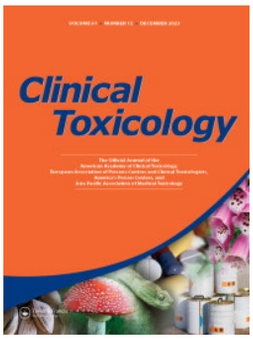

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CLINICAL RESEARCH

The role of QRS complex prolongation in predicting severe toxicity in single-xenobiotic overdose

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ABSTRACT

Objective: The QRS complex duration is commonly used to prognosticate severity, predict outcomes, and indicate treatment in overdose. However, literature to support this practice is mixed in tricyclic antidepressant overdoses and absent in non-tricyclic antidepressant overdoses. Our objective was to assess the validity of QRS complex duration as a prognostic marker in overdose.

Methods: This was a secondary analysis of cases reported to the Toxicology Investigators Consortium between January 1, 2010, and December 31, 2022. Cases were assessed to determine the six xenobiotics most associated with QRS complex prolongation. All cases involving these six xenobiotics, regardless of QRS complex duration, constituted the study cohort. Inclusion criteria were cases of patients older than 12 years old with single-xenobiotic exposures. Clinical outcomes evaluated were seizure, ventricular dysrhythmia, metabolic acidosis, and death.

Results: Of 94,939 total cases, diphenhydramine, amitriptyline, bupropion, quetiapine, nortriptyline, and cocaine were most associated with QRS complex prolongation. Inclusion criteria were met by 4,655 cases of exposure to these xenobiotics. QRS complex prolongation was associated with increased odds ratio of seizure in all included xenobiotics, of ventricular dysrhythmia in all included xenobiotics except nortriptyline, and of metabolic acidosis or death in all included xenobiotics except nortriptyline and quetiapine. A normal QRS complex duration had a negative predictive value of greater than or equal to 93.0 percent of developing metabolic acidosis and 98.0 percent of developing a ventricular dysrhythmia or death from the xenobiotics studied.

Discussion: This study demonstrates that patients with QRS complex prolongation from all six xenobiotics studied had an increased prevalence and odds of developing severe outcomes. Furthermore, patients who did not develop QRS complex prolongation were unlikely to develop a ventricular dysrhythmia, metabolic acidosis, or death. These findings were noted in six xenobiotics that mechanistically can cause QRS complex prolongation through sodium channel or gap junction inhibition.

Conclusion: Identification of patients at risk for severe outcomes after overdose can be aided by measuring the QRS complex duration. If prospectively validated, these outcomes have implications on risk stratification, disposition level of care, and appropriateness of treatments.

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Sodium channel blocking; overdose; seizure; ventricular dysrhythmia; QRS complex

Introduction

Early identification of patients at risk of severe toxicity after overdose has widespread implications for clinical management. Given the prevalence and mortality of tricyclic antidepressant overdoses in the second half of the twentieth century, numerous studies sought to identify early markers of severe tricyclic antidepressant toxicity. Multiple studies demonstrate that the sodium channel blocking effects of tricyclic antidepressant toxicity slows phase 0 depolarization of the cardiac action potential through impaired His-Purkinje and myocardial conduction velocity leading to QRS complex prolongation [1–4]. The QRS complex duration was proposed by Boehnert et al. [5] as a means of prognosticating the clinical course for these patients. Their study demonstrated that patients with a maximum limb lead QRS complex duration of 100 milliseconds (ms) or greater were at increased risk of seizures, while only patients with a QRS complex duration of 160 ms or greater were at risk of ventricular dysrhythmias [5]. Several follow-up studies supported the prognostic ability of QRS complex duration in tricyclic antidepressant toxicity [6,7]. In a canine model, increased amitriptyline concentrations lead to QRS complex prolongation, and a QRS complex greater than 110 ms was associated with ventricular dysrhythmias [6]. In a retrospective analysis of patients with tricyclic antidepressant ingestions, a QRS complex duration greater than 100 ms was one of the multiple markers found to have an elevated odds ratio of major toxicity [7].

