primary outcome without improvement in secondary outcomes such as urine results and HIV risk behaviour may in fact be a marker of buprenorphine diversion (25). However, there is a reliable body of evidence showing that treatment engagement can be used as a surrogate measure for reduced mortality and decreased criminal activity (26, 27). The study has also been criticised for purporting to show that EDIB reduces illicit opioid use, yet the rate of positive urine tests was similar across the groups (28). Urine toxicology results, however, should be interpreted cautiously. A positive urine results only shows illicit opioid use in the last 72 hours, does not indicate the frequency or intensity of use and is not an ideal marker for OUD which is better measured by self-report (29). Complete abstinence from illicit opioids is not a useful primary goal of treatment and in patients not on OAT has been be associated with an increased risk of fatal overdose due to reduced tolerance (2, 30).
Subsequent analysis of longer-term outcomes, however, revealed the benefits of EDIB did not persist beyond 2 months, after which participant’s care was transferred to a community provider or they opted to discontinue treatment (11). Buprenorphine is most effective at reducing mortality and hospitalisation when maintained for at least 12 months compared to discontinuation within five months (31). This disparity between the 2 and 6 and 12-month results show the importance of not only initiating buprenorphine but facilitating its maintenance by direct and supportive communication to community care (32). This has been termed a “warm handover”.

Despite the authors making attempts to reduce bias by blinding care providers to participant’s answers and verbally ensuring confidentiality, it remains unclear whether the self-reports were confounded by a social desirability bias.

In the RCT by D’Onofrio et al., patients were provided with take home doses to initiate themselves. This is unlikely to be immediately feasible in many EDs. A barrier to implementation in both the US and Australia is likely to be emergency physicians’ lack of confidence in prescribing an unfamiliar drug (33). Dedicated training of physicians would be required before this intervention could be applied to EDs universally.
Risk of Bias

These studies by D’Onofrio et al. were assessed for bias according to the Cochrane Risk of Bias (RoB) criteria (Figure 2). With regards to selection bias, random sequence generation and allocation concealment was used, D’Onofrio et al.’s study demonstrates a low risk of bias. As an open label study, neither the participants nor the clinicians were blinded to the intervention, so performance bias is possible. This can be mitigated by the authors having used objective outcome measures. Data on all outcomes were collected by researchers not involved in the patient’s care, mitigating any effects of detection bias.

D’Onofrio’s 2015 study was low risk for attrition bias. For the primary outcomes the statistical method accounted for all available data and included those with missing data. However, in the subsequent paper, few urine drug samples were obtained, accounting for a noteworthy amount of missing data with only the 2- and 6-month data reported. However, the utility of urine toxicology as an outcome measure, has been discussed (28). The analysis of longer-term outcomes completed in 2017 was conducted on 88% of the original sample. The population did not differ on variables such as gender, insurance and types of drugs used, subsequently this reduced bias. Both 2015 and 2017 papers are low risk for reporting bias because the outcomes prospectively identified are the same as those that were reported in the final paper.

In summary, this assessment demonstrates that D’Onofrio et al.’s RCT and its follow-up analysis are pieces of high-quality, level II evidence that show that buprenorphine initiated in
the ED is a more effective treatment than brief intervention and referral for up to 2 months post discharge. Furthermore, the treatment group had reduced use of inpatient addiction services, so it is possible that EDIB may be a cost-effective treatment. For 27% of participants, this was their first experience with treatment, hence EDIB may engage patients in treatment who might otherwise be unable to access OAT.

Srivastava et al. conducted an RCT in a single centre in Canada. This study compared the efficacy of buprenorphine to clonidine for the treatment of opioid withdrawal (23). The outcome measures were: a) the participant’s attendance at a rapid access addiction clinic in the five days after their ED visit and b) their OAT status one month after randomisation (Table 1). The authors found that those who received buprenorphine in the ED were more likely to be engaged in OAT at one month.

The most striking limitation of this study is its small sample size (n=26) with consequent risk of type 1 error. In addition, unlike the previous study, Srivastava et al. did not track or screen all eligible ED patients. Instead, the study relied on ED physicians to enrol patients. Consequently, there is a high risk of confounding and selection bias. Moreover, there was a considerable amount of missing data resulting in attrition bias. Despite its limitations, this study provided some evidence that buprenorphine is a better choice of drug than clonidine in the ED.

