Journal of Medical Toxicology
https://doi.org/10.1007/s13181-021-00855-2

ORIGINAL ARTICLE

Delayed QT Prolongation: Derivation of a Novel Risk Factor for Adverse Cardiovascular Events from Acute Drug Overdose

Siri Shastry[1] · Eleanor R. Aluise[1] · Lynne D. Richardson[1,2] · Rajesh Vedanthan[3] · Alex F. Manini[4]

Received: 15 March 2021 / Revised: 18 June 2021 / Accepted: 19 July 2021

Abstract

Introduction In ED patients with acute drug overdose involving prescription medication and/or substances of abuse, severe QTc prolongation (> 500 ms) is predictive of adverse cardiovascular events (ACVE), defined as myocardial injury, ventricular dysrhythmia, shock, or cardiac arrest. However, it is unclear whether delayed severe QTc prolongation (dsQTp) is a risk factor for ACVE and if specific clinical factors are associated with occurrence of dsQTp.

Methods A secondary analysis of a prospective cohort of consecutive adult ED patients with acute drug overdose was performed on patients with initial QTc < 500 ms. The predictor variable, dsQTp, was defined as initial QTc < 500 ms followed by repeat QTc ≥ 500 ms. The primary outcome was occurrence of ACVE. Multivariable logistic regression was performed to test whether dsQTp was an independent predictor of ACVE and to derive clinical factors associated with dsQTp.

Results Of 2311 patients screened, 1648 patients were included. The dsQTp group ($N = 27$) was older than the control group ($N = 1621$) (51.6 vs 40.2, $p < 0.001$) and had a higher number of drug exposures (2.92 vs 2.16, $p = 0.003$). Following adjustment for age, sex, race/ethnicity, number of exposures, serum potassium, and opioid exposure, dsQTp remained an independent predictor of ACVE (aOR: 12.44, $p < 0.0001$). Clinical factors associated with dsQTp were age > 45 years and polydrug (≥ 3) overdoses.

Conclusion In this large secondary analysis of ED patients with acute drug overdose, dsQTp was an independent risk factor for in-hospital occurrence of ACVE.

Keywords Overdose · QT prolongation · Adverse cardiovascular events

Introduction

Drug overdose represents a major source of mortality and morbidity within the USA, with over 67,000 deaths due to drug overdose in 2018 alone [1].Drug overdose deaths increased by nearly 10% from 2016 to 2017. [2] Over this same time period, there were over 900,000 nonfatal overdoses managed within the Emergency Department (ED) setting [2].

Adverse cardiovascular events (ACVE) in the setting of drug overdose have been well-described [3, 4] and include myocardial injury, shock, ventricular dysrhythmias, or cardiac arrest. ACVEs are frequently implicated in morbidity and mortality associated with drug overdose [5] and have been shown to occur in approximately 10% of all ED patients with drug overdose [3]. In ED patients presenting with acute drug overdose involving prescription medication and/or substances of abuse, severe QTc prolongation (defined as QTc > 500 ms) in association with various drug exposures

Supervising Editor: David M. Wood, MD

✉ Siri Shastry
Siri.Shastry@mountsinai.org

[1] Department of Emergency Medicine, Icahn School of Medicine At Mount Sinai, Mount Sinai Hospital, 555 West 57th Street, 5th Floor, New York, NY 10019, USA

[2] Department of Population Health Science and Policy, Icahn School of Medicine At Mount Sinai, New York, NY, USA

[3] Department of Population Health, New York University Grossman School of Medicine, New York, NY, USA

[4] Division of Medical Toxicology, Department of Emergency Medicine, Icahn School of Medicine At Mount Sinai, Elmhurst Hospital Center, New York, NY, USA

Published online: 27 August 2021

has been previously described [6]. Severe QTc prolongation in ED patients with overdose has also been shown to be a predictor of adverse cardiovascular events (ACVE) [4, 7, 8]. Prior studies have noted an over tenfold increase in odds of ACVE in the patient population with QTc prolongation upon ED presentation [7].

Delayed severe QTc prolongation (defined as a QTc > 500 ms on repeat ECG following an initial normal QTc) following specific drug exposures is a phenomenon that has been noted in the literature with prior case series detailing delayed severe QTc prolongation due to citalopram and methadone and recent characterization of delayed severe QTc prolongation by drug class [6, 9–12]. However, this phenomenon has not been studied systematically. Delayed severe QTc prolongation may occur due to intracellular potassium shifts, which may result from bicarbonate administration; a rise in serum pH is accompanied by potassium movement into the cells to maintain electroneutrality [13, 14]. dsQTp may also occur due to delayed absorption from co-ingestions, pharmacokinetics and/or toxicokinetics of the drugs involved, or drug-drug interactions. Currently, it is unknown if delayed severe QTc prolongation (dsQTp) can be as predictive as initial QTp for identifying those at risk for ACVE in this patient population. If indeed dsQTp is identified as a novel ACVE risk factor, this could have substantial clinical practice implications related to identifying those at risk for subsequent cardiovascular decompensation.