However, other studies have questioned the prognostic ability of the QRS complex duration in tricyclic antidepressant overdose, and literature to support this practice in non-tricyclic xenobiotics is nearly nonexistent [8–11]. In the years following the publication by Boehnert et al. [5] multiple studies displayed

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an inconsistent association between QRS complex duration and severe outcomes such as ventricular dysrhythmias, seizures, and death [8–10]. A 2004 meta-analysis of 18 studies by Bailey et al. [11] reported that the sensitivity and specificity of a QRS complex duration greater than 100 ms for seizures, ventricular dysrhythmias, and death ranged from 46% to 81%. While they concluded that electrocardiogram (ECG) findings poorly predicted complications after tricyclic antidepressant overdose, they acknowledged that "anecdotal clinical experience suggests that the ECG is a far better prognostic test than that indicated by the results" [11]. There are multiple possible explanations for this conclusion. This includes the time-dependent relationship between overdose and ECG, which was inconsistent between studies, and the use of alternate QRS complex duration thresholds other than 100 ms.

Despite these mixed results, QRS complex duration is commonly used to prognosticate severity, predict severe outcomes, inform level of care decisions, and as an indication for hypertonic sodium bicarbonate therapy in tricyclic antidepressant overdoses [12]. The mechanistic justification for this practice stems from the known inhibition of tricyclic antidepressants for voltage-sensitive sodium channels in the heart, which leads to QRS complex prolongation as well as the potential to change the morphology of the R wave in lead aVR, alter the axis of the terminal 40 ms frontal QRS complex plane, produce a right bundle branch block-like pattern, or unmask a Brugada pattern [13–18]. Through this same mechanism, the use of QRS complex duration to predict clinical outcomes and guide management is commonly extrapolated to non-tricyclic sodium channel blocking xenobiotics. Literature to support this practice in non-tricyclic xenobiotics is exceptionally sparse for several xenobiotics and nonexistent for most [19–21]. This is despite the prevalence and potential severity of non-tricyclic sodium channel blocking xenobiotics. For example, diphenhydramine, which is a known sodium channel blocker, had the second most medical outcomes of moderate, major, or death in the 2022 National Poison Data System Annual Report after paracetamol (acetaminophen) [22,23]. Therefore, research is needed to guide whether the practices of prognostication based on QRS complex duration should be used in tricyclic antidepressant or non-tricyclic xenobiotic ingestions.

We hypothesized that QRS complex prolongation is associated with severe clinical features in overdose on tricyclic antidepressant and non-tricyclic xenobiotics with sodium channel-blocking properties. The first objective was to determine if patients with QRS complex prolongation were at increased risk of severe clinical features compared to patients without QRS complex prolongation after tricyclic antidepressant and non-tricyclic xenobiotic overdoses. The second outcome was to determine how well QRS complex prolongation performs in predicting severe clinical features.

Methods

Study design and setting

This was a secondary analysis of cases reported to the Toxicology Investigators Consortium (ToxIC) Core Registry. The ToxIC Core Registry is a database of patient cases that received medical toxicology consultation at approximately 50 participating sites in the United States and internationally [24]. This data source collects de-identified data. This project was exempt from review by our Institutional Review Board and was approved by the ToxIC research committee. De-identified case data was provided on standardized spreadsheets (Microsoft Excel 2022, version 16.70).

Patient population

We studied all cases of QRS complex prolongation in the ToxIC Core Registry, regardless of the xenobiotic, reported between January 1, 2010, and December 31, 2022. These cases were analyzed to obtain the six most frequent single-xenobiotic exposures associated with QRS complex prolongation (Figure 1). Cases of xenobiotic withdrawal were not included.

All cases involving one of the six most commonly associated xenobiotics, regardless of the QRS complex duration, constituted our study cohort. The inclusion criteria were patients older than 12 years of age with single-xenobiotic exposures to one of these six xenobiotics. All routes of exposure were included. Patients 12 years old or younger or without a specified age were excluded to minimize exploratory exposures. Multiple-xenobiotic exposures were excluded to minimize confounding.

Variables

The clinical outcomes evaluated were seizure, ventricular dysrhythmia, metabolic acidosis, and death. These clinical outcomes were chosen as markers of severe toxicity due to their clinical importance and based on their utilization in prior studies evaluating the role of QRS complex duration in overdose [5,8,19]. Variables were defined based on the ToxIC Core Registry documentation criteria including QRS complex prolongation as greater than 120 ms and metabolic acidosis as a pH of less than 7.2 that is metabolic in nature. The ToxIC Core Registry does not specify a standard QRS complex duration measurement method. Therefore, QRS complex duration measurements may be manual or computer-generated depending on the treating provider's discretion.

