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Drug-specific risk of severe QT prolongation following acute drug overdose

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ABSTRACT

Background: Severe QT prolongation (SQTP) has been identified as a strong predictor of adverse cardiovascular events in acute drug overdose, but drug-specific causes of SQTP in the setting of acute drug overdose remain unclear. We aimed to perform the most definitive study to date describing drug-specific risk of SQTP following acute drug overdose.

Methods: This was a prospective multicenter cohort study at >50 hospital sites across the US using the ToxIC Registry between 2015 and 2018. Inclusion criteria were adults (>18 years) receiving medical toxicology consultation for acute drug overdose. The primary outcome was SQTP, which was defined using the computer automated Bazett QT correction (QTc) on the ECG with the previously validated cut point of 500 milliseconds. Mean difference in QTc was also calculated for specific drugs. Drugs associated with SQTP were analyzed using multivariable logistic regression to control for known confounders of QT risk (age, sex, race, cardiac disease).

Results: From 25,303 patients screened, 6473 met inclusion criteria with SQTP occurring in 825 (13%). Drugs associated with increased adjusted odds of SQTP included Class III antidysrhythmics (sotalol), sodium channel blockers (amitriptyline, diphenhydramine, doxepin, imipramine, nortriptyline), antidepressants (bupropion, citalopram, escitalopram, trazodone), antipsychotics (haloperidol, quetiapine), and the antiemetic serotonin antagonist ondansetron.

Conclusions: This large US cohort describes drug-specific risk of SQTP following acute drug overdose. Healthcare providers caring for acute drug overdoses from any of these implicated drugs should pay close attention to cardiac monitoring for occurrence of SQTP.

Introduction

Cardiovascular morbidity and mortality due to drug overdose continues to be a major public health problem in the US as illustrated from a variety of survey, secondary clinical and vital statistics data sources [1–3]. Nearly half of all emergency department (ED) visits in the US are related to substance use disorders [4], and the last estimate from the Drug Abuse Warning Network (2011) reported over 5 million drug related ED visits in the US annually [5], of which 2.3 million involved adverse events [2], a number which has likely increased over the interval time period. Of drug-related ED visits, about one half are due to the nonmedical use of prescription drugs [2].

It has previously been shown that 15% of patients hospitalized with acute drug overdose suffer adverse cardiovascular events (ACVE) which require additional medical treatment, rehabilitation, and/or cause death [6]. Prediction of ACVE in this patient population may be aided by simple clinical risk factors [7], and findings from the initial ECG [8]. The most useful ECG finding for this purpose is the QTc interval; it was previously demonstrated that QTc >500 ms on the initial ECG conferred over 10-fold higher odds of ACVE in this patient population [8].

Because severe QT prolongation (SQTP) has been identified as a strong predictor of ACVE in acute drug overdose [8,9], drug-specific causes of SQTP, especially in overdose, are of vital importance for the stratification of risk of ACVE. The objective of this study was to utilize a national toxico-vigilance database, Toxicology Investigators Consortium (ToxIC), to determine the drug-specific causes of SQTP in the setting of acute drug overdose.

Materials and methods

Study design and setting

This was a prospective cohort study of patients entered into the ToxIC registry database between April 15, 2015 to July 15, 2018. The ToxIC Registry contains data collected prospectively from all clinical cases cared for in-person by medical toxicologists at participating sites [10,11]. To enter patients into the ToxIC Registry, participating medical
Toxicologists use an online interface to upload information including substance involved, demographics, encounter circumstances, toxidrome, signs and symptoms, treatment, and outcomes, derived as part of the standard toxicology bedside consult. The study protocol was approved with waiver of consent by both the Western Institutional Review Board (central IRB for ToxIC sites) and the Program for the Protection of Human Subjects at the Icahn School of Medicine at Mount Sinai (PI’s institution).

