Toxicity of Bupropion Overdose Compared with Selective Serotonin Reuptake Inhibitors

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Abbreviations: SSRI – selective serotonin reuptake inhibitor; FDA – Food & Drug Administration; NPDS – National Poison Data System; MMD – moderate/major/death outcomes; ECG – electrocardiogram; TCA – tricyclic antidepressant; CPR – cardiopulmonary resuscitation; ECMO – extra-corporeal membrane oxygenation; GI – gastrointestinal; ICU – intensive care unit; AMA – against medical advice

Table of Contents Summary
Fluoxetine and escitalopram are FDA-approved prescription medications for pediatric depression, but not the only agents used. We examine adolescent overdose risks of bupropion and SSRIs.

What's Known on This Subject
Adolescents who attempt self-harm by overdose often choose medications of convenience, and frequently have access to antidepressants. SSRIs are the drugs of choice in pediatric depression; however, bupropion is also prescribed. A recent study highlighted bupropion's toxicity in adolescents.[8]

What This Study Adds
This study compares the effects of bupropion and SSRIs 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.

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Contributors' Statement Page

Drs. Overberg and Wagner conceptualized and designed the study, collected data, drafted the initial manuscript, and reviewed and revised the manuscript.

Ms. Morton carried out 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. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Abstract

Objective
Adolescent depression and attempted and completed suicide are increasing in the United States. Since suicide is often impulsive, the means of self-harm are frequently items of convenience like medication. A recent study compared TCA overdose to bupropion. Fluoxetine and escitalopram are the only agents with FDA approval for pediatric depression, but off-label bupropion prescriptions are common. We sought to compare the effects of 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%, $p<0.001$) or serious outcome (58.1% vs. 19%, $p<0.001$), as well as the ten most common clinical effects, including seizures (27.0% vs. 8.5%, $p<0.001$) and hallucinations (28.6% vs. 4.3%, $p<0.001$). Bupropion exposure was significantly associated with need for CPR (0.51% vs. 0.01%, $p<0.001$), intubation (4.9% vs 0.3%, $p<0.001$), vasopressors (1.1% vs 0.2%, $p<0.001$), and benzodiazepines (34.2% vs. 5.5%, $p<0.001$). There was a significant increase in all exposures and in proportion of serious outcomes over time.

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

Introduction

In the United States, suicide is the second leading cause of death in adolescents aged 15-19 and the third leading cause in those aged 10-14.[1] According to National Poison Data System data, intentional exposures first begin to outnumber unintentional exposures in the 13-19 year age group,[1] an effect which 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 U.S. in recent years, regardless of age; cases coded "suspected suicide" rose from 10.5% of national Poison Center cases in 2013 to 12.2% in 2016.[1,3]

The 13-19 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 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 non-suicidal 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]

SSRIs are among the most commonly prescribed antidepressants in adolescents.[13] Only fluoxetine (age $\geq$ 8 years) and escitalopram (age $\geq$12 years) are FDA-approved for treatment of pediatric depression; however, citalopram and sertraline are also widely used.[14] Fluoxetine ($\geq$7 years), sertraline ($\geq$6 years), and fluvoxamine ($\geq$8 years) are also FDA-approved for 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, while more severe poisonings are associated with serotonin syndrome, drowsiness, tremor, nausea, vomiting, decreased consciousness, seizures, and ECG 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 re-uptake.[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 due to 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. showed that poison center cases with bupropion exposure were associated with significantly higher rates of morbidity than TCA cases[8]; therefore, we postulated that bupropion would also present an unfavorable safety profile in comparison to 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 the National Poison Data System. This data is 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 U.S. Poison Centers involving an adolescent (10-19 years) 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 "other types of SSRI," which includes 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 following 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, as 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 extra-corporeal 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 IRB review.

