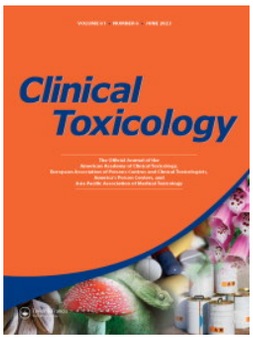

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CLINICAL RESEARCH

Sodium bicarbonate treatment for QRS widening in bupropion overdoses

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ABSTRACT

Introduction: Bupropion cardiotoxicity widens QRS complexes by inhibiting cardiac gap junctions. Sodium bicarbonate is the standard treatment for QRS widening from sodium channel blockade, but its effect on QRS widening in bupropion cardiotoxicity is not well-studied.

Methods: This is a retrospective cohort study of bupropion overdoses from 10 hospitals between January 2010 and June 2022. Patients with documented administration of sodium bicarbonate and QRS duration > 100 milliseconds on pre-bicarbonate electrocardiogram were included. Patients with no electrocardiogram within four hours of treatment or with baseline pre-overdose wide QRS and < 10 milliseconds widening from baseline were excluded. The primary outcome was a change in QRS duration between the pre-bicarbonate electrocardiogram and the first electrocardiogram after initial bicarbonate administration. Secondary outcomes included prevalence of post-bicarbonate QRS < 100 milliseconds, change in electrocardiogram intervals after total bicarbonate administration, and change in metabolic parameters and hemodynamics. Wilcoxon signed-rank testing was performed on the primary outcome. Linear regression modeling was performed to test for an association between change in QRS and bicarbonate dosing.

Results: Thirteen patients were included for final analysis. The median age was 32 years, and 54% were male. Six patients developed seizures; one developed ventricular tachycardia, and four received vasopressors. The median QRS and QTc pre-bicarbonate were 116 and 495 milliseconds, respectively. The median change in QRS duration was −2.0 milliseconds, which was not statistically significant ($P = 0.42$). The median bicarbonate dose administered before the first post-bicarbonate electrocardiogram was 100 milliequivalents. We did not identify an association between QRS change and bicarbonate dosing ($P = 0.9$, R-squared = 0.001). No patient had a QRS duration < 100 milliseconds after the initial bicarbonate dose. There was minimal change in QTc, electrolytes, heart rate, or blood pressure; alkalemia post-bicarbonate was achieved in eight patients.

Conclusion: Sodium bicarbonate did not significantly decrease QRS duration in this small retrospective cohort of bupropion overdoses.

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Bupropion; cardiotoxicity; QRS; sodium bicarbonate; gap junctions

Introduction

The aminoketone antidepressant bupropion causes seizures, sympathomimetic toxicity, and cardiotoxicity in overdose [1–3]. Bupropion cardiotoxicity presents as conduction delay, ventricular dysrhythmias, and hemodynamic instability [3–5]. Cardiac conduction delay often manifests on electrocardiogram (ECG) as a widening of the QRS complex and prolongation of the corrected QT interval (QTc). Xenobiotic-induced QRS widening is most frequently due to sodium channel blockade, for which hypertonic sodium bicarbonate is the preferred treatment [6–8].

The role of hypertonic sodium bicarbonate in bupropion cardiotoxicity is not well defined. Sodium bicarbonate improves sodium channel blocker conduction delay by increasing extracellular sodium concentrations and serum pH. The effect of increased extracellular sodium is unclear in bupropion cardiotoxicity, as bupropion's cardiac effects appear to be mediated by inhibition of gap junctions rather than sodium channels [9]. While some xenobiotics are shifted towards nonionized forms (less able to bind sodium channels) at increasing serum pH, bupropion's binding is unlikely to be influenced by changes in ionization *via* serum alkalinization, given its pKa of 7.9 [10]. The current clinical literature consists of case reports with conflicting results as to whether sodium bicarbonate affects QRS widening in the setting of bupropion toxicity [4,5,11–15].

We conducted a retrospective cohort study to evaluate the effect of sodium bicarbonate on QRS duration in bupropion overdoses, assess for a dose-response relationship, and describe changes in QTc interval, metabolic parameters, and hemodynamics.

Methods

Study design

We conducted a retrospective cohort study using the Research Patient Data Registry query tool. The Research

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Patient Data Registry is a centralized clinical data registry that obtains data from various electronic medical records and billing systems of ten hospitals in Massachusetts, including urban academic and community hospitals. This study was deemed exempt by the sponsoring institution's Institutional Review Board.

