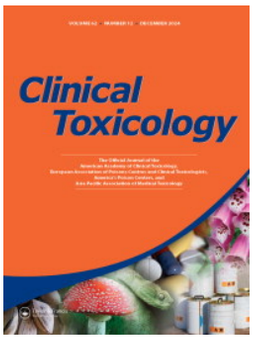

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POISON CENTRE RESEARCH



# Does the time between doses in an unintentional double dose bupropion exposure affect the incidence of adverse effects? A retrospective cohort study

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**ABSTRACT**

**Introduction:** Unintentional therapeutic errors with bupropion are common. The impact of the timing of the second dose in a double dose exposure on adverse effects is not well studied. This study aims to compare adverse effects between double doses separated by <720 min and ≥720 min.

**Methods:** This was a retrospective cohort study of unintentional double dose bupropion ingestions in patients reported to a regional poison center between January 2018 and December 2022. Patients were included if the double dose was their own medication, unintentional, and a single substance exposure. Data collected included age, gender, bupropion formulation, prescribed home dose, dosing error details, time between doses, caller site, referral to the emergency department, patient observation at healthcare facilities, clinical effects, and outcome.

**Results:** Among 663 cases screened, 294 met inclusion criteria. The majority involved extended-release preparations (69.0%). Seventy-four were observed in a healthcare facility and monitored for 24 h from initial dose. The incidence of seizures was 5.3%, including one case not observed for a full 24 h. There was no significant difference in the incidence of seizures (2.7% versus 7.7%), tachycardia (27.0% versus 30.8%), hypertension (18.9% versus 38.5%) other signs/symptoms (27.0% versus 23.1%), or any signs/symptoms (48.6% versus 61.5%) between double doses of extended release bupropion separated by <720 min and those separated by ≥720 min, respectively.

**Discussion:** In patients with double dose exposures to extended-release bupropion, it does not appear that the timing of the second dose can be used to risk-stratify patients. Our data are limited by sample size.

**Conclusion:** In this study, the time between double doses of bupropion did not affect the incidence of seizure, tachycardia, hypertension, other signs/symptoms, or any signs/symptoms. Larger, prospective studies investigating this difference would strengthen our understanding and management of these patients.

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Bupropion; double dose; poison center; seizure; therapeutic error

## Introduction

Bupropion is an antidepressant approved by the United States (US) Food and Drug Administration (FDA) for the treatment of depression, seasonal affective disorder, smoking cessation, and as a combination product with naltrexone for weight loss [1–5]. Bupropion was first approved by the US FDA in 1985 but was subsequently withdrawn from the market due to increased seizure risk. After modifying the dose recommendations, bupropion immediate release (three times per day dosing) was re-introduced in 1989 [6]. A sustained-release formulation (twice per day dosing) was introduced in 1996, and an extended-release formulation (once per day dosing) was introduced in 2003 [7].

At the current approved dosing regimen of a maximum of 450 mg/day, seizures occur in up to 0.4% of patients taking immediate release and sustained release formulations [1,2,8]. The risk of seizures is dose dependent, increasing to 2.2–2.8% when doses exceed 450 mg/day [8–10]. When the dose is kept at 300 mg/day, the risk of seizures with the sustained release formulations is only 0.1% [2,11]. The exact incidence of seizures with the extended release formulation has not been evaluated but is assumed to be comparable to the immediate release and sustained release formulations [3].

The incidence of seizure is greater after overdose, and was reported as greater than 30% in one study [12]. Seizures can begin in a delayed fashion, up to 24 h after ingestion [12–14]. However, with therapeutic errors, for which seizure would be the most concerning adverse effect, the incidence of seizures was markedly lower at 0.6–0.8% in two studies [6,15]. Despite this relatively lower incidence, due to the risk of delayed seizures, our poison center typically recommends 24 h observation even for isolated double dose ingestions of bupropion.

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The necessity of this lengthy observation period is challenged by some authors based on the low incidence of serious adverse effects [14,15].

One question that requires further investigation is the impact of the timing of the second dose in an unintentional double dose ingestion on the incidence of adverse events. We hypothesize that the incidence of adverse effects in unintentional double dose bupropion ingestions separated by at least 720 min (12 h) will be less frequent than doses taken less than 720 min apart.

