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향정신성 약물 중독에 의한 QTc 연장과 그 위험성에 대한 고찰

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QTc Prolongation due to Psychotropic Drugs Intoxication and Its Risk Assessment

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Purpose: The aims of the present study were twofold. First, the research investigated the effect of an individual' s risk factors and the prevalence of psychotropic drugs on QTc prolongation, TdP (torsades de pointes), and death. Second, the study compared the risk scoring systems (the Mayo Pro-QT risk score and the Tisadale risk score) on QTc prolongation.
Methods: The medical records of intoxicated patients who visited the emergency department between March 2010 and February 2019 were reviewed retrospectively. Among 733 patients, the present study included 426 psychotropic drug-intoxicated patients. The patients were categorized according to the QTc value. The known risk factors of QTc prolongation were examined, and the Mayo Pro-QT risk score and the Tisadale risk score were calculated. The analysis was performed using multiple logistic regression, Spearman correlation, and ROC (receiver operating characteristic).
Results: The numbers in the mild to moderate group (male: 470≤QTc<500 ms, female: 480≤QTc<500 ms) and severe group (QTc≥500 ms or increase of QTc at least 60ms from baseline, both sex) were 68 and 95, respectively. TdP did not occur, and the only cause of death was aspiration pneumonia. The statically significant risk factors were multidrug intoxications of TCA (tricyclic antidepressant), atypical antipsychotics, an atypical antidepressant, panic disorder, and hypokalemia. The Tisadale risk score was larger than the Mayo Pro-QT risk score.
Conclusion: Multiple psychotropic drugs intoxication (TCA, an atypical antidepressant, and atypical antipsychotics), panic disorder, and hypokalemia have been proven to be the main risk factors of QTc prolongation, which require enhanced attention. The present study showed that the Tisadale score had a stronger correlation and predictive accuracy for QTc prolongation than the Mayo Pro-QT score. As a result, the Tisadale risk score is a crucial assessment tool for psychotropic drug-intoxicated patients in a clinical setting.

Keywords: Psychotropic drugs, QTc prolongation, Torsades de pointes, Mayo Pro-QT score

INTRODUCTION

South Korea occupies first place among OECD countries with suicide rates standing at 23/100,000 in 2017[1]. Self-poisoning is the most frequently chosen suicidal method among Koreans accounting about 56.3% in 2018, and the ratio is progressing year by year (2012-52.4%, 2013-56%)[2]. Physical access to psychotropic drug via prescription is associated with choice of psychotropic drug intoxication as suicide method (36%, 10158/27876)[3]. As a result, Korean emergency department (ED) physicians commonly experience patients who attempt to suicide through psychotropic drug intoxication.

Psychotropic drug intoxication displays various clinical features both fatal and nonfatal. QT prolongation is one of them. The QT interval is defined as the interval from the

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onset of the QRS complex and reflects ventricular repolarization[4]. The QTc is a heart rate-corrected value that represents the time between the onset of electrical depolarization and the end of repolarization. The QTc prolongation is known for causing Torsades de pointes (TdP), a polymorphic ventricular arrhythmia that can progress to ventricular fibrillation and sudden cardiac death[5].

According to the systemic review of Chan et al., the QT interval nomogram for determining 'at risk' QT-heart rate pairs was highly sensitive and specific for cases of drug-induced TdP. Almost all TdP cases fell under QT nomogram and Bazett' s formula ($QTc=QT/\sqrt{RR}$) where QTc=500 ms is similar to the QT nomogram[6].

The previous studies have agreed that QTc prolongation depends on many risk factors such as gender, electrolytes, drug concentration, underlying disease, genetic susceptibility[7-9]. It is assumed that the more someone takes QTc prolonging drugs, the higher drug concentration would be presented, and the risk of QTc prolongation and TdP would increase. Especially, unlike any other QTc prolonging drugs, psychotropic drugs tend to be routinely taken and prescribed for long period with multiple drug therapy, so patients may take large amount of it. The hypothesis of the study is resumed at: when suicide attempters take overdose of psychotropic drugs, the QTc prolongation and TdP will frequently occur.

As far as we know, there is no study about multiple psychotropic drug intoxication and how often psychotropic drug-induced QTc prolongation progresses to TdP. The cause is explained by the fact that TdP rarely occurs and it occasionally carries dramatic consequences as ventricular fibrillation and death. As a result, the research method rules out clinical trials and relies only on retrospective studies. Thus, the current study collected medical records of psychotropic drug intoxication and investigated the patients who experienced QTc prolongation, TdP, and/or death. And, we compared two kinds of risk scoring system to estimate the utility of them.

MATERIALS AND METHODS

1. Study population

The present study retrospectively reviewed the medical records of all patients who visited the emergency center due to drug intoxication between March 2010 and February 2019. The emergency center is a local emergency center located in Seoul and see about 30.000 patients annually. During this period, 733 patients visited our emergency center because of drug intoxication without reference to suicide attempt. Almost all patients have received adequate hydration, gastric lavage and activated charcoal on necessity. Psychiatric consultation and diagnosis of psychiatric disease have been completed.