Study population

To maximize results from the query tool, three queries were performed. Each query identified patients over 17 years of age with documented administration of intravenous sodium bicarbonate during a hospital encounter between January 2010 and June 2022. The first query included patients with a "Reason for Visit" of "Drug Overdose" within the same encounter where they received sodium bicarbonate. The second query included patients with ICD10 codes T43.291A, T43.292A, T43.293A, T43.294A, or T43.295A for the same encounter for which they received sodium bicarbonate. The third query included patients with a discharge summary that included the phrases "bupropion overdose," "bupropion ingestion," "bupropion toxicity," "Wellbutrin overdose," "Wellbutrin ingestion," "Wellbutrin toxicity," "Wellbutrin XL overdose," "Wellbutrin XL ingestion," or "Wellbutrin XL toxicity," within the same encounter where the patient received sodium bicarbonate.

The Research Patient Data Registry queries generated patient encounters. Duplicates were removed by listwise deletion. The electronic medical record was reviewed, and cases were eligible for inclusion if there was documentation of bupropion overdose or toxicity by history in the emergency department (ED) note, admission history and physical examination, or discharge summary. Time, dose in milliequivalents (mEq), infusion rate, and formulation of sodium bicarbonate administration were identified in the medication administration record. Patients were included if the encounter included an ECG with a computer-measured QRS duration greater than 100 milliseconds (ms) [8,16,17]—or 10 ms greater than baseline if the patient had pre-overdose ECGs with a QRS duration $>$ 100 ms—prior to receiving sodium bicarbonate, and there was a repeat ECG documented within four hours of receiving sodium bicarbonate.

Chart review

Study authors were trained in chart abstraction and reviewed all charts using a standardized data abstraction form (Appendix 1). Electrocardiograms uploaded to the electronic medical records were reviewed, and intervals were recorded both as measured by the ECG computer and hand measured by study authors. Data were recorded from the ECG proximal to the administration of sodium bicarbonate through up to three ECGs (if available) after the last sodium bicarbonate administration. Data surrounding demographics, exposure (co-ingestions, dosage, and formulation of bupropion), and clinical characteristics (seizures, ventricular dysrhythmias, cardiac arrest, and death) were obtained from provider documentation if known. Administration of vasopressors, hypertonic saline, lidocaine, or lipid emulsion was identified in the medication administration record and documentation. Blood pressure and heart rate were obtained from the Flowsheet section of the electronic medical records; mean arterial pressure was calculated by investigators. Serum sodium, potassium, bicarbonate, and pH values were obtained from basic metabolic panels and venous or arterial blood gases during the encounter. To evaluate for interrater reliability, study authors one and two independently reviewed the first ten patients that met all inclusion criteria, and percent agreement was calculated [18]. Disagreements were resolved by consensus with senior author three.

Primary and secondary outcomes

The primary outcome was the change in QRS duration between the pre-sodium bicarbonate ECG and the first ECG after the initial administration of sodium bicarbonate. Based on previous literature and our clinical experience in our practice environment, secondary outcomes for hypothesis generation included the prevalence of QRS narrowing after initial sodium bicarbonate dose, defined as a QRS duration less than 100 ms in the post-sodium bicarbonate ECG [16,19]; association between QRS change and sodium bicarbonate dosing; change in QRS duration and QTc from the pre-sodium bicarbonate ECG to the ECG after total cumulative administration of sodium bicarbonate [20]; and change in heart rate, mean arterial pressure, serum pH, and serum electrolyte concentrations after initial sodium bicarbonate [6,7].

Statistical analysis

Clinical characteristics were reported as medians with interquartile ranges (IQR) or counts with percentages. Differences in primary and secondary outcomes after sodium bicarbonate were calculated and reported as medians with IQR. Serum pH values on venous blood gases were converted to arterial blood gas values for direct comparison by adding 0.05 [21]. Wilcoxon signed-rank testing was performed to evaluate for statistically significant changes in QRS duration after sodium bicarbonate. Linear regression modeling was utilized to test for an association between QRS change and sodium bicarbonate dosing, using QRS change as the dependent variable. The main analyses were conducted with computer-measured intervals confirmed by cardiologist interpretation as part of routine ECG review; we conducted a sensitivity analysis using hand-measured QT intervals corrected by Bazett's formula. Cases with missing primary outcome data were not included as per inclusion criteria; missing secondary outcome data were assumed to be missing at random and removed from the analysis by listwise deletion. All statistical analysis was performed with R Studio 7.1 (Boston, MA). All tests were two-sided, and alpha was defined as $<$ 0.05.