## Methods

An institutional review board exemption was granted for this study. We performed a retrospective cohort study of patients with an unintentional double dose bupropion exposure reported to a single large regional poison center. We reviewed case narratives of a convenience sample of all closed human exposure cases from 1 January 2018 to 31 December 2022 with single substance exposures to bupropion with "reason for the exposure" coded as "unintentional-general", "unintentional-therapeutic error", "unintentional-unknown", "adverse reaction – drug", or "unknown reason." The National Poison Data System® (NPDS) generic code 0310019 was used to capture all bupropion formulations.

Data were collected by the principal investigator (MK), and four additional reviewers (AA, PA, SM, JM). All reviewers were trained by MK for uniform data extraction.

Cases were excluded if (1) there was any report in the narrative of an intentional component to the exposure, (2) the medication did not belong to the patient, (3) the exposure was greater than a double dose, (4) the dosing error also involved other medications, or (5) the bupropion was insufflated.

For included cases we recorded age, gender, bupropion formulation, and typical home dose if known. The dosing error was described in free text by the reviewer, including the total dose if known. We recorded the approximate time between doses. If the exact time was not documented, but the error was described as taking a morning dose followed by an additional dose in the evening (or vice versa), we recorded the time as 720 min (12 h). Likewise, if the error was described as taking the additional dose shortly after the first dose without giving an exact time, we recorded the time as 0 min. We recorded caller site, whether home callers were referred into the emergency department, whether referred callers presented to the emergency department, and whether the patient was observed at the healthcare facility for 24 h after initial bupropion dose (if appropriate).

For cases evaluated at a healthcare facility and monitored for 24 h from first dose, additional data collected included: seizure, tachycardia (defined as a heart rate >100 beats/min or greater than age-adjusted norms per Pediatric Advanced Life Support, hypertension (defined as a systolic blood pressure greater than 140 mmHg, a diastolic blood pressure greater than 90 mmHg, or greater than age adjusted norms per Pediatric Advanced Life Support). Other coded or described effects were coded as "other signs/symptoms". We recorded whether the patient received benzodiazepines or activated charcoal. Coded medical outcomes were recorded using standard definitions utilized by the NPDS®.

For the cases that were evaluated at a healthcare facility and monitored for 24 h from first dose, we divided all cases involving an extended-release product for which the time between doses was coded into <720 min (12 h) and ≥720 min (12 h). The groups were compared for incidence of seizures, tachycardia, hypertension, other signs/symptoms (any other coded or described sign/symptom), or any sign/symptoms (seizure, tachycardia, hypertension, or other sign/symptoms). The groups were also compared for differences in rates of activated charcoal administration and benzodiazepine administration.

### *Statistics*

Descriptive statistics were calculated. Comparisons were analyzed with the chi-squared test or Fisher's exact test, with Fisher's exact test being used if the expected value in >20% of the cells was <5 [16,17]. Significance was set at a *P*-value of 0.05.

### *Inter-reviewer assessment*

Reviewers were encouraged to be specific in free text areas, and to note if any coding needed clarification by MK. To ensure accurate data extraction, a minimum of 10% of each reviewers' assigned cases were reviewed. One author (MK) reviewed the cases of AA, PA, JM, and SB. Another author (AA) reviewed the cases of MK. Any discrepancies were addressed, and the final decision was made by MK. All seizure cases were reviewed in detail to ensure accuracy. Also, MK reviewed the exposure narrative in all cases included in the comparison between doses <720 min and ≥720 min to ensure accuracy in inclusion in each respective group.

## Results

A total of 663 cases were screened and 294 met inclusion criteria. Of those meeting inclusion criteria, 74 were seen in a health care facility and monitored for 24 h from first dose (Figure 1).

Table 1 provides demographic data and descriptive statistics of the included cases. The largest number of included cases came from 2022 data (26.2%), followed by 2020 (24.5%). The most common age was "unknown adult ≥20 years," with 28.2% of the cases. Of the specific age groups, the most common was 20s, with 18.7% of cases. Most patients (72.4%) were female. Most cases involved extended-release products (69.0%).

Most calls (87.4%) were from home or "other" sites. Our poison center referred 79.4% of home calls to a healthcare facility, and 44.6% were confirmed to have arrived at the healthcare facility. When including those patients that had already presented to a healthcare facility at the time of the poison center call, only 43.5% of the total cases were evaluated at a

