Bozinoff *et al. Harm Reduction Journal* 2022, **19**(1):113
https://doi.org/10.1186/s12954-022-00695-5

Harm Reduction Journal

REVIEW

Open Access

Patterns of use and adverse events reported among persons who regularly inject buprenorphine: a systematic review

Nikki Bozinoff[1,2,3*], Vitor Soares Tardelli[4,5], Dafna Sara Rubin-Kahana[5,6,7] and Bernard Le Foll[2,3,5,6,8,9,10]

Abstract

Background and Aims: Given the ongoing opioid crisis, novel interventions to treat severe opioid use disorder (OUD) are urgently needed. Injectable opioid agonist therapy (iOAT) with diacetylmorphine or hydromorphone is effective for the treatment of severe, treatment-refractory OUD, however barriers to implementation persist. Intravenous buprenorphine for the treatment of OUD (BUP iOAT) has several possible advantages over traditional iOAT, including a safety profile that might enable take-home dosing. We aimed to characterize injecting practices among real-world populations of persons who regularly inject buprenorphine, as well as associated adverse events reported in order to inform a possible future BUP iOAT intervention.

Methods: We conducted a systematic review. We searched MEDLINE, EMBASE, and PsycINFO from inception through July 2020 and used backwards citation screening to search for publications reporting on dose, frequency among persons who regularly inject the drug, or adverse events associated with intravenous use of buprenorphine. The review was limited to English language publications and there was no limitation on study type. Study quality and risk of bias was assessed using the Mixed Methods Appraisal Tool. Narrative synthesis was used in reporting the results.

Results: Eighty-eight studies were included in our review. Regular injection of buprenorphine was identified across diverse settings world-wide. Daily dose of oral buprenorphine injected was < 1–12 mg. Frequency of injection was 0–10 times daily. Adverse events could be characterized as known side effects of opioids/buprenorphine or injection-related complications. Most studies were deemed to be of low quality.

Conclusions: Extramedical, intravenous use of buprenorphine, continues to be documented. BUP iOAT may be feasible and results may inform the development of a study to test the efficacy and safety of such an intervention. Future work should also examine acceptability among people with severe OUD in North America. Our review was limited by the quality of included studies.

Keywords: Buprenorphine, Opioid use disorder, Opioids, iOAT, Overdose, Intravenous, Misuse, Abuse

Introduction

The opioid overdose crisis continues unabated in the USA and Canada. In 2020, over 6300 people died in Canada and over 90,000 died in the USA of opioid-related overdose [1, 2]. Reports across multiple jurisdictions have confirmed that the COVID-19 pandemic has exacerbated the crisis [3–5].

Injectable diacetylmorphine has been used in the UK and Europe for decades [6, 7], and is effective for the

*Correspondence: nikki.bozinoff@camh.ca

[1] Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, ON, Toronto, Canada
Full list of author information is available at the end of the article

treatment of severe OUD, not responsive to oral opioid agonist therapy (OAT) [6, 8–11]. Injectable hydromorphone has also emerged as a novel therapy for OUD following the publication of a randomized controlled trial that demonstrated non-inferiority compared with diacetylmorphine for severe, treatment-refractory OUD [9]. Benefits of injectable OAT (iOAT) in this population include improved retention in treatment compared with oral methadone alone, and reduction in the use of non-prescribed opioids [9, 10]. Multiple studies have also demonstrated iOAT to be cost-effective for severe OUD [12–15].

Despite the urgent need for treatment options in the setting of a toxic drug supply and mounting overdose deaths across the North America, the widespread implementation of iOAT has not taken place [16]. A recent environmental scan of iOAT programs across Canada revealed only 14 programs with total capacity for 420 clients. Barriers to the scale up of iOAT identified included, the high cost of infrastructure and personnel required to operate a program that directly supervises people who inject multiple times daily, and lack of government funding for high-dose liquid hydromorphone or diacetylmorphine in multiple provinces [16].

Given the ongoing opioid crisis, there remains a need for novel treatment options for persons not benefitting from oral OAT. Buprenorphine is a partial mu-opioid receptor agonist which is indicated as a first-line treatment for OUD owing to its favorable safety profile—it carries a much lower risk of respiratory depression and overdose when compared to full opioid agonists [17]. In Canada, buprenorphine is available for the treatment of OUD as a sublingual tablet co-formulated with naloxone (hereinafter BNX), and as a buccal film. As a result of its safety profile, it is feasible and non-inferior to methadone to provide BNX with a large number of take-home doses [18]. Two long acting formulations are also available: extended-release buprenorphine for subcutaneous injection by a medical provider at 4 week intervals, and buprenorphine subdermal implants lasting 6 months in duration [19]. Transdermal buprenorphine patches are also available however, are only approved in the treatment of pain.

Interestingly, several preclinical [20–22] and clinical studies [23–25] have shown that buprenorphine can produce reinforcing and rewarding effects under appropriate conditions. Specifically, where intravenous buprenorphine was administered to detoxified persons with opioid use disorder, participants reported euphoria, liking the drug's effects, and a desire to continue taking it [23–25]. In countries in which buprenorphine is widely available, cohorts of people who use intravenous buprenorphine as a drug of choice have been described [26–29]. In fact, it was concerns regarding early reports of extramedical use of buprenorphine [30, 31] that led to the creation of BNX [22, 32], the "abuse-deterrent" formulation most commonly used in the USA and Canada. Despite the widespread use of this "abuse-deterrent" formulation, regular intravenous use of BNX has been well-described [33–35].

Injectable buprenorphine as an alternative to injectable diacetylmorphine or hydromorphone has a number of possible benefits. Most significantly, BUP iOAT could be a safer form of iOAT owing to lower risk of respiratory depression and overdose [36], could potentially be disseminated in low barrier settings (e.g. take-home doses), may be associated with reduced stigma, and may facilitate transition to traditional oral OAT. In France, a recent cross-sectional survey among people with OUD not responsive to oral treatments indicated a strong willingness to consider treatment with BUP iOAT were it available (83% of respondents) [37].

Nevertheless, no clinical trials on the use of BUP iOAT as a novel iOAT exist, it is unclear what dose and frequency of injection would be required to retain people in treatment, and adverse events related to injection of this medication are important to understand. Given the urgency of the opioid crisis, and the need for novel therapeutic options for people with severe refractory OUD, we undertook a systematic review to characterize injecting practices among real-world persons who regularly inject buprenorphine, as well as associated adverse events reported.

Methods

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guideline in conducting and reporting this systematic review [38]. The protocol was registered on PROSPERO [39]. We searched the following electronic bibliographic databases from inception: MEDLINE, EMBASE, PsycINFO and also hand searched the reference lists of included studies from the initial search. We searched all available record fields using natural language search terms capturing three conceptual areas relevant to our search: (1) "Buprenorphine" (2) "injection" and (3) "misuse" (see Additional file 1: Appendix 1 for full search strategy). The initial search was conducted in July 2020.

Titles and abstracts of studies retrieved using the search strategy above were screened independently by two review authors (NB and DRK) to identify studies that potentially met the inclusion criteria. The full text of these potentially eligible studies was retrieved and independently assessed for eligibility by two team members (NB and VST). Any disagreements at screening were resolved through discussion with a third member of the study team. Studies were included if they reported on

the dose or frequency of intravenous buprenorphine use among real-world populations of persons with opioid use disorder who regularly inject buprenorphine, or if they reported on adverse events associated with intravenous use of buprenorphine. There was no restriction on study type; however lab-based studies and studies related to the use of buprenorphine in the management of pain were excluded. Studies related to extended-release formulations of buprenorphine where subcutaneous administration is appropriate were excluded. Owing to resource limitations, only English language publications were included. Data was managed in Covidence systematic review software (2021), Veritas Health Innovation, Melbourne, Australia.

A standardized data abstraction form was developed and used to extract data from the included studies for evidence synthesis. Extracted information included: bibliographical information, study setting, study population, year of data collection, details about the outcomes (including dose, frequency, formulation of buprenorphine used and adverse event(s) reported). Descriptions of adverse events were taken verbatim from the text and no attempt to verify causality was made. Two reviewers extracted data independently and discrepancies were resolved through discussion (with a third author where necessary). For studies reporting on either dose or frequency of use, where one element was missing, we attempted to request this data from the authors via email. Where information remained missing, it was left blank in the table.

Study quality and risk of bias was assessed using the Mixed Methods Appraisal Tool (MMAT), which provides a set of criteria for appraising methodological quality of quantitative, qualitative and mixed methods studies [40, 41]. Quality scores were calculated independently by two reviewers using the MMAT tool. For mixed methods studies, we used the lowest score from amongst the study components. Any conflicts were resolved by a third reviewer. Scores of ≤ 3 were considered to be of low quality and at high risk of bias [42].

Because we anticipated significant heterogeneity in the way results were reported, data across studies were summarized using narrative synthesis. We adhered to the guidance on narrative synthesis in systematic reviews developed by Popay et al., (2006), which provides guidance on maintaining transparency, trustworthiness and avoiding bias in the composite of findings [43].

Results

Figure 1 describes the search and selection process using the PRISMA flow diagram. Five thousand, three-hundred and twenty-four studies were found in the search and imported for screening. After duplicates were removed, 4308 studies were included in first stage screening and titles and abstracts were reviewed. Two-hundred and thirteen studies passed first-stage screening and full texts were assessed for inclusion. After second stage screening, 77 studies were included and 11 additional studies were included after reviewing the reference lists of included studies for a total of 88 included studies. The included studies were published between 1984 and 2020 and were from multiple cities across Australia, Bangladesh, China, Finland, France, Georgia, India, Iran, Malaysia, Nepal, New Zealand, Scotland, Singapore, Spain, Turkey, and the USA (Table 1, 2).

After reviewing the included studies, we chose to group them as studies primarily reporting on dose and frequency of use among regular buprenorphine injectors in Table 1 and those reporting on adverse events in Table 2. Where studies reported on both of those outcomes, they are included in both tables.

