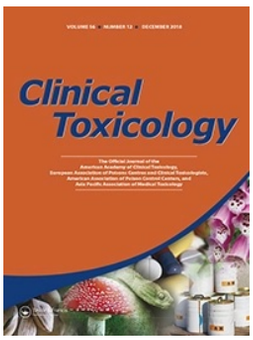

Clinical Toxicology

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

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**To cite this article:** Fariba Farnaghi , Narges Gholami , Hossein Hassanian-Moghaddam , Rebecca McDonald , Reza Zamanzadeh & Nasim Zamani (2021): Unintentional buprenorphine and methadone poisoning in children: a matched observational study, Clinical Toxicology, DOI: 10.1080/15563650.2020.1869755

**To link to this article:** https://doi.org/10.1080/15563650.2020.1869755

Published online: 21 Jan 2021.

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2020.1869755

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CLINICAL RESEARCH



# Unintentional buprenorphine and methadone poisoning in children: a matched observational study

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**ABSTRACT**

**Objective:** To compare accidental pediatric poisoning from methadone vs. buprenorphine in terms of clinical indicators and in-hospital morbidity.

**Methods:** A matched observational study conducted on children aged ≤12 years admitted to our center between March 2018 and March 2019 with acute poisoning from methadone or buprenorphine. Data were extracted from the electronic patient files of the pediatric methadone poisoning cases, and buprenorphine poisoning cases were followed from ED, during the study period. Cases were compared regarding rates of bradypnea/apnea (primary outcome), the need for antidote therapy and intubation, duration of hospital stay, miosis, loss of consciousness, blood gas analyses, and mortality (secondary outcomes).

**Results:** A total of 90 methadone- and 30 buprenorphine-poisoned children were evaluated. Methadone cases had significantly higher rates of apnea (20/90 methadone vs. 0/30 buprenorphine; OR = 17.7, 95% CI 1.1, 302.8; $p = 0.047$), but there was no group difference in bradypnea (39/90 methadone vs. 10/30 buprenorphine; $p$ = ns). 28 (31%) methadone and 3 buprenorphine (10%) cases had been referred to as fully awake ($p = 0.013$). Methadone cases required higher median naloxone doses for initial bolus (0.4 vs. 0.02 mg; $p = 0.014$) and maintenance infusion (14.4 vs. 2.4 mg; $p < 0.001$). 20 apnea cases (all from the methadone group) had miotic pupils, and miotic pupils were seen in 44 (90%) cases with bradypnea (OR = 3.2, 95% CI 1.1, 9.3; $p = 0.026$). Intubation was needed in only 5 methadone cases (5.5%; $p$ = ns). All patients survived.

**Conclusion:** Compared to children poisoned with methadone, buprenorphine cases had higher rates of loss of consciousness on admission but subsequently experienced fewer complications during hospital treatment, which is likely due to the buprenorphine partial antagonist effect. Our findings suggest that methadone exposure is more toxic than buprenorphine in pediatric populations.

**ARTICLE HISTORY**
Received 21 August 2020
Revised 11 December 2020
Accepted 22 December 2020

**KEYWORDS**
Pediatric; opioids; agonist; antagonist; overdose

## Introduction

Poisoning accounts for about 2% of all child deaths in the developed world, and over 5% in developing countries [1]. Opioid toxicity is one of the most common life-threatening forms of pediatric poisoning which can lead to loss of consciousness, respiratory suppression, apnea, coma, and eventually death [2]. The incidence of pediatric opioid poisonings is increasing worldwide [3], typically caused by accidental exposure to opioids that a child's parents or live-in relatives use licitly or illicitly.

Methadone (MTD) is the medication most commonly used for the treatment of opioid use disorder. Several previous studies have evaluated MTD toxicity in children. In a meta-analysis performed on 38 studies involving MTD toxicity in children, Alotaibi et al. concluded that MTD exposure led to severe poisoning in children, with ingestion of minute amounts being potentially lethal in this age group [4]. The authors recommended patient education, supervision of MTD consumption, dispensing MTD doses in child-proof bottles, and storage of MTD in safe places to decrease rates of poisoning in children [4].