ToxIC maintained the core case registry for the present study in which participating sites agree to record all cases seen at local hospitals and EDs where a bedside consultation by a medical toxicologist was provided to aid clinical care. The term consultation as used herein refers to activities carried out by the medical toxicologist as either a consultant or the admitting physician. The core registry as of May 1, 2018 contained data from over 65 US hospitals in 47 US cities nationwide, representing exposures to over 1100 different toxicological agents. This represents 40 university medical centers, 23 States, and all 10 Federal Districts. Many ToxIC investigators work in one or more academic medical center, as well as in hospitals in smaller and/or distant community health care facilities. Many of the participating referral medical centers regularly receive transfers of unknown or unrecognized toxicity from drug use. This feature extends the reach of ToxIC into urban, suburban, and rural areas while preserving its ability to collect community-level adverse event data associated with drug overdose. This current analysis excluded the small number of cases from non-US sites (total 4 sites contributing 433 cases of any type over this period).

**Selection of patients**

Adults (≥18 years) with acute (or acute-on-chronic) pharmaceutical drug exposures were eligible from the registry. Patients were included for analysis only if there were signs and symptoms diagnosed by medical toxicologists as most likely due to drug overdose. Exclusion criteria were lack of an ECG during the ED stay, children (<18 years), missing ECG or clinical data, non-drug exposures, or lack of signs or symptoms of drug overdose as determined at the bedside by the consulting medical toxicologist. Exclusions for “no toxic exposure,” “no signs or symptoms,” and “unknown/unlikely toxic exposure” were based on the determination of the attending medical toxicology consultant. Those with polydrug ingestion were not excluded from the study since the majority of real-world drug overdoses involve multiple co-exposures. However, each drug class was analyzed separately to account for SQTP associations.

**Methods of measurement**

ToxIC registry top-level data collection tools were setup prior to enrollment for the present study in order to collect the appropriate data in prospective fashion. Available patient demographics included age, sex, race and Hispanic ethnicity. Medical toxicologists provided bedside consultation for each patient and independently reported the primary agent(s) responsible for drug toxicity, which was used for the drug-specific QT analysis. Cardiovascular signs and symptoms were collected for each patient, including initial QTc values.

We used the QTc provided by the bedside medical toxicologist as recorded in the ToxIC database. QT intervals were corrected for heart rate (QTc) using the computer-generated value (i.e., not overread by a cardiologist) from Bazett’s correction equation (QTc = QT/RR1/2) in >98% of patients (<2% used an alternate QTc method and these values were included). ECG printouts are not uploaded to the ToxIC database. Manual QT measurement or QTc “over-reads” were not performed by study investigators for the purposes of this study. Patients with atrial fibrillation/flutter were excluded from QTc analysis. Patients with QRS widening were included in accordance with prior overdose cohort studies which evaluated QTc for risk prediction [8,9]. Individual drug associations with ΔQTc (difference between mean QTc in drug exposure compared with mean of entire cohort) as well as odds ratios (OR) for the primary outcome (SQTP), were calculated for all individual drugs with at least three occurrences of SQTP in the database.

Data are collected and managed using REDCap (Research Electronic Data Capture) tools hosted at the Vanderbilt University Medical Center, Institute for Clinical and Translational Research core [12]. REDCap is a secure web-based application which was utilized to support data capture for the study with an intuitive interface for validated data entry, audit trails for tracking data manipulation, and procedures for centralized data quality control performed by a full-time project manager (SC). Quality assurance of ToxIC registry data is maintained in accordance with current best-practices [13] including database logical checks, pilot testing, procedure manuals, paperless e-forms, data cleaning, data tracking, secure encryption, and user training in accordance with current guidelines [14].

**Outcome measures**

The primary outcome for this analysis was SQTP, defined using the previously validated cut point of 500 milliseconds [8]. SQTP could occur at any point during the hospital stay, but the majority of occurrences in this study were the initial ECG assessed in the ED.