2. Data collection of ECGs, Associated risk factors

The ECG and blood samples of almost all intoxicated patients have been retrieved on arrival. Well trained medical interns have collected almost all ECGs. Based on patient' s previous ECG, we have evaluated patients as baseline QTc provided the absence of any other disturbing factors. If patients have been admitted to our hospital, we obtained daily ECG and checked normalized QTc values after recovery from intoxication. QTc morphology was analyzed on 12-lead ECGs by computer algorithm. The QT interval was corrected for heart rate using the Bazett' s formula.

The present study has analyzed the descriptive features and the amount of psychotropic drugs. The data has been collected based on patient' s or companion' s statement, prior prescription, remnant medicine packet or paper-bundle, and Tox drug screen test (by Quidel Tirage Tox Drug Screen). Because of patient' s altered mentality, understatement of drug ingestion, and lack of information, it was hard to comprehend toxicity, but we calculated it as far as we can.

The following risk factors associated with QTc prolongation were collected: sex, age, heart disease, electrolyte imbalance such as hypokalemia (serum potassium〈3.5 mEq/L), hypocalcemia (serum calcium〈8.5 mEq/dL), hypomagnesemia (serum magnesium〈1.8 mEq/dL), chronic kidney disease, liver disease, hypothyroidism, treatment with diuretics[7-9].

3. Study protocol

Among 733 patients, 307 patients have been excluded thus the final sample consisted of 426 patients. The reasons for exclusion were non-psychotropic drug intoxication, separate unknown psychotropic drug, missing or incorrect medical records, lack of ECG. In addition, patients who have recent acute coronary syndrome, recent cerebrovascular accident, congestive heart failure, hypothyroidism, diuretics treatment also have been excluded (Fig. 1). Because the subjects which have conditions mentioned above, was too small to analyze and the conditions are known risk factors that can influence QTc value. And we put together renal dialysis and

hepatic impairment that are related to drug concentration. From a pharmacokinetical point of view, liver and kidneys are principal organs of drug metabolism and excretion, thus dysfunctions of them are related to drug concentration. The excluded subjects did not display TdP. Among the patients included in the study, 263 were normal group (male: QTc ⟨470 ms, female: QTc ⟨480 ms), 68 were mild to moderate group (male: 470≤QTc ⟨500 ms, female: 480≤QTc ⟨500 ms), 95 were Severe group (QTc≥500 ms and/or increase of QTc 60 ms from baseline) (Fig. 1). In the severe group, the number of population QTc≥500 was 70 and the number of QTc increase over 60 was 25. The cutoffs were based on AHA/ACCF statement[10].

Psychotropic drugs were divided into categories: BZD (benzodiazepine), SSRI (serotonin selective reuptake inhibiter), SNRI (serotonin-norepinephrine reuptake inhibitor), TCA (tricyclic antidepressant), atypical antidepressant, typical antipsychotic, atypical antipsychotic, anticonvulsant, non-benzodiazepine sedative, and others (psychostimulant, lithium, propranolol, donepezil). The frequencies of individual medication use and risk classification are shown in Table 1[11]. The present study has classified drug history into subgroup according to dose and multiplicity: monodrug ingestion, monodrug intoxication, multidrug ingestion, multidrug intoxication. The cutoffs determining ingestion or intoxication were based on daily maximal dose by Korea Pharmaceutical Information center[12]. The Mayo Pro-QT risk score[13] and the Tisadale risk score[14] have been calculated accordingly. The Mayo Pro-QT risk score was set according to all ECGs and QTc prolongation of a single center, thus the population is highly randomized[13]. However, the Tisadale risk score has been calculated based on the population sample of patients only admitted to cardiac care unit[14]. Lack of studies concerning the population with psychiatric drug intoxication has motivated us to compare the risk scoring systems that need to be utilized in clinical setting.

4. Data analysis

Chi-square test has been performed to evaluate the difference between the effect of demographic variables (sex, age, suicide attempt, Mayo Pro-QT risk score, Tisadale risk score), presence or absence of drugs, and psychiatric disorders on QTc prolongation.

Furthermore, multiple logistic regression has been carried out to check the causal relationship of other variables such as sex, age, others, HTN, DM, on QTc prolongation, in addition to the dose and multiplicity of drugs. At this point, the research has applied the penalized likelihood method originally proposed by Firth to consider the rare events.

Lastly, Spearman correlation has been applied to verify the correlation of QTc prolongation with the Mayo Pro-QT