Non-Randomised Observational Studies
Our search revealed eight non-randomised observational studies, mostly performed in the last two years (see Table 2). These have demonstrated that when buprenorphine is initiated in the ED with a warm handover (direct communication) to outpatient care, there is substantial engagement in formal addiction treatment in the following months (34-40). In some cases, this was achieved by utilising peer workers, social workers and rapid access bridge clinics; a model that is likely to overcome the extra workload perceived by physicians and prevent loss to follow up during this high-risk period (33, 34, 39, 40).

In all studies, the majority of participants presented to their first follow up appointment, and at 30 days more than two thirds of participants were retained (35-39). In one study, 37% of participants were still in active treatment at 6 months (37). Notable strengths of some include their large sample sizes and multicentre implementation (34, 40). However, for all studies, their largely retrospective design and lack of comparison groups leaves them vulnerable to bias and so can only offer level IV evidence.

Additionally, Hu et al. found that patients maintained on buprenorphine had significantly fewer ED visits at 3 and 6-months compared to those who did not attend their first follow up or who stopped and re-started treatment (37). This mirrors the earlier findings of Berg et al. that buprenorphine, when given to relieve withdrawal symptoms in the ED, decreased 30-day ED attendance, compared to symptomatic treatment (41). This is level III evidence highlighting a health benefit of EDIB for the individual and a resource benefit for the health
service. In the small Dunkley et al. cohort (n=19), 47% of participants were identified as homeless, exhibiting the feasibility of this model in a vulnerable population (35).

In many of these studies, a large proportion of participants attended the ED specifically seeking treatment for OUD. This indicates that they are at the preparation stage of behaviour change and may be more likely to engage in treatment. It is possible that this treatment may not be transferable to EDs outside of North America where fewer people present to ED for treatment of OUD. In Australia and New Zealand, there are not large numbers of presentations to EDs that are seen in North American studies where only a very small proportion of people with OUD seek treatment and access to opioid agonist treatment is severely limited. These studies demonstrate the feasibility of ED initiated buprenorphine in the North American context. There is a gap in the literature for Australian-based evidence.

Discussion

The current review illustrates similar findings to those of Chen et al. in which the evidence from one well conducted trial supported the practise of EDIB(42). This model by D’Onofrio’s has been replicated and successfully implemented in EDs in a diverse range of hospitals throughout North America (43). In 2019, the American College of Medical Toxicology (ACMT) published a position statement supporting EDIB that was endorsed by the American College of Emergency Physicians (ACEP) (44).
Additional Considerations

Implementation of Emergency Department-Initiated Buprenorphine

The reviewed literature has identified factors that limit the implementation and success of EDIB including extra physician workload (33). This is reflected in the lack of treatment focus for OUD in the acute care setting. In addition, when patients are engaged in long-term treatment, they are less likely to present to ED with other drug-related presentations such as overdose, cellulitis or endocarditis (37, 45). Australian EDs are constrained by significant time pressures, so EDIB protocols need to be efficient and make best use of available resources. In many tertiary hospitals in Australia there are addiction medicine consultant liaison services that have the potential to facilitate “warm handovers” and educate and support emergency physicians. Although there may be concern from clinicians that EDIB might increase ED presentations, this has not been reported in America (45). In Australia there is not a large population seeking treatment through EDs. EDIB may increase presentations to already overcrowded Australian EDs. Alternatively, novel community-based approaches such as rapid-access clinics could also alleviate the demand for OAT. It is possible that employing a combination of community and ED strategies could be further studied and employed in Australia. EDs are well placed to provide treatment in a time-responsive manner and are “open all hours”. Buprenorphine is a simple to use and relatively safe intervention to rapidly treat people with OUD.
A number of Level II evidence implementation studies are currently underway. D’Onofrio et al. are set to complete an implementation study by 2021, and a multicentre trial has been commenced by Melnick et al. (46, 47). Moreover, Kawasaki et al. have had successful preliminary results from their Hub and Spoke model of EDIB (48). Resources to promote uptake include peer workers, social workers, ED-based pharmacists and user-centred clinical decision support programs (47, 49). From a review of the available literature, it is clear that the benefits of initiating buprenorphine within ED outweigh any risks that have been identified.

Long-Acting Injectable Buprenorphine (LAIB)

Future research could examine whether pathways from sublingual to LAIB in the ED are more effective for long-term treatment. A multi-site community study with a small Australian arm (10%) demonstrated the benefit of LAIB over SL buprenorphine with higher retention rates and lower levels of illicit opioid use (50). While a further study showed that LAIB had high satisfaction (88%) and a 7% increase in employment rates (17).