Conversely, pediatric poisoning from buprenorphine (BUP; also commonly named B2 in Iran, in reference to BUP 2-mg tablet formulation), which is another medication for opioid use disorder, has been far less investigated. Recent studies suggest that the number of phone calls reporting accidental BUP poisoning in children has dramatically increased in the US, especially in children younger than six years of age [5,6]. However, the recent introduction of child-resistant single-dose packaging has been associated with a slight decrease [5,6].

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The referenced studies have already described BUP and MTD poisonings in children. However, to the best of our knowledge, there is no published study that offers a direct case-by-case comparison regarding clinical severity. In the present study, we aimed to compare pediatric cases of BUP and MTD poisoning referred to a toxicology center in Iran in terms of clinical indicators, complications, and outcomes.

## Methods

### Design

This investigation was a matched observational study of pediatric poisoning cases admitted to Loghman-Hakim Hospital Poison Center (LHHPC) in Tehran, Iran in the year between March 21st, 2018 and March 20th, 2019. Affiliated with Shahid Beheshti University of Medical Sciences, LHHPC is the only tertiary hospital for poisoned children in Tehran and the largest in the country [2]. The ethics committee of Shahid Beheshti University of Medical Sciences approved this study (IR.SBMU.RETECH.REC.1398.018).

### Cases

Eligible cases were defined as children up to 12 years of age that were admitted for acute poisoning from MTD (tablet or syrup formulation) or sublingual (SL) BUP in the study period. SL BUP refers to the tablet formulation for SL administration, not necessarily to the route of exposure. The route of BUP exposure (oral ingestion, licking, or sucking) as well as the MTD formulation (syrup vs. tablet) was obtained via the parents' or caregivers' verbal report. Patients were included in the study after the pediatrician in charge was able to confirm a definite diagnosis of unintentional opioid poisoning (either from MTD or SL BUP), based on history, clinical manifestation, and positive urine screening tests for MTD or BUP, respectively. Children were excluded from the study if they were admitted (1) for intentional/criminal poisoning, (2) with multidrug poisonings, or (3) with unknown intent of ingestion (see Figure 1).

### Measures

An attending pediatrician conducted chart reviews for all eligible patients. A standardized data collection instrument was purpose-developed for the study and completed for all patients. For patients with sublingual (SL) BUP poisoning, data collection was conducted prospectively by the first author. For MTD poisoning cases, the second author reviewed patient charts and completed the data collection instrument retrospectively.

The two pediatricians (i.e., the first and the second authors) conducting data collection were blind to each others' dataset (i.e., the pediatrician collecting data for BUP cases did not have access to the MTD dataset and vice versa) to ensure objectivity. The complete dataset was only available to and accessed by the corresponding author.

Patient demographics as well as primary outcomes (frequency of bradypnea/apnea), and the secondary outcomes (loss of consciousness, impaired blood gas analyses, administered naloxone dose, intubation (yes vs. no), miotic puplis (yes vs. no), hospital stay, and death) were recorded.

Age-related vital signs with normal variations were predefined, using the ranges recommended by Bernstein et al. and Kliegman et al. [8,9]. Any respiratory rate (RR) below the age-related normal range was considered bradypnea. Apnea was defined as the cessation of breathing. Mean arterial pressure (MAP) was defined based on systolic pressure (1/3) plus diastolic pressure (2/3). Level of consciousness (LOC) was determined based on AVPU (Alert, Verbal, Pain, Unresponsive) score and Glasgow Coma Scale (GCS).

### Consent

Written informed consent was provided by the parents (or caregivers) of all SL BUP cases. Since the study was retrospective for MTD cases, the requirement for written informed consent was waived by our local ethics committee at Shahid Beheshti University of Medical Sciences.

### Intervention

Following our hospital protocol, all patients with a diagnosis of MTD or SL BUP poisoning were admitted to the pediatric ward and/or the medical toxicology intensive care unit (ICU) after stabilization in the emergency department (ED). Diagnoses of MTD and SL BUP poisoning were confirmed by history, clinical manifestation, and urine screening tests for MTD/BUP, respectively. Patients were visited twice daily by the attending pediatrician(s) and received routine management. Vital signs were checked in all patients at least four times a day.