According to AAPCC guidelines, clinical effect is stratified as follows:

Minor effect: the patient develops minimally bothersome symptoms that resolve rapidly without lasting effects. This category includes GI 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: 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]

Statistical Analysis

Differences between the two 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 gender were assessed using chi-squared or Fisher's exact tests. The percent of cases per month who were intubated, received vasopressors, experienced a single seizure, experienced multiple seizures, or who had an MMD

outcome 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 0.05 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, 3,504 were exposures to bupropion and 26,522 were exposures to an SSRI. The average age was 15.8 years, and females constituted the majority of both groups. (Table 1). The most common SSRIs implicated were sertraline and fluoxetine, which accounted for 59% of the cases. (Table 2). Proportionally, there were more males in the bupropion case group than the SSRI group (25.1% vs 16.2%, Figure 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 outcome (58.1% vs 19%) compared to those involving an SSRI. (Table 3).

Considering the ten most commonly reported effects among cases with an MMD outcome, 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%, figures 2 and 3), and hallucinations (28.6% vs. 4.3%). All were significant at the level of $p < 0.001$ except for conduction disturbance ($p = 0.005$). SSRI cases were significantly associated with development of

hypertension (25.3% vs. 17.6%, $p < 0.001$) (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 bupropion were associated with significantly higher rates of each of the ten most common reported effects ($p < 0.001$, except $p = 0.002$ for abdominal pain). (Table 5). Bupropion cases were also associated with significantly higher rates of medical therapy, including intubation (4.9% vs 0.3%, figure 4), vasopressor use (1.1% vs 0.2%, figure 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%), $p < 0.001$ for all. Three cases required treatment with ECMO, 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. (Figure 6). The percentage of poison center cases involving bupropion that resulted in MMD outcomes also significantly increased in each year. (Figure 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 showed that poison center cases involving adolescents who attempt self-harm with bupropion had significantly higher rates of serious outcome or death than those involving SSRIs. Patients in the bupropion cases, compared to 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 4-fold 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 healthcare utilization, fewer ICU admissions, and decreased total costs to the healthcare system. [26]

Relative to poison center cases with reported SSRI exposure, cases with reported bupropion exposure had higher rates of acute neuropsychiatric sequelae, including a nearly 7-fold risk for developing hallucinations and an approximately 2-fold 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 more than three times as often with poison center cases involving bupropion than with SSRIs. This analysis of NPDS data shows that neuropsychiatric effects are not the 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 usage of aggressive management such as intubation, vasopressors, CPR, and ECMO.

Sheridan et al. conducted a study that also used NPDS data to compare adolescent poison center cases involving exposure bupropion to those involving tricyclic antidepressants, although during a slightly different time-period and allowing co-ingestion of ethanol.[8] 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 MMD outcomes and need for hospitalization when compared to either TCA or SSRI cases. We did find that hypertension was more frequent in the SSRI cases than the bupropion cases, while Sheridan et al found that hypertension was more common in the bupropion cases than the TCA cases. They also found that TCA cases had a higher rate of

intubations than bupropion cases, while we found that bupropion cases were more likely to be associated with intubation compared to SSRI cases. Both the bupropion and TCA cases had a 0.3% mortality rate in the Sheridan 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. A large population-based cohort study estimated this risk at 32-fold compared to matched controls without a history of self-poisoning at one year following index attempt. The effect was also durable, with a risk of at least 10-fold persisting out to 12 years after 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 to consult with a Poison Center. Second, while 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 "lost to follow-up/left AMA," which imprecisely describes, and possibly obscures, a range of possible outcomes. Fourth, it is possible that our data is biased toward more symptomatic patients, as 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, as 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 post-ingestion 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 or less.

Our analysis is unable to determine whether 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, though there are nuances in the toxicities of individual agents. For instance, paroxetine is the most anticholinergic, while 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. One study of single-agent vilazodone ingestion using NPDS data found considerable toxicity with this agent; 2% of patients required intubation, 2% had one or more 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 SSRI” in NPDS data, and it is therefore highly likely that our data contains 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.

Conclusion

This study of Poison Center data shows 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 to 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.