Conclusion

These findings comprise Level I evidence supporting a recommendation for uptake of EDIB. EDIB has the potential to improve the management of people with OUD attending Australian EDs, provided linkages to community care are facilitated by a warm handover.
References

14. Harm Reduction Australia and ScriptWise. NATIONAL MATOD SUMMIT REPORT: Medication Assisted Treatment for Opioid Dependence (MATOD) in Australia. 2018
28. Murimi I, Murimi IB. Capsule Commentary on D’Onofrio et al., Emergency Department-Initiated Buprenorphine for Opioid Dependence with Continuation in Primary Care: Outcomes During and After Intervention. JGIM: Journal of General Internal Medicine. 2017;32(6):683-.
<table>
<thead>
<tr>
<th>Study</th>
<th>Setting, Design, Population</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>D‘Onofrio 2025</td>
<td>USA, Single Urban ED 2009-2013, RCT, 13-week follow up</td>
<td>Opioid dependent adults, DSM criteria (N=68) and opioid positive urine result. 50% identified through screening, 50% were seeking treatment for opioid dependence. 62% presented to the ED within overdose. 53% interoventive drug use, 25% prescription opium only.</td>
<td>329 (124/125/171/114/144 referrals) Buprenorphine</td>
<td>Brief intervention and ED-initiated buprenorphine with continuation in primary care for 10 weeks.</td>
<td>Primary: addiction treatment at 30 days Secondary: Self-reported illicit opioid use, urine toxicology only risk behavior, use of addiction treatment services.</td>
<td>ED-initiated buprenorphine significantly increased engagement in addiction treatment at 30 days (78%) (95% CI 75.8-80.1%) compared to buprenorphine (34%) (95% CI 30.4-37.6%) and naltrexone/DEPREN (36%) (95% CI 32.3-40.7%).</td>
</tr>
<tr>
<td>D‘Onofrio 2017</td>
<td>As above, RCT, 6 and 12 month follow up</td>
<td>Patients from D‘Onofrio et al 2013 who completed at least one follow up assessment. (38% of the randomized sample above).</td>
<td>As above</td>
<td>21.2 weeks of primary care-based services to community-based OAK program or were provided detoxification over a 5-week period. This was based on their stability, insurance and preferences.</td>
<td>As above</td>
<td>At 3 months, there were significantly more participants engaged in addiction treatment in the buprenorphine group (78%) (95% CI 73.5-82.6%) compared with placebo (47%) (95% CI 37.6-56%) and referral group (53%) (95% CI 42.6-64.3%).</td>
</tr>
<tr>
<td>Schuetafter 2020</td>
<td>Canada, Single Urban Emergency Department, RCT</td>
<td>Patients presenting to the ED, and/or those who were in, opioid withdrawal. 30/33 Buprenorphine/13 Clonidine</td>
<td>Clonidine in ED</td>
<td>Opioid treatment status at 1 month.</td>
<td>Patients who received buprenorphine in the ED were significantly more likely to be receiving CART 1 month later compared to those who received clonidine (63% vs 8%).</td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Randomised Control Trials of Emergency Department-Initiated Buprenorphine
Table 2. Non-Randomised Observational studies on Emergency Department-initiated Buprenorphine