Studies included in Table 1, that is, those reporting on persons who regularly inject buprenorphine were of diverse design, but largely quantitative descriptive studies (surveys or incidence/prevalence studies without a comparison group) and were published between 1984 and 2018. Both oral buprenorphine-alone and BNX formulations were reportedly injected, and in countries in which the liquid formulation is available (Iran, India for example), injection of ampoules was also described. There was heterogeneity related to the frequency of injection among regular buprenorphine users. Our results revealed a report of injecting a maximum of 10 times daily however more common were reports of injecting 2–4 times daily. Among studies reporting injection of buprenorphine ampoules, doses ranged from < 1 mg/day to 24 mg/day. Among those studies reporting on the injection of oral buprenorphine or BNX, doses reported were between < 1 mg to 12 mg daily. Sixty-seven percent of (28/42) studies included in Table 1 had MMAT scores ≤ 3 indicating low quality and high risk of bias. Many were limited by selection bias and measurement bias.

Adverse events associated with buprenorphine injection are reported in Table 2. Adverse events described were generally either known side effects associated with opioids/buprenorphine (overdose, precipitated withdrawal), injection-related complications (endocarditis, cellulitis etc.) or theorized to be as a result of excipients in the buprenorphine/BNX tablets [44]. Adverse events were associated with injection of oral formulations of buprenorphine/BNX although one case report described adverse events associated with injection of buprenorphine from a transdermal patch. The quality of included studies is presented in Table 2. Most studies (53/67, 79%) were of low quality based on MMAT scores ≤ 3 and were judged to be at high risk bias.

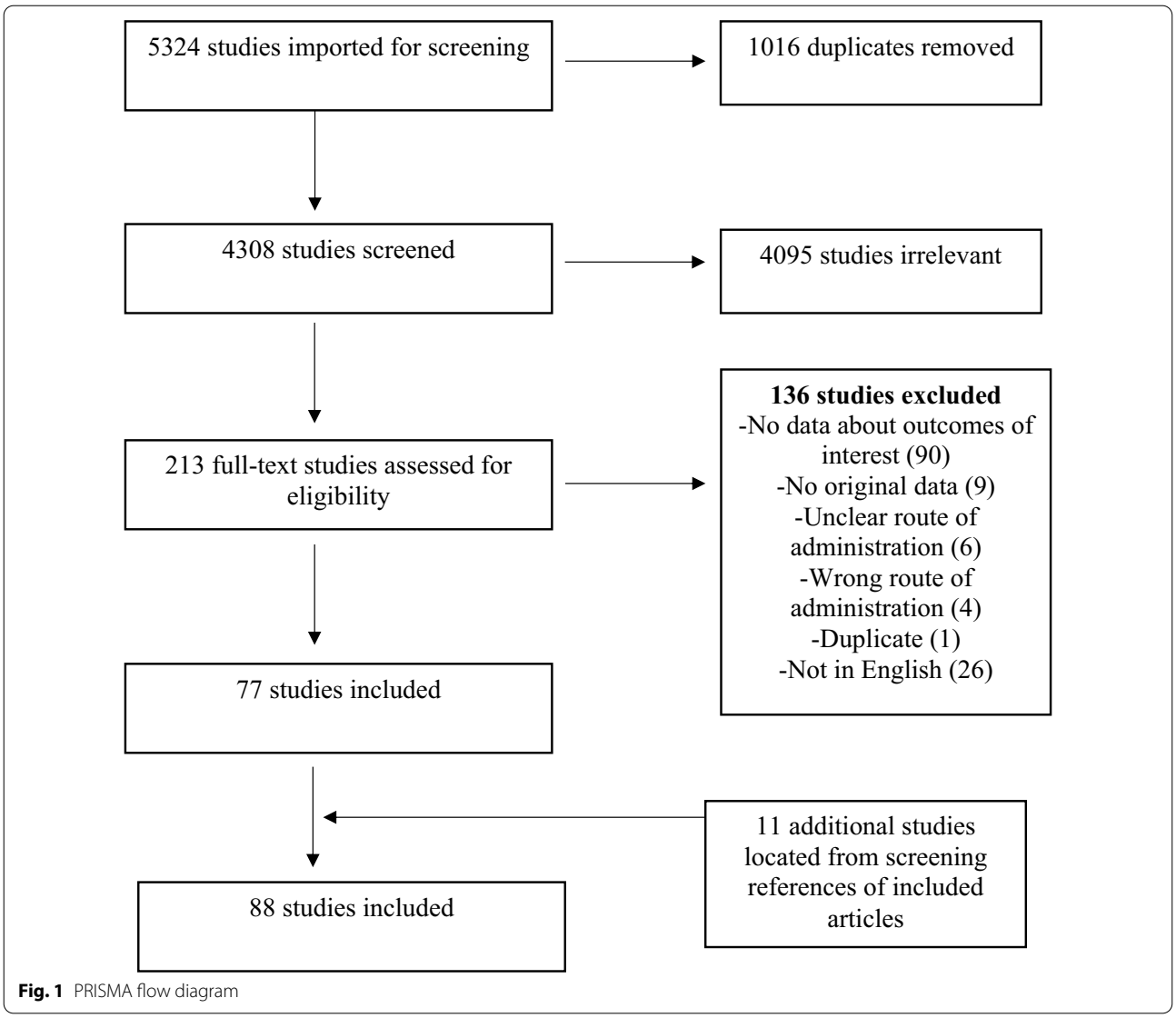

Fig. 1 PRISMA flow diagram

Discussion

Although existing literature has synthesized and described the extent and motivations for extramedical buprenorphine use [33, 45, 46], our review is the first to systematically document patterns of injection and adverse events among people who inject buprenorphine regularly. The studies summarized here could be characterized as coming from countries where either diverted oral buprenorphine is easily accessible (i.e. France [47, 48], Singapore [49]), or, from countries in which more desirable opioids (ie. heroin) are difficult, expensive, or dangerous to obtain (ie. India [50], Bangladesh [51], Finland [52, 53]).

Whereas most people who use buprenorphine extramedically do so irregularly and to manage or mitigate opioid cravings or withdrawal [33, 45, 54–56], our findings demonstrate that there is a smaller subset of persons who inject extramedical buprenorphine for its reinforcing properties. The use of buprenorphine in this way across multiple jurisdictions suggests that BUP iOAT may be an acceptable treatment option for persons with severe, refractory OUD that is non responsive to traditional OAT, or who are not interested in OAT. Possible acceptability of BUP iOAT is further supported by a recent cross sectional study from France among 353 persons with treatment-refractory OUD, 83% of whom indicated they would be willing to consider BUP iOAT were it available [57]. Factors positively associated with willingness to receive BUP iOAT included a history of > 5 injection-related complications, history of regular buprenorphine injection (compared with heroin and prescription opioids), and no

Table 1 Studies discussing dose and frequency of intravenous buprenorphine use

Study citation	Location	Study population	Study design	Year data was collected	Buprenorphine formulation injected	Dose/frequency of use reported	Quality Assessment [1–5]
Aalto [52]	Kotka, Finland	27 people who use IV buprenorphine	Quantitative descriptive	2004–2005		Dose: 8.1 mg/day	2
Ahmadi[a,%] [67]	Shiraz, Iran	204 males who use IV buprenorphine	Clinical trial	2002	Buprenorphine ampoules	Dose: mean = 3.86 amps/day (SD = 2.61), range 1–19 amps/day. *1 amp contains 0.3 mg of buprenorphine in 1 ml, therefore a mean daily dose of 1.16 mg/day (SD = 0.78), range 0.3–5.7 mg/day	3
Ahmadi[b,%] [26]	Shiraz, Iran	204 males who use IV buprenorphine	Clinical trial	2002	Buprenorphine ampoules	Dose: mean = 3.7 amps/day (SD = 2.6), range 1–19 amps/day. *1 amp contains 0.3 mg of buprenorphine in 1 ml, therefore a mean daily dose of 1.1 mg/day (SD = 0.78), range 0.3–5.7 mg/day	3
Ahmadi[c] [68]	Shiraz, Iran	108 males who use IV buprenorphine	Clinical trial	2002	Buprenorphine ampoules	Dose: mean = 4.6 amps/day (SD = 3.1), range 1–17 amps/day. *1 amp contains 0.3 mg of buprenorphine in 1 ml, therefore a mean daily dose of 1.38 mg/day (SD = 0.93), range 0.3–5.1 mg/day	3
Ahmed [51]	Dhaka, Bangladesh	30 males with extramedical use of buprenorphine	Quantitative descriptive	1995	Buprenorphine ampoules	Dose: Range < 1–10 amps/day, 60% used 2–5 amps per day. *1 amp contains 0.6 mg of buprenorphine in 2 ml therefore range of < 0.6–6 mg/day, 60% used 1.2–3 mg/day; Frequency range 1–10 times/day, 86.7% used 2–5 times daily	2
Aich [69]	Bhairahawa, Nepal	76 people with OUD	Quantitative descriptive	2003–2004	Buprenorphine ampoules	Dose: 0.6 mg/injection; Frequency: 2–4 times/day	4
Aitken [27]	Melbourne, Australia	316 PWID	Quantitative descriptive	2005–2006	SL buprenorphine (spitbacks)	Dose: 2-12 mg/day; Frequency: 10.4–10.5 times /week	3

Table 1 (continued)