Results

The three queries returned 206 results. Once duplicates were eliminated, 182 unique patients remained for chart review. Thirty-seven patients had a documented bupropion overdose, and ultimately 13 patients were included in the final analysis (Figure 1). Interrater reliability was demonstrated with 95% agreement. One patient did not receive an ECG after conclusion of the sodium bicarbonate infusion; the latest recorded ECG and the dose of sodium bicarbonate administered by that time were used instead for the relevant secondary outcomes.

The median patient age was 32 years, and seven (54%) patients were male (Table 1). All 12 patients in whom the formulation was documented were exposed to the extended-release (XL) formulation. Of eight patients with a documented exposure dose, the median dose was 2,250 mg. Nine (69%) patients had documented co-ingestions, and one (8%) was also diagnosed with a pulmonary embolism on presentation. Six (46%) patients developed seizures, one developed a ventricular dysrhythmia and cardiac arrest (pulseless ventricular tachycardia), and four (31%) were treated with vasopressors. No patients died. One patient received 3% hypertonic saline between ECGs; the QRS duration did not decrease after hypertonic saline.

Several patients had documented co-ingestion of xenobiotics known to affect QRS duration and QTc intervals, notably cocaine, propranolol, and loperamide [7,22]. Co-ingestions for individual patients are outlined in Table 2.

Primary outcome

The ECG intervals before and after sodium bicarbonate are described in Table 2. The median pre-sodium bicarbonate QRS duration and QTc were 116 ms (IQR: 110–124 ms) and 495 ms (474–521 ms), respectively. The median change in QRS duration from the pre-sodium bicarbonate ECG to the first ECG after initial sodium bicarbonate administration was −2.0 ms (-8.0 to 4.0 ms), which was not statistically significant ($P = 0.42$). We performed a *post hoc* subgroup analysis of patients with pre-treatment QRS duration $\geq$ 120 ms and