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Setting</th>
<th>Design</th>
<th>Participants</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Limitations/risks of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beeg et al 2007</td>
<td>UI: Single urban ED</td>
<td>Retrospective chart review</td>
<td>Ref for addiction medicine ref, social work or treating physicians</td>
<td>118/384/1</td>
<td>ED triage time from arrival and referral to treatment</td>
<td>Inpatient treatment for withdrawal ED</td>
<td>NA</td>
<td>Difficult to comment on the efficacy of buprenorphine, symptomatic treatment for alleviating withdrawal symptoms, no information about rates of treatment engagement.</td>
</tr>
<tr>
<td>Bagnall et al 2010</td>
<td>U: Multicentre (three hospital) ED</td>
<td>Retrospective chart review after pilot implementation program</td>
<td>Universal screening using NIDA quick screen followed by AUDIT-C or DAST-10</td>
<td>241</td>
<td>1. Identified patients with OUD with universal screening, brief intervention and referral to treatment (SBIRT) performed by patient navigators (2010)</td>
<td>NA</td>
<td>7% (287) attended next day follow-up, 10% (231) of patients remained in treatment 30 days later.</td>
<td></td>
</tr>
<tr>
<td>Durville et al 2019</td>
<td>U: Single centre, urban centre ED</td>
<td>Retrospective, chart review</td>
<td>Opioid use on ED visit (addiction and patient addictions) prior to ED visit (addiction and patient addictions)</td>
<td>30</td>
<td>ED triage time from arrival to ED</td>
<td>NA</td>
<td>5% (12) attended initial follow-up, 4% (16) achieved treatment at 30 days, 13% (35) achieved treatment at 6 months.</td>
<td></td>
</tr>
<tr>
<td>Edwards et al 2020</td>
<td>U: Single centre, community hospital ED</td>
<td>Prospective, observational cohort study</td>
<td>Participants presented to ED on ED visit (buprenorphine)</td>
<td>82</td>
<td>ED triage time from arrival and referral to treatment</td>
<td>NA</td>
<td>51% (30) attended initial follow-up, 48% (24) achieved treatment at 30 days, 12% (18) achieved treatment at 6 months.</td>
<td></td>
</tr>
<tr>
<td>Hu et al 2019</td>
<td>Canada, Multicentre Four community EDs</td>
<td>Retrospective, chart review</td>
<td>Opioid use on ED visit (addiction and patient addictions)</td>
<td>45</td>
<td>ED triage time from arrival to ED</td>
<td>NA</td>
<td>5 month follow-up, 34% (15) attended initial follow-up at 30 days, 15% (6) achieved treatment at 30 days, 10% (4) achieved treatment at 6 months.</td>
<td></td>
</tr>
<tr>
<td>Kuester et al 2019</td>
<td>U: Single city, urban ED</td>
<td>Retrospective, chart review</td>
<td>Opioid use on ED visit (addiction and patient addictions)</td>
<td>259</td>
<td>ED triage time from arrival to ED</td>
<td>NA</td>
<td>45% (30) achieved treatment at 30 days, 5% (15) achieved treatment at 30 days.</td>
<td></td>
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<tr>
<td>Kiley et al 2020</td>
<td>U: Single urban ED</td>
<td>Retrospective, chart review</td>
<td>Opioid use on ED visit (addiction and patient addictions)</td>
<td>259</td>
<td>ED triage time from arrival to ED</td>
<td>NA</td>
<td>5% (15) achieved treatment at 30 days, 15% (6) achieved treatment at 6 months.</td>
<td></td>
</tr>
<tr>
<td>Murphy et al 2020</td>
<td>U: Single urban ED</td>
<td>Retrospective, chart review</td>
<td>Opioid use on ED visit (addiction and patient addictions)</td>
<td>259</td>
<td>ED triage time from arrival to ED</td>
<td>NA</td>
<td>48.7% (125) of patients attended first visit with buprenorphine treatment visit.</td>
<td></td>
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Appendix

Appendix 1: Search Strategy

<table>
<thead>
<tr>
<th>Search History (1)</th>
<th>View Search</th>
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<tr>
<td># of Searches</td>
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<td>5647</td>
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<td>8107</td>
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Figure 1. Flow diagram of record review selection

- **Identification**: 602 records identified from databases
- **Screening**: 252 duplicates excluded
- **Eligibility**: 264 records excluded; records not relevant to research question
- **Included**: 71 records excluded; 37 conference abstracts, 18 editorials/letters/comments/reviews, 9 literature reviews, 7 other case study, incomplete trials, implementation studies
- **Included**: 11 articles included in final review
  - 3 randomised control trials
  - 7 retrospective observational studies
  - 1 prospective observational study
Figure 2. Cochrane Risk of Bias Tool for RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>Risk of bias domains</th>
</tr>
</thead>
<tbody>
<tr>
<td>D'Onofrio 2015</td>
<td>D1: +, D2: +, D3: +, D4: -, D5: -, Overall: +</td>
</tr>
<tr>
<td>D'Onofrio 2017</td>
<td>D1: +, D2: +, D3: -, D4: -, D5: -, Overall: -</td>
</tr>
</tbody>
</table>

Domains:
D1: Bias arising from the randomization process
D2: Bias due to deviations from intended intervention.
D3: Bias due to missing outcome data.
D4: Bias in measurement of the outcome.
D5: Bias in selection of the reported result.