**Primary data analysis**

Drugs associated with SQTP were analyzed with chi-squared, incidence (%) and 95% confidence intervals (CI). In addition, a t-test for the difference of means was conducted on the drug specific mean QTc versus the mean population QTc. Based on a previously validated prediction model for ACVE, the occurrence of SQTP was calculated as a measure of effect, and adjusted ORs were calculated using multivariable logistic regression adjusting for literature-based known confounders: age, sex, race, Hispanic ethnicity [15], and previous history of cardiovascular disease [8,9]. Study sample size was calculated a priori, based on a 10% prevalence of drug class
exposure predictor variables, as well as 10% baseline of SQTP risk based on prior registry data. Using these assumptions, we calculated the need to enroll 5138 patients to have 90% power to detect a 50% increase in adjusted odds. Analyses were performed using SPSS v24 software (IBM, Chicago, IL).

Results

Enrollment

From the 25,303 patients entered into ToxIC over this 37-month study period, 7790 cases met our screening criteria, representing 43.7% of all adult acute drug exposure patients receiving medical toxicology consultation by a ToxIC investigator. Based on the determination of the attending medical toxicologist, patients presenting with no clinical toxicity, or who were displaying signs/symptoms unrelated to the suspected exposure, were also excluded (n = 1317). This resulted in a final inclusion cohort of 6473 patients. Enrollment and specific exclusion criteria are outlined in Figure 1.

Patient characteristics

The demographic breakdown for these adult patients is summarized in Table 1. The primary reason for the overdose was either an attempt at self-harm or misuse/abuse in 86.9%. Suicidal intent was reported in over half of the patients.

Drug classes

The five most common drug classes were sedative-hypnotics and muscle relaxants (n = 1545), antidepressants (n = 1540), analgesics (n = 1447), opioids (n = 1220), and sympathomimetics (n = 885), which accounted for 56.5% of all the drugs. As the most common class, sedative-hypnotics were reported in 1545 cases, representing 13.2% of all exposures. The most common sedative-hypnotics were alprazolam (5.1% cases) and clonazepam (4.6% cases). 51.9% of patients reported a common sedative-hypnotics were alprazolam (5.1% cases) in 1545 cases, representing 13.2% of all exposures. The most

QTc analysis

The mean reported QTc interval for the study population was 457.7 ms (SD 49.86), with the overall incidence of SQTP of 12.7%. Individual drug associations with ΔQTc were summarized in Table 3. Drugs with significantly increased ΔQTc were the following (in descending order): sotalol (+96.5), ondansetron (+43.8), doxepin (+30.3), nortriptyline (+23.2), citalopram (+21.7), quetiapine (+14.1), fluoxetine (+12.2), trazodone (+12.0), diphenhydramine (+11.5), bupropion (+7.8), and cocaine (+7.3). The only drug associated with significantly decreased ΔQTc was synthetic cannabinoids (−9.2). Drugs associated with significantly higher incidence (%) of SQTP were the following (in descending order): imipramine (75), sotalol (63), nortriptyline (41), doxepine (33), citalopram (25), haloperidol (24), trazodone (24), amitriptyline (23), escitalopram (23), diphenhydramine (21), quetiapine (20), and bupropion (19). The only drug with significantly lower incidence (%) of SQTP was synthetic cannabinoids (7). Drugs with significantly increased ΔQTc but no association with SQTP incidence were the following: cocaine (+7.3), fluoxetine (+12.2), and ondansetron (+43.8).

SQTP adjusted model

Multivariable logistic regression was performed to calculate adjusted ORs (aOR), for all drugs with ≥3 SQTP occurrences in the database, using the following covariates based on prior literature: age, sex, race/ethnicity, and prior cardiovascular disease [8,9,15]. Findings of the adjusted model are summarized in Table 3. Drugs associated with significantly higher adjusted odds (aOR) of SQTP were the following (in descending order): imipramine (21.3), sotalol (9.8), ondansetron (4.7), nortriptyline (4.5), doxepin (3.1), haloperidol (2.6), citalopram (2.2), trazodone (2.1), escitalopram (1.99), diphenhydramine (1.97), amitriptyline (1.95), quetiapine (1.87), and bupropion (1.66). Adjusting for confounding in the SQTP model did not change positive associations for any drugs, but synthetic cannabinoids lost its unique univariate association with decreased incidence of SQTP (aOR 0.67, CI 0.34–1.34). The only drug that gained significance with adjustment was ondansetron (aOR 4.7, CI 1.11–20.2).

