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Authors
Manini, Alex F
Stimmel, Barry
Vlahov, David

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Racial Susceptibility for QT Prolongation in Acute Drug Overdoses Authors

Alex F. Manini, MD, MS[1], **Barry Stimmel, MD**[2], and **David Vlahov, RN, PhD.**[3]

[1] Division of Medical Toxicology, the Icahn School of Medicine at Mount Sinai, New York, NY, USA.

[2] Cardiology Division, the Icahn School of Medicine at Mount Sinai, New York, NY, USA.

[3] School of Nursing, University of California at San Francisco, CA.

Abstract

Background and Purpose—QT prolongation independently predicts adverse cardiovascular events in suspected poisoning. We aimed to evaluate the association between race and drug-induced QT prolongation for patients with acute overdose.

Methods—This was a cross-sectional observational study at two urban teaching hospitals. Consecutive adult ED patients with acute drug overdose were prospectively enrolled over a two year period. The primary outcome, long-QT, was defined using standard criteria: QTc >470ms in females and >460ms in males. The association between race and drug-induced QT prolongation was tested, considering several confounding variables.

Results—In 472 patients analyzed (46% female, mean age 42.3), QT prolongation occurred in 12.7%. Blacks had two-fold increased odds of drug-induced QT prolongation (OR 2.01, CI 1.03-3.91) and Hispanics had 48% decreased odds of drug-induced QT prolongation (OR 0.52, CI 0.29-0.94).

Conclusions—We found significant racial susceptibility to drug-induced QT prolongation in this large urban study of acute overdoses.

Keywords

Overdose; QT prolongation; racial differences

Introduction

With nearly 100 deaths per day since 2007 (1), the United States is currently experiencing its worst drug overdose epidemic of all time. The death rate of 11.8 per 100,000-population in 2007 was roughly three times the rate in 1991 (2). Poisoning, defined as exposure to any

Corresponding Author: Alex Manini MD, MS, the Icahn School of Medicine at Mount Sinai, Department of Emergency Medicine, One Gustave L. Levy Place, Box 1620, New York, NY 10029. alex.manini@mountsinai.org..

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drug, chemical, or toxin that results in injury, is the leading cause of injury-related fatality in the United States as of 2008 (3). There are over 2.5 million poisonings reported to Poison Control Centers in the United States each year (4). Despite the above statistics, many recommendations for the emergency cardiovascular care of poisoned patients are based only on expert consensus alone (5).

In the general population, the average heart rate-corrected QT interval is longer in women than in men, race-dependent, and increased with age (6-7). Determinants of the QT interval include a complex interplay of electrical current across the myocardial cell membrane involving ion channels of sodium, calcium, and potassium. Specific factors that have been associated with an individual's baseline QT interval include the following: age (increased by 10 ms each decade), gender (females > males by 10 ms), race (Whites > Blacks by 5-10 ms), and genetic markers on chromosomes 7 and 11 (6-7). However, Blacks with Congenital Long QT Syndrome (LQTS) have significantly longer QTc than Whites without corresponding differences in cardiac event rates (8). Thus, it remains unclear if the factors which determine an individual's baseline QT interval (age, race, etc.) also extrapolate to represent susceptibility for adverse clinical outcomes such as acquired changes to the QTc interval.

Drug-induced QT prolongation occurs when exposure to a drug results in alteration of the myocardial current involved in generation of the QT interval via interference with key ion channels, particularly the potassium rectifier current (9). QT prolongation is considered to be a reliable surrogate for the potentially fatal dysrhythmia known as torsades de pointes (TdP), because TdP is generally preceded by QT prolongation. Previously, QT prolongation has been identified as a strong predictor of adverse cardiovascular events in suspected poisoning from drug overdose (10).

The goals of this investigation were to determine whether racial differences had any effect on susceptibility for drug-induced QT prolongation in acute drug overdose. We therefore assessed the association between race and drug-induced QT prolongation, while controlling for drug class, in patients with acute overdose presenting to tertiary care centers that are geographically located in the most racially-diverse zip codes in the United States.