Judgement:
- High
- Some concerns
- Low
<table>
<thead>
<tr>
<th>Study</th>
<th>Setting, Design</th>
<th>Baseline Characteristics</th>
<th>Population</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcomes</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>D’Onofrio 2015</td>
<td>USA, Single Urban ED 2009-2013</td>
<td>Opioid-dependent adults, DSM criteria (initial and opioid tapering tolerance result, 60% identified through screening, 30% were seeking treatment for opioid dependence in ED, 5% presented to the ED without overdose, 5% intravenous drug use, 20% prescription opioids only)</td>
<td>329/134/111/88/104 referral</td>
<td>Brief intervention and ED-initiated buprenorphine with continuation in primary care for 10 weeks. Buprenorphine 4mg on day 1 and 16mg on days 2 and 3. 57% provided with take-home naloxone as not in withdrawal</td>
<td>1. Brief intervention and facilitated referral to community-based treatment 2. Screening and referral to treatment service</td>
<td>Primary: addiction treatment at 30 days Secondary: Self-reported illicit opioid use, urine toxicology only risk behavior, use of addiction treatment services.</td>
<td>ED-initiated buprenorphine significantly increased engagement in medication treatment at 30 days (78%) (p = 0.06-0.89) compared to (81% (p = 0.06-0.89) and referral group (91%) (p = 0.06-0.89)</td>
<td></td>
</tr>
<tr>
<td>D’Onofrio 2017</td>
<td>As above, RCT 6 and 12 month follow-up</td>
<td>Patients from the 2009-2013 cohort completed at least one follow-up assessment (38% of the randomized sample retained). No significant differences compared to the original randomized sample.</td>
<td>As above</td>
<td>After 12 weeks of primary care-based buprenorphine, participants were also transitioned to community-based OAT program or were provided medication over a 2-week period. This was based on their stability, insurance and preference.</td>
<td>As above</td>
<td>Primary: self-reported engagement in medication treatment at 3, 6 and 12 months from enrolment. Secondary: days of illicit drug use, OPI risk (2, 4, and 12 months) and urine toxicology (4, 8 months).</td>
<td>At 12 months, there were significantly more participants engaged in medication treatment in the buprenorphine group (78% (p = 0.06-0.89) compared with the 47% (p = 0.06-0.89) in the referral group (75% (p = 0.06-0.89). Differences were not significant at six months or 12 months.</td>
<td></td>
</tr>
<tr>
<td>Schatschneider 2020</td>
<td>Canada, Single Urban Emergency Department</td>
<td>Patients presenting to the ED, or in need to be in, opioid withdrawal.</td>
<td>36/33 Buprenorphine/OAT Clonidine</td>
<td>Buprenorphine up to 15mg in ED. Prescription for 3 days supply on discharge.</td>
<td>Clonidine in ED and a prescription for five days supply on discharge.</td>
<td>Attendees at the outpatient addiction clinics within 5 days of the index ED visit. Opiate agonist treatment status at 1 month.</td>
<td>Participants who received buprenorphine in the ED were significantly more likely to start receiving OAT 1 month later compared to those who received clonidine. (p = 0.001)</td>
<td></td>
</tr>
</tbody>
</table>
Table 2. Non-Randomised Observational studies on Emergency Department-initiated Buprenorphine