Study citation	Location	Study population	Study design	Year data was collected	Buprenorphine formulation injected	Dose/frequency of use reported	Quality Assessment [1–5]
Alho [70]	Helsinki, Finland	176 people needle exchange clients	Quantitative descriptive	2005	SL buprenorphine and BNX	Dose: 7 mg/day; Frequency: 81.8% daily users (41.6% 3–4 injections/day)	3
Ambekar [28]	Multiple sites in India	902 male PWIDs at harm reduction centres	Quantitative descriptive		Buprenorphine ampoules	Frequency: 48.9% daily injectors; 66.2% more than one injection/day on using days	3
Basu [71]	Chandigarh, India	3 males (30, 26, 25 years) who use IV buprenorphine	Case series		Buprenorphine ampoules	1st case: 0.3 mg 2–3 times per day, escalating to 2–4 times that dose; 2nd case: 1.8 mg daily; case 3: 2.4 mg daily	1
Basu [72]	Chandigarh, India	94 males with extramedical use of buprenorphine	Quantitative descriptive	1987–1993	Buprenorphine ampoules	Dose: 1.8 mg/day	2
Bruce [73]	Kuala Lumpur, Malaysia	19 males who use IV buprenorphine	Case series	2006	SL buprenorphine	Dose: 1-4 mg/injection; Frequency: 2–4 times/day	2
Bruce [35]	Kuala Lumpur, Malaysia	41 people who use IV buprenorphine	Quantitative descriptive	2007	SL buprenorphine and BNX	Dose: 1.9 mg/day before BNX, 2.5 mg/day with BNX; Frequency: 3.9–4.3 injections/day	3
Chowdhury [74]	Guwahati, India	38 year old male	Case study		SL buprenorphine	Dose: 0.8–1.6 mg/day	1
Feeney [75]	Brisbane, Australia	24 year old female	Case study		SL buprenorphine	Dose: 8 mg/injection	1
Horyniak [76]	Melbourne, Australia	23 people who use IV buprenorphine	Mixed methods	2006	SL buprenorphine and BNX (mixed with saliva or lemon juice)	Frequency: up to four times/day among daily injectors	4
Kulaksızoglu [77]	Antalya, Turkey	19 year old male	Case study	2018	SL BNX (dissolved in hot water)	Dose: 10 mg/day	1
Kumar [50]	Madras, India	100 PWIDs	Quantitative descriptive	1998	SL buprenorphine	Frequency: 92.8% 1–3 times/day; 7.1% more than 4 times/day	4
Lavelle [78]	Glasgow, Scotland	78 clients from residential drug treatment centres	Quantitative descriptive	1989–1990	SL buprenorphine	Dose: 1.5 mg/day; Frequency: 243 using days/year; 58% 5–7 days/week	3
Lee [79]		mid-40 s female	Case study		SL buprenorphine (dissolved in hot water)	Dose: 1–3 tablets/injection	1
Liu [80]	Multiple sites in China	1235 people with OUD and a history of buprenorphine use for at least three days	Quantitative descriptive	2000–2001	SL buprenorphine	Dose: 0.5–0.8 mg/injection; Frequency: 2.0–2.8 times/day	4

Table 1 (continued)

Study citation	Location	Study population	Study design	Year data was collected	Buprenorphine formulation injected	Dose/frequency of use reported	Quality Assessment [1–5]
Nizamie (1990)	India	32 year old male	Case study	1988	Buprenorphine ampoules	Dose: 2–4 amps/day	1
Ng [81]	Singapore, Singapore	120 people who use IV buprenorphine	Quantitative descriptive	2005–2006	SL buprenorphine	Dose: 7.4–9.0 mg/day	3
Obadia [82]	Marseille, France	343 PWIDs	Quantitative descriptive	1997	SL buprenorphine	Frequency: 60.2–76.8% inject once a day or more	5
Otiashvili [83]	Multiples sites in Georgia	381 PWIDs	Quantitative descriptive	2007	SL buprenorphine	Dose: 1-8 mg/injection (44% injected 1 mg, 45.8% 2 mg, 9% 4 mg, 0.56% 8 mg)	3
Peyrière [60]		33 year old male and 50 year old male	Case series	2007	SL buprenorphine	Dose: 4 mg/injection; frequency: 3–5 times/day	2
Piralishvili [84]	Tbilisi, Georgia	80 people who use IV buprenorphine	Clinical trial	2011	SL BNX	Dose: 1.75 mg/day; Frequency: 15.2 days in the past 30 days	4
Quigley [31]	West Perth, Australia	24 year old male who uses IV buprenorphine	Case report	1983	Buprenorphine ampoules	Dose: 4.5 mg/day	1
Robinson [34]	Wellington, New Zealand	2 consecutive surveys (54 and 44 people respectively) presenting for OUD treatment	Quantitative descriptive	1990–1992	SL buprenorphine and BNX	Dose: 0.6 mg of buprenorphine/injection on first survey, 0.4/0.34 mg of BNX/injection on second survey	3
Roux [47]	Multiple sites in France	111 clients receiving OAT with buprenorphine	Quantitative descriptive	2004–2005	SL buprenorphine	Frequency: 5% reported at least daily injection	5
Roux [57]	Multiple sites in France	371 PWID with OUD	Quantitative descriptive	2015	SL buprenorphine	Dose: median of 12 mg/day; Frequency: median of 3 injections/day (IQR: 2–4)	4
San [85]	Barcelona, Spain	188 (1988) and 197 (1990) heroin-dependent individuals	Quantitative descriptive	1988 and 1990	SL buprenorphine	Dose: 0.6–0.8 mg/day (1990) and 1.4–4.1 mg/day (1988)	5
Singh [86]	India	24 year old male	Case study		Buprenorphine ampoules	Dose: 24 mg/day, later 2.4–3.6 mg/day; Frequency: 5–6 injections/day	1
Singh [87]	Chandigarh, India	18 people with extramedical buprenorphine use	Case series	1987–1990	Buprenorphine ampoules	Dose: mean = 3 mg/day, range = 1-7 mg/day Frequency: 3–4 injections/day	3

Table 1 (continued)

Study citation	Location	Study population	Study design	Year data was collected	Buprenorphine formulation injected	Dose/frequency of use reported	Quality Assessment [1–5]
Torrens [88]	Barcelona, Spain	22 buprenorphine and 45 heroin-dependent individuals	Quantitative descriptive	1988–1989	SL buprenorphine	Dose: 1.9 mg/day; Frequency: 3–4 times/day	4
Valenciano [89]	Multiple sites in France	1004 clients at syringe-exchange programs	Quantitative descriptive	1998	SL buprenorphine	Frequency: 1 injection/day	4
Vicknasingam [90]	Multiple sites in Malaysia	276 people who use IV buprenorphine; for the second wave 77/276 were re-interviewed 77/276 and additional 171 new participants included	Mixed methods	2006–2007	SL buprenorphine for first survey, BNX in second survey	Dose: first wave—96% used up to 2 mg/injection, second wave 81% used up to 2 mg/using day; Frequency: first wave—63% reported at least daily use, second wave—34% reported at least daily use	3
White [91]	Multiple sites in Australia	16 people who inject BNX films	Qualitative	2012–2013	Buccal BNX (films; spitbacks)	Frequency: 37.5% used daily, of which 83.4% (31.2% of the total) used > 5 times/day	5
Winslow [92]	Singapore, Singapore	120 people with extramedical use of buprenorphine, enrolled in treatment	Quantitativedescriptive	2005–2006	SL buprenorphine	Dose: 7.7 (SD 4.8) mg/day	3
Winslow [93]	Singapore, Singapore	106 PWIDs presenting to an addictions management programme	Quantitative descriptive	2005–2006	SL buprenorphine	Frequency: "many" injected 3–4 times/day	5
Winstock [94]	Multiple sites in Australia	442 clients receiving methadone and 66 receiving supervised buprenorphine at community pharmacies	Quantitative descriptive	2005	SL buprenorphine	Dose: median amount injected on last injection was 6 mg (mean = 5.8; SD = 3.1; range = 2–10 mg)	4
Yeo [95]	Singapore, Singapore	8 clients aged 26–46	Case series	2005	SL buprenorphine (tablets dissolved in hot water)	Dose: 1-2 mg/injection (one of the cases)	2

BNX buprenorphine/naloxone, *IV* intravenous, *IQR* Interquartile range, *OAT* opioid agonist therapy, *OUD* opioid use disorder, *PWID* people who inject drugs, *SD* standard deviation, *SL* sublingual

% = these two studies report on the same study population with outcome measures at different time points. Dose and frequency of IV buprenorphine use was measured at baseline in both cases

Table 2 Studies discussing adverse events associated with intravenous buprenorphine use

Study citation	Location	Study population	Study design	Year data was collected	Buprenorphine formulation injected	Adverse event(s)	Quality Assessment [1–5]
Aboltins [96]	Melbourne, Australia	28 year old female	Case study		SL buprenorphine (spitbacks)	Fungal endophtalmitis	1
Aich [69]	Bhairahawa, Nepal	76 people with OUD	Quantitative descriptive	2003–2004	Buprenorphine ampoules	Thrombophlebitis, HIV, cellulitis, abscess	4
Alvarez [97]	Barcelona, Spain	32 year old male	Case study		SL buprenorphine	S. marcescens endopthalmitis resulting in blindness	1
Ambekar [28]	Multiple sites in India	902 male PWIDs at harm reduction centres	Quantitative descriptive		Buprenorphine ampoules	Abscess, blocked veins, overdose	3
Berson [61]	Clichy, France	33 year old male, 27 year old male, 28 year old male, 31 year old male	Case series	1996–1998	SL buprenorphine	Acute hepatitis in the context of chronic HCV	2
Boggs [98]	USA	29 year old female and 30 year old female	Case series		SL buprenorphine/BNX	Anaphylaxis and death	1
Bouquie [99]	Nantes, France	33 year old male	Case study	2014	SL buprenorphine	Livedo-like dermatitis with necrotic lesion	1
Boyd [100]	Helsinki, Finland	Records of 308 people with opioid overdose	Case series	1996–2002	SLbuprenorphine	Overdose	3
Bruce [35]	Kuala Lumpur, Malaysia	41 people who use IV buprenorphine	Quantitative descriptive	2007	SL buprenorphine/BNX	Opioid withdrawal	3
Cassoux [101]	France	22 year old male, 25 year old male, 27 year old male, 30 year old male	Case series		SL buprenorphine (spitbacks, dissolved tabs in lemon juice)	Ocular candidiasis, septicemia, skin abscess, cervical lymphadenopathy, scalp nodules, wrist arthritis, folliculitis, chorioretinal lesion	2
Chai [102]	Singapore, Singapore	92 hospitalized patients	Case series	2003–2005	SL buprenorphine	Bacteremia, endocarditis, septic pulmonary emboli	2
Chew [103]	Singapore, Singapore	30 F, 35 M, 40 M, 60 M	Case series	2006	SL buprenorphine	Deep venous thrombosis, hand ischemia (thrombosis of brachial artery); epidural, limbs, and popliteal fossa abscesses	2
Chong [104]	Singapore, Singapore	12 clients aged 22–49	Case series	2005–2006	SL buprenorphine	Endocarditis, pneumonia, abscesses, septic shock, disseminated intravascular coagulation, acute heart and renal failure, among others	2