Analysis

Statistical analyses were performed using odds ratios, positive predictive value (PPV), and negative predictive value (NPV) calculations. Odds ratios (OR) were calculated using contingency analysis of categorical variables. Statistical significance was defined using 95% confidence intervals (CI). Predictive values were chosen as the appropriate statistical measurement to assess whether QRS complex duration could stratify patients for developing clinical outcomes. The JMP® Pro 16.0.0 statistical software was used for analyses.

Results

Characteristics of study subjects

During the study period, there were 94,939 total cases reported to the ToxIC Core Registry (Figure 1). QRS complex

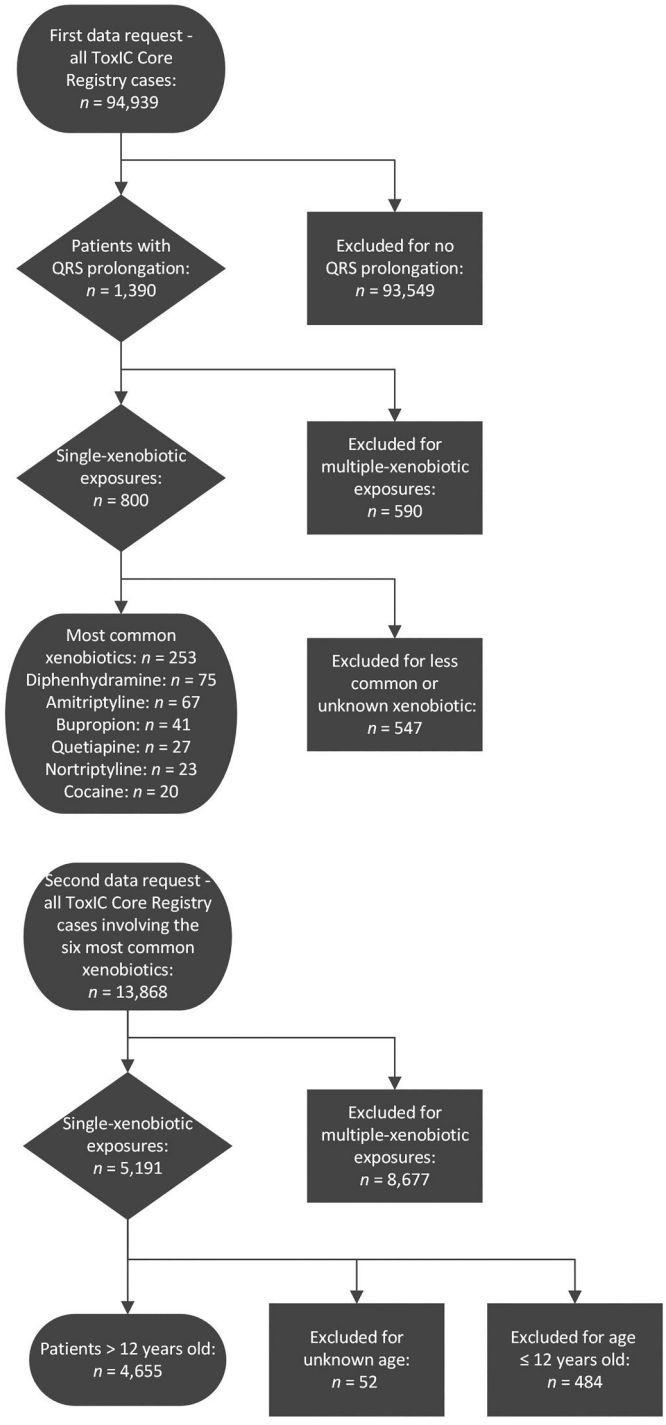

Figure 1. Flow diagram for patients included in the study.

prolongation occurred in 1,390 (1.5%) of these cases; 800 single-xenobiotic exposures and 590 multiple-xenobiotic exposures. The most frequent single-xenobiotic exposures associated with a prolonged QRS complex duration were diphenhydramine ($n = 75$), amitriptyline ($n = 67$), bupropion ($n = 41$), quetiapine ($n = 27$), nortriptyline ($n = 23$), and cocaine ($n = 20$).