Discussion

This large US-based prospective cohort represents the most definitive study to date describing drug-specific risk of SQTP following acute overdose. Patients with acute drug overdose from class III antidysrhythmics, sodium channel blockers, several antidepressants and antipsychotics, as well as the antiepileptic serotonin antagonist ondansetron, have been demonstrated by the present study to be at risk for SQTP. Unexpected drug-associations with QTc prolongation were few but included trazodone. Notable drugs without any association included lithium, cyclobenzaprine, oxycodone, methadone, and olanzapine. Our data suggests that healthcare providers caring for acute drug overdoses from any of these implicated drugs should pay close attention to cardiac monitoring as SQTP is associated with ACVE, including ventricular dysrhythmia and death [8,9,16].

Drug overdose related QTc prolongation

The findings of the present study are consistent with, and add significantly to, existing literature on drug overdose related QTc prolongation. A recent prospective validation cohort study evaluated adult ED patients with acute drug overdose at two urban university hospitals over 5 years. Several characteristics from the initial ECG (ectopy, QT prolongation, non-sinus rhythm, ischemia/infarction) were associated with ACVE in these ED patients [8,9]. These previously derived criteria were highly predictive of ACVE, with QT correction >500 ms as the highest risk feature (OR 11.2, CI 4.6–27) [8]. While severe QTc prolongation may occur for a
variety of reasons, this cohort is the first to prospectively identify common high-risk drugs associated with SQTP.

Generalizability of ToxIC

The ToxIC Registry features two characteristics that allowed for collection of robust and unique data for the present study. First, all patients in the registry are seen at the bedside by highly trained, board certified medical toxicologists. No other surveillance system contains clinical information obtained by physicians with this degree of toxicologic expertise. The second is the ability to collect high quality prospective data on drug exposures, signs, symptoms, and treatments received. The study inclusion/exclusion criteria are likely superior to simply using a positive urine/serum drug screen, as these are fraught with false positives, false negatives, and are not recommended for routine use in ED patients with drug exposures [17]. However, this study characterizes patients seen at the bedside by medical toxicologists and may represent the higher severity illness or susceptible individuals following drug exposure due to typical consulting patterns for severe overdoses. Therefore, ToxIC registry cases likely are not representative of the toxicological exposures that were not hospitalized or had minimal signs or symptoms of toxicity. However, the study cases are representative of the most severe exposed individuals, meaning those who are likely to have taken high doses of the implicated drug and are at higher risk for SQTP.

Class III anti-dysrhythmics

Some drug-associations observed in the present study were expected, such as with sotalol, a Class III anti-dysrhythmic which is a potent competitive inhibitor of rapid delayed

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**Table 1.** Patient characteristics among 6473 cases of acute drug overdose reports from the US ToxIC Registry, April 15, 2015 to July 30, 2018.

| Demographics                | Sex, n (%)        | Male     | 3254 (50.3) |
|                            | Male              | 3254 (50.3) |
| Race, n (%)                 | American Indian/Alaskan Native | 88 (1.4) |
| Previous medical history, n (%) | Coronary artery disease | 258 (4.0) |
| Hispanic ethnicity, n (%)   | Coronary artery disease | 258 (4.0) |
| Coronary artery disease     | Coronary artery disease | 258 (4.0) |
| Congestive heart failure    | Congestive heart failure | 170 (2.6) |

\( n = \) number of cases; \%: percent eligible cases; \( y = \) years; IQR: interquartile range.
Table 2. Exposure characteristics including intent for drug misuse/abuse, self-harm and/or suicidal intent among 6473 patients with acute drug overdose from the US ToxIC Registry, April 15, 2015 to July 30, 2018.

