Toxicity of Bupropion Overdose Compared With Selective Serotonin Reuptake Inhibitors

Adam Overberg, PharmD,[a] Shannon Morton, MPH,[a] Emily Wagner, MD,[b] Blake Froberg, MD[a,c]

abstract

OBJECTIVES: Adolescent depression and attempted and completed suicide are increasing in the United States. Because suicide is often impulsive, the means of self-harm are frequently items of convenience like medication. Authors of a recent study compared tricyclic antidepressant overdose to bupropion overdose. Fluoxetine and escitalopram are the only agents with Food and Drug Administration approval for pediatric depression, but off-label bupropion prescriptions are common. We sought to compare the effects of selective serotonin reuptake inhibitors (SSRIs) and bupropion in overdose.

METHODS: This was an analysis of the National Poison Data System from June 2013 through December 2017 for adolescent (ages 10–19) exposures to SSRIs or bupropion coded as "suspected suicide." Demographics, clinical effects, therapies, and medical outcome were analyzed.

RESULTS: There were 30 026 cases during the study period. Sertraline and fluoxetine accounted for nearly 60%, whereas bupropion was reported in 11.7%. Bupropion exposure was significantly associated with death (0.23% vs 0%; $P < .001$) or serious outcome (58.1% vs 19%; $P < .001$) as well as the 10 most common clinical effects, including seizures (27.0% vs 8.5%; $P < .001$) and hallucinations (28.6% vs 4.3%; $P < .001$). Bupropion exposure was significantly associated with the need for cardiopulmonary resuscitation (0.51% vs 0.01%; $P < .001$), intubation (4.9% vs 0.3%; $P < .001$), vasopressors (1.1% vs 0.2%; $P < .001$), and benzodiazepines (34.2% vs 5.5%; $P < .001$). There was a significant increase in all exposures and in proportion of serious outcomes over time.

CONCLUSIONS: Adolescents who attempt self-harm are at higher risk for serious morbidity and poor outcomes with bupropion than with SSRIs. These risks, and the patient's propensity for self-harm, should be evaluated when therapy with bupropion is considered.

[a]*Indiana Poison Center, Indianapolis, Indiana; and Departments of* [b]*Emergency Medicine and* [c]*Pediatrics, School of Medicine, Indiana University, Indianapolis, Indiana*

Drs Overberg and Wagner conceptualized and designed the study, collected data, drafted the initial manuscript, and reviewed and revised the manuscript; Ms Morton conducted the initial analyses and drafted, reviewed, and revised the manuscript; Dr Froberg conceptualized and designed the study, coordinated and supervised data collection, and critically reviewed the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2018-3295

Accepted for publication May 6, 2019

Address correspondence to Adam Overberg, PharmD, Indiana Poison Center, 1701 N Senate Ave, Room B402, Indianapolis, IN 46202. E-mail: aoverberg@iuhealth.org

WHAT'S KNOWN ON THIS SUBJECT: Adolescents who attempt self-harm by overdose often choose medications of convenience and frequently have access to antidepressants. Selective serotonin reuptake inhibitors are the drugs of choice in pediatric depression; however, bupropion is also prescribed. A recent study highlighted bupropion's toxicity in adolescents.

WHAT THIS STUDY ADDS: In this study, we compare the effects of bupropion and selective serotonin reuptake inhibitors after adolescent single-agent suicidal ingestion. It may serve as guidance to practitioners when weighing benefits and risks of off-label antidepressant prescribing in adolescents who are at risk for self-harm.

To cite: Overberg A, Morton S, Wagner E, et al. Toxicity of Bupropion Overdose Compared With Selective Serotonin Reuptake Inhibitors. *Pediatrics.* 2019;144(2):e20183295

In the United States, suicide is the second leading cause of death in adolescents aged 15 to 19 and the third leading cause in those aged 10 to 14.[1] According to National Poison Data System (NPDS) data, intentional exposures first begin to outnumber unintentional exposures in the 13- to 19-year age group,[1] an effect that persists throughout the adult age categories. Intentional exposures also represent the most common self-harm method leading to hospital presentation among adolescents.[2] This mirrors a larger trend in the United States in recent years, regardless of age; cases coded "suspected suicide" rose from 10.5% of nationwide poison center cases in 2013 to 12.2% in 2016.[1,3]

The 13- to 19-year age group is the most likely to choose antidepressants in a self-harm attempt by overdose, representing 28.9% of single-agent suspected suicide antidepressant ingestions.[4] This is a major issue of interest to both medical and public health professionals, who have made it the focus of multiple studies.[4–9] As a result, in 2004, the Food and Drug Administration (FDA) added a black box warning to prescribing information for all antidepressants noting increased risk of suicide in children, adolescents, and young adults.[10]

It has been suggested that adolescents who attempt suicide may have greater impulsivity than their nonsuicidal peers.[11] Access to antidepressants may lead to increased potential for adolescent self-harming ingestions; indeed, restriction of access to lethal methods of suicide, such as medication, has been shown to be a viable strategy to reduce completed suicides.[12]

Selective serotonin reuptake inhibitors (SSRIs) are among the most commonly prescribed antidepressants in adolescents.[13] Only fluoxetine (age ≥8 years) and escitalopram (age ≥12 years) are FDA-approved for treatment of pediatric depression; however, citalopram and sertraline are also widely used.[14] Fluoxetine (age ≥7 years), sertraline (≥6 years), and fluvoxamine (≥8 years) are also FDA-approved for the treatment of pediatric obsessive-compulsive disorder, which may increase SSRI availability in this age group.[15] Alternative therapy with non-SSRI agents such as venlafaxine and bupropion makes up a significant minority of prescribing in this population, reflecting similar patterns in adults. In a study of adult prescriptions for depression, bupropion was the second most common non-SSRI prescribed after trazodone.[16]

When taken alone, SSRIs are rarely fatal in overdose. Mild-to-moderate ingestions are associated with minor or no symptoms, whereas more severe poisonings are associated with serotonin syndrome, drowsiness, tremor, nausea, vomiting, decreased consciousness, seizures, and electrocardiogram changes.[17] Bupropion is a monocyclic aminoketone that is structurally and pharmacologically a member of the synthetic cathinone class. Similar to other cathinones, it is an amphetamine-like stimulant and inhibitor of norepinephrine and dopamine reuptake.[18] Bupropion is well known to lower the seizure threshold at both therapeutic and supratherapeutic doses.[5,19–21] In mild-to-moderate poisoning, patients commonly experience agitation, hallucinations, tachycardia, and tremor. In more severe poisoning, effects may include coma, hypotension, QRS interval widening, QT interval prolongation, status epilepticus, ventricular dysrhythmias, and death.[22] Notably, the QRS widening caused by bupropion is because of myocardial gap junction blockade rather than sodium channel blockade and is therefore often not responsive to usual therapy with sodium bicarbonate boluses.[23]