There were 13,868 total cases of exposure to diphenhydramine, amitriptyline, bupropion, quetiapine, nortriptyline, or cocaine during the study period. This included 5,191 single-xenobiotic exposures, which were included, and 8,677 multiple-xenobiotic exposure, which were excluded. Cases were then excluded for patients 12 years old or younger ($n = 484$) or without a specified age ($n = 52$). The inclusion criteria were met by 4,655 cases, which formed our study cohort.

The demographics of these patients are shown in Table 1. The median, interquartile range, and range of ages are reported due to the non-normally distributed age of the patient population. The route of exposure was known in 3,515 (75.5%) cases. For cases with a known exposure route, oral was the most common route ($n = 3,299$, 93.9%) and was more common than all non-oral routes combined ($n = 216$, 6.1%). Most non-oral exposures were exposure to cocaine ($n = 180$, 83.3%). This included 83 inhalational cases, 74 intranasal cases, 19 parenteral cases, 3 rectal cases, and 1 other exposure case, which were 30.3%, 27.0%, 6.9%, 1.1%, and 0.4% of the overall cocaine cases with a known exposure route, respectively.

Main results

Comparative analyses between patients with normal and prolonged QRS complex durations for each xenobiotic are shown in Tables 2–5. There were increased overall rates of seizure, ventricular dysrhythmia, metabolic acidosis, and death in patients with QRS complex prolongation compared to patients with normal QRS complex duration for all xenobiotics, except for metabolic acidosis and death in quetiapine exposures. Additionally, QRS complex prolongation was associated with increased odds of seizure in all included xenobiotics, of ventricular dysrhythmias in all included xenobiotics except nortriptyline, and of metabolic acidosis or death in all included xenobiotics except nortriptyline and quetiapine (Figure 2).

The predictive value of QRS complex duration is also shown in Tables 2–5. The PPV of QRS complex prolongation for these clinical outcomes was generally low for the six xenobiotics, although the exact values varied by outcome and xenobiotic. The NPV of a normal QRS complex duration was strongest in predicting the absence of ventricular dysrhythmias, metabolic acidosis, and death. A normal QRS complex duration had a NPV of 93.0% or greater that patients did not develop metabolic acidosis and 98.0% or greater that patients did not develop ventricular dysrhythmia or death from all xenobiotics.

Discussion

The role of QRS complex prolongation in predicting severe toxicity in overdose has implications for the management and disposition of the poisoned patient. These results suggest that patients with a prolonged QRS complex duration have increased odds of seizure, metabolic acidosis, ventricular dysrhythmias, and death for these xenobiotics with few exceptions. These exceptions are potentially due to low incidence rates of certain outcomes for certain xenobiotics. For instance, none of the 26 patients with a prolonged QRS complex duration after quetiapine exposure developed metabolic acidosis or death, which led to a lower rate of these outcomes than in patients with a normal QRS complex duration.

Table 1. The demographics of patients in the study cohort who met inclusion criteria.

	Diphenhydramine		Bupropion		Amitriptyline		Nortriptyline		Quetiapine		Cocaine	
	Prolonged QRS	Normal QRS	Prolonged QRS	Normal QRS	Prolonged QRS	Normal QRS	Prolonged QRS	Normal QRS	Prolonged QRS	Normal QRS	Prolonged QRS	Normal QRS
Total cases	75	1,504	39	951	66	431	20	38	26	926	19	560
Age (years)												
Median	17	17	19	19	42	31	23.5	36.5	34	31	40	41
Interquartile range	14.75 – 27.25	15–29	15 – 31.5	16–32	17–54	17–46	15.75 – 42.75	19.5 – 49.75	23.5 – 46.5	18 – 46	32.5 – 47	30 – 51
Range	13–69	13–86	14–62	13–78	13–81	13–81	13–61	15–64	14–72	13 – 87	16 – 60	14 – 89
Sex												
Female	41 (54.7%)	964 (64.1%)	26 (66.7%)	627 (65.9%)	46 (69.7%)	298 (69.1%)	14 (70.0%)	25 (65.8%)	20 (76.9%)	497 (53.7%)	5 (26.3%)	133 (23.8%)
Male	32 (42.7%)	525 (34.9%)	13 (33.3%)	313 (32.9%)	20 (30.3%)	132 (30.6%)	6 (30.0%)	13 (34.2%)	6 (23.1%)	423 (45.7%)	14 (73.7%)	425 (75.9%)
Transgender	2 (2.7%)	14 (0.9%)	0	9 (0.9%)	0	1 (0.2%)	0	0	0	4 (0.4%)	0	0
Unknown	0	1	0	2	0	0	0	0	0	2	0	2
Self-Harm Attempt												
Yes	65 (86.7%)	1259 (83.7%)	36 (92.3%)	826 (86.9%)	58 (87.9%)	215 (49.9%)	19 (95.0%)	9 (23.7%)	22 (84.6%)	847 (91.5%)	1 (5.3%)	21 (3.8%)
No	8 (10.7%)	179 (11.9%)	1 (2.6%)	83 (8.7%)	2 (3.0%)	33 (7.7%)	1 (5.0%)	3 (7.9%)	3 (11.5%)	51 (5.5%)	18 (94.7%)	505 (90.2%)
Unknown	2	66	2	42	6	183	0	26	1	28	0	34