Table 2 (continued)

Study citation	Location	Study population	Study design	Year data was collected	Buprenorphine formulation injected	Adverse event(s)	Quality Assessment [1–5]
Chowdhury [74]	Guwahati, India	38 year old male	Case study		SL buprenorphine	Koro (acute anxiety due to the perception of intraabdominal penile retraction/shrinkage and fear of impending death)	1
Chua [105]	Singapore, Singapore	Mid-20 s male and mid-30 s female	Case series		SL buprenorphine	Cellulitis	1
DelGiudice [106]	Fréjus, France	13 clients aged 25–43	Case series	1996–2001	SL buprenorphine	Injection-site abscesses, cellulitis in multiple sites, thrombophlebitis in multiple sites, cutaneous necrosis	2
Eiden a [107]	Montpellier, France	31 clients (median age: 39)	Quantitative descriptive	2012–2013		Skin and soft-tissue infection, sepsis, endocarditis, spondylitis, meningitis, pulmonary abscess, candidemia	2
Eiden b [108]	Montpellier, France	192 clients (median age: 34)	Quantitative descriptive	2002–2012	SL buprenorphine	Cutaneous abscesses, osteoarticular infections, pulmonary infections, venous infections, endocarditis, hepatitis, sepsis, puffy hand syndrome	3
Eiden [109]	Languedoc-Roussillon region, France	198 people with extramedical use of buprenorphine	Quantitative descriptive	2002–2012	SL buprenorphine	Cutaneous abscess, venous infection, puffy hand syndrome, osteoarticular infections, endocarditis, pulmonary infections, sepsis, hepatitis	5
Espitia [110]	Nantes, France	33 year old male	Case study			Nicolau Syndrome (necrotic-centre lesion with nerve ischemia and motor deficiency)	1
Feeney [75]	Brisbane, Australia	24 year old female	Case study		SL buprenorphine	Femoral abscess with groin tissue necrosis	1
Gautschi [111]	Perth,Australia	30 year old male	Case study			Groin tissue abscess and myositis	1

Table 2 (continued)

Study citation	Location	Study population	Study design	Year data was collected	Buprenorphine formulation injected	Adverse event(s)	Quality Assessment [1–5]
Hakkinen [112]	Finland	225 postmortem toxicology cases with a urine sample positive for buprenorphine, norbuprenorphine or naloxone and background information supporting drug use	Quantitative descriptive	2010–2011		Fatal overdose	3
Ho [113]	Singapore, Singapore	131 people who use IV buprenorphine	Quantitative descriptive	2004–2006	SL buprenorphine	Cellulitis, abscess, necrotizing fasciitis, false aneurysms, thrombophlebitis, hematoma, lymphadenopathy, infection of specific site	4
Horyniak [76]	Melbourne, Australia	23 people who use IV buprenorphine	Mixed methods	2006	SL buprenorphine/BNX (mixed with saliva or lemon juice)	Nausea, vomiting, abscesses, vein damage	4
Jenkinson [62]	Melbourne, Australia	156 PWID	Quantitative descriptive	2002	SL buprenorphine	Overdose, abscesses/infections, scarring/bruising, thrombosis	4
Joethy [114]	Singapore, Singapore	29 year old male	Case study		SL buprenorphine	Mechanical nerve injury	1
Kintz [115]	Multiple sites in France	38 and 79 fatalities involving buprenorphine	Quantitative descriptive	1996–2000	SL buprenorphine	Fatal overdose	3
Kintz [116]	Strasbourg, France	13 fatalities involving buprenorphine	Quantitative descriptive	2000–2001	SL buprenorphine	Fatal overdose	2
Kluger [117]	Montpellier, France	31 year old male	Case study		SL buprenorphine	Penile and scrotal skin necrosis	1
Kriikku [63]	Finland	775 toxicology cases positive for buprenorphine upon death	Quantitative descriptive	2010–2014	SL buprenorphine/BNX	Overdose	5
Kulaksızoglu [77]	Antalya, Turkey	19 year old male	Case study	2018	SL BNX (dissolved in hot water)	Depressive symptoms	1
Kumar [50]	Madras, India	100 PWIDs	Quantitative descriptive	1998	SL buprenorphine	HCV, HIV, Hepatitis B	4
Lee [79]		mid-40 s female	Case study		SL buprenorphine (dissolved in hot water)	Blurred vision, bacterial endocarditis, mild cognitive impairment	1
Lee [118]	Singapore, Singapore	25 year old male	Case study		SL buprenorphine	Endocarditis, protein-losing enteropathy, tricuspid regurgitation, and heart failure	1

Table 2 (continued)

Study citation	Location	Study population	Study design	Year data was collected	Buprenorphine formulation injected	Adverse event(s)	Quality Assessment [1–5]
Lim [119]	Singapore, Singapore	7 males aged 28–53	Case series		SLbuprenorphine	Loss of consciousness, left/right hemispheric syndrome (including hemianopia, gaze deviation, hemineglect, and aphasia), head injury, thrombophlebitis, arm cellulitis	2
Liu [80]	Multiple sites in China	1235 people with OUD and a history of buprenorphine use for at least three days	Quantitative descriptive	2000–2001	SL buprenorphine	Opioid withdrawal	4
Lo [44]	Singapore, Singapore	53 people with extramedical use of buprenorphine (mean age 34.5)	Case series	2005	SL buprenorphine	Skin infections; limb abscesses, ischaemia, and gangrene; necrotising fasciitis; septic arthritis; pseudoaneurysm of the femoral artery; infective endocarditis; withdrawal symptoms, hepatitis C; syncope/seizure; atypical chest pain; pulmonary tuberculosis	2
Loo [120]	Singapore, Singapore	4 males aged 22–55	Case series	2005	SL buprenorphine	Large thenar abscess, ischemic hand, subclavian vein thrombosis, sepsis, wet gangrene of the digits, paralysis of thenar muscles, carpal tunnel, amputation	2
Marka [121]	New Hampshire, USA	29 year old female and 37 year old male	Case series		SL BNX	Crospovidone reactions (skin foreign body reaction)	1
Nielsen [122]	Melbourne, Australia	250 people who had experience with OAT	Quantitative descriptive	2004–2005	SL buprenorphine	Overdose	3
Ojha [123]	Kathmandu, Nepal	300 PWIDs	Quantitative descriptive		SL buprenorphine	HIV infection	4
Partanen [124]	Helsinki, Finland	25 PWIDs ages 20–39	Case series	2000–2005	SL buprenorphine	Acute limb ischemia, limb infection (osteomyelitis), and amputation	2
Peyrière [60]	Montpellier, France	33 year old male and 50 year old male	Case series	2007	SL buprenorphine	Exacerbation of chronic HCV	2
Power [36]	Sydney, Australia	15,832 individuals who use IV buprenorphine	Quantitative descriptive	2001–2016	SL buprenorphine/BNX	Overdose	5
Prosser [125]	Sydney, Australia	32 year old male	Case study		Buprenorphine transdermal patch	Tubulo-interstitial nephritis	1

Table 2 (continued)

Study citation	Location	Study population	Study design	Year data was collected	Buprenorphine formulation injected	Adverse event(s)	Quality Assessment [1–5]
Puolakka [126]	Finland	6 men aged 16–21	Case series		SL buprenorphine	Cervical myelopathy and neck muscle rhabdomyolysis	1
Reynaud [127]	Alsace and Auvergne, France	6 cases of fatalities involving consumption of buprenorphine-benzodiazepine combinations	Case series	1996–1997	SL buprenorphine	Fatal overdose	1
Robinson [128]	Wellington, New Zealand	2 cohorts (54 and 44 people respectively) presenting for OUD treatment	Quantitative descriptive	1990–1992	SL buprenorphine/ BNX	Opioid withdrawal	3
Roux [47]	Multiple sites in France	111 clientsreceiving OAT with buprenorphine	Quantitative descriptive	2004–2005	SL buprenorphine	Overdose	5
Roux [57]	Multiple sites in France	371 PWID with OUD	Quantitative descriptive	2015	SL buprenorphine	Hand swelling, vein obstruction, rolling veins, cotton fever, and cutaneous abscesses	4
Seet[%] [59]	Singapore, Singapore	18 year old male	Case study		SL buprenorphine (dissolved in water)	Diffuse cystic leukoencephalopathy	1
Seet[%] [129]	Singapore, Singapore	27 year old male and 31 year old male	Case series		SL buprenorphine (dissolved in hot water)	Sciatic neuropathy, severe myositis, and rhabdomyositis	1
Seet[%] [130]	Singapore, Singapore	51 people who use IV buprenorphine	Case series	2002–2005	SL buprenorphine	Cellulitis, endocarditis, myositis, abscesses; withdrawal, seizures, limb ischemia, respiratory failure, rhabdomyolysis, thrombosis, renal failure, leukoencephalopathy	3
Sharma [131]	Singapore, Singapore	32 year old male	Case study		SL buprenorphine (dissolved in hot water)	Myofasciitis (thighs) and polyneuritis	1
Singh [86]	India	24 year old male	Case study		Buprenorphine ampoules	Generalized tonic–clonic seizures; withdrawal; premature ejaculation	1
Singh [87]	Chandigarh, India	18 people with extramedical buprenorphine use	Case series	1987–1990	Buprenorphine ampoules	Concurrent use of benzodiazepines; pain, insomnia, nasal symptoms, irritability, restlessness, muscle twitching, diarrhea, palpitations (withdrawal); gastric antral erosions	3