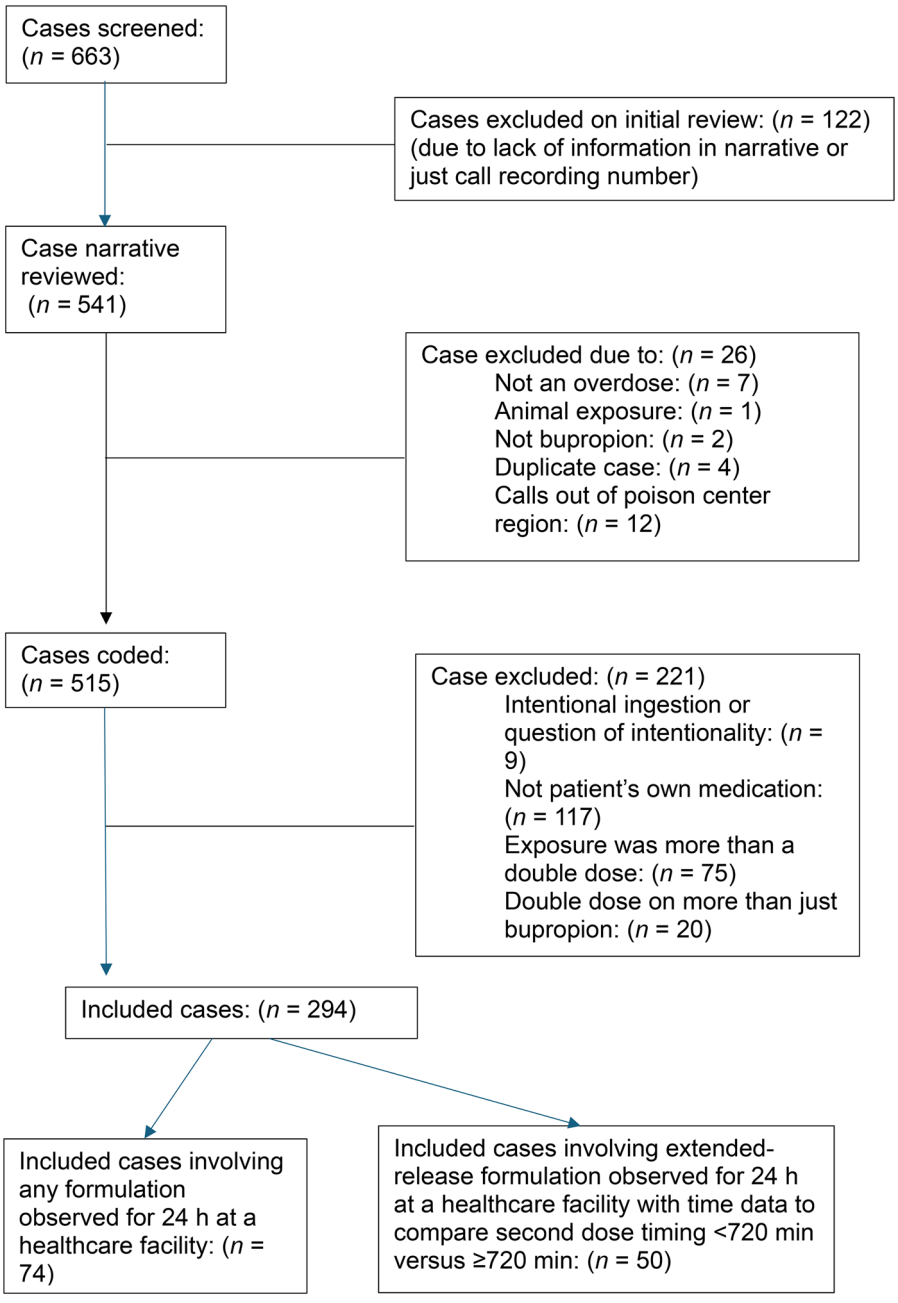


Figure 1. Breakdown of included/excluded cases.

healthcare facility. Of the cases seen at a healthcare facility, 57.8% were monitored for 24 h from first dose.

Table 2 describes the clinical effects of double dose bupropion exposures which were seen at a healthcare facility and monitored for 24 h from first dose (all formulations included). The incidence of seizures was 4.1% ($n = 3$). However, there was one case that had a seizure but was not monitored for a full 24 h. If this case is included, the incidence is 5.3% ($n = 4$). The incidence of tachycardia among all cases observed in a healthcare facility and monitored for 24 h was 29.7%, and the incidence of hypertension was 29.7%. The incidence of other signs/symptoms was 29.7% and the incidence of any sign or symptom was 55.4%. Regarding the medical outcome, most cases were coded as no effect (58.1%), followed by minor effect (25.7%). No cases were coded as major effect.