Materials and Methods

Study Design and Setting

This cross-sectional study prospectively enrolled consecutive adult Emergency Department (ED) patients with acute drug (medication and illicit) overdose over a 24 month period. EDs from two urban, tertiary-care hospitals (“Hospital A, Hospital B”) were used for enrollment. The combined annual visit volume for both EDs is in excess of 200,000 and both are staffed 24 hours per day with board certified emergency physicians. The zip code surrounding “Hospital B” is geographically the most racially-diverse neighborhood in the United States according to the 2010 U.S. Census Bureau (11).

Study Population

ED patients with suspected acute drug overdose 24 hours per day were initially screened for inclusion by on-site research assistants. All eligible patients underwent reporting to the Poison Control Center (PCC) as per the public health law in “Blinded City”. To ensure completeness of enrollment, PCC records were periodically queried by the PI to ensure research assistants included all PCC-reported overdoses. The study protocol was approved by the Program for the Protection of Human Subjects for all participating institutions with a waiver of informed consent.

Following screening of eligibility, we applied formal inclusion and exclusion criteria to determine whether patients would be analyzed further. Inclusion criteria were both of the following: acute presentation (presentation within 24 hours of exposure), and suspected overdose (i.e. illicit drug dose sufficient to cause symptoms or any drug exposure greater than its therapeutic dose). Exclusion criteria were the following: alternative diagnosis (per primary clinical team, e.g. trauma or infection), chronic presentation (i.e. not acute), non-drug overdose (e.g. plant), dermal or inhalational exposures only, age <18 years, anaphylaxis, atrial fibrillation (due to confounding effects on QTc measurement), and subjects with incomplete data (left against medical advice, transferred to an outside institution, or left from the hospital prior to planned discharge).

Data Collection

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 (12). Using a standardized data collection instrument, we collected information on demographics (age, gender, race), exposure information (number, drug class, urine/serum drug concentrations if available), and clinical variables (vital signs, serum potassium concentration). We did not gather data about patients' reported dose of exposure because obtaining an accurate history in this regard is limited from patients with altered mental status or suicidal ideation. Racial classification was extracted from the medical record based on patient or family self-report as one of the following: White, Black, Hispanic, Asian, or Other. The database was de-identified and stored with password protection.

ECG Measurements

All 12-lead ECGs were performed during the initial ED presentation using a standard paper speed of 25 mm/s with standard lead positions. 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 ($QT/RR^{1/2}$). Long QTc was the primary outcome and was defined using standard criteria: QTc ≥ 470 ms in females and ≥ 460 ms in males (13).

Drug Classification

Multi-drug exposures were defined as exposure to >1 drug of any kind, including two drugs of the same drug class (e.g. exposure to lorazepam and clonazepam counted as two drug exposures but only one drug class). The Arizona Center for Education and Research on Therapeutics (CERT) is a non-profit organization that maintains a free accessible website (www.qtdrugs.org) that provides evidence-based recommendations regarding specific drugs with substantial QT and TdP risk (17). Drug exposures in this study were thus dichotomously classified as a positive CERT listing if it met any of the following three criteria, according to the most updated version of the CERT database: (A) definite risk of TdP, (B) possible risk of TdP, and (C) conditional risk of TdP (17). The fourth CERT classification, "drugs to avoid in patients with congenital long QT syndrome", was not utilized for the purposes of this study of acquired long QT syndrome.

Analysis

We calculated overall prevalence rates of QT prolongation by dividing the number of patients with QT prolongation in the study population by the total number of included drug overdoses. 95% confidence intervals were calculated using the estimated standard error method (Wilson procedure). Normality testing of demographic data (e.g. age) was confirmed using the Shapiro-Wilk test. Chi-squared (with Fisher's exact test when appropriate) and t-test were calculated for categorical and continuous variables, respectively,

with 5% alpha (2-tailed). Associations between race and the primary outcome were calculated using stepwise, multivariable logistic regression analysis. Additionally, as a secondary analysis we analyzed bivariate associations with QT prolongation according to the following drug-related criteria: (A) drug class or mechanism of action, (B) specific CERT drugs, and (C) all CERT listed drugs. Computer analysis was performed with SPSS v 19 (IBM, Chicago, IL).