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		Bupropion n=3,504	%	SSRIs n=26,522	%	Overall n=30,026	%
Mean Age (SD)		16.17 (1.87)		15.75 (1.9)		15.8 (1.9)	
Sex							
	Female	2,622	74.83	22,222	83.79	24,844	82.72
	Male	881	25.14	4,271	16.10	5,152	17.29
Chronicity							
	Acute	1,866	53.25	13,266	50.02	15,132	50.40
	Acute-on-Chronic	1,469	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							
	ICU	1,534	43.94	3,010	11.43	4,544	15.23
	Non-ICU	855	24.49	3,231	12.27	4,086	13.70
	Treat/Release	449	12.86	8,421	31.97	8,870	29.74
	Psychiatric Care	412	11.80	9,111	34.59	9,523	31.93
	Lost to Follow-Up/ Left AMA	189	5.41	1,995	7.57	2,184	7.32
	Declined Referral	52	1.49	569	2.16	621	2.08

SD = Standard Deviation, HCF = Health Care Facility, AMA = Against Medical Advice

Table 1. Demographic data.

	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**	

Table 2. Breakdown of SSRIs by agent.

	Bupropion n = 3,504	%	SSRI n = 26,522	%	p
No Effect	413	11.8	9234	34.8	<0.001
Minor Effect	752	21.5	8804	33.2	<0.001
Moderate Effect	1447	41.3	4767	18	<0.001
Major Effect	580	16.6	260	0.98	<0.001
Death	8	0.23	0	0	<0.001

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

Table 3. Outcomes by substance.

	Bupropion n = 2,035	%	SSRI n = 5,027	%	Overall n = 7,062	%	p
Tachycardia	1704	83.73	3011	59.90	4715	66.77	<0.001
Hypertension	358	17.59	1273	25.32	1631	23.10	<0.001
Vomiting	504	24.77	1035	20.59	1539	21.79	<0.001
Drowsiness/Lethargy	419	20.59	1044	20.77	1463	20.72	0.902
Nausea	396	19.46	1060	21.09	1456	20.62	0.132
Tremor	438	21.52	1000	19.89	1438	20.36	0.105
Conduction Disturbance	406	19.95	857	17.05	1263	17.88	0.005
Agitated/Irritable	410	20.15	587	11.68	997	14.12	<0.001
Seizure, Single	549	26.98	429	8.53	978	13.85	<0.001
Other	239	11.74	631	12.55	870	12.32	0.339
Hallucinations/Delusions	582	28.60	214	4.26	796	11.27	<0.001

Table 4. Clinical effects, moderate/major/death outcomes only.

	Bupropion n = 3,504	%	SSRI n = 26,522	%	Overall n = 30,026	%	p
Tachycardia	2276	63.29	6295	22.30	8571	26.93	<0.001
Nausea	562	15.63	3598	12.74	4160	13.07	<0.001
Vomiting	654	18.19	3345	11.85	3999	12.56	<0.001
Drowsiness/Lethargy	545	15.16	3349	11.86	3894	12.23	<0.001
Hypertension	403	11.21	1640	5.81	2043	6.42	<0.001
Other	323	8.98	1344	4.76	1667	5.24	<0.001
Tremor	464	12.90	1138	4.03	1602	5.03	<0.001
Agitated/Irritable	469	13.04	1062	3.76	1531	4.81	<0.001
Dizziness/Vertigo	204	5.67	1177	4.17	1381	4.34	<0.001
Conduction Disturbance	415	11.54	948	3.36	1363	4.28	<0.001
Abdominal Pain	99	2.75	1039	3.68	1138	3.58	0.002

Table 5. Clinical effects, all outcomes.

	Bupropion n = 3,504	%	SSRI n = 26,522	%	Overall n = 30,026	%	p
Charcoal	635	18.12	4,846	18.46	5,481	18.25	0.772
Benzodiazepines	1,198	34.19	1,430	5.45	2,628	8.75	<0.001
Oxygen	288	8.22	205	0.78	493	1.64	<0.001
Sedation	193	5.51	98	0.37	291	0.97	<0.001
Intubation	172	4.91	71	0.27	243	0.81	<0.001
Ventilator	161	4.59	66	0.25	227	0.76	<0.001
Anticonvulsants	66	1.88	19	0.07	85	0.28	<0.001
Vasopressors	40	1.14	6	0.02	46	0.15	<0.001
CPR	18	0.51	3	0.01	21	0.07	<0.001
ECMO	3	0.09	0	0.00	3	0.01	0.002

Table 6. Selected therapies, all outcomes.