For patients with respiratory depression (i.e., bradypnea or apnea), emergency management of the airway, breathing, and circulation was performed according to the specified age range (see above) and/or primary respiratory acidosis ($pH < 7.32$ and $pCO2 > 50$ mmHg) in venous blood gas (VBG) analysis [10]. All patients with respiratory depression or loss of consciousness also received treatment with intravenous naloxone (0.01–0.1 mg/kg). Patients who did not respond to naloxone or were unstable were ventilated using an ambo bag and/or were intubated.

### Early presentations only

Children who were admitted within two hours of opioid exposure (i.e., MTD or SL BUP) underwent "gastric washing" if they were stable with a secured airway. Following insertion of a 22- to 28-Fr nasogastric tube, the stomach was flushed with saline solutions (10–15 cc/kg to a maximum of 250 cc) until complete clearance of the gastric content was achieved. A single dose of activated charcoal was then administered using the nasogastric tube.

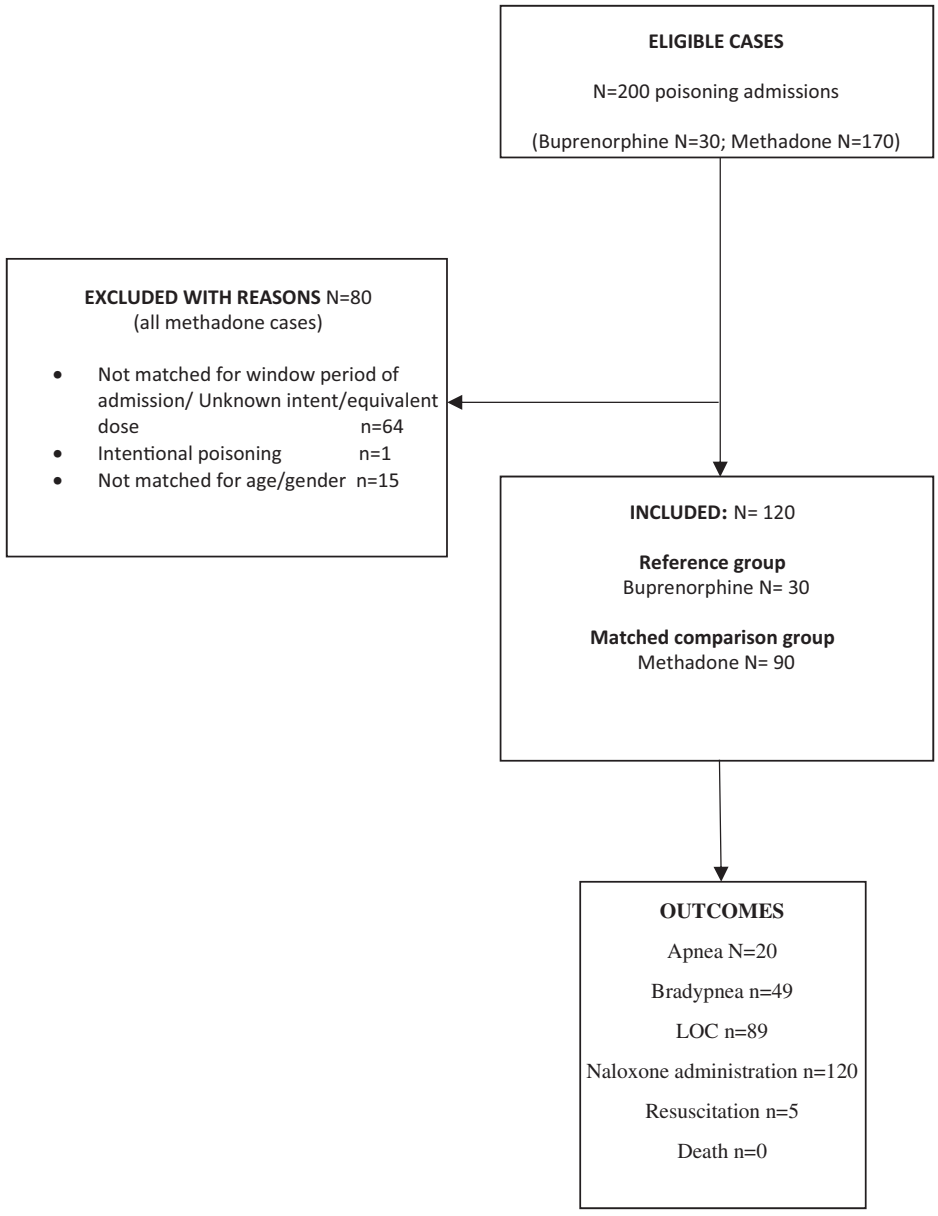


Figure 1. STROBE diagram for inclusion and selection of patients involving buprenorphine and methadone.

## Analyses

### Matching procedure

Methadone-poisoned children were matched to BUP cases by age, gender, an equivalent dose of ingestion (see below), and time of referral (i.e., within 72 h of admission of a BUP case). We considered controlling for matching factors in the analysis [11].

### Determination of equivalent dose

The ingested dose of MTD or SL BUP was calculated based on the ingested volume of MTD syrup (5 mg/mL) or the ingested dose of the MTD or SL tablets (5, 20 and 40 mg for MTD; 0.4, 2 and 8 mg for SL BUP tablets, as BUP or BUP/naloxone), as commercially available on the Iranian market. The total dose ingested was then adjusted by the patient's weight (mg/kg). To achieve an equivalent dose of SL BUP relative to MTD, each unit-dose of 0.8 mg SL BUP was considered equal to 10 mg oral MTD [7].

### Statistical analysis

For the description of quantitative continuous variables with non-normal distribution, median and interquartile range (IQR) were used. For qualitative categorical variables, percent of frequency was provided. To compare continuous variables between the two groups, Mann–Whitney *U* test was used. $\chi^2$-test was used to evaluate the association between categorical variables. Odds