Table 2 (continued)

Study citation	Location	Study population	Study design	Year data was collected	Buprenorphine formulation injected	Adverse event(s)	Quality Assessment [1–5]
Tan [132]	Singapore, Singapore	15 patients aged 25–58 who underwent surgery for pseudoaneurysms due to chronic injection drug use	Case series	2005–2008	SL buprenorphine	Infected pseudoaneurysm; gangrene; wound infection; rebleeding	3
Teo [133]	Singapore, Singapore	49 year old male	Case study		SL buprenorphine	Tetanus	1
Vicknasingam [90]	Multiple sites in Malaysia	276 people who use IV buprenorphine; for the second wave 77/276 were re-interviewed 77/276 and additional 171 new participants included	Mixed methods	2006–2007	SL buprenorphine for first survey, BNX in second survey	Weight loss, muscle fatigue, difficulty breathing, chest discomfort	3
Victorri-Vigneau [134]	Nantes, France	16 people who use IV buprenorphine	Case series		SL buprenorphine	Pain, burning, necrosis on injection site; thrombosis/livedo	2
White [91]	Multiple sites in Australia	16 people who inject BNX films	Qualitative	2012–2013	Buccal BNX (films; spitbacks)	Injection site problems; puffy hands; perceived heart disturbance; opioid withdrawal	5
Wilson [135]	Kentucky, USA	10 clients evaluated for ischemia of the hand or digits after injection of BNX	Case series	2011–2015	SL BNX	Hand ischemia; dry gangrene	2
Winslow [92]	Singapore, Singapore	120 people with extramedical use of buprenorphine, enrolled in treatment	Quantitative descriptive	2005–2006	SL buprenorphine	Skin and soft tissue infections, gangrene, thrombophlebitis, acute hepatitis, septicaemia with endocarditis, multiple lung abscesses, opioid withdrawal, embedded foreign body removal	3
Winslow [93]	Singapore, Singapore	106 PWIDs presenting to an addictions management programme	Quantitative descriptive	2005–2006	SL buprenorphine	HCV	5
Yang [136]	Singapore, Singapore	48 year old M and 30 year old female	Case series		SL buprenorphine	Septic sacroiliitis (progressive back pain, limitation of movement, fever)	1
Yeo [95]	Singapore, Singapore	8 clients aged 26–46	Case series	2005	SL buprenorphine (tablets; dissolved in hot water)	Arterial pseudoaneurysm, infective venous thrombus, venous thrombus, end arterial spasms, and sympathetic dystrophy; amputation of lower limb	2

BNX buprenorphine/naloxone, *HCV* Hepatitis C virus, *HIV* Human Immunodeficiency Virus, *IV* intravenous, *OAT* opioid agonist therapy, *OUD* opioid use disorder, *PWID* people who inject drugs, *SL* sublingual

% = Seet (2007) appears to contain data that is also presented in Seet (2005) and Seet (2006)

lifetime overdose [57]. Among those willing to receive BUP iOAT, willingness to receive supervised dosing was positively associated with injecting heroin, older age, and not having stable housing [57].

Our review documented daily doses of injected SL buprenorphine between < 1 mg-12 mg daily, which is less than the oral buprenorphine doses that best retain persons with OUD in treatment (> 16 mg [58]), likely reflecting higher effective doses when injected. These doses suggest that a BUP iOAT program may be feasible with the existing formulations of buprenorphine and would not require crushing and injecting large volumes of tablets or liquid. It should be noted however that most of these studies occurred in the pre-fentanyl era and therefore required doses for BUP iOAT would likely be higher among fentanyl-dependent persons.

The frequency of use reported among regular buprenorphine injectors (many reporting 2–4 times daily) is similar to the range in frequency of heroin typically injected. Taken together, the dosing and frequency of use of injected buprenorphine revealed in this review provide a starting place for possible dosing were a pilot BUP iOAT clinical trial established.

The adverse events documented as associated with injection of buprenorphine were largely known side effects associated with opioids/buprenorphine (overdose, precipitated withdrawal), injection-related complications (endocarditis, cellulitis etc.), or theorized to be as a result of excipients in the buprenorphine/ BNX tablets [44, 59]. Reports of acute hepatitis in the context of chronic hepatitis C are worth noting [60, 61]. Although overdose was reported, it was most-commonly reported in the context of concurrent sedative use [62, 63]. Consistent with buprenorphine's known ceiling effect with respect to respiratory depression, observational studies suggest that extramedical use of buprenorphine is actually protective for overdose—data considering incidence of overdose following buprenorphine injection at a supervised consumption facility in Australia has demonstrated a significant protective effect associated with injecting buprenorphine compared with injection of heroin or other opioids [36]. Similarly, a recent study in Ohio, US found that higher frequency of extramedical buprenorphine use among people with OUD was associated with a lower risk of drug overdose [64]. Lower likelihood of overdose is a possible major benefit of a BUP iOAT intervention both for participants as well as for the broader community given concerns [65] that diverted doses could end up in the hands of children or other persons without opioid tolerance. However, properly powered trials would be needed to ensure the safety of such an intervention compared with usual treatment. With respect to the infectious complications reported, these are known injection-related complications and could be minimized with harm reduction education and provision of harm reduction supplies. Interestingly, precipitated withdrawal was not a commonly reported adverse-event. This may reflect publication bias, or alternately may reflect proficiency in timing other opioid use among regular buprenorphine injectors. As with SL buprenorphine induction, novel induction methods such as micro-dosing and macro-dosing may be useful for a potential BUP iOAT intervention in order to avoid precipitated withdrawal and retain persons who use fentanyl in treatment [66].

There are several limitations to this systematic review. Firstly, we included only English language publications, and did not search the grey literature, therefore, our review may have missed some relevant publications. Secondly, owing to the heterogeneity of the results, no attempt at meta-analysis was made. The studies included were generally of low quality. Individual studies were subject to selection bias, measurement bias and overall the dataset is subject to outcome reporting bias and language bias. Finally, the majority of the publications included are from outside of North America, and many were published decades ago. It is therefore unclear whether the findings would be applicable to persons with opioid use disorder in North America, and in the current context of a fentanyl-dominated drug supply.

Given the ongoing opioid crisis and increasingly toxic drug supply, there remains an urgent need for novel therapies for the treatment of OUD among persons not responsive to traditional therapies and/or among those not interested in them. Our results paint a clearer picture of the patterns of use of buprenorphine among real-world populations who regularly inject the drug, and could inform the development of a BUP iOAT intervention. Our results suggest that a BUP iOAT intervention could be safe and feasible. Importantly, although people who inject drugs in France demonstrated strong willingness to consider this type of therapy, it remains unclear if it would be acceptable to persons with OUD in the US or Canada. Take-home doses, and availability of liquid formulations may increase the acceptability of BUP iOAT among people with OUD in North America. Future research should work with persons with lived experience to explore acceptability, and consider testing the feasibility, efficacy and safety of BUP iOAT compared with traditional OAT and iOAT.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12954-022-00695-5.

Additional file 1. **Appendix 1**. Search strategy.

Acknowledgements
The authors gratefully acknowledge Elnathan Mesfin for her assistance with data extraction.

Author contributions
NB: Conceptualization, methodology, formal analysis, data curation, writing—original draft. VST: Investigation, data curation, writing—review and editing. DSR-K: Investigation, data curation, writing—review and editing. BLF: Conceptualization, writing—review and editing, supervision. All authors read and approved the final manuscript.

Funding
This review was not funded.

Availability of data and materials
All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate
As this is a review, no institutional ethics approval was required.

Competing interests
Dr. Bozinoff has received grant funding from Canadian Institutes of Health Research, the Academic Health Sciences Alternate Payment Plan, and Womenmind for work outside of this study. Dr. Bernard Le Foll has obtained funding from Pfizer Inc. (GRAND Awards, including salary support) for investigator-initiated projects. Dr. Le Foll has obtained funding from Indivior for a clinical trial sponsored by Indivior. Dr. Le Foll has in-kind donations of cannabis products from Aurora Cannabis Enterprises Inc. and study medication donations from Pfizer Inc. (varenicline for smoking cessation) and Bioprojet Pharma. He was also provided a coil for a Transcranial magnetic stimulation (TMS) study from Brainsway. Dr. Le Foll has obtained industry funding from Canopy Growth Corporation (through research grants handled by the Centre for Addiction and Mental Health and the University of Toronto), Bioprojet Pharma, Alcohol Countermeasure Systems (ACS), Alkermes and Universal Ibogaine. Lastly, Dr. Le Foll has received in kind donations of nabiximols from GW Pharmaceuticals for past studies funded by CIHR and NIH. He has participated in a session of a National Advisory Board Meeting (Emerging Trends BUP-XR) for Indivior Canada and has been consultant for Shinogi. He is supported by CAMH, Waypoint Centre for Mental Health Care, a clinician-scientist award from the department of Family and Community Medicine of the University of Toronto and a Chair in Addiction Psychiatry from the department of Psychiatry of University of Toronto. The other authors declare no competing interests.

