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QT interval prolongation noted in one percent of 2553 Asian patients with schizophrenia: Findings from the REAP-AP survey

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Abstract

Although the association between antipsychotic use and corrected QT interval (QTc) prolongation has been repeatedly confirmed, the relationship has been rarely studied in a practical setting. Using data from the Research on Asian Psychotropic Prescription Patterns for Antipsychotics (REAP-AP) survey, our study aimed to investigate the prevalence and clinical correlates of QTc prolongation in 2553 Asian patients with schizophrenia. After adjusting for the potential effect of confounding factors, the baseline and clinical characteristics of the schizophrenia patients with and without QTc prolongation were compared using analyses of covariance and binary logistic analyses. In addition, a binary logistic analysis model with a forward selection method was used to identify the distinctive clinical correlates of QTc prolongation. QTc prolongation was noted in 1.1% of Asian patients with schizophrenia. Schizophrenia patients were characterized by lower proportions of disorganized speech and negative symptoms; higher use of amisulpride and clozapine; and higher proportions of rigidity, hypercholesterolemia, and sedation than those without QTc prolongation. Finally, a binary logistic mode showed that amisulpride, clozapine, rigidity, and

hypercholesterolemia might be the distinctive clinical correlates of QTc prolongation in Asian patients with schizophrenia. These findings indicate the clinical implications that the uses of amisulpride and clozapine and the occurrences of rigidity and hypercholesterolemia may be potential risk factors for QTc prolongation of schizophrenia patients.

KEYWORDS

Asian, hypercholesterolemia, rigidity, QTc prolongation, schizophrenia

1 | INTRODUCTION

A dose-response relationship exists between antipsychotic drugs and potential prolongation of the rate-corrected QT interval (QTc).[1] Inhibition of the hERG-encoded potassium channels has been proposed as a possible mechanism of the potential effects of most antipsychotics on QTc prolongation.[2,3] QTc prolongation may be caused by antipsychotics, such as chlorpromazine, haloperidol, pimozide, quetiapine, risperidone, thioridazine, and ziprasidone; and antidepressants, such as, bupropion, duloxetine, fluoxetine, and paroxetine.[4] In addition, QTc prolongation has been observed in some newer antidepressants rather than tricyclic antidepressants.[5] However, an association between antipsychotic polypharmacy and QTc prolongation has been inconsistently reported.[1] Moreover, in a study with a large sample population of 2366 subjects, it was reported that age, sex, alcohol misuse, and concurrent intake of the implicated drug acted as mediating variables between first generation antipsychotic use and QTc interval.[6] A QTc interval of >500 ms is considered to be a risk factor for torsade de pointes, which is a life-threatening arrhythmia, associated with sudden cardiac death.[7] However, the prevalence and clinical correlates of QTc prolongation have rarely been reported, especially in patients with schizophrenia in a practical clinical situation. The Research on Asian Psychotropic Prescription Patterns for Antipsychotics (REAP-AP) survey is the largest survey in the realm of psychiatry in Asia.[8,9] In this study, using data from the REAP-AP survey, we aimed to evaluate the prevalence and clinical correlates of QTc prolongation in Asian patients with schizophrenia.

2 | SUBJECTS AND METHODS

2.1 | Study participants and design

As described earlier,[8,9] an aim of the REAP-AP survey was to investigate psychotropic prescription patterns and their clinical correlates as well as explore ways to improve prescription patterns in patients with schizophrenia in Asian countries/special administrative areas. During the study period of March–June 2016, 3744 consecutive patients with schizophrenia were enrolled from 71 REAP-AP4 survey centers in 15 Asian countries and areas, namely Bangladesh, China, Hong Kong, India, Indonesia, Japan, Korea, Malaysia, Myanmar, Pakistan, Singapore, Sri Lanka, Taiwan, Thailand, and Vietnam. The United Nations classification was used to categorize the 15 Asian countries/special administrative areas into three groups as follows: Eastern Asia (China, Hong Kong, Japan, Korea, and Taiwan); Southern Asia (Bangladesh, India, Pakistan, and Sri Lanka); and Southeastern Asia (Indonesia, Malaysia, Myanmar, Singapore, Thailand, and Vietnam). The World Bank list of economies was used to classify the 15 Asian countries/special administrative areas into three groups based on income as follows: high income (Hong Kong, Japan, Korea, Singapore, and Taiwan); upper middle income (China, Malaysia, and Thailand); and lower middle income (Bangladesh, India, Indonesia, Myanmar, Pakistan, Sri Lanka, and Vietnam). The institutional review boards of Taipei City Hospital, Taipei, Taiwan (receipt number: TCHIRB-10412128-E) and other centers approved the protocol for the REAP-AP survey. All study participants, or their authorized representatives, provided written informed consent prior to participation. Prior to initiation of the study, a conference meeting was held to improve the consistency of data collection and diagnosis of schizophrenia among the survey centers. Demographic data and clinical and treatment-related details as per protocol were collected by trained study coordinators supervised by clinical psychiatrists at the survey centers. Data on the study subjects were collected using the predefined questionnaires as per protocol and stored on the REAP-AP study website.