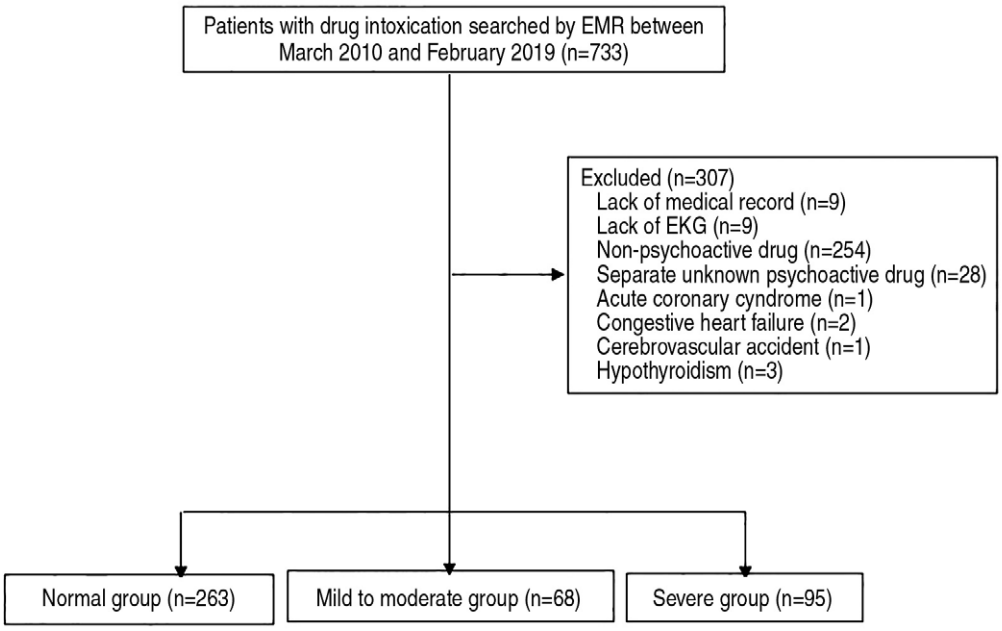

Fig. 1. Diagram of patient categories. Each groups were categorized by QTc value:
Normal- male: QTc<470 ms, female: QTc<480 ms
Mild to moderate group - male: 470≤QTc<500 ms, female: 480≤QTc<500 ms
Severe group - QTc≥500 ms and/or increase of QTc at least 60 ms from baseline, both sex

Table 1. Psychoactive drugs and types in the present study and risk category based on the CredibleMeds Classification system[11)]

Category	Drug	N	CredibleMeds risk
BZD(Benzodiazepine)	Alprazolam	111	Not classified
	Bromazepam	20	Not classified
	Chlordiazepoxide	5	No matching record found
	Clonazepam	35	Not classified
	Clotiazepam	6	Not classified
	Diazepam	48	Not classified
	Etizolam	19	No matching record found
	Flunitrazepam	14	Not classified
	Flurazepam	12	No matching record found
	Lorazepam	72	Not classified
	Loflazepate	7	No matching record found
	Tofisopam	3	No matching record found
SSRI (Serotonin selective reuptake inhibitor)	Atomoxetine	1	Possible risk of TdP
	Citalopram	4	Known risk of TdP
	Escitalopram	31	Known risk of TdP
	Fluoxetine	12	Conditional risk of TdP
	Fluvoxamine	3	Conditional risk of TdP
	Paroxetine	22	Conditional risk of TdP
	Serteraline	8	Conditional risk of TdP
	Vortioxetine	1	Not classified
SNRI (Serotonin norepinephrine reuptake inhibitor)	Desvenlafaxine	6	Not classified
	Duloxetine	7	Not classified
	Venlafaxine	4	Possible risk of TdP
TCA (Tricycle antidepressants)	Amitriptyline	18	Conditional risk of TdP
	Cyclobenzaprine	4	Not classified
	Doxepin	9	Conditional risk of TdP
	Imipramine	3	Possible risk of TdP
	Nortriptyline	15	Possible risk of TdP
	Quinupramine	1	No matching record found
Atypical antidepressant	Bupropion	15	Not classified
	Hyperici	1	No matching record found
	Mirtazepine	15	Possible risk of TdP
	Tianeptine	4	No matching record found
	Trazodone	50	Conditional risk of TdP
Typical antipsychotics	Chlorpromazine	4	Known risk of TdP
	Haloperidol	5	Known risk of TdP
	Perphenazine	11	Possible risk of TdP
Atypical antipsychotics	Amisulpride	5	Conditional risk of TdP
	Aripiprazole	15	Possible risk of TdP
	Blonanserin	1	No matching record found
	Clozapine	2	Possible risk of TdP
	Olanzapine	6	Conditional risk of TdP
	Paliperidone	3	Possible risk of TdP
	Quetiapine	59	Conditional risk of TdP
	Risperidone	10	Conditional risk of TdP
	Ziprasidone	1	Conditional risk of TdP
	Zotepine	4	Possible risk of TdP
Anticonvulsants	Baclofen	3	Not classified
	Carbamazepine	10	Not classified
	Gabapentin	5	Not classified
	Lamotrigine	9	Not classified
	Phenobarbital	1	No matching record found
	Phenytoin	2	Not classified
	Topiramate	14	Not classified
	Valproate	22	Not classified

(Continued to the next page)

Table 1. Continued

Category	Drug	N	CredibleMeds risk
Nonbenzodiazepine sedatives	Buspirone	4	Not classified
	Melatonin	3	No matching record found
	Zolpidem	135	Not classified
Psychostimulants	Methylphenidate	6	Special risk for patients with congenital Long QT
	Phentermine	7	
	Phendimetrazine	1	
	Diethylpropion	1	
	Methamphetamine	1	
Etc	Selegilline	1	No matching record found
	Lithium	16	Possible risk of TdP
	Propranolol	45	Not classified
	Donepezil	2	Known risk of TdP
	Unknown	12	

* Known Risk of TdP - These drugs prolong the QT interval and are clearly associated with a known risk of TdP, even when taken as recommended.