Given the increasing incidence of drug overdose in the USA and the substantial role of ACVE in associated morbidity and mortality, an improved understanding of predictors of ACVE in this patient population is vital to improve risk stratification and management. Identifying clinical factors associated with dsQTp may allow for identification of ED patients potentially requiring serial repeat ECG screening. Accordingly, the present study aims to: (1) define clinical factors associated with dsQTp in ED patients with acute drug overdose and (2) test whether dsQTp is an independent predictor of ACVE in this patient population.

Methods

Study Design and Setting

This was a secondary data analysis from a prospective cohort study at two academic, urban tertiary care EDs from March 2015 through March 2020. The ED at one site has annual patient volumes of approximately 145,000 visits; the second site has approximately 106,000 ED visits annually. Annual volumes include visits to the psychiatric ED, pediatric ED, and urgent cares. IRB approval was obtained with waiver of consent prior to data collection at the study institutions.

Study Population

Patients in the parent cohort (which aims to validate a previously derived risk prediction tool for prediction of adverse cardiovascular events [4]) are consecutive ED patients over the age of 18 with acute overdose or poisoning; of these, a secondary data analysis was performed on those with an initial QTc < 500 ms upon presentation [15]. ED patients with suspected acute drug overdose were screened prospectively by trained research assistants based on presenting chief complaint. Patients were enrolled consecutively 24 h a day over the study period. Exclusion criteria from the cohort were as follows: initial ECG with QTc ≥ 500, age under 18, an alternative diagnosis (e.g., stroke, sepsis), non-drug exposure (e.g., caustic, plant), dermal exposure (due to the self-limiting nature of these exposures), chronic toxicity (i.e., symptom onset not within prior 24 h), prisoner status, do not resuscitate/do not intubate (DNR/DNI) status, missing data, or transfer of patient to other hospital/care facility.

Measures

Data were abstracted from the medical chart by several trained research assistants for the original prospective cohort study. Data collection from the medical chart occurred in accordance with accepted guidelines for valid medical chart abstraction, including training of abstractors and 95% agreement of a random sampling of ten test charts prior to mass data abstraction [16]. Abstractors were blind to study hypothesis.

Data collected included demographics, drug exposure, medication administration, initial (upon arrival to ED) and repeat ECG data, lab data (during presenting ED visit, generally within 1–2 h of initial ECG), and outcome measures. dsQTp was defined as presence of initial QTc < 500 ms followed by repeat ECG with QTc ≥ 500 ms. Prior large cohort studies have validated a cutoff of 500 ms as being most predictive of adverse cardiovascular events in ED patients with acute drug overdose [4, 7]. Based on prior literature [8], the computer-generated corrected QT interval (Bazett's corrected QTc, $QT/\sqrt{RR}$) was used as it has been previously validated for this purpose [6–8, 15]. There was no defined time interval for the repeat ECG, as it was obtained as part of routine clinical care. For patients who had multiple repeat ECGs, the ECG during the hospital stay with the longest QTc interval was recorded. Repeat ECGs with normal QTc were not recorded in the database. Cohort patients were grouped on the basis of dsQTp; patients with a repeat ECG with QTc ≥ 500 ms were the dsQTp group, while control patients were patients

with repeat ECG with QTc < 500 ms or who did not have a repeat ECG performed. Enrolled subjects were then prospectively followed to hospital discharge for occurrence of the study outcomes (below).

Outcomes

The primary study outcome was the occurrence of adverse cardiovascular events (ACVE). ACVE was defined according to prior literature [3, 4] as the composite in-hospital occurrence of any of the following: (A) myocardial injury (serum troponin elevation > 0.10 ng/mL); (B) ventricular dysrhythmias (defined as ventricular tachycardia (VT), ventricular fibrillation (VF) or Torsades des Pointes (TdP)); (C) cardiac arrest (loss of pulse requiring CPR); or (D) shock (hypotension requiring administration of vasopressors).

Analysis

Univariate statistics were employed to evaluate for associations between demographic/clinical characteristics and dsQTp. Demographic factors examined included age, sex, and race/ethnicity. Clinical characteristics included underlying coronary artery disease (CAD) and/or congestive heart failure (CHF), serum electrolytes (potassium, calcium and bicarbonate), serum pH, number of exposures, drug class, and administration of antipsychotic agent for agitation within the ED. Chi-squared tests were performed for categorical variables, and *t*-tests or ANOVA were employed for continuous variables. Chi-squared analysis was utilized to test for association between dsQTp and the composite outcome of ACVE as well as each ACVE subgroup (myocardial injury, shock, ventricular dysrhythmia, cardiac arrest).

We performed a multivariable logistic regression to further evaluate demographic and clinical predictors of dsQTp. Demographic and clinical characteristics that were found to have significant associations on bivariate analysis as well as characteristics of interest a priori were included in the model. We generated receiver operating characteristic (ROC) curves for continuous variables found to be predictive of dsQTp. We identified optimal cutoff points for these predictive variables by identifying the point which yielded the maximum value for the sum of sensitivity and specificity. Multivariable logistic regression was subsequently used to further evaluate the association between ACVE and dsQTp with adjustment for age, sex, race/ethnicity, number of exposures, and exposure to an opioid. Predictors for inclusion in the regression model were chosen based on significant associations on bivariate analysis as well as variables of interest a priori. A second multivariable logistic regression model was used to evaluate the association between ACVE and dsQTp following adjustment for known risk factors for ACVE. History of cardiac disease, serum bicarbonate, and age were included as covariates as these characteristics have been previously associated with ACVE [4].