<table>
<thead>
<tr>
<th>Reason for encounter, n (%)</th>
<th>n</th>
<th>% Cases: # cases reporting specific drug/total number of cases (N = 6473).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication of misuse/abuse</td>
<td>1931 (29.9)</td>
<td></td>
</tr>
<tr>
<td>Indication of self-harm</td>
<td>3633 (56.1)</td>
<td></td>
</tr>
<tr>
<td>Indication of misuse/abuse and self-harm</td>
<td>59 (0.9)</td>
<td></td>
</tr>
<tr>
<td>No Indication misuse/abuse or self-harm</td>
<td>850 (13.1)</td>
<td></td>
</tr>
<tr>
<td>Encounters with indication of self-harm, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicidal intent</td>
<td>3234 (50.0)</td>
<td></td>
</tr>
<tr>
<td>No Suicidal intent</td>
<td>130 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Unknown if suicidal intent</td>
<td>327 (5.1)</td>
<td></td>
</tr>
<tr>
<td>Missing</td>
<td>1 (0.0)</td>
<td></td>
</tr>
</tbody>
</table>

Agents reported – single and multiple drug exposures combined

Ten most common drug classes reported | n | % Agent fields | % Cases |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sedative-hypnotic/muscle relaxant</td>
<td>1545</td>
<td>13.2</td>
<td>23.9</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>1540</td>
<td>13.1</td>
<td>23.8</td>
</tr>
<tr>
<td>Analgesic</td>
<td>1447</td>
<td>12.3</td>
<td>22.4</td>
</tr>
<tr>
<td>Opioid</td>
<td>1220</td>
<td>10.4</td>
<td>18.8</td>
</tr>
<tr>
<td>Symptomaticalictic</td>
<td>885</td>
<td>7.5</td>
<td>13.7</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td>854</td>
<td>7.3</td>
<td>13.2</td>
</tr>
<tr>
<td>Anticholinergic/antihistamine</td>
<td>822</td>
<td>7.0</td>
<td>12.7</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>655</td>
<td>5.6</td>
<td>10.1</td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td>493</td>
<td>4.2</td>
<td>7.5</td>
</tr>
<tr>
<td>Psychostimulant</td>
<td>322</td>
<td>2.7</td>
<td>5.0</td>
</tr>
</tbody>
</table>

Fifteen most common drugs reported | n | % Agent fields | % Cases |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>776</td>
<td>6.6</td>
<td>12.0</td>
</tr>
<tr>
<td>Diphenhydramine</td>
<td>499</td>
<td>4.3</td>
<td>7.7</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>472</td>
<td>4.0</td>
<td>7.3</td>
</tr>
<tr>
<td>Cocaine</td>
<td>348</td>
<td>3.0</td>
<td>5.4</td>
</tr>
<tr>
<td>Heroin</td>
<td>335</td>
<td>2.9</td>
<td>5.2</td>
</tr>
<tr>
<td>Alprazolam</td>
<td>332</td>
<td>2.8</td>
<td>5.1</td>
</tr>
<tr>
<td>Bupropion</td>
<td>325</td>
<td>2.8</td>
<td>5.0</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>296</td>
<td>2.5</td>
<td>4.6</td>
</tr>
<tr>
<td>Methamphetamine</td>
<td>293</td>
<td>2.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>263</td>
<td>2.2</td>
<td>4.1</td>
</tr>
<tr>
<td>Trazadone</td>
<td>250</td>
<td>2.1</td>
<td>3.9</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>239</td>
<td>2.0</td>
<td>3.7</td>
</tr>
<tr>
<td>Amitryptline</td>
<td>158</td>
<td>1.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>148</td>
<td>1.3</td>
<td>2.3</td>
</tr>
<tr>
<td>Lithium</td>
<td>144</td>
<td>1.2</td>
<td>2.2</td>
</tr>
</tbody>
</table>

rectifier potassium channels [18]. Previously, sotalol serum concentrations were found to correlate with QT prolongation following intravenous and oral sotalol administration [19]. In the present study, sotalol overdose was associated with an aOR of 9.6 (CI 2.5–40.6) for SQTP and was thus one of the highest-risk drugs in the entire cohort, albeit a rare overdose.