Sheridan et al[8] showed that poison center cases with bupropion exposure were associated with significantly

TABLE 2 Breakdown of SSRIs by Agent

	n (%)
Sertraline	8969 (33.8)
Fluoxetine	7395 (27.9)
Escitalopram	4036 (15.2)
Citalopram	3385 (12.8)
Other SSRI	1704 (6.42)
Paroxetine	920 (3.47)
Fluvoxamine	113 (0.43)
Total	26 522 (100)

TABLE 1 Demographic Data

	Bupropion (*N* = 3504)	SSRIs (*N* = 26 522)	Overall (*N* = 30 026)
Age, mean (SD), y	16.17 (1.87)	15.75 (1.9)	15.8 (1.9)
Sex, *n* (%)			
Female	2622 (74.83)	22 222 (83.79)	24 844 (82.72)
Male	881 (25.14)	4271 (16.10)	5152 (17.29)
Chronicity, *n* (%)			
Acute	1866 (53.25)	13 266 (50.02)	15 132 (50.40)
Acute-on-chronic	1469 (41.92)	12 319 (46.45)	13 788 (45.92)
Unknown	138 (3.94)	744 (2.81)	882 (2.94)
Chronic	31 (0.88)	193 (0.73)	224 (0.75)
Highest level of care, *n* (%)			
ICU	1534 (43.94)	3010 (11.43)	4544 (15.23)
Non-ICU	855 (24.49)	3231 (12.27)	4086 (13.70)
Treat and release	449 (12.86)	8421 (31.97)	8870 (29.74)
Psychiatric care	412 (11.80)	9111 (34.59)	9523 (31.93)
Lost to follow-up or left AMA	189 (5.41)	1995 (7.57)	2184 (7.32)
Declined referral	52 (1.49)	569 (2.16)	621 (2.08)

AMA, against medical advice.

higher rates of morbidity than tricyclic antidepressant (TCA) cases; therefore, we postulated that bupropion would also present an unfavorable safety profile in comparison with SSRIs. Wider awareness of the toxicity of available antidepressants may help practitioners who treat adolescents with depression to limit access and therefore limit severe clinical effects and poor outcomes.

METHODS

This was a retrospective observational study using data from NPDS. These data are collected by member poison centers and maintained in a near real-time, de-identified database by the American Association of Poison Control Centers. Demographics, clinical effects, therapies provided, and medical outcome are coded from phone calls in a standardized manner by trained Certified Specialists in Poison Information at individual poison centers.

All human exposure cases reported to US poison centers involving an adolescent (10–19 years of age) with single-substance exposure to an SSRI or bupropion and coded as suspected suicide were included. Cases with any co-ingestion were excluded. The SSRIs studied were citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, and, as categorized by NPDS coding, "other types of SSRI[s]," which include vilazodone and vortioxetine. Bupropion was included in "other types of TCA" in NPDS coding until it was given its own substance code on January 30, 2013. Analysis of cases reported in the months after this date revealed that poison centers were consistently coding bupropion exposures using its specific substance code by the end of May 2013. Therefore, we elected to consider data from June 1, 2013, through December 31, 2017. Each case was considered an independent occurrence because it was not possible to link the de-identified data to potential repeat patients. Analyses of demographic characteristics, clinical effects, highest level of care required, therapies provided, and severity of medical outcome were performed. Specific therapies of interest were intubation, mechanical ventilation, vasopressors, benzodiazepines, sedation, oxygen, anticonvulsants, activated charcoal, cardiopulmonary resuscitation (CPR), and extracorporeal membrane oxygenation (ECMO). This study was deemed by the Indiana University Institutional Review Board to be quality improvement research using de-identified data and thus not required to undergo review from the Indiana University Institutional Review Board.

According to American Association of Poison Control Centers guidelines, clinical effect is stratified as follows:

TABLE 3 Outcomes by Substance

	Bupropion (N = 3504), n (%)	SSRI (N = 26 522), n (%)	P
No effect	413 (11.8)	9234 (34.8)	<.001
Minor effect	752 (21.5)	8804 (33.2)	<.001
Moderate effect	1447 (41.3)	4767 (18)	<.001
Major effect	580 (16.6)	260 (0.98)	<.001
Death	8 (0.23)	0 (0)	<.001

Rows will not add up to 100%. Columns may not add up to 100%, but percent is calculated by columns.

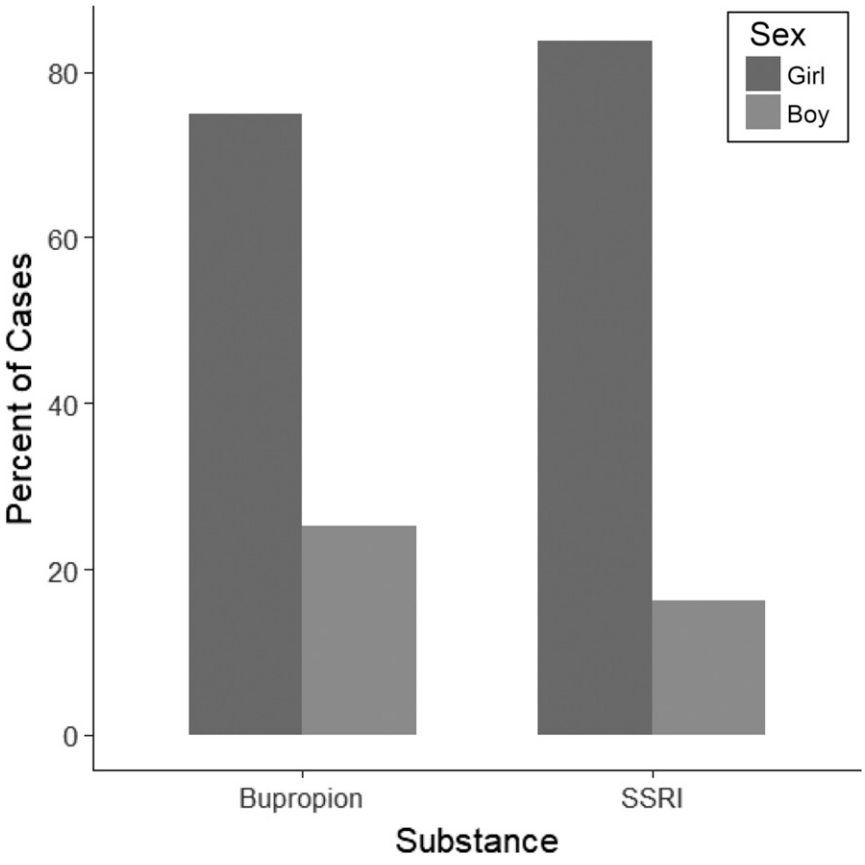

FIGURE 1
Distribution of sex by substance.