Sensitivity analysis was performed to account for potential confounding by ED administration of antipsychotic agents for sedation. We compared rates of dsQTp among patients given antipsychotic agents within the ED and analyzed for univariate associations according to specific antipsychotic agents.

With a fixed sample size of 1648, we calculated that we would have > 97% power to show a threefold increase in adjusted risk of ACVE in those with dsQTp, with 0.05 alpha. Statistical analyses were performed using SAS University Edition v.9.4 (SAS Institute, Cary, NC) and SPSS v. 24 (IBM, Armonk, NY).

Results

Enrollment and Demographics

Out of 2311 patients screened, 663 were excluded leaving 1648 patients for analysis. Patient enrollment and inclusion/exclusion details are summarized in Fig. 1. The dsQTp group ($N = 27$, 1.6% of total included patients) was found to be older than the control group ($N = 1621$) (51.6 vs 40.2 $p < 0.001$). The dsQTp group was also found to have a significantly higher number of exposures (2.92 vs 2.16 $p = 0.003$). However, there were no significant differences with regard to sex, race/ethnicity, pH, baseline potassium, or baseline calcium ($p =$ NS for all). Additionally, baseline rates of underlying coronary artery disease (CAD) or congestive heart failure (CHF) were similar between the two groups. A comparison of patient demographics and clinical characteristics between groups is presented in Table 1.

Drug Exposures

The most common drug classes reported by ED patients were opioids, stimulants, benzodiazepines, other sedatives (including alcohol), and anti-depressants. There was a significantly higher number of opioid exposures in the dsQTp group when compared to the control group (67% of exposures versus 35%, $p = 0.001$); there were no other significant differences in other drug classes. The most common opioid exposures were methadone ($N = 8$) and heroin ($N = 2$). Other opioid exposures in the dsQTp group included tramadol ($N = 1$) and hydromorphone ($N = 1$). A full summary of drug classes is presented in Table 2, and time to dsQTp by specific patient is presented in Fig. 2.

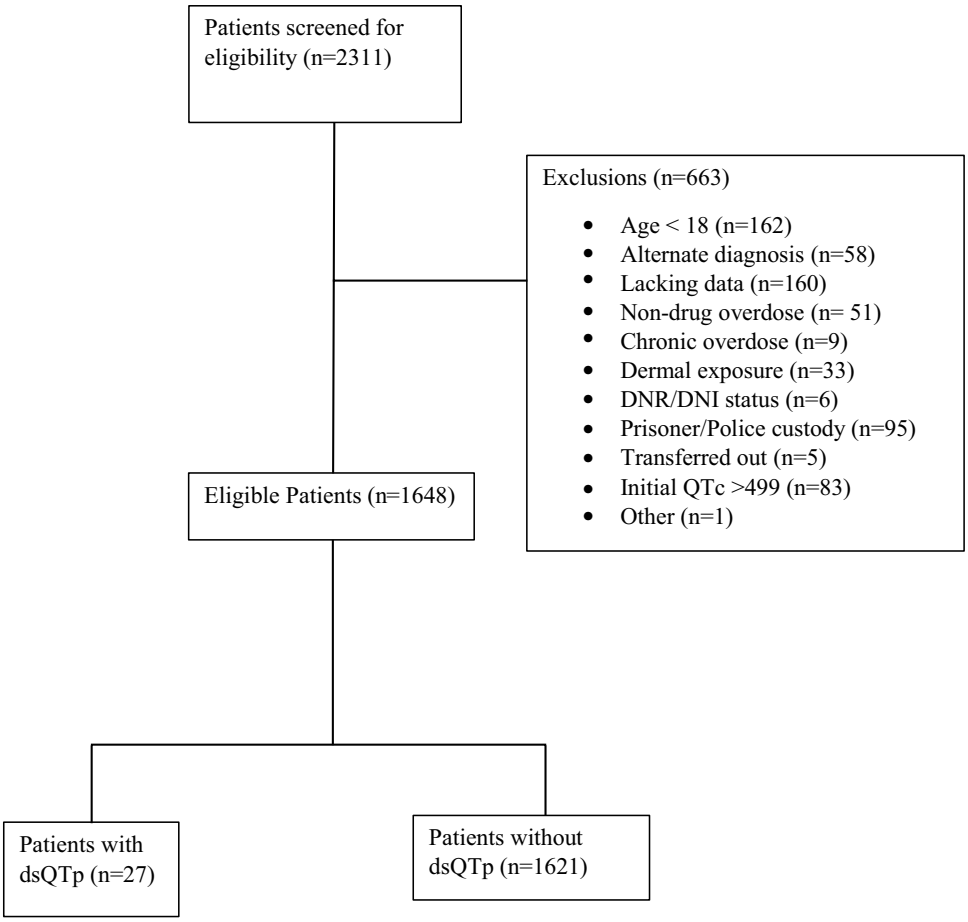

Fig. 1 Study enrollment and inclusion/exclusion criteria. Abbreviations: DNR, do not resuscitate; DNI, do not intubate; dsQTp, delayed severe QTc prolongation.