† Possible Risk of TdP - These drugs can cause QT prolongation but currently lack evidence for a risk of TdP when taken as recommended.

‡ Conditional Risk of TdP - These drugs are associated with TdP but only under certain conditions of their use (e.g. excessive dose, in patients with conditions such as hypokalemia, or when taken with interacting drugs) or by creating conditions that facilitate or induce TdP (e.g. by inhibiting metabolism of a QT-prolonging drug or by causing an electrolyte disturbance that induces TdP).

§ Drugs to Avoid in Congenital Long QT Syndrome (cLQTS) - These drugs pose a high risk of TdP for patients with cLQTS and include all those in the above three categories (KR, PR & CR) plus additional drugs that do not prolong the QT interval per se but which have a Special Risk (SR) because of their other actions.

risk score, and the Tisadale risk score. Receiver Operating Characteristic (ROC) has been performed to estimate the cut-off value of the Mayo Pro-QT risk score, and the Tisadale risk score during diagnosis of QTc prolongation. The cut-off value has been estimated according to Euclidean distance, expressed as min ($\sqrt{(1\text{-specificity})^2+(1\text{-sensitivity})^2}$), while considering sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), accuracy during application of Mcnemar test.

All statistical analyses were performed using the SAS 9.4 (Statistical Analysis System version, SAS Institute, Cary, NC, USA), SPSS 23 (IBM Corporation, Chicago, IL, USA). A value of $p<0.05$ was considered a statistically significant.

RESULTS

A total of 426 patients had a median age of 41 years (interquartile range [IQR], 29-54 years), and there were 317 (74.41%) female patients. The number of subjects who committed suicide attempts stands at 371 (87.08%). The most common psychiatric disease and psychotropic drug were major depressive disorder (MDD) (n=273, 64.08%) and BZD (n=281, 65.96%). During 10 year-record of accumulation of drug intoxication cases in the ED, TdP did not occur. The only case of death was caused by aspiration pneumonia. All baseline patient characteristics are summarized in Table 2.

The demographic characteristics by QTc interval are summarized in Table 3. Female sex and old age are known risk factors of QTc prolongation, but they do not seem to show linear relation. Suicide attempt has prominent ratio (n=91, 95.79%) in the severe group. The MDD and BZD, the most common psychiatric disease and drug, each other, did not show correlation with QTc severity (p=0.7508 and p=0.0856). However, the study has emphasized a strong correlation between QTc prolongation and panic disorder, TCA, atypical antipsychotics, atypical antidepressant.

Adjusted by sex, age, other underlying conditions, multiple logistic regression revealed, the risk factors of QTc prolongation (male≥470, female≥480, increase of QTc 60 ms from baseline) were TCA multidrug intoxication, atypical antipsychotics multidrug ingestion, multidrug intoxication, atypical antidepressant multidrug intoxication, panic disorder, and hypokalemia (Table 4). Less than daily maximal dose and monodrug exposure are relatively safe from all kinds of psychotropic drug. Suicide attempt has not been found to be statistically significant (OR, 1.09 [95% CI, 0.60-1.97; p=0.7788]). According to spearman correlation, the Tisadale risk score pointed a stronger correlation of QTc prolongation (ρ=0.28 vs ρ=0.51, $p<.0001$) (Fig. 2). ROC curves of the Mayo Pro-QT risk score and the Tisadale risk score are presented in Fig.

Table 2. Characteristics of the study population

Age (y), median (IQR)	41 (29-54)
Age≥60 y, no. (%)	83 (18.24)
Sex	
Male, no. (%)	109 (25.58)
Female, no. (%)	317 (74.41)
Suicide attempt, no. (%)	371 (87.08)
Admission, no. (%)	272 (63.84)
QTc (ms), median (IQR)	465 (446-488)
Underlying conditions	
HTN, no. (%)	74 (17.37)
DM, no. (%)	29 (6.8)
Others (%)	10 (2.3)
Psychiatric disorders	
MDD, no. (%)	273 (64.08)
BD, no. (%)	40 (9.3)
Schizophrenia, no. (%)	17 (3.9)
Anxiety disorder, no. (%)	21 (4.9)
Panic disorder, no. (%)	37 (8.6)
Insomnia, no. (%)	58 (8.6)
Adjustment disorder, no. (%)	86 (13.61)
Acute stress reaction, no. (%)	34 (20.18)
Psychotropic drug exposures	
BZDs, no. (%)	281 (65.96)
SSRIs, no. (%)	84 (19.71)
SNRIs, no. (%)	18 (4.22)
TCAs, no. (%)	48 (11.26)
Atypical antidepressants, no. (%)	76 (17.84)
Typical Antipsychotics, no. (%)	20 (4.69)
Atypical antipsychotics, no. (%)	88 (20.65)
Anticonvulsants, no. (%)	61 (14.31)
Nonbenzodiazepine sedatives, no. (%)	142 (33.313)
Lithium, no. (%)	16 (3.75)
Propranolol, no. (%)	45 (10.56)
Unknown, no. (%)	12 (2.81)
Others, no. (%)	19 (4.46)
Electrolytes	
K (mEq/L), median (IQR)	3.8 (3.5-4.1)
Ca (mg/dL), median (IQR)	2.2 (2-2.3)
Mg (mg/dL), median (IQR)	8.9 (8.6-9.2)
Mayo Pro-QT risk score, median (IQR)	2 (1-3)
Tisadale risk score, median (IQR)	5 (3-7)
Gastric lavage, no (%)	80 (18.77)
Activated charcoal, no (%)	194 (45.53)
TdP, no. (%)	0
Death, no. (%)	1 (0.23)