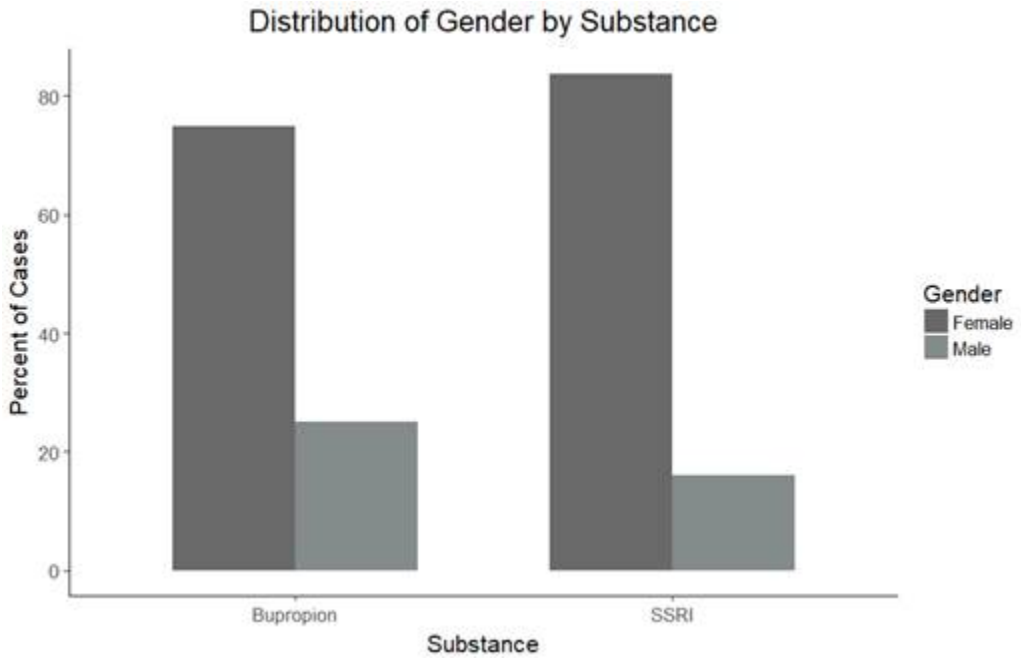
Distribution of Gender by Substance
Percent of Cases
80
60
40
20
0
Bupropion
SSRI
Substance
Gender
Female
Male

Figure 1.

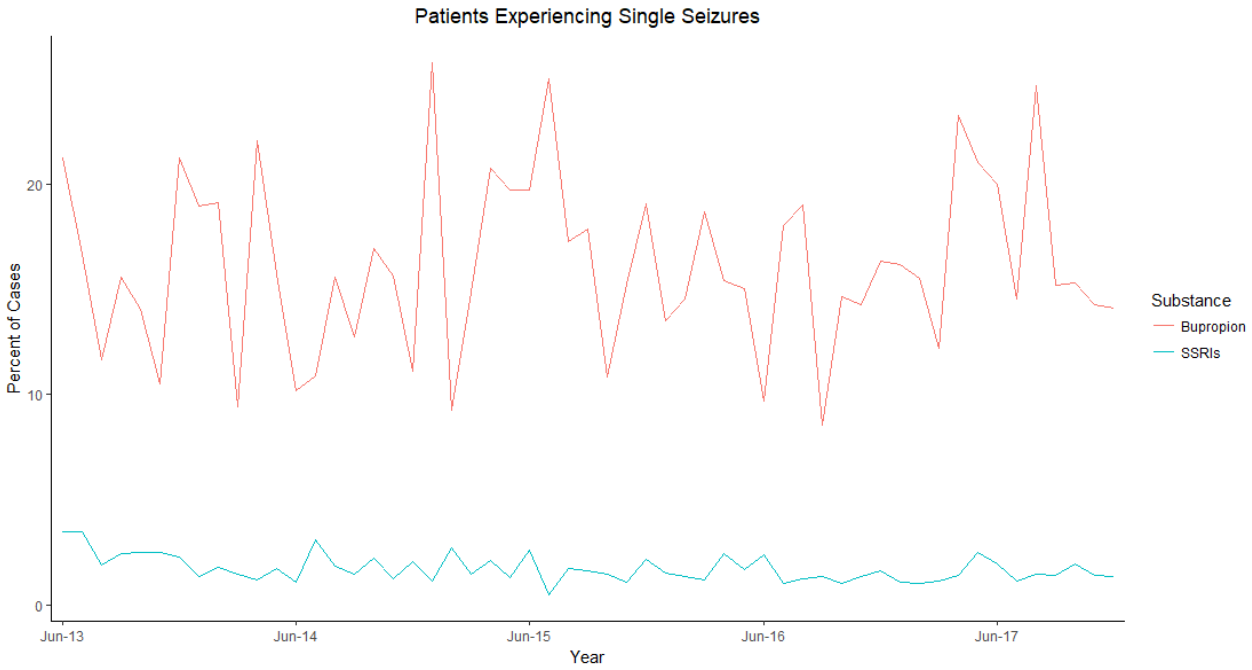
Patients Experiencing Single Seizures
Percent of Cases
20
10
0
Jun-13
Jun-14
Jun-15
Jun-16
Jun-17
Year
Substance
Bupropion
SSRIs