Table 1 Demographic and clinical characteristics of ED overdose patients.

Patient characteristic	dsQTp ($n=27$)	No dsQTp ($n=1621$)	p Value
Age, mean (SD)*	51.6 (18.7)	40.2 (16.3)	$p<0.01^{+}$
Female (*N*, %)	16 (59.3%)	657 (40.6%)	$p=$NS
Race/ethnicity (*N*, %)			$p=$NS
White	11 (42.3%)	437 (27.0%)	
Black	6 (23.1%)	223 (13.8%)	
Asian	2 (7.7%)	112 (6.9%)	
Other/unknown	7 (26.9%)	848 (51.9%)	
Hispanic	6 (24.0%)	455 33.3%	
Underlying cardiac disease (*N*, %)	2 (7.4%)	60 (3.7%)	$p=$NS
Potassium, mean (mEq/L)	4.20	4.02	$p=$NS
Calcium, mean (mg/dl)	8.79	9.20	$p=$NS
Bicarbonate, mean (mEq/L)	24.4	25.3	$p=$NS
pH, mean	7.32	7.35	$p=$NS
Number of ingestions, mean*	2.92	2.16	$p<0.01^{+}$

*$p<0.05$, $^{+}$A t-test was utilized to test for significance

dsQTp delayed severe QTc prolongation, *NS* not significant

Factors Associated with dsQTp

We performed a multivariable logistic regression to identify demographic and clinical factors associated with dsQTp following adjustment for potential confounders. Our model included age, sex, race, ethnicity, number of exposures, opioid exposure, and serum potassium as predictors. Age (aOR, 1.04; 95% CI, 1.01, 1.06) and number of exposures

Table 2 Reported drug class exposures in ED overdose patients.

Drug class	dsQTp *N* (%) (*n* = 27)	No dsQTp *N* (%) (*n* = 1621)	Cohort total *N* (%) (*n* = 1648)	*p* Value
Opioid*	18 (66.7%)	574 (35.1%)	592 (35.9%)	$p < 0.01^{+}$
Benzodiazepine	11 (40.7%)	406 (24.8%)	417 (25.3%)	*p* = NS
Other sedative (including EtOH)	10 (37.0%)	573 (35.1%)	583 (35.4%)	*p* = NS
Stimulant	9 (33.3%)	387 (23.7%)	396 (24.0%)	*p* = NS
Anti-depressant	6 (22.2%)	189 (11.6%)	195 (11.8%)	*p* = NS
Analgesic (OTC non-opioid)	6 (22.2%)	347 (21.2%)	353 (21.4%)	*p* = NS
Cannabinoids	5 (18.5%)	238 (14.6%)	243 (14.7%)	*p* = NS
Antipsychotic	4 (14.8%)	129 (7.9%)	133 (8.1%)	*p* = NS
Cardiovascular (CCB, BB, digoxin, ACE-i)	3 (11.1%)	83 (5.1%)	86 (5.2%)	*p* = NS
Anti-epileptics	3 (11.1%)	83 (5.1%)	86 (5.2%)	*p* = NS
Metals	0 (0%)	2 (0.1%)	2 (0.1%)	*p* = NS
Caustics	0 (0%)	21 (1.3%)	21 (1.3%)	*p* = NS
Toxic alcohol	0 (0%)	1 (0.06%)	1 (0.06%)	*p* = NS
Diabetes medications	0 (0%)	35 (2.1%)	35 (2.1%)	*p* = NS
Diuretics	0 (0%)	3 (0.2%)	3 (0.2%)	*p* = NS
Other	2 (7.4%)	278 (17.0%)	280 (17.0%)	*p* = NS
Unknown	1 (3.7%)	54 (3.3%)	55 (3.3%)	*p* = NS

*$p < 0.05$; +A Chi-squared test was utilized to test for significance

Numbers do not sum to 100% due to majority of patients having polydrug exposures

ACE-i ACE inhibitor, *BB* beta-blocker, *CCB* calcium channel blocker, *dsQTp* delayed severe QTc prolongation, *EtOH* ethyl alcohol, *NS* not significant, *OTC* over-the-counter