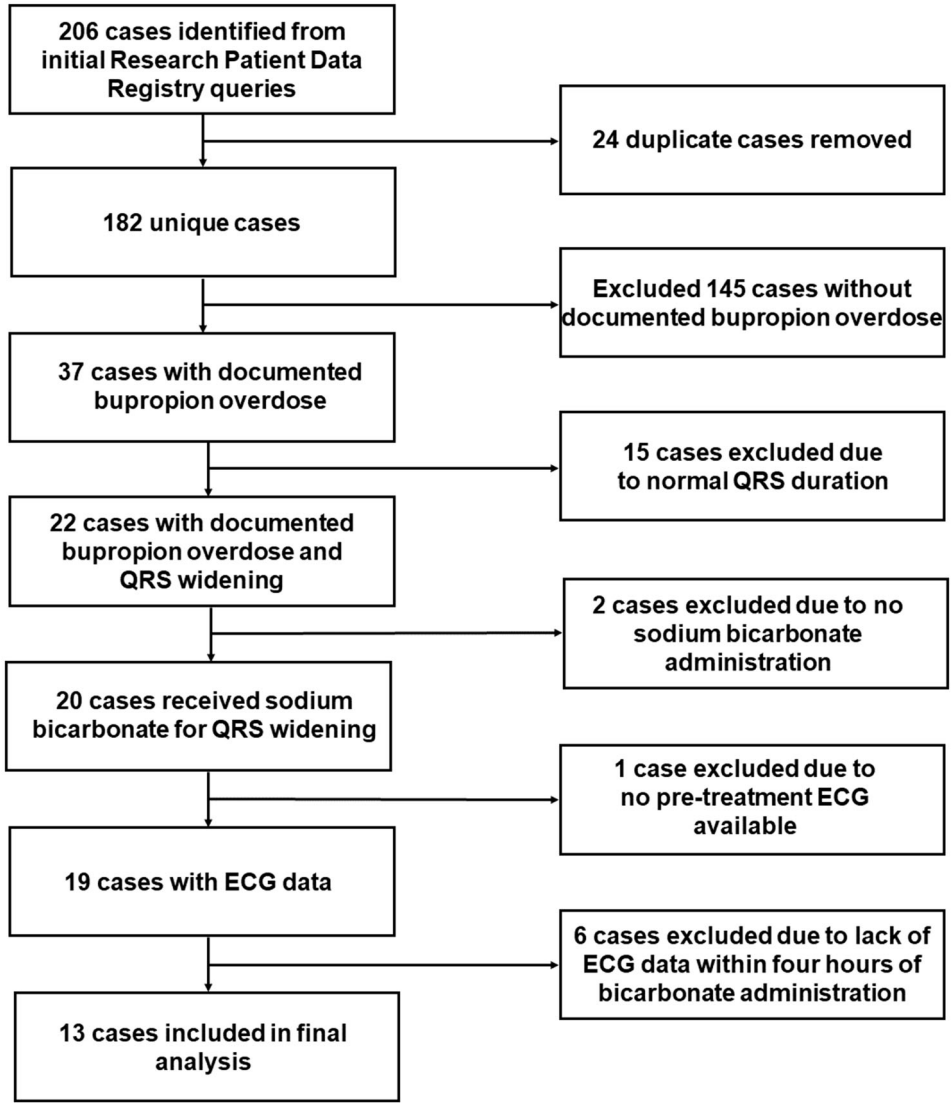

Figure 1. Study inclusion flow chart.

Table 1. Study sample clinical characteristics.

Characteristic	Cases, n[a]
Age (years): median (IQR)	32 (31–40)
Gender	
Male	7 (54%)
Female	6 (46%)
Bupropion ingested dose (mg): median (IQR)	2,250 (1,125–9,000)
Formulation of bupropion ingestion	
Extended-release tablet	12 (92%)
Not available	1 (8%)
Documented co-ingestions	
Yes	9 (69%)
No	4 (31%)
Pre-treatment heart rate in beats per minute: median (IQR)	94 (80-105)
Pre-treatment mean arterial pressure (mmHg): median (IQR)	91 (81-105)
Pre-treatment serum pH: median (IQR)	7.46 (7.41-7.47)
Pre-treatment serum bicarbonate concentration (mEq/L): median (IQR)	24 (22–25)
Pre-treatment serum sodium concentration (mEq/L): median (IQR)	140 (138–140)
Pre-treatment serum potassium concentration (mEq/L): median (IQR)	3.7 (3.6–3.9)
Seizures	
No	7 (54%)
Yes	6 (46%)
Ventricular dysrhythmia	
No	12 (92%)
Yes	1 (11%)
Treatment with vasopressors	
No	9 (69%)
Yes	4 (31%)
Cardiac arrest	
No	12 (92%)
Yes	1 (11%)
Death	
No	13 (100%)
Yes	0 (0%)
Other treatments for QRS widening	
Hypertonic saline	1 (8%)
Lidocaine	0 (0%)
Lipid emulsion	0 (0%)

[a]Total sample size = 13 patients.

those with pre-treatment QRS duration $\geq$ 140 ms. Among patients with pre-treatment QRS duration $\geq$ 120 ms, the median change in QRS duration was −1.0 ms (-4.0–1.0 ms) ms; in the two patients with pre-treatment QRS duration $\geq$ 140 ms, the median change in QRS duration was −6.0 ms.

Secondary outcomes

No patient had a QRS duration < 100 ms on the first ECG after initial sodium bicarbonate administration. The median initial dose of sodium bicarbonate was 100 mEq (IQR 93-100 mEq); eight (62%) patients were started on an infusion. Sodium bicarbonate dosing in individual patients is detailed in Table 3. Because the change in QRS duration had a skewed distribution, logarithmic transformation was applied *post hoc* to QRS duration values for the linear regression model to meet statistical assumptions. The model did not demonstrate an association between change in logarithmic transformed QRS duration and sodium bicarbonate dose ($P = 0.90$, R-squared = 0.001).

The median changes in QRS duration and QTc from pre-sodium bicarbonate ECG to the ECG after the total cumulative sodium bicarbonate administration were −2.0 ms (IQR-6.0–2.0 ms) and −6.0 ms (IQR-24–15 ms), respectively (Table 2).