Figure 2.

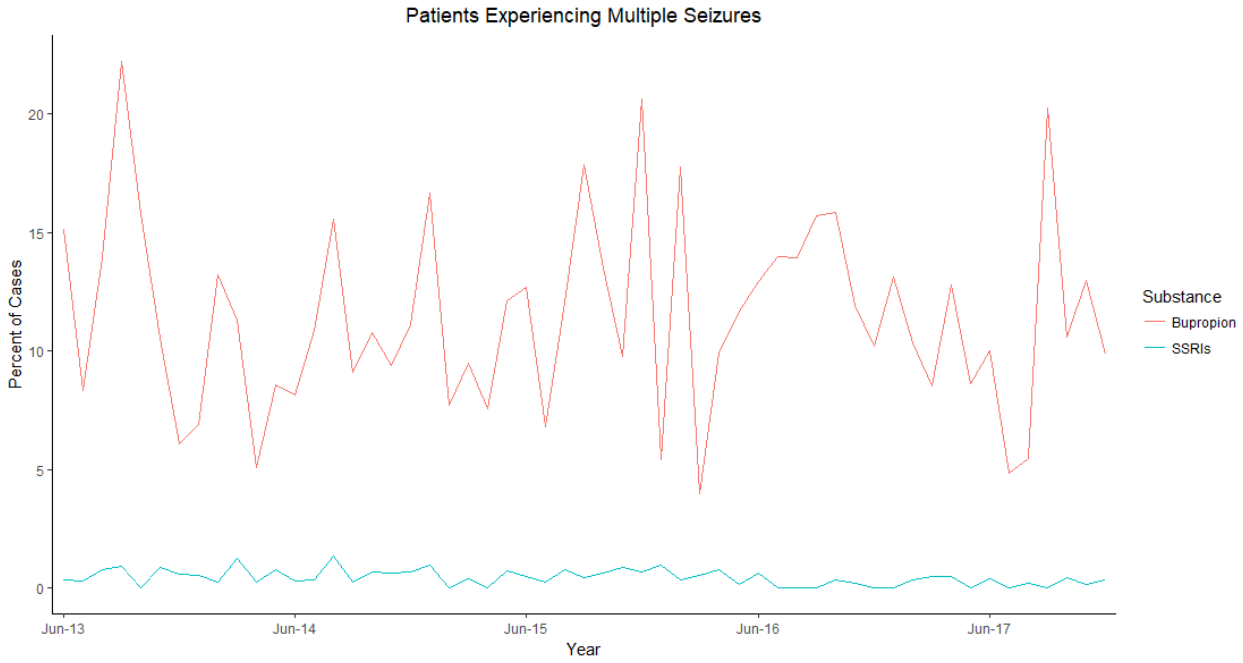
Patients Experiencing Multiple Seizures
Percent of Cases
20
15
10
5
0
Jun-13
Jun-14
Jun-15
Jun-16
Jun-17
Year
Substance
Bupropion
SSRIs

Figure 3.