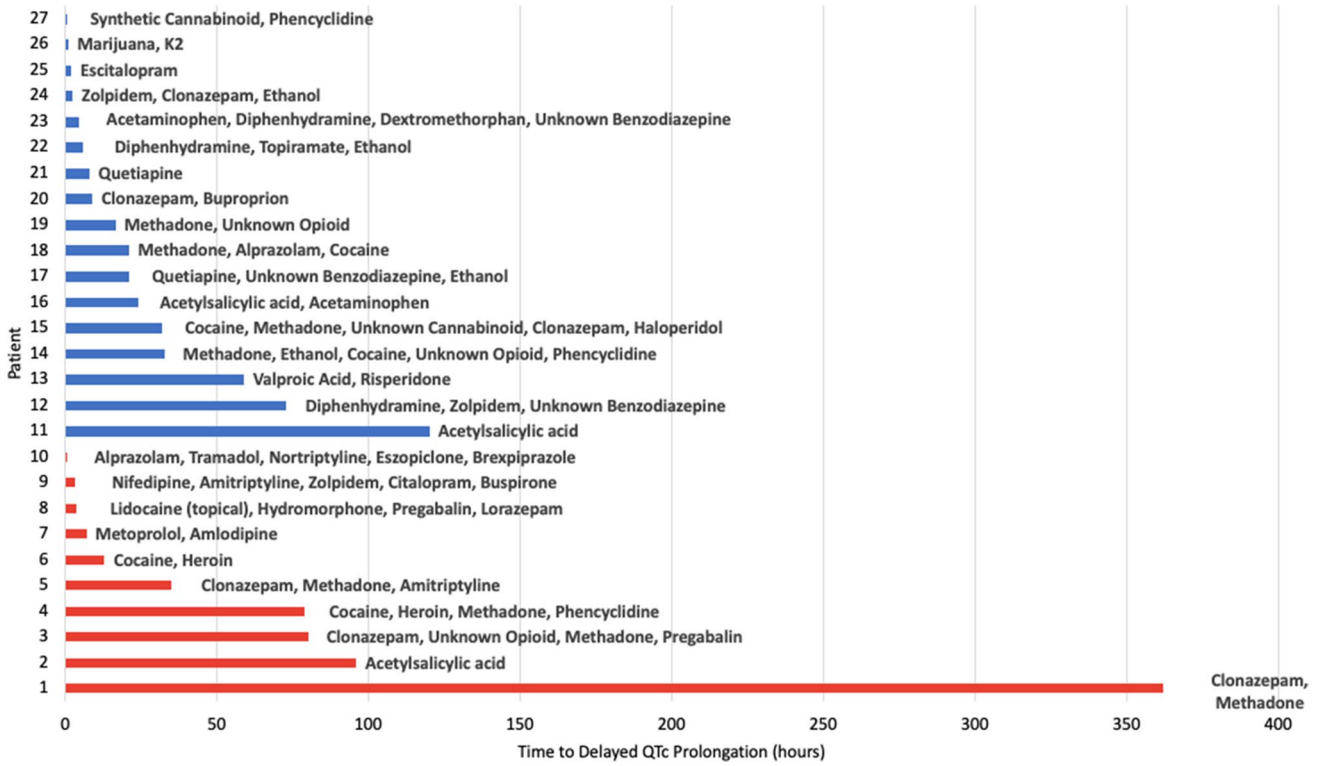

Fig. 2 Timeline of delayed QTc prolongation in ED overdose patients. Bars in red represent patients who experienced an ACVE, while bars in blue represent patients with no ACVE. Abbreviations: ACVE, adverse cardiovascular event.

(aOR, 1.24; 95% CI, 1.00–1.54) were found to be predictive of dsQTp on adjusted analysis. Optimal cutpoints for these two variables based on ROC curve analysis were as follows: age > 45 years and number of exposures ≥ 3 drugs. Opioid exposure was not significantly associated with dsQTp after controlling for confounders. Serum potassium also was not significantly associated with dsQTp. Full results are summarized in Table 3.

Timing of ED Presentation and Delayed QTc Prolongation

The mean time to ED arrival following overdose was 7.3 (SD: 9.6) hours in the control group and 8.3 (SD: 8.9) hours in the dsQTp group. There was no significant difference in time to ED arrival between groups (p = NS). The mean time to delayed QTc prolongation was 40.3 (SD 70.1) hours from the time of ED arrival. Time to delayed QTc ranged from 15 min to 362 h. Time to dsQTp was under 6 h in 29.6% (8/27) of patients, 6 to 12 h in 14.8% (4/27), 12 to 24 h in 18.5% (5/27) and over 24 h in 37% (10/27).

Table 3 Multivariable logistic regression of clinical characteristics associated with delayed severe QTc prolongation.

Clinical characteristic	Adjusted OR (95% CI)
Age	1.04 (1.01, 1.06)
Sex	0.63 (0.28, 1.46)
Race/ethnicity	
Black[+]	1.29 (0.42, 3.98)
Asian[+]	1.25 (0.26, 6.11)
Hispanic[^]	1.01 (0.22, 4.59)
Number of ingestions	1.24 (1.00, 1.54)
Opioid ingestion	2.70 (0.71, 10.26)
Serum potassium	1.32 (0.82, 2.14)

[+]White as reference, ^non-Hispanic as reference

Main Analysis

On unadjusted analysis, we found that dsQTp was significantly associated with occurrence of ACVE with 37.0% (10/27) of patients with dsQTp experiencing an ACVE as compared to 4.3% (70/1621) of patients without dsQTp (OR, 13.03; 95% CI, 5.76–29.50). dsQTp was also significantly associated with myocardial injury (OR, 12.26; 95% CI, 4.93–30.46), shock (OR, 22.34; 95% CI, 8.67–57.61), cardiac arrest (OR, 9.09; 95% CI, 2.55–32.41), and death (OR, 18.30; 95% CI, 4.80–69.78). dsQTp was not significantly associated with ventricular dysrhythmias (OR, 6.20; 95% CI, 0.77–50.19). Full results are summarized in Table 4.