Author details
[1]Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, ON, Toronto, Canada. [2]Department of Family and Community Medicine, University of Toronto, Toronto, ON, Canada. [3]Addictions Division, Centre for Addiction and Mental Health, Toronto, ON, Canada. [4]Departamento de Psiquiatria, Universidade Federal de Sao Paulo, São Paulo, Brazil. [5]Translational Addiction Research Laboratory, Centre for Addiction and Mental Health, Toronto, ON, Canada. [6]Department of Psychiatry, University of Toronto, Toronto, ON, Canada. [7]Child, Youth, and Family Services, Centre for Addiction and Mental Health, Toronto, ON, Canada. [8]Division of Neurosciences and Clinical Translation, Department of Psychiatry, University of Toronto, Toronto, ON, Canada. [9]Department of Pharmacology and Toxicology, University of Toronto, Toronto, ON, Canada. [10]Waypoint Research Institute, Waypoint Centre for Mental Health Care, Penetanguishene, ON, Canada.

Received: 3 August 2022 Accepted: 30 September 2022
Published: 13 October 2022

References

1. Opioid and Stimulant-related Harms in Canada. Ottawa: Public Health Agency of Canada; 2021.
2. Ahmad F, Rossen L, Sutton P. Provisional drug overdose death counts. National Center for Health Statistics; 2022.
3. Gomes T, Murray R, Kolla G, Leece P, Bansal S, J B, et al. Changing circumstances surrounding opioid-related deaths in ontario during the COVID-19 pandemic. Ontario: Ontario Drug Policy Research Network; 2021.
4. Holland KM, Jones C, Vivolo-Kantor AM, Idaikkadar N, Zwald M, Hoots B, et al. Trends in US emergency department visits for mental health, overdose, and violence outcomes before and during the COVID-19 pandemic. JAMA Psychiat. 2021;78(4):372–9.
5. Mason M, Arukumar P, Feinglass J. The pandemic stay-at-home order and opioid-involved overdose fatalities. JAMA. 2021.
6. Strang J, Groshkova T, Uchtenhagen A, van den Brink W, Haasen C, Schechter MT, et al. Heroin on trial: systematic review and meta-analysis of randomised trials of diamorphine-prescribing as treatment for refractory heroin addiction†. Br J Psychiatry. 2015;207(1):5–14.
7. Strang J, Groshkova T, Metrebian N, European Monitoring Centre for Drugs and Drug A. New heroin-assisted treatment: recent evidence and current practices of supervised injectable heroin treatment in Europe and beyond: Publications Office of the European Union Luxembourg; 2012.
8. Haasen C, Verthein U, Degkwitz P, Berger J, Krausz M, Naber D. Heroin-assisted treatment for opioid dependence: randomised controlled trial. Br J Psychiatry. 2007;191:55–62.
9. Oviedo-Joekes E, Guh D, Brissette S, Marchand K, MacDonald S, Lock K, et al. Hydromorphone Compared With Diacetylmorphine for Long-term Opioid Dependence: A Randomized Clinical Trial. JAMA Psychiatry. 73. United States 2016. p. 447–55.
10. Ferri M, Davoli M, Perucci CA. Heroin maintenance for chronic heroin-dependent individuals. Cochrane Database Syst Rev. 2011;2011(12):Cd003410.
11. Oviedo-Joekes E, Brissette S, Marsh DC, Lauzon P, Guh D, Anis A, et al. Diacetylmorphine versus methadone for the treatment of opioid addiction. N Engl J Med. 361. United States: 2009 Massachusetts Medical Society; 2009. p. 777–86.
12. Bansback N, Guh D, Oviedo-Joekes E, Brissette S, Harrison S, Janmohamed A, et al. Cost-effectiveness of hydromorphone for severe opioid use disorder: findings from the SALOME randomized clinical trial. Addiction. 2018;113(7):1264–73.
13. Nosyk B, Guh DP, Bansback NJ, Oviedo-Joekes E, Brissette S, Marsh DC, et al. Cost-effectiveness of diacetylmorphine versus methadone for chronic opioid dependence refractory to treatment. CMAJ. 2012;184(6):E317–28.
14. Byford S, Barrett B, Metrebian N, Groshkova T, Cary M, Charles V, et al. Cost-effectiveness of injectable opioid treatment v. oral methadone for chronic heroin addiction. Br J Psychiatry. 2013;203(5):341–9.
15. Dijkgraaf MG, van der Zanden BP, de Borgie CA, Blanken P, van Ree JM, van den Brink W. Cost utility analysis of co-prescribed heroin compared with methadone maintenance treatment in heroin addicts in two randomised trials. BMJ. 2005;330(7503):1297.
16. Eydt E, Glegg S, Sutherland C, Meador K, Trew M, Perreault M, et al. Service delivery models for injectable opioid agonist treatment in Canada: 2 sequential environmental scans. CMAJ Open. 2021;9(1):E115–24.
17. Bruneau J, Ahamad K, Goyer M, Poulin G, Selby P, Fischer B, et al. Management of opioid use disorders: a national clinical practice guideline. CMAJ. 2018;190(9):E247–57.
18. Jutras-Aswad D, Le Foll B, Ahamad K, Lim R, Bruneau J, Fischer B, et al. Flexible Buprenorphine/Naloxone Model of Care for Reducing Opioid Use in Individuals With Prescription-Type Opioid Use Disorder: An Open-Label, Pragmatic, Noninferiority Randomized Controlled Trial. Am J Psychiatry. 2022:appiajp21090964.
19. Ng K, Kim J, Veljovic S, Zhang M. Buprenorphine for Opioid Use Disorder Treatment: Focus on New Formulations and Alternative Induction Protocols: PharmacyConnection.ca; 2020 [Available from: https://pharmacyconnection.ca/opioid-use-disorder-treatment-spring-summer-2020/.
20. Mello NK, Lukas SE, Bree MP, Mendelson JH. Progressive ratio performance maintained by buprenorphine, heroin and methadone in Macaque monkeys. Drug Alcohol Depend. 1988;21(2):81–97.
21. Winger G, Skjoldager P, Woods JH. Effects of buprenorphine and other opioid agonists and antagonists on alfentanil-and