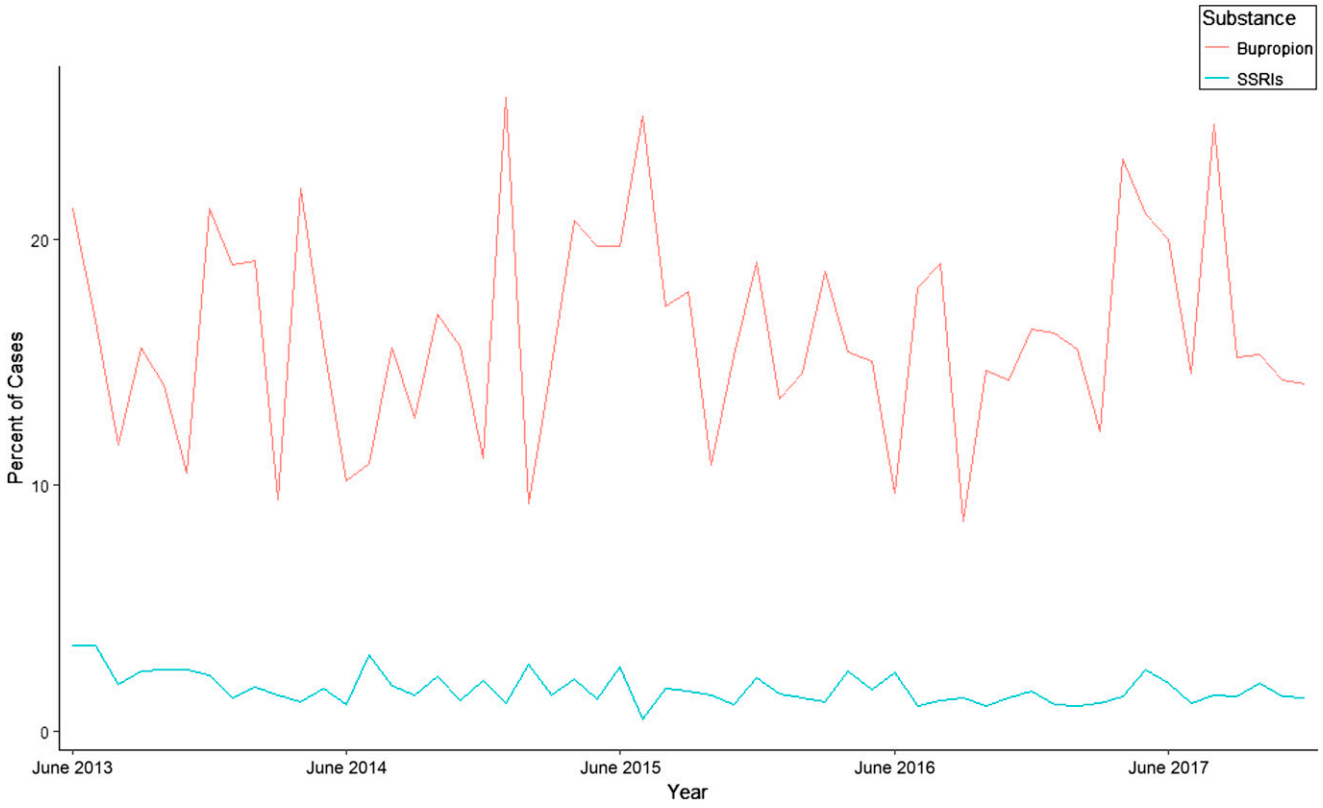

FIGURE 2
Patients experiencing single seizures.

Minor effect: The patient develops minimally bothersome symptoms that resolve rapidly without lasting effects. This category includes gastrointestinal symptoms, drowsiness, oral irritation, and sinus tachycardia without hypotension.

Moderate effect: Effects of an exposure are more pronounced, prolonged, or systemic and often require treatment but are not life-threatening and resolve without lasting effects. This includes acid-base disturbance, disorientation, hypotension, isolated seizures, and conduction disturbances without hypotension.

Major effect: The patient experiences life-threatening symptoms or has significant permanent dysfunction as a result of the exposure. This includes status epilepticus, symptomatic ventricular tachycardia, coma with hypotension, cardiac or respiratory arrest, ventricular fibrillation, renal failure, and rhabdomyolysis.

Death: This includes patients who die as a direct result of the exposure, from a complication of the exposure, or for whom the exposure was a contributing factor in the death.[1]

Differences between the 2 groups in clinical effects in cases with any outcome, clinical effects in cases with moderate or major outcome or death (MMD), selected therapies as listed above, the highest level of care required, chronicity of exposure, and sex were assessed by using χ^2 or Fisher's exact tests. The percent of patients per month who were intubated, received vasopressors, experienced a single seizure, experienced multiple seizures, or who had an MMD were analyzed by logistic regression. All-severity outcome frequencies were assessed with Poisson regression. Logistic regression was used to assess trends in exposures over time. An interaction term was used to assess the differences in reported clinical effects, outcomes, and therapies between SSRIs and bupropion ingestions over time. A level of significance of .05 was used for all statistical tests. All statistical analyses were performed in R and were completed using RStudio version 1.1.383 (RStudio, Inc, Boston, MA).

RESULTS

There were 30 026 poison center case records that met inclusion criteria. Of these, 3504 were exposures to bupropion and 26 522 were exposures to an SSRI. The average age was 15.8 years, and girls constituted the majority of both groups (Table 1). The most common SSRIs implicated were sertraline and fluoxetine, which accounted for 59% of the cases