Sample Size

Sample size was calculated a priori. Assuming 20% demographic factor prevalence and a 10% rate of QT prolongation, we calculated the need to analyze at least 466 patients for 80% power to detect a two-fold odds difference.

Results

Enrollment

In 766 patients screened, we excluded 294 (age < 18, lack of ECG, missing data); thus 472 patients were analyzed with QT prolongation occurring in 12.7% overall. Severe QT prolongation >500 ms occurred in only 14 patients (3%). The enrollment algorithm with inclusion and exclusion criteria is illustrated in **Figure 1**.

Demographics

Study subjects were 46% female with a mean age of 42.3 ±0.8 years. There were similar proportions of QT prolongation across age and gender in this study. Racial composition of all subjects was 41.3% Hispanic, 31.8% Whites, 16.5% Blacks, 8.7% Asians, 1.7% other. On bivariate analysis, Hispanics had a significantly lower proportion of QT prolongation (8.7%, $p<0.05$), while Blacks displayed a trend towards higher risk (19.2%, $p<0.10$). All the baseline clinical demographics are summarized in **Table 1**.

Drug Exposures

The top five most common drug classes in the study, in descending order, were opioids (N=102), benzodiazepines (96), sympathomimetics (79), anti-depressants (66), and anti-psychotics (59). There were 131 overdoses involving CERT drugs, of which 108 were part of multi-drug exposures. Overdoses involving CERT drugs were not more likely than non-CERT overdoses to cause QT prolongation (12.9% vs. 12.7%, chi-squared p=NS). The only drug class significantly associated with QT prolongation was the opioid class (20%, $p<0.05$), and the only individual drug associated with QT prolongation was oxycodone (26%, $p<0.05$). Multi-drug exposures involving methadone were significantly associated with QT prolongation (24%, $p<0.05$). A full summary of QT prolongation according to drug exposures and CERT classification is displayed in **Table 2**.

Main Analysis

In the main analysis for the effect of racial differences on susceptibility to drug-induced QT prolongation, we controlled for confounding factors by performing stepwise multivariable logistic regression. The final model utilized four covariates with prior literature evidence of associations with QT prolongation: age, gender, CERT listing, and serum potassium concentration (in mEq/L, drawn at the bedside during the ED visit for overdose) (2,6-7,17). Model fit was assessed by the Nagelkerke method with $R^2 = 0.64$. On the resultant regression analysis, Blacks had significantly increased risk of drug-induced QT prolongation (adjusted OR 2.01, CI 1.03-3.91) while Hispanics had significantly decreased risk (adjusted OR 0.52, CI 0.29-0.94). Odds of QT prolongation for all races is illustrated in **Table 3**.

Sensitivity Analyses

To more conservatively account for the effect of heart rate on QTc (given the known limitations of the Bazett's QT correction), we performed a sensitivity analysis accounting for heart rate as an additional linear covariate in the regression model. With this correction, Hispanics still had significantly decreased risk (adjusted OR 0.43, CI 0.23-0.82) and Blacks still had increased risk (adjusted OR 1.97, CI 1.00-3.92) of drug-induced QT prolongation.

To account for possible QRS effects on QTc, we performed a sensitivity analysis excluding patients with QRS >120 ms (n=16). In this analysis, Hispanics still had decreased risk (adjusted OR 0.59, CI 0.30-1.14) and Blacks still had increased risk (adjusted OR 1.61, CI 0.76-3.38) of drug-induced QT prolongation.

To account for a less stringent definition of QT prolongation, we used a less stringent cutpoint of 450 ms for men and 460 ms for women. In this analysis, Hispanics still had significantly decreased risk (adjusted OR 0.44, CI 0.26-0.75) and Blacks still had significantly increased risk (adjusted OR 2.1, CI 1.2-3.8) of drug-induced QT prolongation.

Given the challenges of racial classification in a protocol utilizing medical records with waiver of consent, we performed a sensitivity analysis to assess for the impact of a reasonable degree of racial misclassification. Assuming up to 10% racial misclassification, and keeping the degree of QT prolongation constant in the dataset at 12.7%, Hispanics would have similar reduction in risk (OR 0.62, CI 0.33-1.0, $p<0.05$) and Blacks would have similarly increased risk (OR 1.9, CI 1.02-3.5, $p<0.05$).