Of the 12 patients with complete vital sign data (one missing pre-treatment mean arterial pressure), the median heart rate and mean arterial pressure before sodium bicarbonate were 94 beats per minute (IQR 80–105 beats per minute) and 91 mmHg (IQR 81–105 mmHg). The median change in heart rate was −6 beats per minute (IQR-11–2 beats per minute), and the median change in mean arterial pressure was −2 mmHg (-16–6 mmHg) (Table 4).

Median pre-treatment electrolyte values are described in Table 1; values for individual patients are described in Table 4. pH values, rather than changes, are presented in Table 4 due to the high prevalence of missing pre-treatment data. The median post-sodium bicarbonate serum pH was 7.48 (IQR 7.45–7.51). The median change in serum bicarbonate concentration was 3 mEq/L (IQR-1–7 mEq/L). The median change in serum sodium and potassium concentrations were 1 mEq/L (IQR-3–3 mEq/L) and −0.1 mEq/L (-0.3–0.4 mEq/L), respectively.

Sensitivity analysis

In the sensitivity analysis using hand-calculated interval values, the median change in QRS after sodium bicarbonate was 0 (IQR-10.0—0.0) ms ($P = 1$) (Supplemental Table 1). The linear regression model again did not demonstrate an association between sodium bicarbonate dose and change in logarithmic transformed QRS ($P = 0.46$, R-squared = 0.05). In the sensitivity analysis, the median change in QTc after total cumulative administration of sodium bicarbonate was 10.0 (IQR-29–36) ms.

Table 2. Ingestion characteristics and ECG intervals before and after sodium bicarbonate.

Patient	Bupropion ingestion (mg)	Formulation	Co-ingestions	Pre-bicarbonate QRS (ms)	Post-bicarbonate QRS (ms)	Time from bicarboate to post-bicarbonate ECG (min)	ΔQRS (ms) bicarbonate[b]	ΔQRS (ms) total bicarbonate[c]	Pre-bicarbonate QTc (ms)	Post-bicarbonate QTc (ms)	ΔQTc (ms) bicarbonate[d]	ΔQTc (ms) total bicarbonate[e]
1	9,000	XL[a]	Fluoxetine, amfetamine	108	114	208	6	−22	452	497	45	−24
2	2,400	XL	None	140	138	20	−2	10	474	613	139	18
3	NA[g]	XL	Lisinopril, amlodipine, clopidogrel, clonazepam	116	150	184	34	12	492	544	52	51
4	NA	XL	Propranolol	112	104	74	−8	−14	481	545	64	15
5	NA	XL	Seroquel	118	106	111	−12	0	520	430	−90	−90
6	NA	XL	Venlafaxine	108	112	33	4	−6	521	523	2	60
7	900	XL	Loperamide	134	134	39	0	8	561	519	−42	−11
8	1,200	XL	Fluoxetine	110	110	80	0	−2	451	458	7	−19
9	9,000	XL	Alprazolam, ethanol	108	102	60	−6	6	495	512	17	−6
10	2,100	NA	Cocaine, benzodiazepines	110	108	1	−2	0	510	469	−41	8
11	40,500	XL	None	152	142	2	−10	0	569	436	−133	−133
12	900	XL	None	124	128	23	4	0	467	461	−6	−6
13	NA	XL	None	118	104	4	−14	0	630	479	−151	−151

[a]Extended-release tablet.
[b]Change in QRS after initial sodium bicarbonate dose (post- minus pre-bicarbonate).
[c]Change in QRS after total cumulative doses of sodium bicarbonate.
[d]Change in QTc after initial sodium bicarbonate dose (post- minus pre-bicarbonate).
[e]Change in QTc after total cumulative doses of sodium bicarbonate.
[f]Not available.

Discussion

Since 2020, bupropion has been the antidepressant associated with the most severe outcomes and fatalities reported to the National Poison Data System, and both exposures and severe outcomes are increasing [23]. Bupropion cardiotoxicity will only become more relevant to clinicians in the coming years, necessitating the identification and implementation of a safe, effective treatment.

We did not identify a statistically significant decrease in the QRS duration after sodium bicarbonate administration. While there is no widely accepted definition of a clinically meaningful change in QRS duration in ms, animal studies of desipramine and cocaine showed 15% and 30% reduction in QRS duration, respectively, in weight-based doses similar to those used in clinical practice [24,25]. There are also case reports of sodium channel blocker-induced QRS widening responding dramatically to 100 mEq sodium bicarbonate [7,26]. Given this existing literature and the authors' clinical experience, we do not consider the 2.0 ms effect size clinically meaningful; even among patients with a QRS duration $\geq$ 140 ms, the QRS duration narrowed by only 6.0 ms.