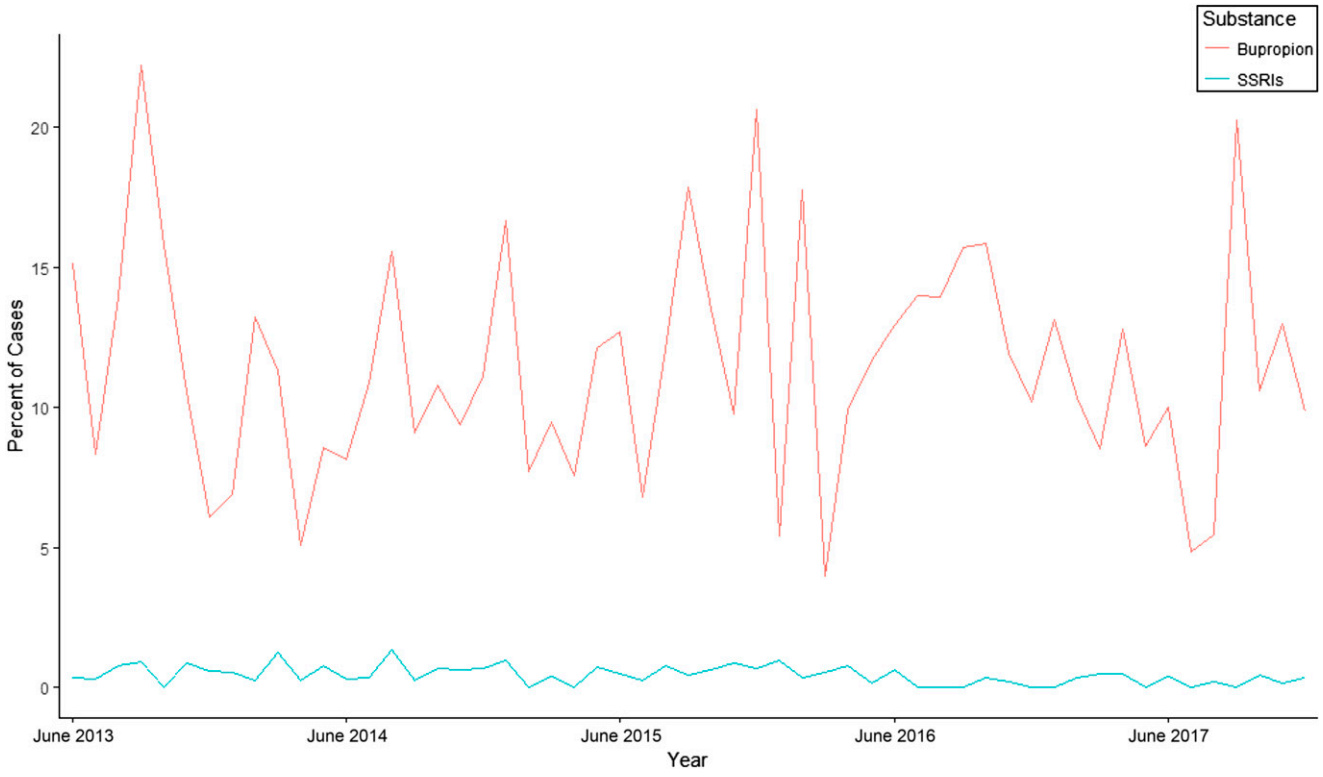

FIGURE 3
Patients experiencing multiple seizures.

(Table 2). Proportionally, there were more boys in the bupropion case group than in the SSRI group (25.1% vs 16.2%; Fig 1). Mortality was rare; all 8 fatalities (0.22%) occurred in the bupropion cases. Poison center cases involving an SSRI were much more likely to result in either minor or no effects from the exposure than those involving bupropion (68% vs 33.2%). By contrast, cases involving bupropion were more likely to have an MMD (58.1% vs 19%) compared with those involving an SSRI (Table 3).

Considering the 10 most commonly reported effects among cases with an MMD, bupropion exposure was significantly more likely to cause tachycardia (83.7% vs 59.9%), vomiting (24.8% vs 20.6%), cardiac conduction disturbances (20.0% vs 17.1%), agitation (20.2% vs 11.7%), seizures (27.0% vs 8.5%; Figs 2 and 3), and hallucinations (28.6% vs 4.3%). All were significant at the level of $P < .001$ except for conduction disturbance ($P = .005$). SSRI cases were significantly associated with the development of hypertension (25.3% vs 17.6%; $P < .001$; Table 4). Proportions of drowsiness, nausea, tremor, and other effects were not significantly different between case groups.

Considering all-severity outcomes, poison center cases involving

TABLE 4 Clinical Effects (MMDs Only)

	Bupropion ($N = 2035$), *n* (%)	SSRI ($N = 5027$), *n* (%)	Overall ($N = 7062$), *n* (%)	*P*
Tachycardia	1704 (83.73)	3011 (59.90)	4715 (66.77)	<.001
Hypertension	358 (17.59)	1273 (25.32)	1631 (23.10)	<.001
Vomiting	504 (24.77)	1035 (20.59)	1539 (21.79)	<.001
Drowsiness and/or lethargy	419 (20.59)	1044 (20.77)	1463 (20.72)	.902
Nausea	396 (19.46)	1060 (21.09)	1456 (20.62)	.132
Tremor	438 (21.52)	1000 (19.89)	1438 (20.36)	.105
Conduction disturbance	406 (19.95)	857 (17.05)	1263 (17.88)	.005
Agitated and/or irritable	410 (20.15)	587 (11.68)	997 (14.12)	<.001
Seizure, single	549 (26.98)	429 (8.53)	978 (13.85)	<.001
Other	239 (11.74)	631 (12.55)	870 (12.32)	.339
Hallucinations and/or delusions	582 (28.60)	214 (4.26)	796 (11.27)	<.001

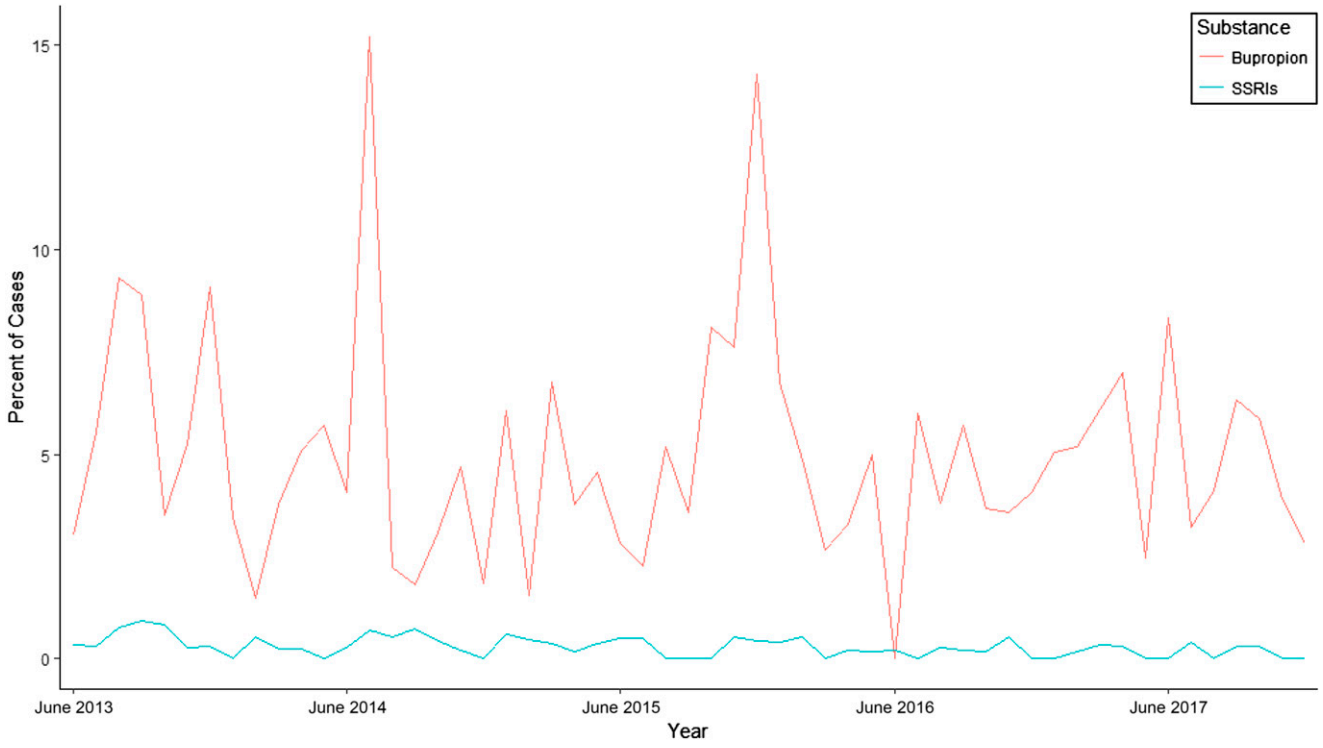

FIGURE 4
Patients requiring intubation.