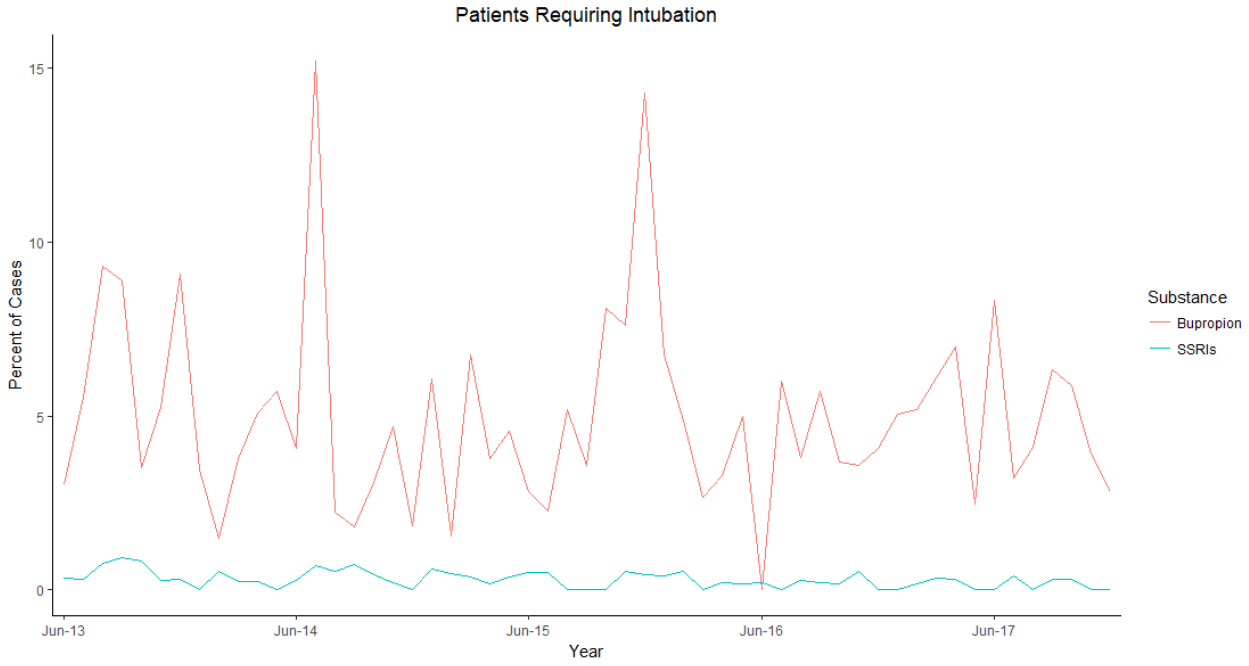
Patients Requiring Intubation
Percent of Cases
15
10
5
0
Jun-13
Jun-14
Jun-15
Jun-16
Jun-17
Year
Substance
Bupropion
SSRIs

Figure 4.