We subsequently performed a multivariable logistic regression to evaluate the association between dsQTp and ACVE after adjusting for potential confounders. Following adjustment for age, sex, race/ethnicity, number of exposures, serum potassium concentration, and opioid exposure, dsQTp was significantly associated with ACVE (aOR, 12.44; 95% CI, 4.78–32.41). Full results are summarized in Table 5.

We utilized a multivariable logistic regression model to examine the association between dsQTp and ACVE following adjustment for known risk factors for ACVE. We included history of cardiac disease, serum bicarbonate, age, and dsQTp as predictors with ACVE as the outcome variable. Following adjustment for cardiac disease, serum bicarbonate, and age, dsQTp remained significantly associated with ACVE (aOR, 9.48; 95% CI, 3.47, 25.92). Full results are summarized in Table 5.

Sensitivity Analysis— Antipsychotics Administered

In order to determine if dsQTp in the study population was iatrogenic due to ED administration of antipsychotics, we performed a sensitivity analysis to determine the association between ED antipsychotic administration and dsQTp. In the dsQTp group, 3 patients (3/27, 11.1%) received haloperidol as compared to 138 patients in the control group

Table 4 Unadjusted analysis of association between dsQTp and ACVE.

Specific outcomes	dsQTp N (%) (n = 27)	No dsQTp N (%) (n = 1621)	Unadjusted OR (95% CI)
Any ACVE*	10 (37.0%)	70 (4.3%)	13.03 (5.76, 29.50)
Shock*	7 (25.9%)	25 (1.5%)	22.34 (8.67, 57.61)
MI*	7 (25.9%)	45 (2.8%)	12.26 (4.93, 30.46)
Ventricular dysrhythmia	1 (3.7%)	10 (0.6%)	6.20 (0.77, 50.19)
Cardiac arrest*	3 (11.1%)	22 (1.4%)	9.09 (2.55, 32.41)
Death*	3 (11.1%)	11 (0.7%)	18.30 (4.80, 69.78)

*$p < 0.05$

ACVE adverse cardiovascular event, *dsQTp* delayed severe QTc prolongation, *MI* myocardial injury

myocardial injury, serum troponin > 0.10 ng/mL; shock, hypotension requiring administration of vasopressors; ventricular dysrhythmia, ventricular tachycardia, ventricular fibrillation, or Torsades des Pointes

Table 5 Multivariable logistic regression model of association between dsQTp and ACVE.

Model covariates	Adjusted OR (95% CI)
Model 1	
dsQTp	12.44 (4.78, 32.41)
Age	1.02 (1.00, 1.04)
Sex	1.60 (0.88, 2.90)
Race/ethnicity	
Black[+]	1.41 (0.64, 3.12)
Asian +	0.73 (0.19, 2.79)
Hispanic^	0.72 (0.31, 1.66)
Number of ingestions	1.19 (1.01, 1.41)
Opioid ingestion	1.81 (0.58, 5.65)
Serum potassium	2.57 (1.77, 3.72)
Model 2	
dsQTp	9.48 (3.47, 25.92)
Age	1.02 (1.01, 1.04)
Underlying cardiac disease	5.37 (2.42, 11.95)
Serum bicarbonate	0.82 (0.78, 0.87)

[+]White as reference; [^]non-Hispanic as reference

ACVE adverse cardiovascular event, *dsQTp* delayed severe QTc prolongation

(138/1621, 8.5%). No patients in the dsQTp group received risperidone as compared to 2 patients in the control group (2/1621, 0.1%). One patient in the dsQTp group received quetiapine (1/27, 3.7%) as compared to 5 patients in the control group (5/1621, 0.3%). There were no significant associations between antipsychotic agent administration and the occurrence of dsQTp (p = NS for all), except for quetiapine ($p = 0.003$).

Discussion

This study found that dsQTp is an infrequent but important finding in ED patients with acute drug overdose. Clinical factors associated with dsQTp were older patient age and polydrug exposures. Our findings add to the existing body of literature which has identified other independent clinical risk factors for ACVE [4, 15, 17]. Based on the findings from the present study, clinicians should consider screening a subset of high-risk ED patients for dsQTp due to its strong association with ACVE. Future studies with protocolized performance of repeat ECGs on this patient population are warranted in order to validate and clarify these findings.

We identified patient age and number of exposures as clinical risk factors for dsQTp. On initial univariate analysis, we also found opioid exposure to be significantly associated with dsQTp. This association may have been in part due to QTc prolongation from methadone use, [12] although this study did not analyze data on opioid subtypes. However, opioid exposure was no longer significantly associated with dsQTp following adjustment for potential confounding factors. This suggests that older age and number of exposures are predictive of dsQTp regardless of drug class involved in overdose. Opioids and benzodiazepines were the most common drug exposures in this study and were frequently involved in polydrug exposures, raising the possibility that the association we identified between greater number of exposures and dsQTp may in part be due to benzodiazepines and opioids slowing gut absorption. Optimal cutpoints for these two variables based on ROC curve analysis were as follows: age > 46 years and number of exposures ≥ 3 drugs. Clinicians may consider serial QTc measurements and aggressive management of overdose in patients above these thresholds based on the potential for ACVE.