The risk of clinical deterioration in sodium channel blocker toxicity appears to increase with a QRS duration greater than 100 ms, and the majority (53%) of United States poison centers utilized 100 ms as the threshold to recommend sodium bicarbonate in a 2003 survey of poison center medical directors [16,19]. Several reviews and expert opinions support this 100 ms threshold, but practice varies with respect to exact clinical and ECG thresholds to initiate sodium bicarbonate treatment [8,17]. The authors practice in the United States, where the aforementioned survey was conducted, and our local practice pattern is to initiate treatment when the QRS duration $>$ 100 ms in the setting of suspected sodium channel blockade. We recognize that practice patterns vary, even within the United States, but our study was designed to reflect our clinical environment. Clinicians might differ as to whether a narrowing to $<$ 100 ms is meaningful, but this was not seen in a single patient, arguing further against the efficacy of sodium bicarbonate.

Practice variation also exists around the dosing and administration (bolus versus infusion) of sodium bicarbonate. An intravenous 50–100 mEq bolus followed by an infusion of 150 mEq in one liter of 5% dextrose in water is a common dosing strategy [7]. Seger et al. [19] reported that over three-quarters of poison centers recommended a bolus dose of 1–2 mEq sodium bicarbonate per kilogram patient weight. Seventy-one percent employed bolus dosing followed by an infusion, while 24% recommended only a bolus. Patients in our study received a median initial dose of 100 mEq, with eight patients out of 13 receiving bolus and infusion and the remainder receiving a bolus alone. The dosing in this study appears consistent with our local practice environment and should be generalizable to medical toxicologists and poison centers in a similar environment. In addition, eight patients' post-treatment serum pH were within the commonly recommended target range of 7.45–7.55 (median 7.48), suggesting adequate alkalinization [7].

Table 3. Sodium bicarbonate dosing.

Patient	Initial bicarbonate bolus (mEq)	Initial bicarbonate dose (mEq)[a]	Started on bicarbonate infusion?	Total dose of bicarbonate administered (mEq)
1	50	168	Yes	1,532
2	100	100	No	100
3	50	93	Yes	480
4	100	100	Yes	542
5	100	126	Yes	239
6	50	50	No	232
7	100	100	Yes	366
8	100	100	No	100
9	100	100	No	250
10	100	100	Yes	482
11	50	50	Yes	429
12	50	50	No	457
13	100	100	Yes	188

[a]Sodium bicarbonate dose used for the primary outcome.

We accounted for the dose of sodium bicarbonate administered using a linear regression model. We did not find an association between the dose of sodium bicarbonate and a change in QRS duration, arguing against the existence of a dose-response relationship. This is again in contrast to previous data and clinical experience with sodium channel-blocking xenobiotics [24].

Sodium bicarbonate appears to reverse hypotension, ventricular dysrhythmias, and QRS widening in sodium channel blocker overdoses [6–8]. Despite similar clinical manifestations—QRS widening from either sodium channel blockade or bupropion toxicity can progress to dysrhythmias and shock—we did not find evidence that sodium bicarbonate improves ECG or clinical parameters in bupropion overdoses [4,27]. Because bupropion's cardiotoxic effects appear independent of sodium channel blockade or pH-dependent ionization, the lack of efficacy of sodium bicarbonate in this setting is not entirely unexpected [9].

Previous case reports have shown varied results utilizing sodium bicarbonate in bupropion toxicity, with most cases suggesting no improvement [5,11–14]. Franco [4] described a patient with a bupropion overdose who developed wide complex tachycardia (QRS 220 ms) after discontinuation of a sodium bicarbonate infusion that returned to sinus rhythm (QRS 120) after restarting the infusion. Infusion and/or bolus dosing was not reported. Livshits et al. [15] described an overdose with elevated serum bupropion concentration that developed grossly widened QRS on ECG (exact duration not reported) that narrowed after a 100 mEq sodium bicarbonate bolus, although hypotension persisted; diphenhydramine co-ingestion may have contributed to the QRS widening. While these two cases suggest QRS narrowing related to bicarbonate administration, the majority of the literature, including the present study, does not support the use of sodium bicarbonate in QRS widening from bupropion overdose.