Furthermore, patients with a prolonged QRS complex duration after nortriptyline exposure did not have statistically different odds ratios of ventricular dysrhythmia, metabolic acidosis, or seizure. However, given that nortriptyline is a metabolite of amitriptyline with the same mechanism of action, a larger sample size for nortriptyline could have yielded similar results to amitriptyline. This has implications on patient disposition as patients with QRS complex prolongation in the setting of overdose are more likely to necessitate a higher level of care and are at greater risk of decompensation.

Another important finding from this study was the NPV of severe outcomes in patients with a normal QRS complex duration. A normal QRS complex duration had a NPV of 93.0% or greater that the patient would not develop metabolic acidosis and 98.0% or greater that a patient would not develop ventricular dysrhythmia or death for each xenobiotic. The clinical importance of this finding is that patients with a normal QRS complex duration are unlikely to develop ventricular dysrhythmias, metabolic acidosis, or death. Therefore, patients who continued to display a normal QRS complex duration were unlikely to have a fatal ingestion or necessitate interventions to treat ventricular dysrhythmias or metabolic acidosis in this study.

As hypothesized, QRS complex prolongation in this study was associated with increased odds of severe outcomes. We believe this is due to the mechanism of toxicity of the xenobiotics. Blocking voltage-sensitive sodium channels in the myocardium and conducting system slows phase 0 (depolarization) of the myocyte action potential. This leads to QRS complex prolongation as well as the other potential electrocardiographic findings mentioned previously. This altered sodium conduction impairs contraction and predisposes patients to the development of ventricular dysrhythmias [3].

Five of the six xenobiotics most frequently associated with QRS complex prolongation in the ToxIC Core Registry have known sodium channel-blocking properties: diphenhydramine [25], amitriptyline [13], quetiapine [26], nortriptyline [27], and cocaine [28]. In contrast, experimental evidence from *in vitro* and animal studies suggests that bupropion induces QRS complex prolongation through myocardial gap junction inhibition rather than sodium channel blockade [29,30]. This slows myocyte electrical impulse communication and therefore slows the rate of depolarization [29,30]. Therefore, all six xenobiotics act through a mechanism that may result in QRS complex prolongation.

Finally, the threshold for a normal QRS duration used in this study was less than 120 ms. Although many prior studies have used 100 ms, we felt that 120 ms was a more appropriate threshold. There is a significant proportion of the population whose baseline QRS complex duration is between 100 ms and 120 ms. A study using cohorts from the Framingham Heart Study identified that 4% of patients had QRS complex durations between 100–120 ms and 3% greater than or equal to 120 ms after excluding patients with pacemakers or taking antidysrhythmics [31]. Furthermore, another study following 2537 healthy 18–30 years old patients with QRS complex durations of less than 100 ms at year 0 found that 11.5% of patients developed QRS complex durations of greater than 100 ms by

Table 2. Statistical analyses for patients with normal and prolonged QRS complex durations for developing seizures.