* Other underlying conditions include renal dialysis, hepatic impairment, diuretics

† Other psychotropic drugs include psychostimulants, monoamine oxidase inhibitor, donepezil

‡ IQR: interquartile, HTN: hypertension, DM: diabetes mellitus, BZD: benzodiazepine, SSRI: serotonin selective reuptake inhibitor, SNRI: serotonin norepinephrine reuptake inhibitor, TCA: tricycle antidepressants

3. The AUROC (Area under receiver operating characteristic) value of the Tisadale risk score was bigger than that of the Mayo Pro-QT score (0.7206 (0.6715-0.7697, 95%CI)〉 0.6191 (0.5633-0.6749, 95%CI)). Optimal cut off values of the Mayo Pro-QT risk score and the Tisadale risk score were 3 and 5, respectively. Predictive accuracy of the Mayo Pro-QT score and the Tisadale score were comparable; but that of the Tisadale score was bigger. (62.44% and 66.43%) (Table 5)

DISCUSSION

The QTc prolongation may be either congenital or acquired. The QTc prolongation usually can be provocated by the presence of extrinsic triggers such as drugs, hypokalemia or hypomagnesemia and bradycardia[10,14,15]. However, acquired QTc prolongation is almost always caused by drugs[15]. Drug-induced QT prolongations can be caused by drugs that block the rapid delayed rectifier potassium current (IKr) in cardiac tissue, which is mediated by the human ether-á-go-go related gene (hERG)[16]. There are common drugs known to cause QTc prolongation and TdP, such as antiarrhythmics, antimicrobials, antipsychotics, antidepressants, antihistamines, and antiemetics[7,8,11]. The CredibleMeds.org is prototype for evidence-based sources of safety information that rank drugs for their risk of a specific form of drug toxicity and drug-induced arrhythmia and it has become the standard reference of drug-induced QT prolongation and TdP[8,11,17].

There are a number of reports stating that the use of an antidepressant causes QTc prolongation[18-20]. The studies analyzing the ECGs of psychotropic drug users pointed that starting TCA increased the QTc interval significantly with 6.9 ms compared with nonusers[20]. Another study about adult patients, who have been prescribed antidepressants, asserts that the SSRI and TCA have significantly influenced QTc prolongation[19]. Despite the fact that the current study revealed similar results about TCA (OR, 3.61 [95% CI, 1.44-9.04; p=0.0062]), it did not show the same results in terms of SSRI multidrug intoxication (OR, 1.20 [95% CI, 0.70-2.08; p=0.5101]). According to Waring et al., atypical antidepressants were not associated with clinically significant increases in QTc intervals at therapeutic doses[21]. Contrary to previous study, the present study is focused on intoxicated patients and atypical antidepressants multidrug intoxication is statistically related to QTc prolongation (OR, 2.57 [95% CI, 1.36-4.84; p=0.0036])

According to a number of studies, demonstrated that therapeutic use of typical antipsychotics, in particular, induce QT prolongation[18,22]. The present study included, only three kinds of typical antipsychotics: chlorpromazine, haloperidol, perphenazine. Another study describing the patients prescribed antipsychotics for schizophrenia, typical antipsychotics chlor-