Sodium channel blockers

An additional drug class with expected findings from this dataset was that of sodium channel blockers. Previously, patch clamp in vitro studies showed reduced hERG currents and disrupted hERG expression [20–23], while another retrospective case series of 13 tricyclic exposures suggested a risk of QT prolongation [24]. In the present study, sodium channel blockers with significantly increased risk of SQTP were overdoses from imipramine (aOR 21.3, CI 2.2–210), followed by nortriptyline (aOR 4.5, CI 2.1–9.9), doxepin (aOR 3.1, CI 1.8–5.6), diphenhydramine (aOR 1.97, CI 1.6–2.5), and amitriptyline (aOR 1.95, CI 1.3–2.9). Mechanistically, this was an expected finding because widening of the QRS via sodium channel blockade prolongs the QT interval, by definition. Interestingly, this suggests that the degree of QRS widening from the above sodium channel blockers follows the same order. Since this is speculative, investigations into the degree of QRS widening based on specific drugs in this class are warranted to help guide management.

Antidepressants

Findings of SQTP from other antidepressant (non-tricyclic) overdoses were also confirmatory of suggestions of QTc prolongation in the existing literature. For example, bupropion has had prior in vitro [25] and multiple case report [26–29] associations with QTc prolongation which were confirmed by significantly increased SQTP risk in the present study (aOR 1.66, CI 1.2–2.2). Both citalopram (aOR 2.2, CI 1.4–3.5) and escitalopram (aOR 1.99, CI 1.2–3.4) had near-equal increased risk of SQTP in the present study, which also confirms data suggested in prior case reports for citalopram [30–33], escitalopram [34–37], and a retrospective citalopram cohort study [38]. Interestingly, this suggests that cardiac monitoring for patients with either citalopram or escitalopram overdose should be managed in the same way.

Antipsychotics

Antipsychotics that were significantly associated with SQTP in the present study were haloperidol (aOR 2.6, CI 1.3–5.4) and quetiapine (aOR 1.87, CI 1.5–2.4), while others such as olanzapine and risperidone had no association. This is consistent with prior in vitro [39,40] and supratherapeutic dosage studies [41–43] of haloperidol. Similarly, these data are consistent with prior studies of quetiapine including a psychiatric cohort of drug-drug interactions [44], and a retrospective case series of overdoses suggesting QTc prolongation [45]. Therefore, future study of post-sedation QT monitoring is warranted to verify and minimize QT risk in patients receiving sedative doses of antipsychotics.

Ondansetron

The antiemetic serotonin antagonist ondansetron had increased risk of SQTP in the present study (aOR 4.7, 1.11–20.2), which is consistent with a wealth of prior literature. Ondansetron blocks calcium-activated potassium channels [46], and QT risk has previously been reported in a variety of settings, including overdose involving an infant [47], therapeutic dose in ED patients [48], therapeutic dose in PICU patients [49], and drug-drug-interactions in the ICU [50]. While ondansetron overdose is rare, these findings should not be extrapolated to therapeutic dosing of ondansetron when treating patients with QT-drug overdose who are experiencing nausea.

Trazodone

An unexpected drug-association with SQTP was the atypical antidepressant, trazodone (aOR 2.1, CI 1.6–2.9). This drug has
been reported to cause QTc prolongation in only four human cases in the known medical literature [51–54]. However, there is in vitro evidence that suggests potent inhibitory activity on the hERG channel [55]. The findings of the present study validate these in vitro findings using our clinical cohort.