ratios (OR) and 95% confidence intervals (CI) were provided for expressing the strength of this association. Pearson correlation coefficient was used to assess the severity of association between continuous variables. Enter logistic model was performed to determine independent variables predicting apnea/bradypnea or intubation in these patients. A *p*-value of less than 0.05 was considered

statistically significant. Statistical Package for Social Sciences (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA) was used for analysis.

## Results

### Sample determination

A total of 120 poisoning patients, of whom 90 (75%) were MTD-poisoned and 30 (25%) were SL BUP-intoxicated were included in the study (see Figure 1 for STROBE Diagram). After exclusion of ineligible MTD cases, we matched three methadone-poisoned children per SL BUP poisoning case, resulting in a 3:1 ratio. All 30 SL BUP cases that were admitted during the study period were included. 170 cases with MTD poisoning were admitted during the study period, of whom, 90 (source of MTD poisoning was tablet formulation in 29 [32.2%] and syrup formulation in 61 [67.8%]) were matched to BUP cases and included. The remaining 80 MTD cases were excluded since one had intentionally ingested MTD, 64 were not admitted within 72 h of admission of SL BUP cases or the intent was not defined or equivalent dose was not matched, and 15 could not be matched to BUP cases based on age or gender.

### Demographics

Among the study sample of 120 patients, 71 (59.2%) were male. The median age was 24 months [18, 36] (range: 4–96 months), and the median weight was 12 kg [10, 14] (range: 7–23 kg). The demographic characteristics (age, gender, weight) of the two groups did not differ significantly as they were matched regarding these variables ($p > 0.05$; see Table 1). 48 (53.3%) MTD and 19 (63.3%) BUP cases were referred from other hospitals/clinics ($p$ = ns).

### Clinical outcomes

#### Primary outcome

The general condition of patients in the two groups changed over time, with MTD-poisoned patients (20/90; 22.2%) developing significantly higher rates of apnea ($p = 0.003$) than BUP patients (0/30; 0%). Further analysis showed that the odds of experiencing apnea in MTD cases was 17.3 times higher than for BUP cases (95% CI 1.1, 302.8; $p = 0.047$). Bradypnea was documented in 39/90 MTD vs. 10/30 BUP cases ($p$ = ns).