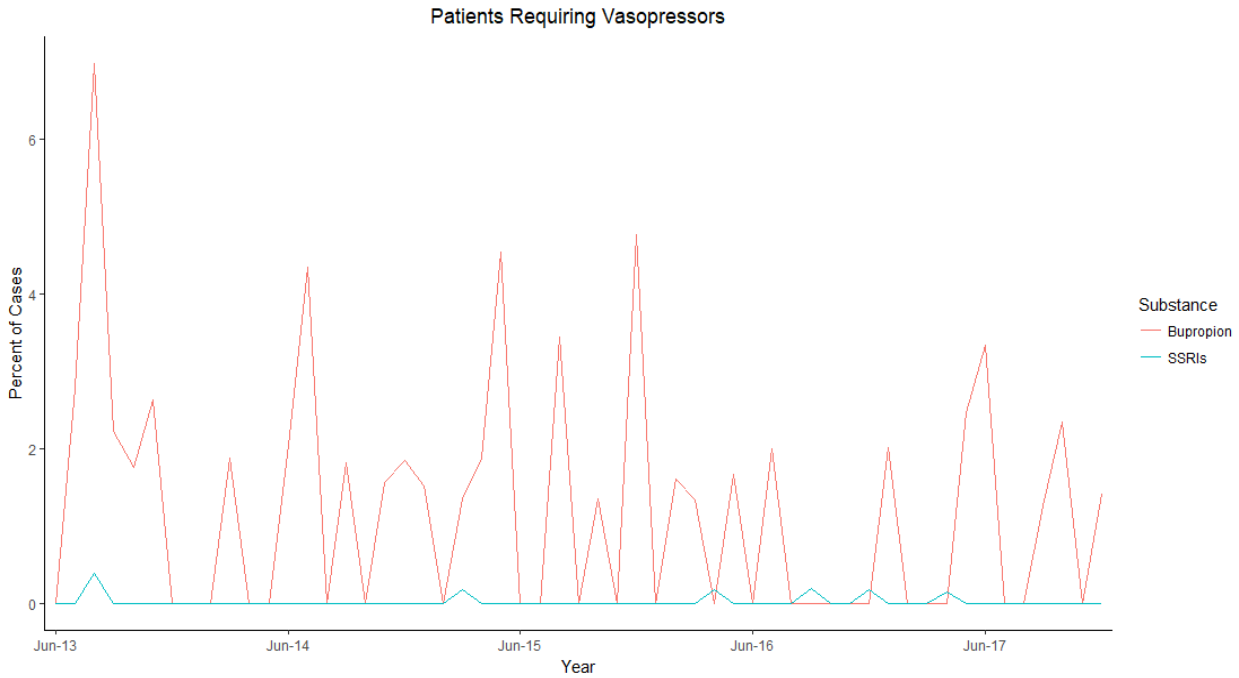
Patients Requiring Vasopressors
Percent of Cases
0
2
4
6
Jun-13
Jun-14
Jun-15
Jun-16
Jun-17
Year
Substance
Bupropion
SSRIs

Figure 5.

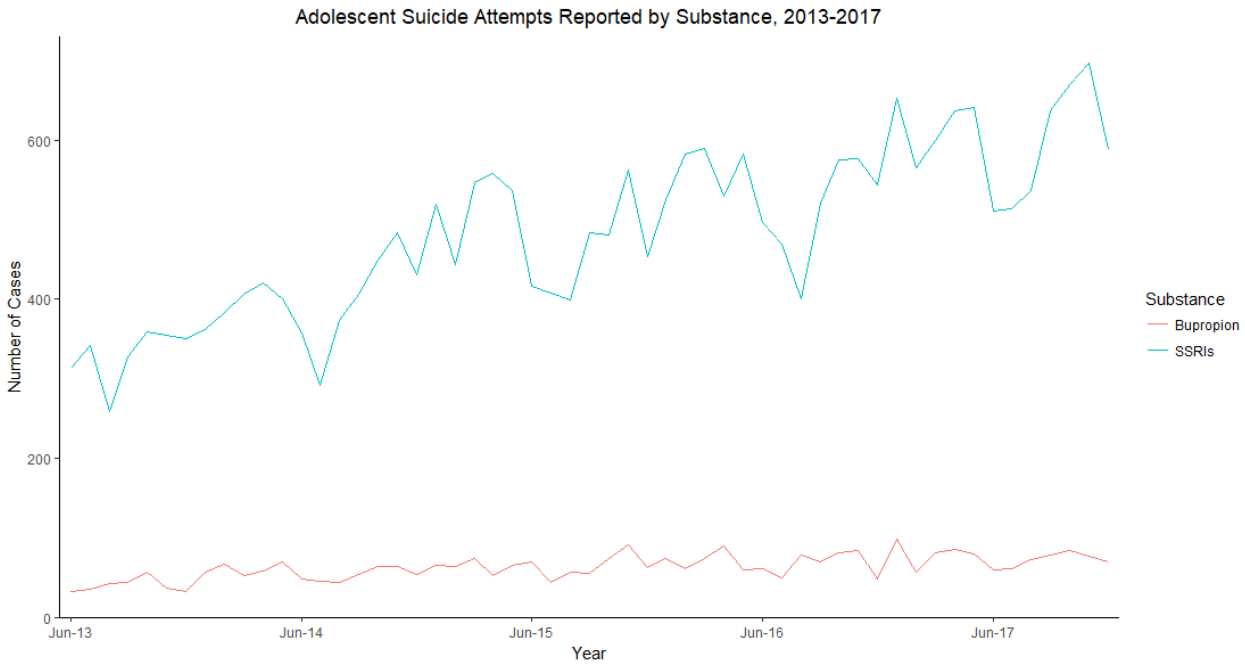
Adolescent Suicide Attempts Reported by Substance, 2013-2017
Number of Cases
600
400
200
0
Jun-13
Jun-14
Jun-15
Jun-16
Jun-17
Year
Substance
Bupropion
SSRIs