	Seizures/total cases with a prolonged QRS	Seizures/total cases with a normal QRS	Odds ratio of a seizure with a prolonged QRS compared to a normal QRS (95% CI)	Positive predictive value of a prolonged QRS for a seizure (95% CI)	Negative predictive value of a normal QRS for a seizure (95% CI)
Diphenhydramine	23/75 (30.7%)	173/1504 (11.5%)	3.4 (2.0 – 5.7)	30.7% (21.7 – 41.4%)	88.5% (88.0 – 89.0%)
Bupropion	24/39 (61.5%)	358/951 (37.6%)	2.7 (1.4 – 5.1)	61.5% (46.0 – 75.1%)	62.4% (61.7 – 63.0%)
Amitriptyline	16/66 (24.2%)	30/431 (7.0%)	4.3 (2.2 – 8.4)	24.3% (16.6 – 34.0%)	93.0% (91.5 – 94.3%)
Nortriptyline	9/20 (45.0%)	7/38 (18.4%)	3.6 (1.1 – 12.1)	45.0% (29.6 – 61.4%)	81.6% (71.2 – 88.8%)
Quetiapine	4/26 (15.4%)	34/926 (3.7%)	4.8 (1.6 – 14.6)	15.4% (6.2 – 33.4%)	96.3% (95.9 – 96.7%)
Cocaine	6/19 (31.6%)	34/560 (6.1%)	7.1 (2.6 – 20.0)	31.6% (15.6 – 53.5%)	93.9% (93.1 – 94.6%)

CI: confidence interval.

Table 3. Statistical analyses for patients with normal and prolonged QRS complex durations for developing ventricular dysrhythmias.

	Ventricular dysrhythmias/total cases with a prolonged QRS	Ventricular dysrhythmias/total cases with a normal QRS	Odds ratio of ventricular dysrhythmias with a prolonged QRS compared to normal QRS (95% CI)	Positive predictive value of a prolonged QRS for ventricular dysrhythmias (95% CI)	Negative predictive value of a normal QRS for ventricular dysrhythmias (95% CI)
Diphenhydramine	12/75 (16.0%)	9/1504 (0.6%)	31.6 (12.9 – 77.8)	16.0% (10.9 – 22.9%)	99.4% (99.0 – 99.6%)
Bupropion	2/39 (5.1%)	6/951 (0.6%)	8.5 (1.7 – 43.6)	5.1% (1.5 – 15.8%)	99.4% (99.1 – 99.6%)
Amitriptyline	12/66 (18.2%)	5/431 (1.2%)	18.9 (6.4 – 55.8)	18.2% (13.0 – 24.8%)	98.8% (97.6 – 99.4%)
Nortriptyline	2/20 (10.0%)	0/38 (0.0%)	Infinity (Incalculable)	10.0% (7.1 – 14.0%)	100.0% (90.8 – 100.0%)
Quetiapine	1/26 (3.9%)	2/926 (0.2%)	18.5 (1.6 – 210.6)	3.9% (0.8 – 17.2%)	99.8% (99.5 – 99.9%)
Cocaine	4/19 (21.1%)	11/560 (2.0%)	13.3 (3.8 – 46.6)	21.1% (9.1 – 41.5%)	98.0% (97.4 – 98.6%)

CI: confidence interval.

Table 4. Statistical analyses for patients with normal and prolonged QRS complex durations for developing metabolic acidosis.

	Metabolic acidosis/total cases with a prolonged QRS	Metabolic acidosis/total cases with a normal QRS	Odds ratio of a metabolic acidosis with a prolonged QRS compared to a normal QRS (95% CI)	Positive predictive value of a prolonged QRS for a metabolic acidosis (95% CI)	Negative predictive value of a normal QRS for a metabolic acidosis (95% CI)
Diphenhydramine	14/75 (18.7%)	24/1504 (1.6%)	14.1 (7.0 – 28.7)	18.7% (12.4 – 27.1%)	98.4% (98.0 – 98.7%)
Bupropion	5/39 (12.8%)	23/951 (2.4%)	5.9 (2.1 – 16.6)	12.8% (5.9 – 25.8%)	97.6% (97.1 – 98.0%)
Amitriptyline	7/66 (10.6%)	12/431 (2.8%)	4.1 (1.6 – 10.9)	10.6% (5.9 – 18.3%)	97.2% (96.1 – 98.0%)
Nortriptyline	1/20 (5.0%)	0/38 (0.0%)	Infinity (Incalculable)	5.0% (3.5 – 7.1%)	100.0% (90.8 – 100.0%)
Quetiapine	0/26 (0.0%)	11/926 (1.2%)	0 (0 - Undefined)	0.0% (0.0 – 100.0%)	98.8% (98.8 – 98.8%)
Cocaine	5/19 (21.1%)	36/560 (6.4%)	5.2 (1.8 – 15.2)	26.3% (11.9 – 48.5%)	93.6% (92.8 – 94.2%)

CI: confidence interval.