Discussion

The main finding of this study is that racial susceptibility is more important than drug class in determining an individual patient's risk of QT prolongation following acute drug overdose. Blacks had greater than two-fold increased risk of drug-induced QT prolongation, while Hispanics had approximately 50% risk reduction for drug-induced QT prolongation. We also found an association with QT prolongation based on specific opioid exposures including the strongest association for oxycodone, a non-CERT drug.

Racial differences in drug-induced QT prolongation provide further evidence of genetic vulnerability within populations. This data raises a particular concern for Black populations with overdose, due to shorter average baseline QT intervals coupled with higher risk of QT prolongation following drug exposure. Another significant finding of the current analysis is that Hispanics were found to be relatively resistant to drug-induced QT prolongation in overdose. These findings may be caused by a differential impact of QT prolonging drugs across races. Aside from genetic differences, a possible alternative explanation for these findings may be that there were racial differences in the fundamental severity of overdose, which led to higher QT risk in some and lower in others. For example there may be differences in the dose of exposure, which may have affected racial differences in this study. We can't say if one group is using more (behaving differently), metabolizing (physiologic), fundamental (genetic), other some other factor. We propose this observation to generate further hypotheses but cannot make a definite conclusion regarding the exact mechanism.

For many reasons, information on racial differences in pharmacokinetics and pharmacodynamics is limited or lacking altogether. Although racial diversity has been included in clinical trials during the past decades, analyses of the data to address questions in various racial/ethnic groups are often lacking. Compounding factors are small numbers of racial subgroups, some races not included in early phase clinical trials, and weight or body mass index (BMI) not being considered. Although not much is documented about racial/

ethnic differences in drug effects, data from drug adverse events have shown that some races more often experience TdP, a potentially fatal arrhythmia (18). QT prolongation is considered to be surrogate for TdP because TdP is generally preceded by QT prolongation. Drug-induced QT prolongation and accompanying TdP are challenging and urgent safety issues because it is not possible to predict which drugs will induce TdP and which patients are susceptible.

It has been well documented that the prevalence of certain ECG findings among individuals free of coronary heart disease (CHD) differs by race (19). In order to assess whether these differences exist independently of CHD risk factors (e.g., hypertension), Vitelli et al. examined over 2,500 ECG tracings in an apparently healthy biracial population of both men and women, and found that the QTc interval was shorter in African-Americans than in whites (6). This finding remained statistically significant after further adjustment for traditional CHD risk factors. These results suggest that racial differences in electrocardiograms may not be explained entirely by differences in established CHD risk factors, and because current diagnostic ECG criteria are largely based on data from middle-aged white men and women, race should be considered in the interpretation of ECG findings.

There are pharmacological differences amongst different races that have important clinical consequences. For several drugs, such as ibutilide (20), there is a higher incidence in racial subgroups of drug-induced QT prolongation and a potentially fatal arrhythmia, TdP. A difference in the racial prevalence of cardiovascular disease may be a factor relating to QT interval variability. For example, racially distinct rates of atherosclerosis may yield differential rates of potentially fatal arrhythmias in clinical studies. Differences in effectiveness of analgesics have been demonstrated, for example for the ability of opioids to provide pain relief having genetic differences that vary by race (21). Drugs may have different pharmacokinetics in certain races because of differences in phase I and phase II enzymes that metabolize drugs. Conflicting results about biological racial differences have been reported for the major drug metabolizing enzyme, cytochrome P450 3A4, and may be related to a role for P-glycoprotein, a cell membrane transporter. Single nucleotide polymorphisms, with varying frequencies by race, are reported as having impact on drug delivery and disposition (22). Ethnic/racial variations have also been demonstrated with the drug metabolizing enzymes CYP2C9 (23), 2C19 (24), and 2D6 (25). Thedata from the present study provides further evidence that racial differences exist in the susceptibility and resistance to acquired long QT syndrome.