Table 3. Demographic characteristics by QTc severity group

Variable	QTc severity group			
	Normal (n=263)	Mild to moderate (n=68)	Severe (n=95)	*p*-value
Sex				0.0036
Male	63 (23.95)	28 (41.18)	18 (18.95)	
Female	200 (76.05)	40 (58.82)	77 (81.05)	
Age				0.0346
<60	210 (82.89)	47 (69.12)	78 (82.11)	
≥60	45 (17.11)	21 (30.88)	17 (17.89)	
Suicide attempt				0.0013
Yes	228 (86.69)	52 (76.47)	91 (95.79)	
No	35 (13.31)	16 (23.53)	4 (4.21)	
Underlying conditions				
HTN	44 (16.13)	18 (26.47)	12 (12.63)	0.0644
DM	18 (6.84)	7 (10.29)	4 (4.21)	0.3145
Other	6 (2.28)	2 (2.94)	2 (2.11)	0.9008
Psychiatric disease				
MDD	166 (63.12)	43 (63.24)	64 (67.37)	0.7508
BD	23 (8.75)	4 (5.88)	13 (13.68)	0.2049
Schizophrenia	12 (4.56)	0	5 (5.26)	0.1454
Anxiety disorder	13 (4.94)	3 (4.41)	5 (5.26)	1.0000
Panic disorder	13 (4.94)	9 (13.24)	15 (15.79)	0.0020
Insomnia	31 (11.79)	15 (22.06)	12 (12.63)	0.0843
Adjustment disorder	54 (20.53)	16 (23.53)	16 (16.84)	0.5625
Psychotropic drug				
BZDs	171 (65.01)	42 (61.76)	68 (71.57)	0.0856
SSRIs	52 (19.77)	12 (17.64)	20 (21.05)	0.9453
SNRIs	9 (3.42)	2 (2.9)	7 (7.37)	0.4663
TCAs	20 (7.60)	7 (10.29)	21 (22.10)	<.0001
Atypical antidepressants	34 (12.92)	7 (10.29)	35 (36.84)	<.0001
Typical antipsychotics	11 (4.18)	4 (5.8)	5 (5.2)	0.4494
Atypical antipsychotics	42 (15.96)	14 (20.58)	32 (33.68)	0.0056
Anticonvulsants	30 (11.40)	8 (11.76)	23 (24.21)	0.0786
Nonbenzodiazepine sedatives	89 (33.84)	25 (36.76)	28 (29.47)	0.1485
Lithium	7 (2.66)	3 (4.41)	6 (6.32)	0.1313
Propranolol	28 (10.65)	4 (5.88)	13 (13.68)	0.9436
Unknown	11 (4.18)	0	1 (1.05)	0.0344
Others	44 (16.73)	8 (11.76)	21 (22.10)	0.2727
Hypokalemia	48 (18.25)	23 (33.82)	29 (30.53)	0.0048
Hypocalcemia	34 (12.93)	18 (26.47)	14 (14.74)	0.0631
Hypomagnesemia	4 (1.52)	4 (5.88)	3 (3.16)	
Mayo Pro-QTc risk score				0.0003
<4	248 (94.29)	57 (83.82)	77 (81.05)	
≥4	15 (5.7)	11 (16.17)	18 (18.95)	
Tisadale risk score				<.0001
<7	215 (81.74)	45 (66.17)	46 (48.42)	
7-11	47 (17.87)	20 (29.41)	37 (38.94)	
≥11	1 (0.38)	3 (4.41)	12 (12.63)	

* Values are presented as number (%).
† By Fisher's exact tests
‡ Normal- male: QTc<470 ms, female: QTc<480 ms
§ Mild to moderate group - male: 470≤QTc<500 ms, female: 480≤QTc<500 ms
‖ Severe group - QTc≥500 ms and/or increase of QTc at least 60 ms from baseline, both sex

promazine and intravenous haloperidol were significant risk factors, whereas atypical antipsychotics such as olanzapine, quetiapine, and risperidone were not[22]. According to a randomized intervention study that measured QTc changes before and after drug administration, atypical antipsychotics olanzapine, risperidone, and quetiapine were safer than typical antipsy-

Table 4. Risk factors of QTc prolongation related to psychotropic drugs by multiple logistic regression analysis

	Adjusted OR	95% CI		*p*-value
		Low	High	
TCAs				
Drug free	Reference	.	.	.
Monodrug ingestion	1.07	0.10	11.38	0.9559
Monodrug intoxication	2.27	0.37	14.03	0.3763
Multidrug ingestion	1.89	0.73	4.92	0.1918
Multidrug intoxication	3.61	1.44	9.04	0.0062
Atypical antidepressants				
Drug free	Reference	.	.	.
Monodrug ingestion	NA	NA	NA	NA
Monodrug intoxication	18.01	0.69	472.39	0.0829
Multidrug ingestion	1.57	0.71	3.48	0.2680
Multidrug intoxication	2.57	1.36	4.84	0.0036
Atypical antipsychotics				
Drug free	Reference	.	.	.
Monodrug ingestion	NA	NA	NA	NA
Monodrug intoxication	0.44	0.01	18.36	0.6663
Multidrug ingestion	2.43	1.12	5.26	0.0244
Multidrug intoxication	2.33	1.30	4.17	0.0044
Panic disorder				
No	Reference	.	.	.
Yes	3.78	1.84	7.75	0.0003
Hypokalemia				
No	Reference	.	.	.
Yes	2.23	1.41	3.54	0.0007

* Firth's method of logistic regression

† Adjusted by sex, age, underlying conditions (HTN, DM, renal dialysis, hepatic impairment, diuretics)