### *Comparison of double dose extended release bupropion exposures separated by <720 min (12 h) versus ≥ 720 min (12 h) observed at a healthcare facility and monitored for 24 h from first dose*

Table 3 specifically compares patients followed in a healthcare facility for 24 h with extended-release bupropion exposures separated by less than 720 min with exposures separated by greater than or equal to 720 min. Cases that did not have a time between doses recorded were excluded from this analysis. There was no statistical difference in the incidence of seizures, tachycardia, hypertension, other signs/symptoms, or any signs/symptoms (seizure, tachycardia, hypertension, or other signs/symptoms) between these two groups. There was one patient with seizure in the <720 min group and one patients with seizure in the ≥720 min group. There was no significant difference between the

Table 1. Demographics and patient characteristics.

| Year | *n* (%) |
|---|---|
| 2018 | 46 (15.6) |
| 2019 | 33 (11.2) |
| 2020 | 72 (24.5) |
| 2021 | 66 (22.4) |
| 2022 | 77 (26.2) |
| Total | 294 |
| **Age (years)** | |
| 6–12 | 3 (1.0) |
| Teenager | 21 (7.1) |
| 20s | 55 (18.7) |
| 30s | 44 (15.0) |
| 40s | 37 (12.6) |
| 50s | 26 (8.8) |
| 60s | 15 (5.1) |
| 70s | 6 (2.0) |
| 80s | 2 (0.7) |
| Unknown adult (≥20) | 83 (28.2) |
| Unknown | 2 |
| **Gender** | |
| Male | 81 (27.6) |
| Female | 213 (72.4) |
| **Formulation** | |
| 12 h, Wellbutrin SR®, Zyban® | 16 (5.4) |
| Extended Release 24 h, Aplenzin®, Forfivo XL®, Wellbutrin XL® | 203 (69.0) |
| Naltrexone HCl/Bupropion HCl | 3 (1.0) |
| Unknown | 72 |
| **Observation** | |
| Caller from home/other | 257 (87.4) |
| Poison center recommended healthcare evaluation | 204 (79.4) |
| Total recommended home cases that presented to healthcare facility | 91 (44.6) |
| Total evaluated at a healthcare facility | 128 (43.5) |
| Total observed by healthcare facility for 24 h from first dose | 74 (25.2) |

Table 2. Clinical effects of bupropion double dose exposures seen at a healthcare facility and monitored for 24 h from first dose (*n* = 74).

| Clinical effects* | *n* (%) |
|---|---|
| Seizure | 4 (5.3)** |
| Tachycardia | 22 (29.7) |
| Hypertension | 22 (29.7) |
| Other sign/symptom | 22 (29.7) |
| Any sign/symptom | 41 (55.4) |
| **Coded outcome** | |
| No effect | 43 (58.1) |
| Minor effect | 19 (25.7) |
| Moderate effect | 9 (12.2) |
| Not related, the exposure was probably not responsible for the effect | 3 (4.1) |

*The total exceeds 74 because patients may have one or more clinical effect.
**One case for which a seizure occurred was not observed for 24 h. Adding this case to the cohort gives an incidence of seizures of 5.3%.

groups in rates of activated charcoal administration or benzodiazepine administration.

### *Seizure cases*

Four cases reported seizures, though the authors question whether a true seizure occurred in case 4. Case narratives are summarized in Table 4.

### *Inter-reviewer assessment*

In reviewing 10% of each reviewer's charts, minimal discordance was identified. The most common errors were noted and addressed by re-review. First, it was noted that two cases were erroneously included that were chronic double doses, and one was included that was a triple dose, not a double dose. Therefore, MK reviewed all the descriptions of dosing error on included cases to ensure any similar oversights were addressed. Second, it was noted that an oversight in the initial exclusion criteria was that cases were not specifically excluded if they originated in a location that may have ultimately been followed by a different poison center (example: out-of-state). This was corrected by re-review by MK.

Other than discussed above, of the 70 cases reviewed in full, only some minor coding errors were noted in four (5.7%) cases: one case had the time between doses changed from 720 min to 780 min, one had the time between doses changed to unknown as it was felt that the narrative was unclear, one case was clarified as it was coded as unknown formulation but the specific formulation was available, and one case had symptoms added (confusion/lightheaded/anxious) that were initially not coded.