bupropion were associated with significantly higher rates of each of the 10 most common reported effects ($P < .001$, except $P = .002$ for abdominal pain; Table 5). Bupropion cases were also associated with significantly higher rates of medical therapy, including intubation (4.9% vs 0.3%; Fig 4), vasopressor use (1.1% vs 0.2%; Fig 5), administration of a benzodiazepine (34.2% vs 5.4%), supplemental oxygen requirement (8.2% vs 0.8%), and CPR (0.5% vs 0.01%), with $P < .001$ for all. Three patients required treatment with ECMO; they were all in the bupropion group (Table 6). Poisson regression indicated that the number of reported poison center cases increased independently and significantly throughout the study period by an average of 807 cases per year for SSRIs and an average of 134 cases per year for bupropion. There was not a significant difference between cases for either substances over time (Fig 6). The percentage of poison center cases involving bupropion that resulted in MMDs also significantly increased in each year (Fig 7).

DISCUSSION

Bupropion's pharmacologic actions and potential for serious toxicity in overdose are well known within toxicology circles but may be under-recognized in the wider pediatric and primary care communities. This study revealed that poison center cases involving adolescents who attempt self-harm with bupropion had

TABLE 5 Clinical Effects (All Outcomes)

	Bupropion ($N = 3504$), n (%)	SSRI ($N = 26\,522$), n (%)	Overall ($N = 30\,026$), n (%)	P
Tachycardia	2276 (63.29)	6295 (22.30)	8571 (26.93)	<.001
Nausea	562 (15.63)	3598 (12.74)	4160 (13.07)	<.001
Vomiting	654 (18.19)	3345 (11.85)	3999 (12.56)	<.001
Drowsiness/lethargy	545 (15.16)	3349 (11.86)	3894 (12.23)	<.001
Hypertension	403 (11.21)	1640 (5.81)	2043 (6.42)	<.001
Other	323 (8.98)	1344 (4.76)	1667 (5.24)	<.001
Tremor	464 (12.90)	1138 (4.03)	1602 (5.03)	<.001
Agitated and/or irritable	469 (13.04)	1062 (3.76)	1531 (4.81)	<.001
Dizziness and/or vertigo	204 (5.67)	1177 (4.17)	1381 (4.34)	<.001
Conduction disturbance	415 (11.54)	948 (3.36)	1363 (4.28)	<.001
Abdominal pain	99 (2.75)	1039 (3.68)	1138 (3.58)	.002

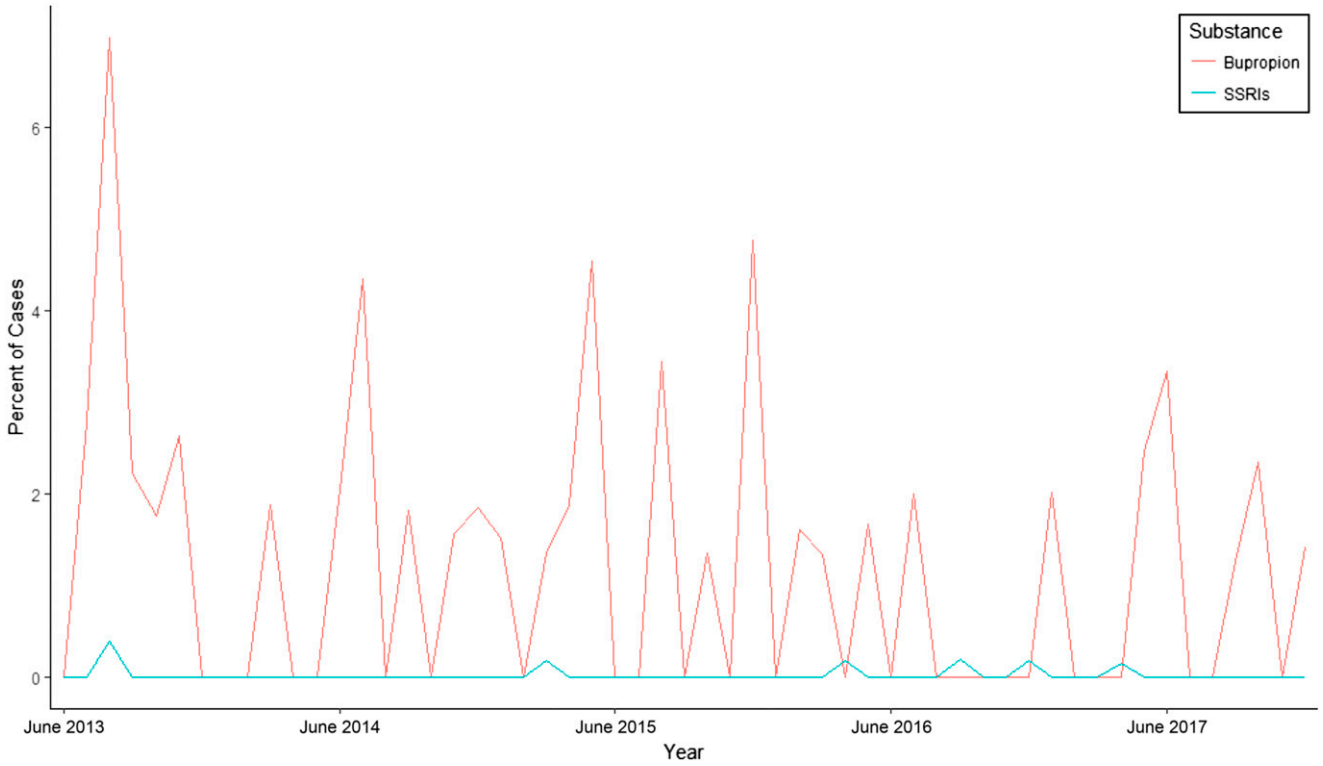

FIGURE 5
Patients requiring vasopressors.

significantly higher rates of serious outcome or death than those involving SSRIs. Patients in the bupropion cases, compared with patients in the SSRI cases, were 2.5 times more likely to have a moderate or major outcome or die and required hospitalization at nearly triple the rate, including a fourfold higher risk of ICU admission. These risks are particularly concerning given the rising rates of total attempts and poor outcomes after ingestion. Overdoses have been shown to vary directly with sales of each agent;[24] therefore, decreases in prescription of bupropion could be expected to decrease the number of serious outcomes in antidepressant overdoses.[25] Downstream effects would include decreased health care use, fewer ICU admissions, and decreased total costs to the health care system.[26]