As noted above, previous literature has identified risk factors for ACVE [6]. The present study has additionally identified dsQTp as a potentially important risk factor for ACVE. The identification of this novel risk factor for ACVE may allow clinicians to better risk stratify and prognosticate the clinical course of ED patients presenting with overdose. Additionally, there is currently a lack of consensus regarding the timing and approach of medical clearance of overdose patients [18]. Based on the findings of this research, clinicians may find it useful to obtain a repeat ECG in the overdose patient population in order to aid in safe cardiovascular medical clearance.

Use of antipsychotic medications has been shown to be a risk factor for QTc prolongation [10]. Antipsychotic medications are frequently utilized in the ED setting to manage patient agitation [19] and may have been used in the management of the patient population within the study cohort. In order to determine if dsQTp in the study population was iatrogenic due to ED administration of antipsychotics, we performed a sensitivity analysis to determine the association between ED antipsychotic administration and dsQTp. We found that other than quetiapine, antipsychotic administration was not associated with dsQTp. Our sensitivity analysis largely confirmed that dsQTp was related to the initial overdose and was not a result of iatrogenic drug administration.

Future studies with performance of routine, protocolized serial ECGs for the purpose of repeat QTc measurement are needed to validate findings from the present study. These studies should utilize a fixed time interval between the initial and repeat ECG as this will remove time to QTc prolongation as a potential confounder and will improve interpretability of findings. Future studies with a larger and broader patient population will also permit generalizing to a larger population and allow for greater elucidation of the role of specific substances in development of dsQTp. Future studies should obtain initial and repeat serum electrolyte levels to

elucidate the association between various serum electrolytes and dsQTp, as this was not performed in the present study.

Limitations

Limitations of the present study warrant some consideration in the interpretation of our results. First, while our findings establish an association between dsQTp and ACVE, this association does not necessarily amount to causation, and results should be interpreted as such. Further, 341 patients in the cohort did not have a repeat ECG obtained (some of which may have been due to discharge prior to repeat ECG—e.g., simple opioid overdoses), since this was not protocolized. Thus, the true number of patients with dsQTp is likely much larger than what is reflected within the study cohort. Additionally, it is possible that those patients who had a repeat ECG obtained generally had more severe overdoses or had already been triaged to closely monitored units such as ICUs; however, we were unable to adjust for this in our analysis given the lack of a validated measure for overdose severity. Further, our study methodology was such that any repeat ECGs performed were not added to the study database if normal. Therefore, our control group could not be narrowed to include only patients with a normal repeat ECG. These limitations may have introduced selection bias. Because we did not collect data on the total number of ED visits over the study period, we do not know the precise proportion of total ED visits represented by our study cohort. We also did not have data on whether patients were symptomatic from the presenting overdose at the time of dsQTp as the data collection instrument did not collect this information.

We additionally did not have serum electrolyte measurements at the time of the repeat ECG for all included patients as serum electrolyte measurement was also not protocolized and serial electrolytes are not routinely obtained as standard clinical practice. We thus did not have serum magnesium levels at the time of dsQTp, and this was not included in our analyses. Accordingly, it is possible that serum potassium, magnesium, or other electrolytes mediated the development of dsQTp. While our study identified strong associations between dsQTp and ACVE, we had wide confidence intervals because only a small number of patients were in the dsQTp group. Finally, the present study relied on patient self-report with regard to exposures, and serum drug concentrations were not obtained. Standard toxicologic screens and APAP levels were sent as necessitated by routine care and were not a formal component of the study protocol. However, this is reflective of real-world clinical practice and, accordingly, makes the present study findings more generalizable.

Conclusions

In conclusion, in this large secondary data analysis of ED patients with acute drug overdose, dsQTp was a significant risk factor for in-hospital occurrence of ACVE. Future study is warranted to determine if serial ECGs add value to the evaluation of specific high-risk overdose patients, especially those with polydrug overdose or older age. Further study is also needed to validate the utility of dsQTp as a risk factor in this patient population, as it may warrant more aggressive and early interventions to prevent ACVE.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13181-021-00855-2.

Author Contribution SS performed data analysis and drafted the manuscript. ER provided assistance with data collection, drafted the abstract, and preliminary data analysis. RV assisted with data analysis and interpretation. LDR provided assistance with study design and data collection. AM conceived the study; obtained funding; and oversaw data collection, analysis, as well as manuscript preparation. All authors helped edit the manuscript and approved the final version of the manuscript.

Sources of Funding The study was made possible, in part, by grant DA037317 (PI: Manini) from the National Institute on Drug Abuse of the National Institutes of Health. Dr. Shastry is supported by an institutional training grant, 1T32 HL129974-01 (PI: Richardson), from the National Heart, Lung & Blood Institute of the National Institutes of Health. Dr. Manini is currently supported by grant R01DA048009 from the National Institute on Drug Abuse of the National Institutes of Health.

Declarations

Conflict of Interest None.