The supposition that drug-induced QT prolongation is a valid surrogate for adverse cardiovascular events, including TdP, has so far held up in the poisoning literature. In a case-control study of 134 undifferentiated acute drug overdoses presenting to an urban emergency department, QT prolongation was found to be associated with increased risk of in-hospital adverse cardiovascular events (shock, dysrhythmia, infarction, death), and could distinguish discrete subgroups at low risk (normal QTc, 3.8% risk), high risk (long QTc, 26% risk), and highest risk (>500 ms, >38% risk) (10). In a meta-analysis of poisoning literature conducted by Chan and colleagues, the same QTc cutoff of 500 ms was diagnostically accurate (93.9% sensitivity, 97.2% specificity) in 129 cases of drug-induced TdP (14). Therefore, ongoing research is urgently warranted to characterize factors associated with drug-induced QT prolongation as a surrogate for adverse cardiovascular outcomes due to drug overdose.

One unexpected finding of this study was the association of QT risk with oxycodone, a non-CERT drug. In our study, oxycodone overdose conferred higher risk of QT prolongation (26%) than methadone (22%) or all CERT-listed drugs combined (12.9%). Previously,

oxycodone was shown to be associated with dose-dependent QTc prolongation in patients and low-affinity inhibition of hERG activity in vitro (26). Our findings are consistent with a recent case series of oxycodone overdoses demonstrating a trend of QT prolongation (27). However, the CERT website does not list oxycodone, perhaps due to limited or absent data linking the drug with cases of TdP. Unfortunately, with only 23 oxycodone cases the present study was not powered adequately to address in-depth subgroup analysis of oxycodone overdose. Nevertheless, based on this study, clinicians should consider ECG screening or inpatient telemetry monitoring for patients with clinically-severe oxycodone overdose.

Based on the findings of this study, future research should explore further the racial association with QT risk in drug overdose. The relationship between QT prolongation and cardiovascular events is complex, as has been demonstrated for patients with LQTS (28). Prospective cohort studies are warranted to confirm and expand upon the associations found in the present study. In addition, drug class associations with CERT drugs should be confirmed. Due to the fact that QT prolongation is a risk factor for cardiac dysrhythmias, future work should attempt to characterize adverse cardiovascular outcomes in addition to QT prolongation. And finally, study on genetic racial differences in expression and functionality of HERG, p-glycoprotein, and CYP enzymes should be explored as possible underlying etiologies of racial susceptibility to drug-induced acquired QT prolongation.

Limitations

There are several limitations of this study that require consideration, including all those inherent to cross-sectional studies including inability to calculate incidence or provide longitudinal follow-up. This study used Bazett's formula for QT correction, rather than more accurate linear correction formulae (29), to enhance this study's generalizability given Bazett's is still the most widely used QTc formula; however, sensitivity analysis using heart rate as an additional covariate did not change the main results. While the number of patients with actual QT prolongation was relatively small and limited statistical power for subgroup analysis (e.g. unadjusted oxycodone QT risk may be confounded by age and sex), parallel data collection is ongoing by the study investigators at regional institutions. The urban affiliate hospitals in this study represent only one medical school (i.e., University A) and thus may not be generalizable to all settings; however, we think the hospitals were appropriate for study of racial differences given that they are located in the most racially diverse zip code in the United States (11).Exposure confirmation through analytical testing was lacking in a subset of patients; however, this was unlikely to be an issue as suspicion of overdose based on history, clinical findings, or ancillary testing was required for inclusion into the study. We did not collect data regarding liver function tests, which may have affected drug metabolism. We did not collect data regarding any time lag between admission and ECG performance; however, ECGs were generally obtained on arrival to the ED for the majority of patients. The baseline QT for a small fraction of patients may have been prolonged regardless of drug overdose; however this was unlikely to represent a large source of error given that congenital long QT syndrome is exceedingly rare. Racial classification in the study was based on the medical record which may have been somewhat inaccurate as compared to true self-reporting; however, we accounted for this limitation with a sensitivity analysis which did not change the conclusions of the study.