Relative to poison center cases with reported SSRI exposure, patients with reported bupropion exposure had higher rates of acute neuropsychiatric sequelae, including a nearly sevenfold risk for developing hallucinations and an approximately twofold risk for becoming agitated. Bupropion is well known for its ability to lower the seizure threshold, sometimes even precipitating new-onset seizures at therapeutic doses.[21] In our study, seizures occurred >3 times as often with poison center cases involving bupropion than with SSRIs. This analysis of NPDS data reveals that neuropsychiatric effects are not the

TABLE 6 Selected Therapies (All Outcomes)

	Bupropion (N = 3504), n (%)	SSRI (N = 26 522), n (%)	Overall (N = 30 026), n (%)	P
Activated Charcoal	635 (18.12)	4846 (18.46)	5481 (18.25)	.772
Benzodiazepines	1198 (34.19)	1430 (5.45)	2628 (8.75)	<.001
Oxygen	288 (8.22)	205 (0.78)	493 (1.64)	<.001
Sedation	193 (5.51)	98 (0.37)	291 (0.97)	<.001
Intubation	172 (4.91)	71 (0.27)	243 (0.81)	<.001
Ventilator	161 (4.59)	66 (0.25)	227 (0.76)	<.001
Anticonvulsants	66 (1.88)	19 (0.07)	85 (0.28)	<.001
Vasopressors	40 (1.14)	6 (0.02)	46 (0.15)	<.001
CPR	18 (0.51)	3 (0.01)	21 (0.07)	<.001
ECMO	3 (0.09)	0 (0.00)	3 (0.01)	.002

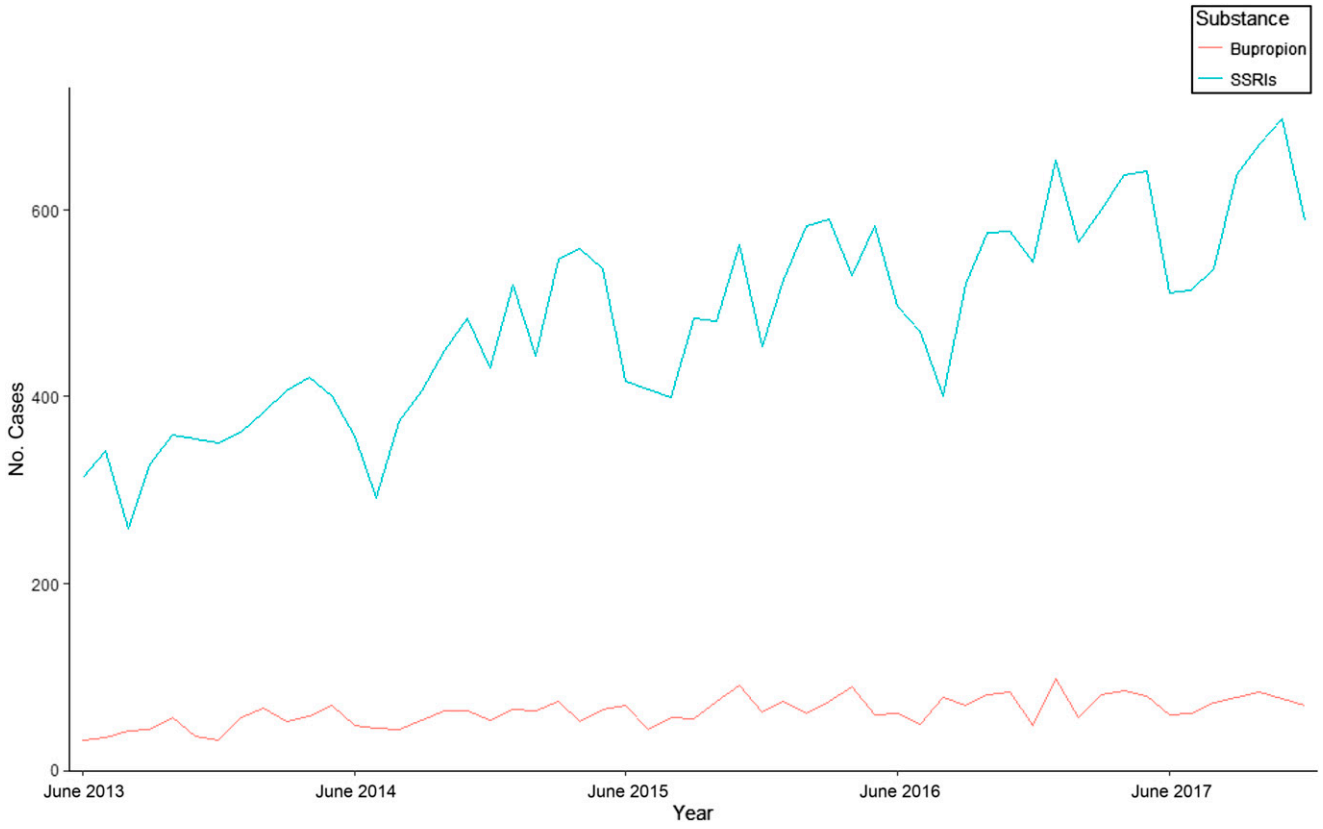

FIGURE 6
Adolescent suicide attempts reported by substance, 2013–2017.

only toxicity of concern with bupropion; in fact, this agent poses a number of additional substantial risks, including tachycardia and malignant dysrhythmias. These adverse effects likely account for the greater requirement for use of aggressive management such as intubation, vasopressors, CPR, and ECMO.

Sheridan et al[8] conducted a study in which they also used NPDS data to compare adolescent poison center cases involving exposure bupropion to those involving TCAs although during a slightly different time period and allowing co-ingestion of ethanol. Their study had many similar findings to ours, including higher rates of hallucinations, seizures, tachycardia, and vomiting in the bupropion cases. Another similarity was the overall finding that bupropion cases were more likely to have MMDs and need for hospitalization when compared with either TCA or SSRI cases. We did find that hypertension was more frequent in the SSRI cases than in the bupropion cases, whereas Sheridan et al[8] found that hypertension was more common in the bupropion cases than in the TCA cases. They also found that TCA cases had a higher rate of intubations than bupropion cases, whereas we found that bupropion cases were more likely to be associated with intubation compared with SSRI cases. Both the bupropion and TCA cases had a 0.3% mortality rate in the Sheridan et al[8] study. We had a similar mortality rate of 0.22% in the bupropion cases but had no deaths reported in the SSRI cases.