**Synthetic cannabinoids**

A possible negative association in the present study was the class of synthetic cannabinoids. While case reports have suggested QTc prolongation in overdose [56], and some class members, such as JWH-030, have been demonstrated to inhibit hERG [16], likely there is significant structural heterogeneity within the drug class to make significant generalizability about pharmacologic activity difficult, either protective or harmful. The present study was underpowered to demonstrate a "protective" effect on SQTP, however further study in larger patient populations is warranted as this was a surprising finding.

**Unexpected findings**

Expected drug-associations that were not observed in this population included lithium (aOR 0.97 [0.6–1.6]), which has been reported to have QTc prolonging effects, both in overdose and therapeutic use [57,58]. Furthermore, methadone (aOR 1.31 [0.8–2.2]) [59–61] and olanzapine (aOR 0.79 [0.4–1.4]) [62] are proven chronic QTc prolonging drugs, but neither demonstrated a significant association in this analysis of acute exposures. Delayed QTc monitoring may thus be required for more sensitive detection of SQTP in this select group of drug exposures. An alternative explanation that could be proposed for the lack of association with methadone is that peak QTc was delayed and/or not reported. Future study that is able to detect delayed, SQTP is therefore warranted to confirm this alternative explanation.

**Validity of Bazett method**

SQTP cutoffs for this population were derived to predict occurrence of ACVE; it was previously demonstrated that a Bazett QTc >500 ms on the initial ECG conferred over 10-fold higher odds of ACVE in this patient population [8]. No other QT method (Fredericia, Framingham, Rautaharju, or nomogram) has been validated to predict ACVE, therefore it would be inappropriate to have "back-calculated" those alternative correction formulae in this study. The QT correction method used by bedside medical toxicology consultants in the present study was the Bazett correction in >98% of patients (<2% used an alternate QTc method and these values were included). This was used, unchanged, in the analysis for two main reasons: (1) this is the most generalizable correction because it is what was used by the real providers in the ToxIC registry in the real world; and (2) Bazett is actually the only QT correction that has been validated for prediction of ACVE in the drug overdose population. Furthermore, a prior study by Othong and colleagues evaluated utility of the
Rautaharju method to predict drug-induced torsade de pointes [63]; however, torsade de pointes is extremely rare and is not the study outcome (i.e., ACVE) from which SQTP cutpoints for this population are relevant [7,8].

**Limitations**

Because timing between drug overdose and obtaining the ECG were not recorded in the ToxIC database, presence or absence of a significant delay may have impacted the ability to detect associations for some drugs with delayed QT effects (e.g., methadone). Serum electrolyte concentrations which may have affected QTc prolongation (potassium, magnesium, calcium) were seldom (<10%) reported in the ToxIC database and were thus not able to be included in the model. The population observed in this study is a relatively young and diverse population, which may influence the associations observed. Additionally, the majority of the encounters described episodes of misuse/abuse or self-harm events and were therefore indicative of potentially high dose exposures and/or repetitive use. Approximately one-half of the included patients had multiple drug exposures, which may introduce further complexity when trying to determine the contribution of each substance to the observed QTc effects. Nevertheless, the observed effects may have implications for prescribing practices to prevent overdose-related cardiovascular morbidity and mortality. QTc prolongation was used as a surrogate for true clinical outcomes (i.e., ACVE) in this study based on prior large validation study [8], which may be viewed as a limitation. Finally, it is well established that at higher heart rates, QTc is over-estimated by most of the QT correction methods (including Bazett’s formula); however, prior cohort studies evaluating QTc in this population did not stratify for heart rate [8,9], and excluding patients with tachycardia would severely limit the study’s generalizability.

**Conclusions**

In this large prospective US cohort, we have comprehensively identified specific drugs with the highest risk of SQTP following acute drug overdose. Drug classes most commonly associated with SQTP were class III antidysrhythmics, sodium channel blockers, antidepressants, and antipsychotics. These findings should be used by clinicians to guide the clinical management of patients with acute drug overdose, as heightened awareness of the need for electrocardiographic monitoring may be required. Timing and duration of electrocardiographic monitoring, as well as implications for prescribing practices to prevent drug-induced QT prolongation, both require further study.

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**References**