Table 3. Patients followed in a healthcare facility for 24 h with extended-release bupropion exposures separated by time between doses (*n* = 50).

| | <720 min (*n* = 37) | ≥720 min (*n* = 13) | |
|---|---|---|---|
| Signs and Symptoms* | *n* (%) | *n* (%) | *P*-value |
| Seizure | 1 (2.7) | 1 (7.7) | Not significant** |
| Tachycardia | 10 (27.0) | 4 (30.8) | Not significant** |
| Hypertension | 7 (18.9) | 5 (38.5) | Not significant** |
| Other signs/symptoms | 10 (27.0) | 3 (23.1) | Not significant** |
| Any signs/symptom | 18 (48.6) | 8 (61.5) | Not significant*** |
| Management | *n* (%) | *n* (%) | |
| Activated charcoal | 15 (40.5) | 5 (38.5) | Not significant*** |
| Benzodiazepine | 4 (10.8) | 1 (7.7) | Not significant** |

*The total exceeds 50 because patients may have one or more clinical effect.
**Fisher's exact test.
***chi-square test.

## Discussion

Therapeutic errors are a common source of calls to poison centers. In 2022, there were 331,539 cases involving therapeutic errors, and 47.2% of those involved either an inadvertent double dose or some other dosing error [18]. Poison centers frequently receive calls regarding bupropion dosing errors and given its narrow therapeutic window, these patients are often referred to healthcare facilities. This study aimed to investigate whether the timing of the second dose in a double dose exposure affected the incidence of seizure and other adverse effects seen after unintentional double doses of bupropion.

We hypothesized that if a patient experienced an unintentional double dose of an extended-release bupropion product with a duration of time between the doses of at least 720 min (12 h), the rates of signs and symptoms would be less. We found that there was no difference in the incidence of seizures, tachycardia, hypertension, other signs/symptoms, or any signs/symptoms. A power calculation was not done, and our sample size was small, so it possible that a difference exists that we were unable to identify (a type II error). However, if this is the case, it is worth noting that the patients in the ≥720 min group seen at a healthcare facility and monitored for 24 h from first dose were not asymptomatic; 30.8% developed tachycardia, 38.5% had hypertension,

**Table 4.** Narrative summary of patients with seizures.

| | |
|---|---|
| Case 1 | A 24-year-old female with a history of bipolar disorder, anxiety, and post-traumatic stress disorder reportedly took bupropion 300 mg extended release at 18:00 and then again at midnight (6 h later), for a total of 600 mg. She felt anxious and tremulous and her husband thought she had a seizure at home. She presented to the emergency department at 04:30 and the poison center was contacted. On arrival, her blood pressure was 152/95 mmHg and her heart rate was 122 beats/min. Her blood work was normal. She received intravenous fluids and was monitored on telemetry. Her heart rate, tremulousness, and anxiety improved. No further seizures occurred. |
| Case 2 | 19-year-old male with a history of attention deficit hyperactivity disorder and bipolar disorder presented to the emergency department after having a seizure lasting 30 s. He vomited once before arrival. The patient was seen at bedside by a medical toxicologist and the poison center was contacted. The patient reported taking bupropion extended release 150 mg in the morning, but that he may have unintentionally taken an additional dose the night before. He had also smoked cannabis in the morning about 3 h prior to the seizure. His vital signs were normal, and his examination was unremarkable. He had a family history of seizures in his brother. The patient was observed for less than 24 h and discharged. |
| Case 3 | 18-year-old male presented after unintentionally taking a second dose of his bupropion 450 mg (presumed to be extended release based on the dose and once a day dosing). As for the timing of the second dose, the exact phrasing was: "he believes he accidentally repeated his bedtime dose of bupropion 450 mg last night at around 9 am. When he woke this morning, he felt odd and knew something was wrong;" [Based on the specific time of 09:00, it was coded as 720 min (dose in the evening and then dose in the morning)]. In the emergency department, he was altered, anxious, and possibly hallucinating per staff, and the poison center was consulted. He was tachycardic at 140 beats/min and hypertensive at 143/73 mm/Hg. He had a brief seizure in the emergency department and received lorazepam. He was admitted, observed, and improved over time and was ultimately discharged. |
| Case 4 | 33-year-old female unintentionally took bupropion 300 mg (unknown formulation) twice, with an unknown amount of time between doses. She presented to the emergency department and the poison center was contacted. Her daughter reported that she had abnormal shaking while she was sleeping, and therefore it was coded as a seizure. She was tachycardic at 127 beats/min which rapidly improved to 89 beats/min. Her blood pressure was 151/89 mmHg. The remainder of her examination was normal. The patient tested positive for COVID-19, and while undergoing an evaluation for a pulmonary embolism, the case was closed at the poison center. |
| | *It is important to note that the documentation in this case was limited. |

23.1% developed other signs or symptoms, and 61.5% developed any sign or symptom.