Adolescents who survive a first overdose are at a greater risk of later successfully completing suicide. Authors of a large population-based cohort study estimated this risk at 32-fold compared with matched controls without a history of self-poisoning at 1 year after the index attempt. The effect was also durable, with a risk of at least 10-fold persisting out to 12 years after the index attempt.[6] It would therefore seem advisable to limit access of adolescents to agents that are less toxic in overdose, particularly for patients who have a history of attempting self-harm.

There are a number of limitations to our study. First, it is a retrospective study of voluntarily reported data; therefore, it is likely that there are qualifying exposures that do not appear in our data set. This may be because patients did not seek medical attention, died before receiving it, did not develop symptoms from their exposure, or because treating medical providers did not deem it necessary

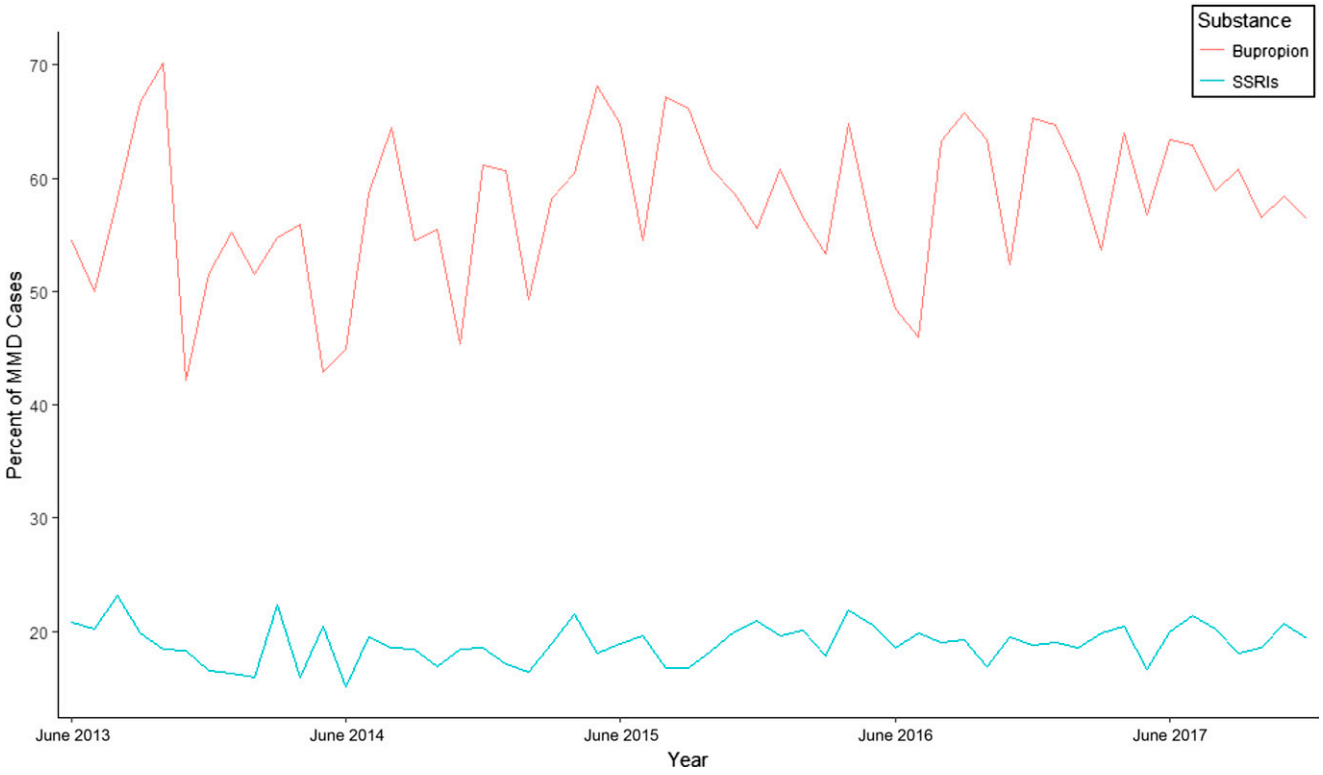

FIGURE 7
Serious patient outcomes by substance.

to consult with a poison center. Second, although poison centers strive to create complete records, it is often difficult to precisely quantify the size of an exposure, and confirmatory testing is often not performed. Third, a number of case records were coded as "lost to follow-up/left [against medical advice]," which imprecisely describes, and possibly obscures, a range of possible outcomes. Fourth, it is possible that our data are biased toward more symptomatic patients because they are more likely to seek or require medical attention for their exposure. Fifth, poison centers are often limited to the medical history and treatment details provided by the treating personnel because they are call center–based and often do not have access to the electronic medical record system of every hospital for which they provide coverage. These factors may create inaccuracies in case records; however, all cases undergo review by medical toxicology faculty to ensure quality and consistency. In addition, we selected the major outcomes of intubation, seizure, CPR, and ECMO and therapies including oxygen and benzodiazepines, because they are objective measures that are more likely to be documented consistently. Sixth, the source of medications used in overdose is often not known; however, some inferences may be made from the chronicity of exposure as recorded in the poison center case. If it is known at presentation or learned during the clinical course that the patient's own prescribed medication was involved, the exposure will be coded as "acute-on-chronic" in NPDS data; by contrast, exposures to medications prescribed to another person or acquired for the purpose of misuse or abuse would be coded as "acute." Finally, a higher proportion of asymptomatic bupropion exposures may be hospitalized because of the well-known risk for delayed seizures up to 18 hours postingestion and the common poison center recommendation for at least 23 hours of observation. By comparison, the recommended observation time for SSRIs is often ≤8 hours.

In our analysis, we were unable to determine if any individual agent was responsible for a disproportionate amount of a given clinical effect, therapy, or outcome. We considered SSRIs as a class when determining their clinical effects in overdose, although there are nuances in the toxicities of individual agents. For instance, paroxetine is the most anticholinergic, whereas citalopram and escitalopram are most likely to cause QT prolongation.[27,28] Vilazodone and vortioxetine are new members of the SSRI class that received FDA approval for use in adults with depression in 2011 and 2013, respectively; they are not approved for pediatric use. Authors of 1 study

of single-agent vilazodone ingestion using NPDS data found considerable toxicity with this agent; 2% of patients required intubation, 2% had ≥1 seizures, 6% had reported confusion, 4% had tremor, and 1% had hyperthermia and muscle rigidity.[29] Both substances are presently coded as other types of SSRIs in NPDS data, and it is therefore highly likely that our data contain some cases with exposure to these medications. It is difficult to determine their overall contribution to the studied clinical effects and outcomes; however, it would most likely have the effect of biasing our data toward worse morbidity with SSRIs.

CONCLUSIONS

This study of poison center data reveals that in reported cases of adolescent self-harm via overdose, bupropion cases had significant increases in rates of serious outcomes, such as seizures, respiratory failure, agitation, conduction disturbance, need for ICU admission, and death when compared with cases involving SSRIs. Suicidal ingestions are increasing steadily, as are the numbers of adolescents treated with medication for depression. In light of bupropion's disproportionately significant morbidity and mortality risk, it would be prudent for practitioners to avoid the use of this medication in adolescents that are at risk for self-harm.