Conclusions

We found significant racial susceptibility to drug-induced QT prolongation in this large urban study of acute overdoses. Drug classifications significantly associated with QT prolongation were oxycodone, methadone, and opioid drug class, while CERT classification showed no association with QT risk. These results imply that genetic factors may play an important role in the susceptibility to drug-induced QT prolongation following overdose and

may outweigh information about the drug of exposure. Future studies that evaluate QT prolongation in the setting of drug overdose should therefore incorporate data on race/ethnicity in addition to other relevant influences on QT risk such as age, gender, drug class, and electrolyte abnormalities.

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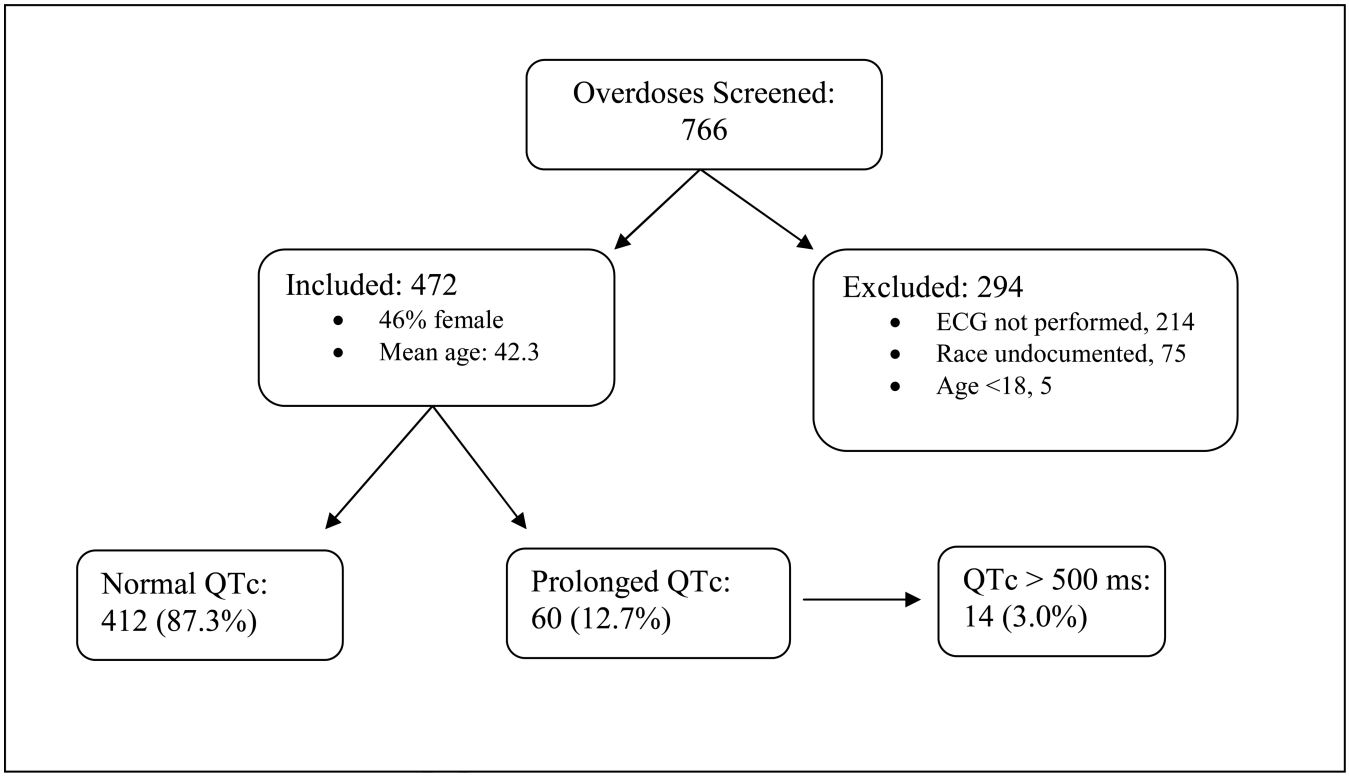

Figure 1.
Screening, Enrollment, and Prevalence of Drug Induced QT Prolongation
Figure 1 Legend: Prolonged QTc defined as >460 ms in men and >470 ms in women.
Figure 1 Abbreviations: ECG = electrocardiogram; QTc = Bazett's corrected QT interval.

Table 1

Demographic Information.