cocaine-reinforced responding in rhesus monkeys. J Pharmacol Exp Ther. 1992;261(1):311–7.
22. Walsh SL, Eissenberg T. The clinical pharmacology of buprenorphine: extrapolating from the laboratory to the clinic. Drug Alcohol Depend. 2003;70(2 Suppl):S13-27.
23. Pickworth WB, Johnson RE, Holicky BA, Cone EJ. Subjective and physiologic effects of intravenous buprenorphine in humans. Clin Pharmacol Ther. 1993;53(5):570–6.
24. Comer SD, Collins ED. Self-administration of intravenous buprenorphine and the buprenorphine/naloxone combination by recently detoxified heroin abusers. J Pharmacol Exp Ther. 2002;303(2):695–703.
25. Comer SD, Collins ED, Fischman MW. Intravenous buprenorphine self-administration by detoxified heroin abusers. J Pharmacol Exp Ther. 2002;301(1):266–76.
26. Ahmadi J, Ahmadi K, Ohaeri J. Controlled, randomized trial in maintenance treatment of intravenous buprenorphine dependence with naltrexone, methadone or buprenorphine: a novel study. Eur J Clin Investig. 2003;33(9):824–9.
27. Aitken CK, Higgs PG, Hellard ME. Buprenorphine injection in Melbourne, Australia—an update. Drug Alcohol Rev. 2008;27(2):197–9.
28. Ambekar A, Rao R, Mishra AK, Agrawal A. Type of opioids injected: does it matter? A multicentric cross-sectional study of people who inject drugs. Drug Alcohol Rev. 2015;34(1):97–104.
29. Torrens M, San L, Camí J. Buprenorphine versus heroin dependence: comparison of toxicologic and psychopathologic characteristics. Am J Psychiatry. 1993;150(5):822–4.
30. Harper I. Temgesic abuse. N Z Med J. 1983;96(741):777.
31. Quigley AJ, Bredemeyer DE, Seow SS. A case of buprenorphine abuse. Med J Aust. 1984;140(7):425–6.
32. Weinhold LL, Bigelow GE, Preston KL. Combination of naloxone with buprenorphine in humans. NIDA Res Monogr. 1989;95:485.
33. Lofwall MR, Walsh SL. A review of buprenorphine diversion and misuse: the current evidence base and experiences from around the world. J Addict Med. 2014;8(5):315–26.
34. Robinson GM, Dukes PD, Robinson BJ, Cooke RR, Mahoney GN. The misuse of buprenorphine and a buprenorphine-naloxone combination in Wellington, New Zealand. Drug Alcohol Depend. 1993;33(1):81–6.
35. Bruce RD, Govindasamy S, Sylla L, Kamarulzaman A, Altice FL. Lack of reduction in buprenorphine injection after introduction of co-formulated buprenorphine/naloxone to the Malaysian market. Am J Drug Alcohol Abuse. 2009;35(2):68–72.
36. Power J, Salmon AM, Latimer J, Jauncey M, Day CA. Overdose risk and client characteristics associated with the injection of buprenorphine at a medically supervised injecting center in Sydney, Australia. Subst Use Misuse. 2019;54(10):1646–53.
37. Roux P, Rojas Castro D, Ndiaye K, Briand Madrid L, Laporte V, Mora M, et al. Willingness to receive intravenous buprenorphine treatment in opioid-dependent people refractory to oral opioid maintenance treatment: results from a community-based survey in France. Subst Abuse Treat Prev Policy. 2017;12(1):46.
38. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372: n71.
39. Bozinoff N, Le Foll B, Dafna K, Tardelli V. Patterns of intravenous buprenorphine use among persons with opioid use disorder. PROSPERO 2020 CRD42020203098. Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020203098
40. Pluye P, Gagnon MP, Griffiths F, Johnson-Lafleur J. A scoring system for appraising mixed methods research, and concomitantly appraising qualitative, quantitative and mixed methods primary studies in mixed studies reviews. Int J Nurs Stud. 2009;46(4):529–46.
41. Hong QN, Pluye P, Fàbregues S, Bartlett G, Boardman F, Cargo M, et al. Mixed methods appraisal tool (MMAT), version 2018.
42. Reporting the results of the MMAT (version 2018). 2020.
43. Popay J, Roberts H, Sowden A, Petticrew M, Arai L, Rodgers M, et al. Guidance on the conduct of narrative synthesis in systematic reviews. Prod ESRC Methods Programme Vers. 2006;1(1): b92.
44. Lo HY, Leong CSL. Surgical complications in parenteral Subutex abusers. Singapore Med J. 2006;47(11):924–7.
45. Yokell MA, Zaller ND, Green TC, Rich JD. Buprenorphine and buprenorphine/naloxone diversion, misuse, and illicit use: an international review. Curr Drug Abuse Rev. 2011;4(1):28–41.
46. Sud A, Salamanca-Buentello F, Buchman DZ, Sabioni P, Majid U. Beyond harm-producing versus harm-reducing: a qualitative meta-synthesis of people who use drugs' perspectives of and experiences with the extramedical use and diversion of buprenorphine. J Subst Abuse Treat. 2022;135: 108651.
47. Roux P, Villes V, Blanche J, Bry D, Spire B, Feroni I, et al. Buprenorphine in primary care: risk factors for treatment injection and implications for clinical management. Drug Alcohol Depend. 2008;97(1–2):105–13.
48. Frauger E, Nordmann S, Orleans V, Pradel V, Pauly V, Thirion X, et al. Which psychoactive prescription drugs are illegally obtained and through which ways of acquisition? About OPPIDUM survey. Fundam Clin Pharmacol. 2012;26(4):549–56.
49. Noroozi A, Mianji F. Singapore's experience with buprenorphine (Subutex). Iran J Psychiatry Behav Sci. 2008;2(1):54–9.
50. Kumar MS, Mudaliar S, Thyagarajan SP, Kumar S, Selvanayagam A, Daniels D. Rapid assessment and response to injecting drug use in Madras, south India. Int J Drug Policy. 2000;11(1–2):83–98.
51. Ahmed SK, Ara N. An exploratory study of buprenorphine use in Bangladesh: a note. Subst Use Misuse. 2001;36(8):1071–83.
52. Aalto M, Halme J, Visapaa J-P, Salaspuro M. Buprenorphine misuse in Finland. Subst Use Misuse. 2007;42(6):1027–8.
53. Aalto M, Visapaa JP, Halme JT, Fabritius C, Salaspuro M. Effectiveness of buprenorphine maintenance treatment as compared to a syringe exchange program among buprenorphine misusing opioid-dependent patients. Nord J Psychiatry. 2011;65(4):238–43.
54. Lofwall MR, Martin J, Tierney M, Fatseas M, Auriacombe M, Lintzeris N. Buprenorphine diversion and misuse in outpatient practice. J Addict Med. 2014;8(5):327–32.
55. Cicero TJ, Ellis MS, Chilcoat HD. Understanding the use of diverted buprenorphine. Drug Alcohol Depend. 2018;193:117–23.
56. Cicero TJ, Ellis MS, Surratt HL, Kurtz SP. Factors contributing to the rise of buprenorphine misuse: 2008–2013. Drug Alcohol Depend. 2014;142:98–104.
57. Roux P, Rojas Castro D, Ndiaye K, Briand Madrid L, Laporte V, Mora M, et al. Willingness to receive intravenous buprenorphine treatment in opioid-dependent people refractory to oral opioid maintenance treatment: results from a community-based survey in France. Subst Abuse Treat Prev Policy. 2017;12:1–11.
58. Mattick RP, Breen C, Kimber J, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev. 2014(2):Cd002207.
59. Seet RC, Rathakrishnan R, Chan BP, Lim EC. Diffuse cystic leucoencephalopathy after buprenorphine injection. J Neurol Neurosurg Psychiatry. 762005. p. 890–1.
60. Peyriere H, Tatem L, Bories C, Pageaux GP, Blayac JP, Larrey D. Hepatitis after intravenous injection of sublingual buprenorphine in acute hepatitis C carriers: report of two cases of disappearance of viral replication after acute hepatitis. Ann Pharmacother. 2009;43(5):973–7.
61. Berson A, Gervais A, Cazals D, Boyer N, Durand F, Bernuau J, et al. Hepatitis after intravenous buprenorphine misuse in heroin addicts. J Hepatol. 2001;34(2):346–50.
62. Jenkinson RA, Clark NC, Fry CL, Dobbin M. Buprenorphine diversion and injection in Melbourne, Australia: an emerging issue? Addiction. 2005;100(2):197–205.
63. Kriikku P, Hakkinen M, Ojanpera I. High buprenorphine-related mortality is persistent in Finland. Forensic Sci Int. 2018;291:76–82.
64. Carlson RG, Daniulaityte R, Silverstein SM, Nahhas RW, Martins SS. Unintentional drug overdose: Is more frequent use of non-prescribed buprenorphine associated with lower risk of overdose? Int J Drug Policy. 2020;79: 102722.
65. Bromley LA. Problems with hydromorphone prescribing as a response to the opioid crisis. Cmaj. 1922020. p. E219–e20.
66. Spadaro A, Long B, Koyfman A, Perrone J. Buprenorphine precipitated opioid withdrawal: prevention and management in the ED setting. Am J Emerg Med. 2022;58:22–6.
67. Ahmadi J, Ahmadi K. Controlled trial of maintenance treatment of intravenous buprenorphine dependence. Ir J Med Sci. 2003;172(4):171–3.