References

1. Wilson N, Kariisa M, Seth P, Smith H IV, Davis NL. Drug and opioid-involved overdose deaths — United States, 2017–2018. MMWR Morb Mortal Wkly Rep. 2020;69(11):290–7. https://doi.org/10.15585/mmwr.mm6911a4.
2. Vivolo-Kantor AM, Hoots BE, Scholl L, Pickens C, Roehler DR, Board A, et al. Nonfatal drug overdoses treated in emergency departments — United States, 2016–2017. MMWR Morb Mortal Wkly Rep. 2020;69(13):371–6. https://doi.org/10.15585/mmwr.mm6913a3.
3. Manini AF, Nelson LS, Stimmel B, Vlahov D, Hoffman RS. Incidence of adverse cardiovascular events in adults following drug overdose. Acad Emerg Med. 2012;19(7):843–9. https://doi.org/10.1111/j.1553-2712.2012.01397.x.
4. Manini AF, Hoffman RS, Stimmel B, Vlahov D. Clinical risk factors for in-hospital adverse cardiovascular events after acute drug overdose. Acad Emerg Med. 2015;22(5):499–507. https://doi.org/10.1111/acem.12658.
5. Gummin DD, Mowry JB, Spyker DA, Brooks DE, Beuhler MC, Rivers LJ, et al. 2018 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS):

36th Annual Report. Clin Toxicol (Phila). 2019;57(12):1220–413. https://doi.org/10.1080/15563650.2019.1677022.
6. Campleman SL, Brent J, Pizon AF, Shulman J, Wax P, Manini AF, et al. Drug-specific risk of severe QT prolongation following acute drug overdose. Clin Toxicol (Phila). 2020;58(12):1326–34. https://doi.org/10.1080/15563650.2020.1746330.
7. Manini AF, Nair AP, Vedanthan R, Vlahov D, Hoffman RS. Validation of the prognostic utility of the electrocardiogram for acute drug overdose. J Am Heart Assoc. 2017;6(2):e004320. https://doi.org/10.1161/jaha.116.004320.
8. Manini AF, Nelson LS, Skolnick AH, Slater W, Hoffman RS. Electrocardiographic predictors of adverse cardiovascular events in suspected poisoning. J Med Toxicol. 2010;6(2):106–15. https://doi.org/10.1007/s13181-010-0074-x.
9. Tampi RR, Balderas M, Carter KV, Tampi DJ, Moca M, Knudsen A, May J. Citalopram, QTc Prolongation, and Torsades de Pointes. Psychosomatics. 2015;56(1):36–43. https://doi.org/10.1016/j.psym.2014.09.002.
10. Beach SR, Celano CM, Sugrue AM, Adams C, Ackerman MJ, Noseworthy PA, Huffman JC. QT Prolongation, Torsades de Pointes, and Psychotropic Medications: A 5-Year Update. Psychosomatics. 2018;59(2):105–22. https://doi.org/10.1016/j.psym.2017.10.009.
11. Kim Y, Kim A, Chung JY. Population pharmacokinetic/pharmacodynamic modeling of delayed effect of escitalopram-induced QT prolongation. J Affect Disord. 2021;285:120–6. https://doi.org/10.1016/j.jad.2021.02.048.
12. Martell BA, Arnsten JH, Krantz MJ, Gourevitch MN. Impact of methadone treatment on cardiac repolarization and conduction in opioid users. Am J Cardiol. 2005;95(7):915–8. https://doi.org/10.1016/j.amjcard.2004.11.055.
13. Fraley DS, Adler S. Correction of hyperkalemia by bicarbonate despite constant blood pH. Kidney Int. 1977;12(5):354. https://doi.org/10.1038/ki.1977.122.
14. Blumberg A, Weidmann P, Shaw S, Gnädinger M. Effect of various therapeutic approaches on plasma potassium and major regulating factors in terminal renal failure. Am J Med. 1988;85(4):507. https://doi.org/10.1016/s0002-9343(88)80086-x.
15. Manini AF, Brent J, Campleman S, et al. Validation of a prediction rule for adverse cardiovascular events from drug overdose. Ann Emerg Med. 2020;76(4):S6. https://doi.org/10.1016/j.annemergmed.2020.09.024
16. Gilbert EH, Lowenstein SR, Koziol-McLain J, Barta D, Steiner J. Chart reviews in emergency medicine research: where are the methods? Ann Emerg Med. 1996;27(3):305–8. https://doi.org/10.1016/s0196-0644(96)70264-0.
17. Carreiro S, Miller S, Wang B, Wax P, Campleman S, Manini AF. Clinical predictors of adverse cardiovascular events for acute pediatric drug exposures. Clin Toxicol (Phila). 2020;58(3):183–9. https://doi.org/10.1080/15563650.2019.1634272.
18. Hollander JE, McCracken G, Johnson S, Valentine SM, Shih RD. Emergency department observation of poisoned patients: how long is necessary? Acad Emerg Med. 1999;6(9):887–94. https://doi.org/10.1111/j.1553-2712.1999.tb01235.x.
19. Gottlieb M, Long B, Koyfman A. Approach to the agitated emergency department patient. J Emerg Med. 2018;54(4):447–57. https://doi.org/10.1016/j.jemermed.2017.12.049.

This study was previously presented at the North American Congress of Clinical Toxicology (NACCT) Annual Meeting (Nashville, TN, September 2019) and American College of Emergency Physicians (ACEP) Annual Meeting (Denver, CO, October 2019).