‡ OR: odd ratio, CI: confidence interval, NA: not applicable

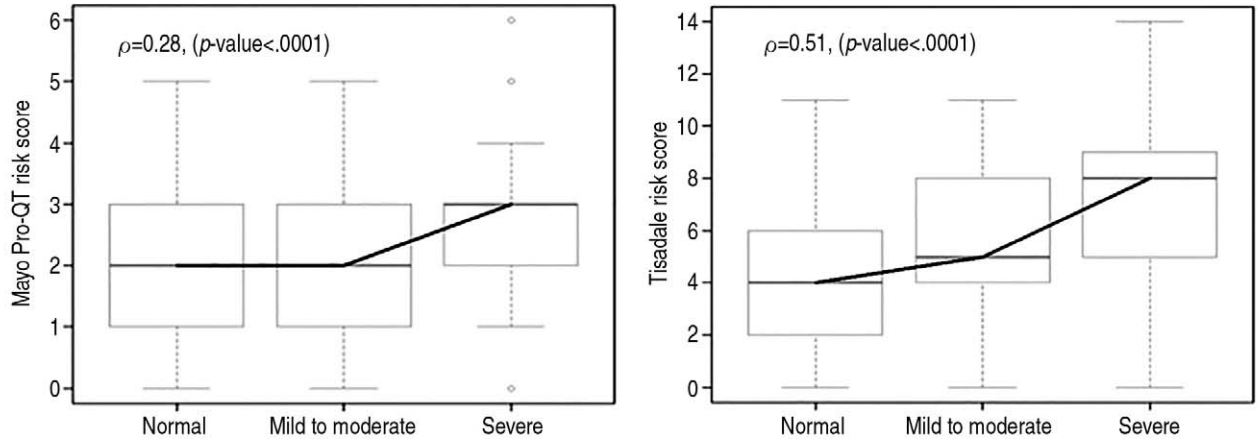

Fig. 2. Comparison of rank correlation analysis of QTc prolongation between the Mayo Pro QT risk score and the Tisadale risk score. Analysis was performed by Spearman rank correlation coefficient. In this graph, X axis displays categorical valuable. ρ value was formulated by continuous variable.

chotics. However, both typical and atypical antipsychotics cause a QT prolongation ranging from 4 ms to 30 ms[23]. Unlike previous study, the present study revealed that typical antipsychotics were not the risk factors of QTc prolongation, and atypical antipsychotics multidrug ingestion and intoxication were risk factors of QTc prolongation (OR, 2.43 [95% CI, 1.12-5.26; p=0.0244] and OR, 2.33 [95% CI, 1.30-4.17; p=0.0044]). The authors of one study indicated that, no significant prolongation of the QT interval was found following monotherapy with an antipsychotic agent, while combination of these drugs

with antidepressants caused a significant QT prolongation[24]. Basically, multidrug intoxication is more likely to induce QTc prolongation.

As started by the present study, almost all psychiatric diseases were not associated with QTc prolongation, except panic disorder. (OR, 3.78 [95% CI, 1.84-7.75; p=0.0003]). At the moment, the lack of research investigated the relationship between panic disorder and QTc prolongation provides little information on the topic. Some studies revealed anxiety and panic disorder increase QT dispersion and QT variability[25,26]. The QT dispersion defined as the difference between the maximum QT and minimum QT. The QT variability is based on the analysis of beat to beat changes in duration and the morphology of ventricular repolarization[27]. The changes in QT interval variability and QT dispersion are linked to autonomic nervous system which can be influenced by anxiety symptom[28,29].

Hypokalemia is common risk factor in drug-induced QTc prolongation. Low extracellular potassium paradoxically reduces IKr by enhanced inactivation or exaggerated competitive block by sodium[30,31]. As a result, hypokalemia prolongs the QT interval. Many previous studies and the present study show identical result.

Up to date, there is no comparative study of risk scoring system for predicting QTc prolongation. A Pro-QTc score of 4 or higher predicted mortality. (hazard ratio 1.72 [95% CI 1.11-2.66; p<0.001])[13]. The Tisadale risk scores of lower than 7, 7-10, and 11 or above were categorized as low, moderate, and high risk respectively. The incidence of QTc interval prolongation in the low, moderate and high groups was 15%, 37%, and 73%, respectively[14]. The most significant difference between the Mayo Pro-QTc risk score and the Tisadale risk score is consideration of weighted scoring for QT prolonging drug[13,14]. As a result, the Tisadale score was more valid tool for risk assessment of psychotropic drug intoxication, despite that the predictive accuracy was not so high.

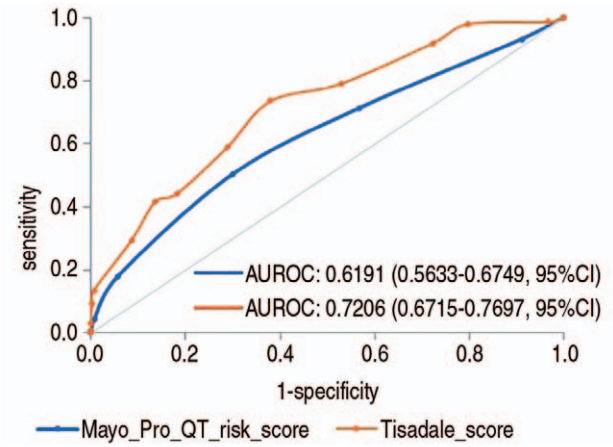

Fig. 3. Receiver operating characteristic (ROC) curves of the Mayo Pro-QT risk score and the Tisadale risk score for QTc prolongation. AUROC (Area under receiver operating characteristics) of each was 0.6191 (0.5633-0.6749, 95%CI) and AUROC: 0.7206 (0.6715-0.7697, 95%CI), respectively

In this 10-year retrospective study, the prevalence of population QTc≥500 ms stands at 16.43% (n=70, out of 426). According to previous studies of psychotropic drug induced QTc≥500 ms, the value is within the range of the 0.9% to 2.6%[32,33]. Those studies targeted population for who followed the routine intake of psychotropic drugs. However, the present study focuses on target population with intentional psychotropic drug intoxication. Despite of significant difference in prevalence of severe QTc prolongation between previous studies and the present study, no cases of TdP have occurred. To support the hypothesis that intentional psychoactive drug intoxication wound tend to show QTc. prolongation, the study relied on larger number of population compared with other studies. However, it was hard to observe TdP. Although, the overall incidence of TdP is unknown, a study estimated the incidence of TdP to be 2.5 per million per year for males and 4 per million per year for females[34].