We selected participants who met all the following inclusion criteria, to ensure appropriate analyses of the data obtained from the REAP-AP survey: (a) schizophrenia diagnosed with the International Classification of Diseases, 10th revision (ICD-10),[10] (b) antipsychotic drugs used for pharmacotherapy, and (c) availability of the presence or absence of QTc prolongation, which was recorded by a standard 12-lead electrocardiography with a paper speed of 25 mm/s. The QTc interval was calculated by Bazett's formula: $QTc = QT/RR^{1/2}$, and QTc prolongation was defined as a duration of >450 ms in men and >470 ms in women.[7,11]

2.2 | Statistical analysis

Thus, 2553 Asian patients with schizophrenia were included for the comparison of the baseline and clinical characteristics of those with and without QTc prolongation. Independent *t*-tests were used for continuous variables and $\chi 2$ tests were used for discrete variables; and the baseline and clinical characteristics of schizophrenia patients with and without QTc prolongation were compared. Moreover, covariance analyses were performed for continuous variables, and

TABLE 1 Baseline characteristics of schizophrenia patients with QTc prolongation (n = 27)

Case number	Age	Sex	BMI (kg/m^2)	Psychopathological characteristics	Psychotropic medications	Other adverse effects[a]
1	14	Male	25.63	Disorganized behavior	Olanzapine 20 mg	Weight gain
2	58	Male	n/a	Disorganized behavior, negative symptoms	Olanzapine 10 mg	None
3	61	Male	22.60	Negative symptoms	Olanzapine 20 mg	Hypercholesterolemia
4	66	Female	22.02	Hallucination	Sulpride 800 mg, estazolam 1 mg	Hypercholesterolemia
5	50	Female	26.89	Hallucination	Aripiprazole 15 mg, estazolam 2 mg	Impaired glucose tolerance
6	40	Female	24.63	Delusion, hallucination	Zotepine 200 mg, clonazepam 2.5 mg	Constipation, oversedation
7	59	Female	22.48	Delusion, hallucination	Clozapine 200 mg, lorazepam 2 mg	Blurred vision
8	48	Female	25.60	Hallucination	Clozapine 300 mg, clonazepam 2 mg	Constipation, excessive salivation, postural hypotension, urinary difficulty, blurred vision
9	71	Female	26.93	Hallucination	Clozapine 300 mg	Constipation
10	56	Female	23.73	Delusion, hallucination, verbal aggression	Clozapine 350 mg, flunitrazepam 2 mg	Constipation, impaired glucose tolerance, hypercholesterolemia
11	30	Male	24.13	Delusion, hallucination	Clozapine 350 mg, valproate 1000 mg	Tremor, constipation, oversedation
12	62	Female	23.01	Delusion	Olanzapine 20 mg, ziprasidone 160 mg, clonazepam 2 mg, Zopiclone 7.5 mg	Constipation, dry mouth, impaired glucose tolerance, hypercholesterolemia
13	63	Male	29.90	Delusion	Amisulpride 400 mg, trihexyphenidyl 8 mg	Akathisia
14	61	Female	29.16	Delusion, hallucination	Amisulpride 400 mg, Valproate 1000 mg, Escitalopram 10 mg	Rigidity, tremor, constipation, hypercholesterolemia, oversedation
15	52	Female	26.98	Delusion, hallucination, disorganized speech	Clozapine 275 mg, valproate 1000 mg, trihexyphenidyl 4 mg	Rigidity, tremor
16	78	Female	25.71	Delusion, hallucination, negative symptoms, verbal aggression	Risperidone 4 mg, trihexyphenidy 2 mg	Rigidity, hypercholesterolemia, oversedation
17	24	Female	27.21	Delusion, hallucination, negative symptoms, verbal aggression	Zotepine 400 mg, carbamazepine 600 mg, trihexyphenidy 5 mg	Rigidity, akathisia, constipation
18	56	Female	18.56	Hallucination, negative symptoms	Olanzapine 20 mg, trihexyphenidy 2 mg	Rigidity, constipation
19	43	Female	23.60	Hallucination, negative symptoms	Amisulpride 800 mg, trihexyphenidy 2 mg	Rigidity, tremor, constipation
20	53	Female	25.35	Delusion, hallucination	Amisulpride 800 mg, trihexyphenidy 10 mg	Rigidity, tremor, constipation
21	69	Female	24.65	Negative symptoms	Risperidone 3 mg, chlorpromazine 250 mg, valproate 500 mg, duloxetine 40 mg, oxazepam 30 mg	Constipation, excessive salivation, dry mouth, postural hypotension, blurred vision, impaired glucose tolerance, weight gain
22	41	Male	36.49	Delusion, hallucination	Clozapine 25 mg, risperidone 4 mg, trihexyphenidy 4 mg	Hypocholesterolemia, weight gain
23	38	Female	21.64	Negative symptoms	Clozapine 275 mg, trihexyphenidy 4 mg	Excessive salivation
24	58	Female	n/a	Disorganized speech	Clozapine 300 mg, fluoxetine 40 mg, clonazepam 1 mg,	Constipation