ABBREVIATIONS

CPR: cardiopulmonary resuscitation
ECMO: extracorporeal membrane oxygenation
FDA: Food and Drug Administration
MMD: moderate or major outcome or death
NPDS: National Poison Data System
SSRI: selective serotonin reuptake inhibitor
TCA: tricyclic antidepressant

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

REFERENCES

1. Gummin DD, Mowry JB, Spyker DA, Brooks DE, Fraser MO, Banner W. 2016 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 34th annual report [published correction appears in *Clin Toxicol (Phila)*. 2017;55(10):1256]. *Clin Toxicol (Phila)*. 2017;55(10):1072–1252
2. Hawton K, Saunders KE, O'Connor RC. Self-harm and suicide in adolescents. *Lancet*. 2012;379(9834):2373–2382
3. Mowry JB, Spyker DA, Brooks DE, McMillan N, Schauben JL. 2014 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 32nd annual report [published correction appears in *Clin Toxicol (Phila)*. 2016;54(7):607]. *Clin Toxicol (Phila)*. 2015;53(10): 962–1147
4. White N, Litovitz T, Clancy C. Suicidal antidepressant overdoses: a comparative analysis by antidepressant type. *J Med Toxicol*. 2008;4(4):238–250
5. Finkelstein Y, Hutson JR, Freedman SB, Wax P, Brent J; Toxicology Investigators Consortium (ToxIC) Case Registry. Drug-induced seizures in children and adolescents presenting for emergency care: current and emerging trends. *Clin Toxicol (Phila)*. 2013;51(8):761–766
6. Finkelstein Y, Macdonald EM, Hollands S, et al; Canadian Drug Safety and Effectiveness Research Network (CDSERN). Long-term outcomes following self-poisoning in adolescents: a population-based cohort study. *Lancet Psychiatry*. 2015;2(6):532–539
7. Sheridan DC, Hendrickson RG, Lin AL, Fu R, Horowitz BZ. Adolescent suicidal ingestion: national trends over a decade. *J Adolesc Health*. 2017;60(2): 191–195
8. Sheridan DC, Lin A, Horowitz BZ. Suicidal bupropion ingestions in adolescents: increased morbidity compared with other antidepressants. *Clin Toxicol (Phila)*. 2018;56(5):360–364
9. Curtin SC, Tejada-Vera B, Warmer M. Drug overdose deaths among adolescents aged 15-19 in the United States: 1999-2015. *NCHS Data Brief*. 2017;(282):1–8
10. Friedman RA, Leon AC. Expanding the black box - depression, antidepressants, and the risk of suicide. *N Engl J Med*. 2007;356(23): 2343–2346
11. Kashden J, Fremouw WJ, Callahan TS, Franzen MD. Impulsivity in suicidal and nonsuicidal adolescents. *J Abnorm Child Psychol*. 1993;21(3):339–353
12. Cash SJ, Bridge JA. Epidemiology of youth suicide and suicidal behavior. *Curr Opin Pediatr*. 2009;21(5):613–619
13. Hales CM, Kit BK, Gu Q, Ogden CL. Trends in prescription medication use among children and adolescents-United States,

1999-2014. *JAMA*. 2018;319(19):2009–2020

14. Lopez-Leon S, Lopez-Gomez MI, Warner B, Ruiter-Lopez L. Psychotropic medication in children and adolescents in the United States in the year 2004 vs 2014. *Daru*. 2018;26(1):5–10
15. Centers for Medicare and Medicaid Services. *Antidepressant Medications: Use in Pediatric Patients*. Washington, DC: US Department of Health and Human Services; 2013
16. Treviño LA, Ruble MW, Treviño K, Weinstein LM, Gresky DP. Antidepressant medication prescribing practices for treatment of major depressive disorder. *Psychiatr Serv*. 2017;68(2):199–202
17. Barbey JT, Roose SP. SSRI safety in overdose. *J Clin Psychiatry*. 1998;59(suppl 15):42–48
18. Lexicomp. *Bupropion. Lexi-Drugs*. Riverwoods, IL: Wolters Kluwer Health, Inc. Available at: http://online.lexi.com. Accessed August 24, 2018
19. Starr P, Klein-Schwartz W, Spiller H, Kern P, Ekleberry SE, Kunkel S. Incidence and onset of delayed seizures after overdoses of extended-release bupropion. *Am J Emerg Med*. 2009;27(8):911–915
20. Shepherd G, Velez LI, Keyes DC. Intentional bupropion overdoses. *J Emerg Med*. 2004;27(2):147–151
21. Pesola GR, Avasarala J. Bupropion seizure proportion among new-onset generalized seizures and drug related seizures presenting to an emergency department. *J Emerg Med*. 2002;22(3):235–239
22. Brown KM, Crouch BI. Bupropion overdose: significant toxicity in pediatrics. *Clin Pediatr Emerg Med*. 2017;18(3):212–217
23. Caillier B, Pilote S, Castonguay A, et al. QRS widening and QT prolongation under bupropion: a unique cardiac electrophysiological profile. *Fundam Clin Pharmacol*. 2012;26(5):599–608
24. Farmer RD, Pinder RM. Why do fatal overdose rates vary between antidepressants? *Acta Psychiatr Scand Suppl*. 1989;354:25–35
25. Isacsson G, Bergman U. Risks with citalopram in perspective. *Lancet*. 1996;348(9033):1033
26. Ramchandani P, Murray B, Hawton K, House A. Deliberate self poisoning with antidepressant drugs: a comparison of the relative hospital costs of cases of overdose of tricyclics with those of selective-serotonin re-uptake inhibitors. *J Affect Disord*. 2000;60(2):97–100
27. Sanchez C, Reines EH, Montgomery SA. A comparative review of escitalopram, paroxetine, and sertraline: are they all alike? *Int Clin Psychopharmacol*. 2014;29(4):185–196
28. Ferguson JM. SSRI antidepressant medications: adverse effects and tolerability. *Prim Care Companion J Clin Psychiatry*. 2001;3(1):22–27
29. Heise CW, Malashock H, Brooks DE. A review of vilazodone exposures with focus on serotonin syndrome effects. *Clin Toxicol (Phila)*. 2017;55(9):1004–1007

Toxicity of Bupropion Overdose Compared With Selective Serotonin Reuptake Inhibitors

Adam Overberg, Shannon Morton, Emily Wagner and Blake Froberg

Pediatrics 2019;144;
DOI: 10.1542/peds.2018-3295 originally published online July 5, 2019;

PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Toxicity of Bupropion Overdose Compared With Selective Serotonin Reuptake Inhibitors

Adam Overberg, Shannon Morton, Emily Wagner and Blake Froberg

Pediatrics 2019;144;
DOI: 10.1542/peds.2018-3295 originally published online July 5, 2019;