#### Secondary outcomes

In terms of presentation on arrival, SL BUP cases had significantly more LOC compared to MTD cases ($p = 0.013$), although deep coma (unresponsive to pain in APUV scale) was more common in MTD patients (ns); see Table 2. No in-hospital fatalities occurred in either group, and all patients were discharged symptom-free. The duration of hospitalization was significantly longer ($p < 0.001$) for MTD cases (median 3.5 days vs. 2 days in the BUP group; see Table 2). pH and $O_2$ saturation were less in MTD patients while the pulse rate was higher. Nose and face itching was more common in BUP cases (Table 2).

#### Naloxone treatment

Forty-eight MTD cases (53.3%) had been treated with naloxone in the prehospital setting or referred hospitals but 5 (10.4%) developed apnea in subsequent hours. The odds of apnea were 4.8 times (95% CI 1.6, 14.6) higher in those who were admitted directly to the hospital compared to those children who had already received naloxone treatment in the prehospital setting or referring hospitals (15 cases; 35.7% vs. 5 cases; 10.4%, $p = 0.004$).

In the hospital ED, 79 cases (65.8%) received naloxone. The odds of receiving naloxone treatment were 2.5 times (95% CI 1.1, 5.7) higher for MTD than BUP cases (64 cases, 71.1% vs. 15 cases, 50%; $p = 0.035$). The administered dose of naloxone was significantly lower in BUP cases. Naloxone infusion was started in all hospitalized MTD and BUP patients, but the dose administered was again significantly lower for BUP cases (2.4 mg [1.6, 3.2] vs. 14.4 [8.0, 24.2]; $p = 0.001$, Table 2).

#### Gastric washing

SL BUP cases had a significantly ($p < 0.001$) earlier presentation to the ED, with a median [IQR] (range) of 1 [0.5, 1.2] hour elapsed between ingestion and hospitalization, relative to 3 [2, 4] (0.5, 12) hours in the MTD group. As follows, SL BUP cases (24/30; 80%) underwent gastric washing significantly more ($p < 0.001$) often than the MTD group (25/90; 27.8%, OR (95% CI) 10.4 (3.8, 28.5). No complications were observed using this technique.

#### Miosis

Out of a total of 120 MTD and SL BUP cases, 96 (80%) referred with miotic/pinpoint pupils. Miosis was significantly more common in MTD patients [79, 88%, vs. BUP: 17, 57%; $p < 0.001$, Table 2]. All 20 MTD patients with apnea had miotic/pinpoint pupils. 76 (79.2%) patients with miotic pupils did not experience apnea ($p = 0.012$). The incidence of miotic pupils in bradypnea cases was 44 (89.8%). The presence of miotic pupils was associated with increased odds (3.2 times) of bradypnea (95% CI 1.1, 9.3, $p = 0.026$).

### Logistic regressions

After performing Enter logistic regression applying all categorical on-arrival variables with significance $p$-value $< 0.2$ (including group [MTD vs. BUP], admission type [direct vs. referral], miosis [yes vs. no], bradypnea [yes vs. no], drug formulation [tablet vs. syrup] and AVPU scale), the only factor that predicted apnea in patients was LOC as per AVPU scale; (OR = 3.8, 95% CI 1.2, 11.6, $p < 0.001$). Odds of apnea were 42.4 times higher (95% CI 4.7, 379.0) in patients unresponsive to pain stimuli on the AVPU scale ($p < 0.001$).