Figure 6.

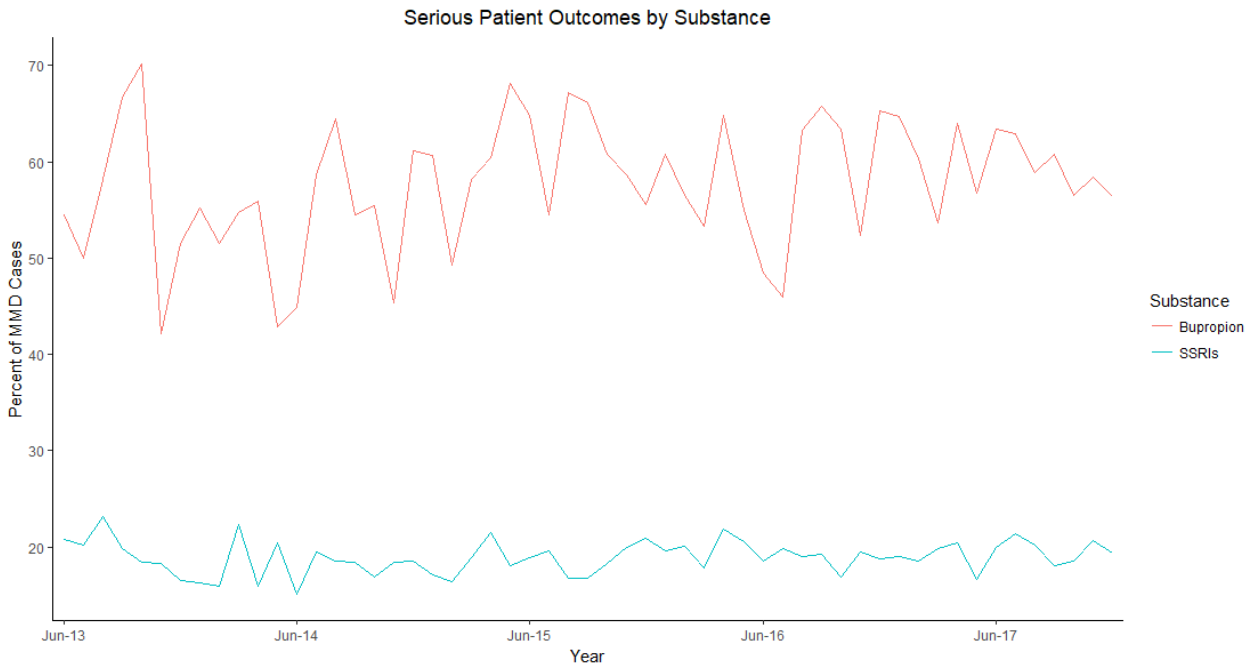
Serious Patient Outcomes by Substance
Percent of MMD Cases
70
60
50
40
30
20
Jun-13
Jun-14
Jun-15
Jun-16
Jun-17
Year
Substance
Bupropion
SSRIs

Figure 7.