Based on risk of QT prolongation due to drugs, between June 1990 and March 2001, 8 non-cardiovascular marketed drugs including antipsychotics are removed from the market in the United States and elsewhere[7-9]. Indeed, some drugs have been withdrawn from the market because they cause TdP result in a mean increase in the QT interval as small as "only" 5 to 10 msec in populations of patients. The drugs removed from the market once approved from clinical trials, despite being tested on a few thousand patients and no cases of TdP have been recorded in a database[9]. The drugs that survived from restriction and withdrawal because of QTc prolongation, are evaluated to relatively safe; however,

Table 5. Predictive accuracy of Mayo Pro-QT score and Tisadale risk score

	Cut off value	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
Mayo Pro-QT risk score	3	50.31	69.96	50.96	69.43	62.44
Tisadale risk score	5	73.62	61.98	54.55	79.13	66.43

* By Mcnemar test

the recruitment of clinical trials usually involve healthy subjects with no pre-existing medical conditions, or patients with specific health conditions.

In accordance with electrophysiological approach, a drug that prolongs action potential duration, induces early afterdepolarizations and ectopic beats, and increases dispersion of ventricular repolarization is presumed to cause TdP. By contrast a drug that does not induce these changes is improbable to cause TdP[35]. Therefore, it appears that QT prolongation alone is insufficient and that heterogeneity of repolarization may also be necessary to produce an arrhythmogenic response[10]. Beach et al. by nonsystemic review, the evidence for clinically meaningful QT prolongation with most classes of psychiatric agents remains minimal[36]. Not all QT-prolonging drugs are associated with risk for TdP[8,10,11,17]. The development of TdP is the consequence of multiple risk factors and QTc prolongation may be just one of them, not a keystone for TdP occurrence.

Concerning about association of TdP, many ED physicians have vague fear of the QTc prolongation and spend their limited medical resources and efforts in monitoring nonfatal patients with psychotropic drug intoxication by admitting patients. Contrary to widespread expectation, it was hard to encounter patients who committed suicide by psychotropic drugs intoxication with QTc prolongation progressed to TdP in clinical practice. In consequence, the present study points out that the risk of QTc prolongation due to psychotropic drugs intoxication is overestimated.

During the examination of patients with acute psychotropic drug intoxication in the ED, physicians are advised to careful risk assessment of psychotropic drug-induced QTc prolongation with precise understanding and consideration of other risk factors. Considering the mechanism and extremely low prevalence of TdP, the intoxicated patients presenting only QTc prolongation without any other risk factors are subject to short term monitoring in the ED. After adequate treatment and evaluation, the physicians are advised to follow the basic admission-discharge process of these patients, avoiding forceful admission.

The present study has several limitations. First, majority of subjects appear to display an improved health status and only few of them suffer from multiple risk factors. Further studies involving the population with more comorbidities such as patients in intensive care unit or coronary care unit are needed. Second, the emergency center under investigation only have screening kit, and does not possess gas chromatography-mass spectrometry that can analyze serum drug concentration. As a result, the research only investigated oral dose depending on statement and deduction, despite the accepted standard that serum drug concentration is the most accurate value to decide whether ingestion or intoxication has occurred. Third, the multidrug ingestion and intoxication were the risk factors of QTc prolongation, while the monodrug ingestion and intoxication were not. However, further studies need to elucidate the drug combinations that cause QTc prolongation. Fourth, panic disorder has been found to be one of the risk factor of QTc prolongation. Further studies are needed to clarify whether the effect of panic disorder alone or in combination with medications causes the QTc prolongation. Fifth, the managements for intoxicated patients to reduce serum drug concentration such as adequate hydration, gastric lavage, and active charcoal intake was not considered. The mediators are predicted to influence drug concentration, QTc value, and tendency to progress TdP[37].

CONCLUSION

Multiple psychotropic drug intoxication - TCA, atypical antidepressant, atypical antipsychotics -, panic disorder and hypokalemia have been proven to be the main risk factors of QTc prolongation which require enhanced attention. In addition to physical factors, psychiatric disease and emotional state must be considered as risk factors of QTc prolongation, though the association between them is subject for debate in further research.

The present study showed that the Tisadale score pointed the stronger correlation and predictive accuracy than that of the Mayo Pro-QT score for QTc prolongation. As a result, the Tisadale risk score becomes a crucial assessment tool for psychotropic drugs intoxicated patients in clinical setting.

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