Applying on-arrival categorical variables with $p$-value $<$ 0.2 including miosis (yes vs. no), apnea (yes vs. no), direct

Table 1. Demographics, opioid exposure, and admission mode.

| | Methadone ($n = 90$) | Buprenorphine ($n = 30$) | $p$-Value | OR (95% CI) | Total ($n = 120$) |
|---|---|---|---|---|---|
| Demographics | | | | | |
| Age (months)[a] | 26 [18, 36] (4, 96) | 24 [18, 36] (9, 96) | 0.463[c] | | 24 [18, 36] (4, 96) |
| Weight (Kg)[a] | 12 [10, 14] (7, 23) | 12 [10, 15] (7, 23) | 0.784[c] | | 12 [10, 14] (7, 23) |
| Gender: male, $n$ (%) | 55 (61) | 16 (53) | 0.453[d] | | |
| Opioid exposure | | | | | |
| Ingested dose (mg/Kg)[a,b] | 1.1 [0.7, 1.8] (0.3, 8) | 0.1 [0.1, 0.2] (0.1, 0.3) | | | |
| Equivalent methadone dose (mg/Kg)[a,b] | 1.1 [0.7, 1.8] (0.3, 8.0) | 1.7 [0.6, 2.4] (0.3, 3.9) | 0.317[c] | | 1.2 [0.6, 2.1] (0.3, 8.0) |
| Route of administration: Ingestion (vs. sucking), $n$ (%) | 90 (100) | 20 (67) | <0.001[e] | 0.67 (0.52, 0.86) | 110 (92) |
| Time elapsed since ingestion (hrs)[a] | 3 [2, 4] (0.5, 12) | 1 [0.5, 1.2] (0.5, 5) | <0.001[c] | | 2 [1, 4] (0.5, 12) |
| Opioid source, $n$ (%) | | | | | |
| Parents (all fathers) | 59 (65) | 20 (67) | 0.053[d] | | 79 (66) |
| Grandparents | 8 (9) | 3 (10) | | | 11 (9) |
| Others | 9 (10) | 7 (23) | | | 16 (13) |
| Unknown | 14 (16) | 0 | | | 14 (12) |
| Mode of hospital admission | | | | | |
| Referral, $n$ (%) (vs. direct admission) | 48 (53) | 19 (63) | 0.339[d] | | 66 (55) |

[a]Median [IQR] (range); [b]31 missing cases in MTD group; [c]MWU: Mann–Whiney $U$ test; [d]Person's Chi-square, [e]Fisher's Exact Test.
OR: odds ratio; CI: confidence interval.

admission (yes vs. no), AVPU scale, MTD poisoning could be independently predicted by the on-admission low level of AVPU scale (OR = 0.3, 95% CI 0.2, 0.8), miotic pupils (OR = 4.8, 95% CI 1.7, 13.3), and apnea (OR = 16.9, 95% CI 1.4, 200.8) ($p < 0.001$).

## Discussion

Based on our results, BUP-poisoned children had referred with higher degrees of loss of consciousness but subsequently experienced less severe toxicity, as indicated by no episodes of apnea and lower doses of naloxone, compared to the MTD group. None of the patients in either group died.

The increased availability of MTD and BUP (as BUP or BUP/naloxone) in households puts young children at risk of exposure to these opioids. Toddlers are highly susceptible to the adverse effects of these compounds [12]. Most of our patients were in the age group of 1-3 year-olds (median age of 2 years), confirming that young children in the phase of object exploration are at greater risk of unintentional drug exposure and poisoning.

Compared to MTD, BUP seems to have the same efficacy as the medication of opioid use disorder [13,14], but has been described to have lower toxicity regarding its pharmacodynamic properties and to present less severe opioid syndromes with a "ceiling effect" for respiratory depression [13,15]. This means that if a certain dose is reached, the ingestion of more BUP does not cause further suppression of the respiratory drive. Our cases of BUP poisoning yield the same conclusion.

BUP has a high affinity for opioid receptors, and therefore it is generally suspected that in acute poisonings, high doses of naloxone are needed to reverse BUP action [16]. One unexpected finding of the current study is, however, that the mean dose of initial bolus naloxone was significantly lower in the SL BUP group. This cannot be explained by the total opioid dose the child had ingested, as there was no significant group difference in the doses of MTD and BUP (converted into morphine equivalent dose). A similar observation had previously been reported by Geib and colleagues where BUP-poisoned children responded to naloxone doses of as low as 0.2 to 0.8 mg [17]. Still, in our study, the median dose of 0.02 mg for the SL BUP group was far below their results. A possible explanation is taking naloxone before ED admission in referral cases and early admission compared to the MTD group (1 vs. 3 h).