Sodium bicarbonate therapy has been associated with complications, including iatrogenic hypokalemia, alkalemia, QTc prolongation, and adverse cardiovascular events [20,28]. We did not identify a clinically meaningful difference in QTc or serum potassium concentration despite alkalinization, possibly due to adequate potassium supplementation. Given the lack of evidence of benefit and known potential harm, future research should focus on alternative therapeutic options.

Major toxicology society guidelines, case reports, and the high lipid solubility of bupropion support the use of lipid emulsion therapy as a potential alternative treatment in severe bupropion toxicity refractory to other treatments [27,29–31]. However, there remains no consensus on treatment for QRS widening before the development of refractory arrhythmias or hemodynamic instability. Lidocaine and hypertonic saline, while effective in sodium channel blockade, are unlikely to be helpful given the underlying pathophysiology of gap junction inhibition. Lidocaine has been used to treat ventricular tachycardia refractory to cardioversion in a bupropion overdose, but a guinea pig heart study found no effect of lidocaine on cardiac gap junctions [32,33].

Several investigational peptides have been identified, including antiarrhythmic peptide 10 and rotigaptide, that increase cardiac gap junction conduction *via* phosphorylation of connexin 43 [34,35]. These drugs represent a possible future therapeutic option but are not currently available for clinical use.

Strengths and limitations

This study has several important limitations. Sodium bicarbonate dosing and timing of ECGs were not standardized, limiting direct comparisons. However, patients received clinically relevant doses of sodium bicarbonate.

Given the small sample size, we performed a *post hoc* power calculation using the mean and standard deviation pre-treatment QRS duration in our sample (119.8 ± 16.7 ms), the final sample size of 13 patients, 80% power, and an alpha of 0.05. This yielded a minimum detectable difference of 13.3 ms; thus, we were not powered to find a difference smaller than this. Clinicians might disagree as to whether a difference of less than 13.3 ms is clinically important. However, the median pre-sodium bicarbonate QRS duration was 116 ms, and thus we should have been able to detect a narrowing of the QRS duration below 100 ms, which was not seen in any patient. Further studies are warranted utilizing prospective, standardized data gathering with a larger sample.

Confirmatory drug testing was not performed in the majority of patients, but by history, many patients had co-ingestions that may have contributed to their QRS widening,

Table 4. Vital signs and metabolic parameters before and after sodium bicarbonate.

Patient	Pre-bicarbonate heart rate (bpm)	ΔHeart rate (bpm)	Pre-bicarbonate mean arterial pressure (mmHg)	Δ Mean arterial pressure (mmHg)	Pre-bicarbonate serum pH	Post-bicarbonate serum pH	Pre-bicarbonate serum bicarbonate concentration (mEq/L)	Δ Serum bicarbonate concentration (mEq/L)	Pre-bicarbonate serum sodium concentration (mEq/L)	Δ Serum sodium concentration (mEq/L)	Pre-bicarbonate serum potassium concentration (mEq/L)	Δ Serum potassium concentration (mEq/L)
1	88	−10	109	−7	NA[b]	7.46	NA	NA	NA	NA	NA	NA
2	124	−11	106	−16	NA	NA	23	−2	140	−1	3.3	0.7
3	96	−10	89	−26	NA	7.51	21	5	126	4	3.4	0.6
4	57	−6	79	−17	7.27	7.44	22	−6	142	−3	4.5	0.4
5	105	−26	70	3	NA	7.48	25	−1	140	2	3.6	0.4
6	125	−3	60	26	NA	7.33	11	15	141	−4	3.7	−0.4
7	80	2	82	22	7.46	7.47	29	−8	140	−4	4.1	−0.1
8	78	10	100	4	NA	NA	25	0	138	3	3.8	−0.2
9	94	35	92	8	NA	7.54	25	4	139	0	3.6	−0.3
10	102	−5	105	−16	7.49	7.51	22	7	139	3	3.9	0
11	63	−12	NA	NA	7.45	7.42	28	2	127	20	1.9	0.4
12	92	−19	119	−20	NA	7.53	24	7	138	4	4.2	−0.4
13	118	4	87	5	NA	7.49	13	11	145	−7	3.6	−0.1

[a]Not available.

and one had a pulmonary embolism that may have contributed by causing right heart strain. However, co-ingestions would overall bias the results toward a positive finding, as most xenobiotics contributing to QRS widening are sodium channel blockers and would respond to sodium bicarbonate.