Table 5. Statistical analyses for patients with normal and prolonged QRS interval durations for deaths.

	Deaths/total cases with a prolonged QRS	Deaths/total cases with a normal QRS	Odds ratio of death with a prolonged QRS compared to a normal QRS (95% CI)	Positive predictive value of a prolonged QRS for death (95% CI)	Negative predictive value of a normal QRS for death (95% CI)
Diphenhydramine	5/75 (6.7%)	8/1504 (0.5%)	13.4 (4.3 – 41.9)	6.7% (3.3 – 12.9%)	99.5% (99.2 – 99.7%)
Bupropion	4/39 (10.3%)	3/951 (0.3%)	36.1 (7.8 – 167.5)	10.3% (5.3 – 19.0%)	99.7% (99.3 – 99.9%)
Amitriptyline	4/66 (6.1%)	1/430 (0.2%)	27.7 (3.1 – 252.2)	6.1% (3.8 – 9.6%)	99.8% (98.7 – 100.0%)
Nortriptyline	1/20 (5.0%)	0/38 (0.0%)	Infinity (Incalculable)	5.0% (3.5 – 7.1%)	100.0% (90.8 – 100.0%)
Quetiapine	0/26 (0.0%)	6/926 (0.7%)	0 (0 - Undefined)	0.0% (0.0 – 100.0%)	99.4% (99.4 – 99.4%)
Cocaine	2/19 (10.5%)	11/560 (2.0%)	5.9 (1.2 – 28.6)	10.5% (2.9 – 31.4%)	98.0% (97.5 – 98.4%

CI: confidence interval.

year 20 [32]. Furthermore, the inclusion of patients with a baseline QRS complex duration of greater than 120 ms in our analysis would likely bias the results toward the null hypothesis, thereby strengthening the positive conclusions of this study.

Ultimately, QRS complex prolongation in these six xenobiotics is predictive of severe toxicity. The QRS complex prolongation is the electrocardiographic representation of the sodium channel blockade and gap junction inhibition that occurs with these xenobiotics. The sodium channel blockade and gap junction inhibition may directly predispose patients to ventricular dysrhythmias. The causes of seizures and metabolic acidosis are multifactorial and partially driven by other mechanisms not related to the QRS complex. However, we demonstrated that the QRS complex prolongation is still predictive of these outcomes, likely because it is a marker of greater xenobiotic toxicity in the patient.

Limitations

There are limitations to this study. First, documentation was based on history, not on laboratory confirmation. Second, the ToxIC Core Registry is limited by the documentation of treating medical toxicologists. The ToxIC quality assurance process