68. Ahmadi J, Maany I, Ahmadi M. Treatment of intravenous buprenorphine dependence. A randomized open clinical trial. German J Psychiatry. 2003;6(1):23–9.
69. Aich TK, Dhungana M, Khanal R. Pattern of buprenorphine abuse among opioid abusers in Nepal. Indian J Psychiatry. 2010;52(3):250–3.
70. Alho H, Sinclair D, Vuori E, Holopainen A. Abuse liability of buprenorphine-naloxone tablets in untreated IV drug users. Drug Alcohol Depend. 2007;88(1):75–8.
71. Basu D, Varma VK, Malhotra AK. Buprenorphine dependence: a new addiction in India. Disabil Impair. 1990;3:142–6.
72. Basu D, Mattoo SK, Malhotra A, Gupta N, Malhotra R. A longitudinal study of male buprenorphine addicts attending an addiction clinic in India. Addiction. 2000;95(9):1363–72.
73. Bruce RD, Govindasamy S, Sylla L, Haddad MS, Kamarulzaman A, Altice FL. Case series of buprenorphine injectors in Kuala Lumpur, Malaysia. Am J Drug Alcohol Abuse. 2008;34(4):511–7.
74. Chowdhury AN, Banerjee G. Recurrent Koro in repeated i.v. buprenorphine withdrawal [1]. Addiction. 1996;91(1):145–6.
75. Feeney GFX, Fairweather P. Groin tissue necrosis requiring skin graft following parenteral abuse of buprenorphine tablets. Drug Alcohol Rev. 2003;22(3):359–61.
76. Horyniak D, Armstrong S, Higgs P, Wain D, Aitken C. Poor Man's Smack: a qualitative study of buprenorphine injecting in Melbourne, Australia. Contemp Drug Probl Interdiscip Q. 2007;34(3):525–48.
77. Kulaksizoglu B, Kara H, Bodur B, Kuloglu M. Intravenous buprenorphine/naloxone and concomitant oral pregabalin misuse: a case report. Neuropsychiatr Dis Treat. 2018;14:3033–5.
78. Lavelle TL, Hammersley R, Forsyth A, Bain D. The use of buprenorphine and temazepam by drug injectors. J Addict Dis. 1991;10(3):5–14.
79. Lee T-S, Yeong B. Multiple embolic phenomenon in the brain associated with parenteral buprenorphine abuse. J Neuropsychiatry Clin Neurosci. 2008;20(2):235–7.
80. Liu ZM, Lu XX, Lian Z, Mu Y, Guo P, An X. Evaluation on drug dependence of buprenorphine. Acta Pharmacol Sin. 2003;24(5):448.
81. Ng WL, Mythily S, Song G, Chan YH, Winslow M. Concomitant use of midazolam and buprenorphine and its implications among drug users in Singapore. Ann Acad Med Singap. 2007;36(9):774–7.
82. Obadia Y, Perrin V, Feroni I, Vlahov D, Moatti JP. Injecting misuse of buprenorphine among French drug users. Addiction. 2001;96(2):267–72.
83. Otiashvili D, Zabransky T, Kirtadze I, Piralishvili G, Chavchanidze M, Miovsky M. Why do the clients of Georgian needle exchange programmes inject buprenorphine? Eur Addict Res. 2010;16(1):1–8.
84. Piralishvili G, Otiashvili D, Sikharulidze Z, Kamkamidze G, Poole S, Woody GE. Opioid addicted buprenorphine injectors: drug use during and after 12-weeks of buprenorphine-naloxone or methadone in the Republic of Georgia. J Subst Abuse Treat. 2015;50:32–7.
85. San L, Torrens M, Castillo C, Porta M, De la Torre R. Consumption of buprenorphine and other drugs among heroin addicts under ambulatory treatment: results from cross-sectional studies in 1988 and 1990. Addiction. 1993;88(10):1341–9.
86. Singh J, Grover S, Basu D. Very high-dose intravenous buprenorphine dependence: a case report. German J Psychiatry. 2004;7(4):58–9.
87. Singh RA, Mattoo SK, Malhotra A, Varma VK. Cases of buprenorphine abuse in India. Acta Psychiatr Scand. 1992;86(1):46–8.
88. Torrens M, San L, Cami J. Buprenorphine versus heroin dependence: comparison of toxicologic and psychopathologic characteristics. Am J Psychiatry. 1993;150(5):822–4.
89. Valenciano M, Emmanuelli J, Lert F. Unsafe injecting practices among attendees of syringe exchange programmes in France. Addiction. 2001;96(4):597–606.
90. Vicknasingam B, Mazlan M, Schottenfeld RS, Chawarski MC. Injection of buprenorphine and buprenorphine/naloxone tablets in Malaysia. Drug Alcohol Depend. 2010;111(1–2):44–9.
91. White N, Flaherty I, Higgs P, Larance B, Nielsen S, Degenhardt L, et al. Injecting buprenorphine-naloxone film: findings from an explorative qualitative study. Drug Alcohol Rev. 2015;34(6):623–9.
92. Winslow M, Ng WL, Mythily S, Song G, Yiong HC. Socio-demographic profile and help-seeking behaviour of buprenorphine abusers in Singapore. Ann Acad Med Singap. 2006;35(7):451–6.
93. Winslow M, Subramaniam M, Ng WL, Lee A, Song G, Chan YH. Seroprevalence of hepatitis C in intravenous opioid users presenting in the early phase of injecting drug use in Singapore. Singap Med J. 2007;48(6):504–8.
94. Winstock AR, Lea T, Sheridan J. Prevalence of diversion and injection of methadone and buprenorphine among clients receiving opioid treatment at community pharmacies in New South Wales, Australia. Int J Drug Policy. 2008;19(6):450–8.
95. Yeo AKS, Chan CY, Chia KH. Complications relating to intravenous buprenorphine abuse: a single institution case series. Ann Acad Med Singapore. 2006;35(7):487–91.
96. Aboltins CA, Daffy JR, Allen P. Fungal endophthalmitis in intravenous drug users injecting buprenorphine contaminated with oral Candida species [1]. Med J Aust. 2005;182(8):427.
97. Alvarez R, Adan A, Martinez JA, Casale A, Miro JM. Haematogenous Serratia marcescens endophthalmitis in an HIV-infected intravenous drug addict. Infection. 1990;18(1):29–30.
98. Boggs CL, Ripple MG, Ali Z, Brassell M, Levine B, Jufer-Phipps R, et al. Anaphylaxis after the injection of buprenorphine. J Forensic Sci. 2013;58(5):1381–3.
99. Bouquie R, Pistorius MA, Wainstein L, Mussini JM, Gerardin M, Deslandes G, et al. Generic buprenorphine injection: the case report highlightening the link between in vitro and in vivo investigations. Fundam Clin Pharmacol. 2015;29(SUPPL. 1):28.
100. Boyd J, Randell T, Luurila H, Kuisma M. Serious overdoses involving buprenorphine in Helsinki. Acta Anaesthesiol Scand. 2003;47(8):1031–3.
101. Cassoux N, Bodaghi B, Lehoang P, Edel Y. Presumed ocular candidiasis in drug misusers after intravenous use of oral high dose buprenorphine (Subutex) [11]. Br J Ophthalmol. 2002;86(8):940–1.
102. Chai LYA, Khare CB, Chua A, Fisher DA, Tambyah PA. Buprenorphine diversion: a possible reason for increased incidence of infective endocarditis among injection drug users? The Singapore experience. Clin Infect Dis. 2008;46(6):953–5.
103. Chew HC. Subutex abuse presenting to the emergency department: a case series. Hong Kong J Emerg Med. 2007;14(3):163–8.
104. Chong E, Poh KK, Shen L, Yeh IB, Chai P. Infective endocarditis secondary to intravenous Subutex abuse. Singap Med J. 2009;50(1):34–42.
105. Chua SM, Lee TS. Abuse of prescription buprenorphine, regulatory controls and the role of the primary physician. Ann Acad Med Singapore. 2006;35(7):492–5.
106. Del Giudice P. Cutaneous complications of intravenous drug abuse. Br J Dermatol. 2004;150(1):1–10.
107. Eiden C, Brunel AS, Reynes J, Diot C, Xatart S, Faucherre V, et al. Bacterial infections related to intravenous substances abuse: new trends. Fundam Clin Pharmacol. 2014;28(SUPPL. 1):58.
108. Eiden C, Leglise Y, Diot C, Faillie JL, Petit P, Peyriere H. Misuse of high-dose buprenorphine: analysis of cases reported to the addictovigilance center of Montpellier. Fundam Clin Pharmacol. 2014;28(SUPPL. 1):48.
109. Eiden C, Nogue E, Diot C, Frauger E, Jouanjus E, Leglise Y, et al. Three complementary approaches to characterize buprenorphine misuse. Subst Use Misuse. 2016;51(14):1912–9.
110. Espitia O, Vigneau-Victorri C, Pistorius MA. Image gallery: Nicolau syndrome after misuse of buprenorphine. Br J Dermatol. 2017;176(4): e35.
111. Gautschi OP, Zellweger R. Images in emergency medicine. Extensive groin abscess and myositis after intravenous cubital buprenorphine injection. Ann Emerg Med. 2006;48(6):656–9.
112. Häkkinen M, Heikman P, Ojanperä I. Parenteral buprenorphine–naloxone abuse is a major cause of fatal buprenorphine-related poisoning. Forensic Sci Int. 2013;232(1–3):11–5.
113. Ho RCM, Ho ECL, Mak A. Cutaneous complications among i.v. buprenorphine users. J Dermatol. 2009;36(1):22–9.
114. Joethy J, Yong FC, Puhaindran M. Another complication of subutex abuse. Singap Med J. 2008;49(3):267–8.
115. Kintz P. Deaths involving buprenorphine: a compendium of French cases. Forensic Sci Int. 2001;121(1–2):65–9.
116. Kintz P. A new series of 13 buprenorphine-related deaths. Clin Biochem. 2002;35(7):513–6.
117. Kluger N, Girard C, Guillot B, Bessis D. Penile and scrotal skin necrosis after injection of crushed buprenorphine tablets. Presse Medicale. 2010;39(5):610–1.

118. Lee LC, Wong R, Raju GC, Khor C, Yip J. Protein-losing enteropathy post-valvular surgery with severe tricuspid regurgitation in Subutex-related endocarditis. Singap Med J. 2009;50(4):e124–6.
119. Lim CCT, Lee SH, Wong Y-C, Hui F. Embolic stroke associated with injection of buprenorphine tablets. Neurology. 2009;73(11):876–9.
120. Loo HW, Yam AKT, Tan TC, Peng YP, Teoh LC. Severe upper limb complications from parenteral abuse of Subutex. Ann Acad Med Singapore. 2005;34(9):575–8.
121. Marka A, Hoyt BS, Dagrosa AT, Barton DT, Kim A, Linos K, et al. Cutaneous crospovidone reaction secondary to subcutaneous injection of buprenorphine. J Cutan Pathol. 2020;47(5):470–4.
122. Nielsen S, Dietze P, Lee N, Dunlop A, Taylor D. Concurrent buprenorphine and benzodiazepines use and self-reported opioid toxicity in opioid substitution treatment. Addiction. 2007;102(4):616–22.
123. Ojha SP, Sigdel S, Meyer-Thompson HG, Oechsler H, Verthein U. 'South Asian cocktail'—the concurrent use of opioids, benzodiazepines and antihistamines among injecting drug users in Nepal and associations with HIV risk behaviour. Harm Reduct J. 2014;11(1):17.
124. Partanen TA, Vikatmaa P, Tukiainen E, Lepantalo M, Vuola J. Outcome after injections of crushed tablets in intravenous drug abusers in the Helsinki University Central Hospital. Eur J Vasc Endovasc Surg. 2009;37(6):704–11.
125. Prosser NJ, Snelling PL, Karim R. A case of tubulo-interstitial nephritis associated with intravenous injection of buprenorphine sourced from a transdermal patch. Pathology. 2019;51(Supplement 1):S96.
126. Puolakka TJ, Honkaniemi J, Vuorialho M, Vaananen P. Cervical myelopathy associated with paravertebral neck muscle rhabdomyolysis following buprenorphine abuse. Acta Anaesthesiol Scand. 2015;59(Supplement 121):4–5.
127. Reynaud M, Petit G, Potard D, Courty P. Six deaths linked to concomitant use of buprenorphine and benzodiazepines. Addiction. 1998;93(9):1385–92.
128. Robinson GM, Dukes PD, Robinson BJ, Cooke RR, Mahoney GN. The misuse of buprenorphine and a buprenorphine–naloxone combination in Wellington, New Zealand. Drug Alcohol Depend. 1993;33(1):81–6.
129. Seet RCS, Lim ECH. Intravenous use of buprenorphine tablets associated with rhabdomyolysis and compressive sciatic neuropathy. Ann Emerg Med. 2006;47(4):396–7.
130. Seet RCS, Oh VMS, Lim ECH. Complications arising from intravenous buprenorphine abuse [2]. QJM. 2007;100(5):312–3.
131. Sharma V, Vasoo S, Ong B. Myofasciitis and polyneuritis related to Buprenorpine abuse. Neurology and Clinical Neurophysiology. 2005;2005((Sharma, Vasoo, Ong) Department of Medicine, National University Hospital, Singapore-119074, Singapore).
132. Tan KK, Chen K, Chia KH, Lee CW, Nalachandran S. Surgical management of infected pseudoaneurysms in intravenous drug abusers: single institution experience and a proposed algorithm. World J Surg. 2009;33(9):1830–5.
133. Teo FSW, Li YH, Lam KNSF, Johan A. Tetanus in an injecting buprenorphine abuser. Ann Acad Med Singapore. 2007;36(12):1021–3.
134. Victorri-Vigneau C, Wainstein L, Bernier C, Guerlais M, Gerardin M, Jolliet P. Cutaneous complications of buprenorphine intravenous drug abuse. Fundam Clin Pharmacol. 2012;26(SUPPL.1):69.
135. Wilson RM, Elmaraghi S, Rinker BD. Ischemic hand complications from intra-arterial injection of sublingual buprenorphine/naloxone among patients with opioid dependency. Hand (New York, NY). 2017;12(5):507–11.
136. Yang SS, Lee K. Unusual complication of intravenous Subutex abuse: two cases of septic sacroiliitis. Singap Med J. 2008;49(12):e343–6.

Publisher's Note