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Year</th>
<th>Setting</th>
<th>Design</th>
<th>Participants</th>
<th>Sample Size</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Limitations/ risk of bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beg et al.</td>
<td>2007</td>
<td>U.K. single urban ED</td>
<td>Retrospective chart review</td>
<td>NHS addiction medicine nurses would make treatment decisions</td>
<td>0/88/94</td>
<td>ED-based treatment and referral to treatment</td>
<td>Symptomatic treatment for withdrawal</td>
<td></td>
<td>Unable to comment on the efficacy of buprenorphine in symptomatic treatment for alleviating withdrawal symptoms. No information about rates of treatment engagement.</td>
</tr>
<tr>
<td>Nagie et al.</td>
<td>2010</td>
<td>U.K. Multiple (three hospitals) ED</td>
<td>Retrospective chart review after plan implementation program</td>
<td>Universal screening using NODS or DS15-T or DAST-20</td>
<td>241</td>
<td>1. Identifying patients with OUD via universal screening. Brief intervention and referral to treatment (SSRT) performed by patient management (pwx) providers. 2. Initiated on a 48-hour sublingual buprenorphine in the ED.</td>
<td>3. Multi-dose discharge medication facilitated rapid community follow-up</td>
<td></td>
<td>79% (95/120) of patients remained in treatment 30 days later. No comparison group.</td>
</tr>
<tr>
<td>Dulhane et al.</td>
<td>2012</td>
<td>U.K. Single centre, tertiary centre ED</td>
<td>Retrospective, chart review</td>
<td>OUD identified by OUD criteria and participants passed clinical decision unit (CDU) and ED (condensed was 24 h) and referred to opioid OAT treatment.</td>
<td>19</td>
<td>0. ED Triage Officer (EDTO) refers patients to OAT and the EDTO doctor notes difficulty in motivating patients to attend the OAT.</td>
<td></td>
<td></td>
<td>95% (12/12) of enrolment follow-up 47% (5) active in treatment at 30 days 23% (4) active in treatment at 6 months Small sample size, no comparison group, poor generalizability.</td>
</tr>
<tr>
<td>Edwards et al.</td>
<td>2020</td>
<td>U.K. Single centre, community hospital ED</td>
<td>Prospective, observational cohort study</td>
<td>OUD identified by OUD criteria. Protocol performance by internal healthcare providers</td>
<td>62</td>
<td>ED-based treatment with rapid referral to OAT. Up to 24 hours at ED pharmacy</td>
<td></td>
<td></td>
<td>53% (32/62) follow-up 95% active at treatment at 30 days 18% (10) treatment attrition No opioid screening, treatment seeking population, no comparison group.</td>
</tr>
<tr>
<td>Hu et al.</td>
<td>2019</td>
<td>Canada, Multicentre Four centres by hospital ED</td>
<td>Retrospective, chart review</td>
<td>OUD identified by OUD criteria. Protocol performance by internal healthcare providers.</td>
<td>65</td>
<td>0. OUD criteria in ED. Prescription for up to 3 days. Community pharmacist discharge and eligibility rapid access community addiction clinic</td>
<td></td>
<td></td>
<td>6-month follow-up 54% (36/65) follow-up appointment at 30s 57% were in treatment (receiving buprenorphine) at 6-month period ED visit Small sample size, no comparison group, narrow screening protocol</td>
</tr>
<tr>
<td>Cochrane et al.</td>
<td>2019</td>
<td>U.K. Single centre, urban ED</td>
<td>Retrospective, chart review</td>
<td>Patients identified by Buprenorphine 75% of those treated in ED</td>
<td>19</td>
<td>ED referral to opioid OAT treatment. 24-hour buprenorphine. Weekly withdrawal managed in in-patient treatment centre in hospital. ETO identified OUD and referred to “spoke” community pharmacy</td>
<td></td>
<td></td>
<td>19% (3/16) active in treatment at 30 days Single criteria generalizability. Market included an estimated 0.48% of opioid-dependent ED patients.</td>
</tr>
<tr>
<td>Galley et al.</td>
<td>2020</td>
<td>U.K. Single urban ED</td>
<td>Retrospective chart review</td>
<td>Adults referred by social work nurses and doctors.</td>
<td>1,30</td>
<td>Social work advice ED with referral to community clinic GP/ED provider within 3 days</td>
<td></td>
<td></td>
<td>57% (73/168) treatment follow-up 95% active in treatment at 30 days Small sample size, no comparison group, narrow screening protocol</td>
</tr>
<tr>
<td>Marshman et al.</td>
<td>2020</td>
<td>U.K. Multicentre ED (29 hospitals)</td>
<td>Retrospective chart review of electronic health record (EHR) data.</td>
<td>All patients screened with the AUDIT-C and evaluating screening questions (Electronic health records) at each hospital.</td>
<td>0/30</td>
<td>1. SORRY by Peer Recovery Coaches. 2. 1:1 buprenorphine-supervised initiation with referral for ongoing treatment to OAT network. 3. Community-based peer services targeting high risk OUD-provider (prescriptions) discharged from the hospital</td>
<td></td>
<td></td>
<td>98.5% (430) attended first outpatient buprenorphine treatment visit. No comparison group. Peer recovery coaches (PRC) were unable to see everyone who screened positive. The number of patients that declined to speak with a PRC was not recorded. Not all patients who received a brief intervention needed or wanted a referral to treatment. No long-term follow-up to determine outcomes.</td>
</tr>
</tbody>
</table>
Review article: Rapid review of the emergency department-initiated buprenorphine for opioid use disorder


http://hdl.handle.net/11343/276469