Although we excluded patients with QRS widening unchanged from pre-overdose ECGs, we considered that some patients may have had incidentally discovered wide QRS durations unrelated to overdose. Almost half of our cohort had documented seizures, and nearly a third received vasopressors, which supports the hypothesis that the bupropion overdoses were severe enough to be a plausible explanation for the QRS widening. However, most of our cohort had only mildly prolonged QRS durations (< 120 ms), and only one developed a ventricular dysrhythmia. Different results may be obtained in a cohort of severe cardiotoxicity, and future studies should examine this patient population.

Several previous studies on QRS duration in overdose have employed hand-measurement of ECG intervals by a blinded cardiologist [36,37]. The ECGs in this study were reviewed by the investigators themselves and thus not blinded. Both computer and manual measured QRS durations suffer from inter-evaluator variability [38,39]. To minimize bias, we chose to utilize computer measurements in our primary analysis. Our sensitivity analysis utilizing hand measurements did not demonstrate a significant difference in interval duration after sodium bicarbonate, lending further support to the primary analysis results.

Conclusions

Sodium bicarbonate did not significantly reduce QRS duration in this small retrospective cohort of bupropion overdoses. Clinically important changes were not observed in QTc interval or vital signs. Prospective evaluations of pharmacologic therapies are urgently needed to guide treatment in bupropion cardiotoxicity.

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Appendix 1. Data abstraction form

Study ID	Age (years)	Sex	Date/Time of ingestion (if unknown, 'NA')	Bupropion dose (mg) (if unknown, 'NA')	Bupropion formulation (if unknown, 'NA')

Please enter data for EKGs below. Enter 3 EKGs post last bicarb administration, if available. Please add more rows if needed.

Pre-bicarb EKG data	Date/Time	Heart rate (bpm):	Calculated QRS (ms):	QRS by hand if available (ms):	Calculated QTc (ms):	QTc Bazett by hand if available (ms):	Any other signs of Na channel blockade; rightward axis, R' in aVR > 3 mm:
EKG 2 data	Date/Time	Heart rate (bpm):	Calculated QRS (ms):	QRS by hand if available (ms):	Calculated QTc (ms):	QTc by hand if available (ms):	Any other signs of Na channel blockade; rightward axis, R' in aVR > 3 mm:
EKG 3 data	Date/Time	Heart rate (bpm):	Calculated QRS (ms):	QRS by hand if available (ms):	Calculated QTc (ms):	QTc by hand if available (ms):	Any other signs of Na channel blockade; rightward axis, R' in aVR > 3 mm:

Please enter data for bicarbonate administration below; 2nd, 3rd, and 4th bicarbonate administrations would refer to multiple boluses given between multiple sets of EKGs; e.g., between EKG 1 and 2 100mEq were given, and then between EKG 2 and 3, another 50 mEq were given

Date/Time of 1st bicarbonate administration	Bicarbonate administered between which EKGs (#)?	Total dose of sodium bicarbonate bolus between EKGs?	Was a bicarbonate infusion started?	If so, what was the composition (e.g., 150 mEqs sodium bicarbonate in 1 L D5W) and rate (e.g., 150 mL/hr)?	If so, date/time of infusion begun?

Please enter date/time and dose of any additional therapies to narrow the QRS (e.g., hypertonic saline, lidocaine, intralipid)

Therapy administered	Date/time of therapy administration	Dose of therapy administration

Please enter the following information regarding the vitals closest to the pre-bicarbonate EKG

HR (bpm)	Date/Time of HR	Systolic/diastolic BP (mmHg)	MAP (mmHg)	Date/Time of BP

Please enter the following information regarding the vitals closest to the POST-bicarbonate EKG but after the bicarbonate was given

HR (bpm)	Date/Time of HR	Systolic/diastolic BP (mmHg)	MAP (mmHg)	Date/Time of BP

Please enter any other pre/post bicarbonate vital signs for additional bicarbonate administrations

HR (bpm)	Date/Time of HR	Systolic/diastolic BP (mmHg)	MAP (mmHg)	Date/Time of BP
HR (bpm)	Date/Time of HR	Systolic/diastolic BP (mmHg)	MAP (mmHg)	Date/Time of BP

Please enter an 'X' if the patient developed any of the following during this hospitalization

Seizures
Hypotension receiving vasopressors
Cardiac arrest
Death