There was no difference in incidence of seizures when the double dose was spaced by ≥720 min, though the study was likely underpowered to identify a difference. There were two seizures identified in the data set that occurred with staggered, double dose ingestions (only one of which was monitored for 24 h from first dose). However, the details of these cases raise some questions. Case 2 involved a patient who self-presented after ingesting 300 mg. However, he also reported using cannabis prior to the seizure. It is possible the patient had smoked something other than cannabis, perhaps a synthetic cannabinoid, which could have contributed to the seizure. For case 3, the reported ingestion was two 450 mg tablets. However, there is some question as to the timing of the two doses in this case based on the documentation, and the double dose may have actually occurred <720 min apart.

In our cohort, the incidence of tachycardia in patients evaluated at a healthcare facility was 30.8%. This value is notably higher than what is described in two similar studies. In a retrospective poison center study, Shepherd and colleagues [6] found tachycardia to occur in 5.5% of patients with bupropion therapeutic errors. Similarly, Beuhler and colleagues [15] found a 12% incidence of tachycardia in patients with non-staggered, acute therapeutic errors of bupropion. However, looking at these studies in detail, most cases were not evaluated at a healthcare facility. Only 26.6% and 43.8% of patients were seen at a healthcare facility, as reported by Shepherd and colleagues [6] and Beuhler and colleagues [15], respectively. We suspect our incidence of tachycardia is higher as we only included cases seen at a healthcare facility with vital signs recorded. It is possible that home calls have undocumented tachycardia, as vital sign monitoring at home is often unavailable.

The rate of seizures in our cohort is 5.3% among all patients evaluated at a healthcare facility (including the one case not monitored for a full 24 h). This is greater than the incidence of seizures described by Beuhler and colleagues [15] of 0.6%, and by Shepherd and colleagues [6] of 0.8%, but lower than the incidence described by Correia and colleagues [19] of 6.1%. It is unclear why this range of seizure incidence exists between these studies. However, it is worth noting that in the three studies compared above, all cases were included, not just cases evaluated in a healthcare facility. The cases in our cohort who did not present to a healthcare facility were usually either not followed at home or were unable to be followed at home, and so we opted to exclude them entirely to limit bias. Further, we only included cases that were monitored for 24 h from first dose of bupropion to prevent missing any potential late seizures.

An optimal approach to the poison center management of bupropion double dose exposures remains difficult given variation in data and risk of seizure. The findings of this study suggest that the time of the second dose of bupropion in unintentional double dose exposures cannot be used to risk-stratify patients. It may be reasonable to discuss an option of home management in select patients, especially if the patient has someone with them at home, they agree to follow standard seizure precautions and agree to proceed to a healthcare facility if they develop symptoms. Further, studies suggest that tachycardia is predictive of a seizure following a bupropion overdose [13,14]. Given the rise in watches and other devices with built in heart rate monitors, the caller could specifically be advised to monitor their heart rate at home, and to proceed to a healthcare facility if they develop tachycardia. Further research is needed to identify an optimal population for and approach to home management in these cases.

There are several limitations to this study. The study is retrospective in nature and so the typical limitations of retrospective chart reviews apply. As discussed above, a power calculation was not done and our sample size was small, posing risk of a type II error. In cases without a specific time interval between ingestions but for which it was reported a second dose was taken that evening or morning, the time frame was estimated to 720 min. Doses may have been further apart or closer together in actuality which could affect

the likelihood of adverse events. There is no confirmation of exposure in these cases. It is possible the patient thought they took a double dose when in fact they did not. The term "extended release" generally refers to the 24 h preparation. However, it is possible that some miscoding occurred when a patient was on a sustained release product. We included only healthcare facility patients in our main analysis. It is possible that this represents a sicker cohort, as patients with symptoms are more likely to present to care. Finally, the reviewers were not blinded to the study question and hypothesis. Therefore, bias may have been present in the narrative reviews.

## Conclusion

We were unable to demonstrate a difference in incidence of seizures, tachycardia, hypertension, other signs/symptoms, or any signs/symptoms in double dose extended-release bupropion exposures based on the timing of dosing error, in patients who were evaluated at a healthcare facility. The incidence of seizures in evaluated patients was 5.3%. We recommend that poison centers should continue to manage patients based on their usual protocol regardless of the timing between doses.

## Disclosure statement

No potential conflict of interest was reported by the authors.

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## Data availability statement

The data that support the findings of this study are available from the corresponding author, MK, upon reasonable request.

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