Clinical Characteristic:	Total	QTP	No QTP
		N (% by row)	
Age (mean ± SE)	42.3±0.8	45.1±1.8	41.9±0.9
Females	217	23 (10.6)	194 (89.4)
Race			
Hispanic*	195	17 (8.7)	178 (91.3)
White	150	22 (14.7)	128 (85.3)
Black**	78	15 (19.2)	63 (80.8)
Asian	41	6 (14.6)	35 (85.4)
Other	8	0 (0)	8 (100)
TOTALS:	**472**	**60 (12.7)**	**412 (87.3)**

Univariate associations with QTP acknowledged with:

Abbreviations: QTP = QT prolongation controlled for gender (>460 ms male, >470 ms female), N = number, SE = standard error.

* $p<0.03$

** $p<0.07$

Table 2

QT Prolongation According to Drug Exposures and CERT Classification

Drug Class Exposed	All Suspected Overdoses	Confirmed by Toxicology‡	Single-drug Exposed	Multi-drug Exposure
	No. (% with QTP)			
Opioids				
Methadone**	41 (22)	23 (26)	3 (0)	**38 (24)†**
Oxycodone	**23 (26)†**	12 (17)	1 (0)	**22 (27)†**
Other	44 (20)	23 (17)	7 (0)	**37 (24)†**
ALL	**102 (20)†**	55 (18)	11 (0)	**91 (22)†**
Sympathomimetics				
Cocaine	63 (14)	35 (9)	9 (22)	54 (13)
Other	16 (38)	8 (50)	6 (33)	10 (40)
ALL	79 (19)	43 (16)	15 (25)	64 (17)
Benzodiazepines				
ALL	96 (17)	58 (17)	10 (10)	**86 (17)†**
Antidepressants				
Es-/Citalopram**	11 (0)	4 (0)	1 (0)	10 (0)
TCA**	10 (10)	2 (0)	3 (33)	7 (0)
Other	45 (16)	18 (11)	7 (29)	38 (13)
ALL	66 (12)	24 (8)	11 (27)	55 (9)
Antipsychotics				
Quetiapine**	31 (10)	15 (7)	6 (0)	25 (12)
Other	28 (7)	10 (0)	6 (33)	22 (0)
ALL	59 (8)	25 (4)	12 (17)	47 (6)
Anticonvulsants				
ALL	31 (3)	16 (6)	10 (10)	21 (0)
Mood-Stabilizers				
Lithium**	8 (13)	8 (13)	5 (20)	3 (0)
OTC Drugs				
Diphenhydramine**	24 (8)	8 (0)	4 (25)	20 (5)
Acetaminophen	61 (15)	61 (15)	6 (17)	55 (15)
Any CERT Drug**	131 (12.9)	60 (13)	23 (17)	108 (12.0)
TOTALS*	472 (12.7)	190 (13.7)	159 (15.1)	313 (11.5)

Abbreviations: OTC = over the counter; QTP = QT prolongation controlled for gender (>460 ms in males, >470 ms in females) ; TCA = tricyclic antidepressants.

†Indicates bivariate $p < 0.05$ for association with QTP, denoted in **BOLD**.

‡"Toxicology Positive:" patients with any positive urine/serum drug concentration/screen.

*Columns individually do not add up to 100% due to involvement of multi-drug exposures.

**CERT listing for TdP risk.

Table 3

Odds of QT Prolongation by Race

Race/Ethnicity	Univariate		Adjusted*	
	OR	CI	OR	CI
Black	1.8	0.97-3.50	**2.01**	**1.03-3.91**
White	1.29	0.73-2.26	1.18	0.65-2.17
Hispanic	**0.52**	**0.29-0.94**	**0.49**	**0.26-0.92**
Asian	1.2	0.48-2.98	1.58	0.61-4.11
Other	0.98	0.97-0.99	0.98	0.97-0.99

Five models are represented, one for each race/ethnicity, with the comparison group being the absence of each race/ethnicity (e.g., comparison group for Black model is non-Black, etc.)

Significant findings listed in **BOLD**.

Abbreviations: OR = odds ratio; CI = 95% confidence intervals.

*Each regression model adjusted for the following covariates: age, gender, CERT listing, and serum potassium.