In both groups, many patients needed naloxone treatment. Additionally, five patients in the MTD group needed intubation, indicating that their poisoning was more severe. However, none of our patients died – maybe due to early referral of the patients with BUP poisoning and prolonged hospitalization and observation of the patients with MTD toxicity. This is also compatible with findings from previous studies which suggest that prolonged overnight observation is beneficial in MTD-poisoned pediatric patients [18].

Our regression analysis showed that apnea and miotic pupils could be detected more commonly in MTD poisoning patients. Only late gastric washing could have a possible role in this finding which seems to be the effect and not the cause of such difference as the MTD-poisoned patients had referred later and therefore had undergone gastric washing less frequently than the BUP group (see Table 2). Meanwhile, the time elapsed between ingestion and presentation could not prognosticate apnea in either group.

The other interesting finding was that miotic pupils were significantly more common in the MTD group, whereas itching and mild to moderate loss of consciousness were recorded more often in the SL BUP group. Since the data from MTD cases were retrieved retrospectively, some variables like itching may have not been recorded systematically and should therefore be interpreted with caution, although this represents an interesting finding itself.

Table 2. Clinical characteristics on arrival, treatment, and duration of hospitalization.

| | Methadone ($n = 90$) | Buprenorphine ($n = 30$) | $p$-Value | OR (95% CI) | Total ($n = 120$) |
|---|---|---|---|---|---|
| Clinical characteristics | | | | | |
| Axillary temperature (°C)[a] | 37.0 [36.6, 37.0] (36.0, 39.0) | 36.8 [36.5, 37.0] (35.9, 37.0) | 0.224[b] | | 36.8 [36.5, 37.0] (35.9, 39.0) |
| pH[a] | 7.35 [7.31, 7.38] (7.00, 7.53) | 7.37 [7.33, 7.41] (7.28, 7.48) | 0.044[b] | | 7.35 [7.31, 7.39] (7.00, 7.53) |
| $O_2$ saturation (%)[a] | 96 [92, 98] (80, 99) | 96 [95, 98] (92, 99) | 0.008[b] | | 96 [93, 98] (80, 99) |
| $pCO_2$ (mmHg)[a] | 35.5 [32.3, 41.3] (23.0, 53.0) | 36.4 [33.4, 42.1] (21.8, 50.0) | 0.896[b] | | 35.6 [32.9, 41.5] (21.8, 53.0) |
| Respiratory rate (per min)[a] | 24 [20, 26] (8, 43) | 22 [20, 27] (14, 40) | 0.692[b] | | 24 [20, 26] (8, 43) |
| Bradypnea, *n* (%) | 39 (43) | 10 (33) | 0.335[c] | | 49 (41) |
| Apnea, *n* (%) | 20 (22) | 0 | 0.003[d] | 1.3 (1.1, 1.4) | 20 (17) |
| Mean arterial pressure (mmHg)[a] | 70 [70, 73] (43, 87) | 70 [67, 73] (53, 85) | 0.297[b] | | 70 [70, 73] (43, 87) |
| Pulse rate (per min)[a] (min, max) | 110 [102, 120] (80, 153) | 105 [90, 116] (80, 140) | 0.045[b] | | 110 [100, 120] (80, 153) |
| Hypotension, *n* (%) | 0 | 1 (3) | 0.250[d] | | 1 (1) |
| Glasgow Coma Scale[a] | 13 [13, 15] (6, 15) | 14 [14, 14] (10, 15) | 0.319[b] | | 13 [14, 15] (6, 15) |
| Level of consciousness, *n* (%) | | | | | |
| Awake | 28 (31) | 3 (10) | 0.013[c] | Cramer's v: 0.299 | 31 (26) |
| Verbal stimulation | **50 (56)** | **22 (73)** | | | 72 (60) |
| Painful stimulation | 5 (6) | 5 (17) | | | 10 (8) |
| Unresponsive | 7 (8) | 0 | | | 7 (6) |
| Miosis, *n* (%) | 79 (88) | 17 (57) | <0.001[c] | 5.5 (2.1, 14.3) | 96 (80) |
| Vomiting, *n* (%) | 48 (53) | 17 (57) | 0.834[c] | | 65 (54) |
| Itching, *n* (%) | 26 (29) | 15 (50) | 0.035[c] | 0.4 (0.1, 0.9) | 41 (34) |
| Treatment | | | | | |
| Median [IQR] Naloxone initial bolus (mg)[a] | 0.4 [0.0, 0.8] (0, 3.2) | 0.02 [0, 0.4] (0, 4) | 0.014[b] | | 0.3 [0, 0.4] (0, 4) |
| Naloxone infusion (mg)[a] | 14.4 [8.0, 24.2] (1.6, 106) | 2.4 [1.6, 3.2] (0.8, 16) | <0.001[b] | | 11.2 [4.8, 20.3] (0.8, 106) |
| Cardiopulmonary resuscitation, *n* (%) | 5 (6) | 0 | 0.330[d] | | 5 (4) |
| Intubation, *n* (%) | 5 (6) | 0 | 0.330[d] | | 5 (4) |
| Ambubag ventilation, *n* (%) | 5 (6) | 0 | 0.330[d] | | 5 (4) |
| Gastric washing, *n* (%) | 25 (28) | 24 (80) | <0.001[c] | 10.4 (3.8, 28.5) | 49 (41) |
| Activated charcoal, *n* (%) | 44 (49) | 19 (63) | 0.170[c] | | 63 (52) |
| Hospitalization | | | | | |
| Duration (days) | 3.5 [3.0, 3.5] (1.5, 5.5) | 2 [1.5, 2.0] (1.0, 3.0) | <0.001[b] | | 3.0 [2.0, 3.5] (1.0, 5.5) |