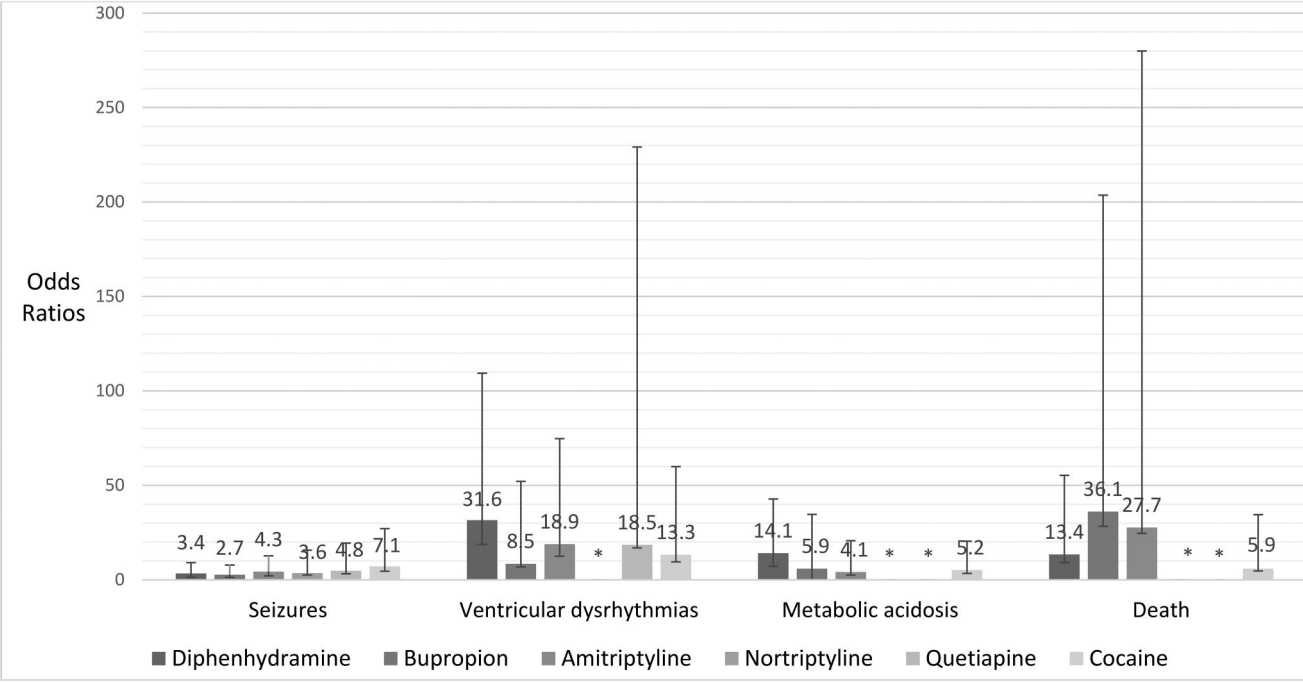

Figure 2. Odds ratios for clinical outcomes in patients with prolonged QRS complex compared to a normal QRS complex duration. Columns with no bar and an asterisk (*) signify an odds ratio where the 95% confidence interval did not show a significant difference in outcomes between patients with a prolonged compared to normal QRS complex duration. The error bars display the 95% confidence interval for each odds ratio, which may also be seen in Tables 2–5.

does not verify ToxIC entries with patients' medical records and undetected errors in data entry might occur. Despite this, there is no reason to believe that there were categorical differences in the histories or data entry between patients with normal and prolonged QRS complex duration. Third, this study utilized QRS complex prolongation on any ECG as a positive finding, but did not associate it with any timeframe. Additionally, the ToxIC database does not specify the method of QRS complex duration measurement and leaves this interpretation to the entering provider. Fourth, all exposure routes were included in this study. We chose to include all exposure routes instead of just oral exposures due to the different patterns of use between xenobiotics. In this study, 93.9% of cases with a known exposure route were oral exposures, although the proportion of oral exposures was lower for cocaine (34.3%). However, this is reflective of a different pattern of cocaine exposures compared to the other xenobiotics studied. Fifth, ToxIC data methodologically represents only a subset of all overdoses that the primary team sought medical toxicology consultation, typically due to case severity or complexity. We expect that this only strengthens the conclusion because even in a population with high rates of severe outcomes, QRS complex prolongation was still largely predictive. Sixth, this study only looks at the six xenobiotics most frequently reported to have QRS complex prolongation in a national database. All these xenobiotics act through a mechanism that could lead to QRS complex prolongation. Therefore, the potential generalizability of this study pertains only to xenobiotics that mechanistically function like these six xenobiotics. Further study is needed to prospectively validate the prognostic value of QRS complex prolongation and to determine if QRS complex prolongation has prognostic value in xenobiotics without a mechanism for QRS complex prolongation.

Conclusions

In summary, the identification of patients at risk of severe clinical outcomes in overdose can be aided by evaluating the QRS complex duration on electrocardiography. Patients with QRS complex prolongation from these xenobiotics had an increased prevalence and odds of developing severe clinical outcomes. Furthermore, patients who did not develop QRS complex prolongation were unlikely to develop ventricular dysrhythmias, metabolic acidosis, or death. If prospectively validated, these outcomes have implications on risk stratification, disposition level of care, and appropriateness of treatments.

Meetings

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Authors' contributions

MS, SK, KM, CH, and JB conceived the study. MS, SK, and KM performed the data request and data analysis. MS drafted the manuscript. MS, SK, KM, CH, and JB contributed substantially to the revisions and rewriting of the manuscript. MS takes responsibility for the paper as a whole.

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Data availability statement

Data for this manuscript was obtained by request from the American College of Medical Toxicology's Toxicology Investigators Consortium: https://www.acmt.net/toxic/

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