[a]Median [IQR] (range); [b]MWU: Mann–Whiney *U* test; [c]Person's Chi-square; [d]Fisher's Exact Test.
OR: odds ratio, CI: confidence interval. Bold numbers are defining the main cause of significance in each category.
Itching was in the face and nose except whole body iching in 2 cases.

In the current study, the number of cases was higher for MTD poisoning than for SL BUP. It may be attributed to more exposure to MTD than SL BUP in the community, but also it may be due to different formulations available in the home environment. MTD has tablet and syrup formulations and we have already shown that syrup formulation may cause more accidental poisoning compared to a tablet, in which it is the only available formulation of SL BUP [19].

Considering all the above-mentioned results emphasizes the fact that such poisonings in children are better to be prevented instead of treated. Although our results with the management of these patients are promising, one cannot be sure that all cases of poisoning can be treated easily and complication-free. This shows the importance of the previously performed studies in this regard and the fact that we still need their recommendations implemented to decrease the risk of poisoning, complications, and deaths due to these intoxications in children [5].

## Limitations

It was impossible to estimate the opioid dose that was absorbed by sucking, licking, or ingestion. Thus, the central limitation of the current study is the fact that we were unable to determine the serum levels of MTD and BUP due to technical limitations with laboratory assays. A second limitation concerns the fact that we selected our MTD group retrospectively. Future prospective studies taking these limitations into consideration are warranted. Extend-release formulations of medications for opioid use disorder (e.g., BUP injection) may reduce rates of pediatric poisoning.

## Conclusion

BUP and MTD are two common medications for opioid use disorder, which are also frequent sources of opioid poisoning, with potentially life-threatening results in pediatric patients. Although BUP-poisoned patients had mild to moderate loss of consciousness on initial presentation, MTD-intoxicated cases were more prone to severe poisoning. This is likely because MTD is a pure agonist with a longer half-life relative to the partial agonist BUP. Our results indicate that, compared to buprenorphine, methadone exposure is more toxic in pediatric populations.

## Acknowledgments

Methadone data were collected based on the specialization thesis by RZ. Funding from SBMU was used to support the design and the conduct of the study.

## Disclosure statement

No potential conflict of interest was reported by the author(s). The sponsor had no role in the collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

## Funding

This study was financially supported by the SBMU Toxicological Research Center [14639].

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