TABLE 1 (Continued)

Case number	Age	Sex	BMI (kg/m^2)	Psychopathological characteristics	Psychotropic medications	Other adverse effects[a]
25	49	Female	21.27	Delusion, hallucination	Clozapine 450 mg, fluoxetine 40 mg, trihexyphenidy 15 mg	Rigidity, tremor
26	43	Male	19.33	Delusion, hallucination	Amisupride 800 mg, clonazepam 3 mg, trihexyphenidy 2 mg	Rigidity, akinesia, dystonia, excessive salivation, oversedation
27	43	Female	23.73	Hallucination, disorganized speech, verbal aggression, physical aggression	Clozapine 200 mg, risperidone 2 mg, trihexyphenidy 2 mg	Tremor, akathisia, constipation, sexual dysfunction, hypercholesterolemia

Abbreviations: BMI, body mass index; QTc, QT interval.
[a]Except QTc prolongation.

binary logistic analyses were performed for discrete variables after adjusting for the potential effects of confounding factors. A binary logistic analysis model, with a forward selection method to avoid multicollinearity, was used to identify the distinctive clinical correlates for QTc prolongation. Statistical significance was set at $P < .01$ (two-tailed) as we aimed to exclude familywise errors due to multiple comparisons. All statistical analyses were conducted using IBM SPSS 24 (IBM Co., Armonk, New York).

3 | RESULTS

As shown in Table 1, the prevalence of QTc prolongation was 1.1% (n = 27) among 2553 Asian patients with schizophrenia. The baseline characteristics (ie, age, sex, body mass index [kg/m^2], psychopathalgical characteristics, psychotropic medications, and other side effects) of schizophrenia patients with QTc prolongation were presented. In addition, as shown in Table 2, participants with QTc prolongation were characterized by a significantly older age ($t = 4.191$, $P < .0001$) and female sex ($\chi^2 = 11.595$, $P = .001$), and a higher proportion of them were inpatients ($\chi^2 = 11.899$, $P = .001$) than those without QTc prolongation. Moreover, participants with QTc prolongation significantly differed from those without QTc prolongation with respect to the distribution of the duration of illness ($\chi^2 = 33.269$, $P < .0001$), regional group ($\chi^2 = 22.517$, $P < .0001$), and income group ($\chi^2 = 26.752$, $P < .0001$). After adjusting for the effect of age, sex, region group, income group, inpatient, and duration of illness for controlling potential effects of confounding factors on the differences in clinical characteristics of the study participants with and without QTc prolongation, those with QTc prolongation were characterized by significantly lower proportions of disorganized speech (adjusted odds ratio [aOR] = 0.290, $P = .029$) and negative symptoms (aOR = 0.345, $P = .025$); higher use of amisulpride (aOR = 4.632, $P = .005$) and clozapine (aOR = 2.974, $P = .010$); and higher proportions of rigidity (aOR = 4.440, $P = .001$), hypercholesterolemia (aOR = 3.699, $P = .005$), and sedation (aOR = 4.955, $P = .005$) than those without QTc prolongation. Although the difference was not statistically significant, the use of antipsychotic polypharmacy was lower in those with QTc prolongation than in those without QTc prolongation (aOR = 0.345, $P = .014$). In addition, between those with and without QTc prolongation, there were no differences in terms of the uses of anticonvulsant (aOR = 0.775, $P = .620$), antidepressant (aOR = 1.226, $P = .720$), anxiolytic (aOR = 0.806, $P = .610$), and antiparkinsonian drugs (aOR = 1.487, $P = .325$).

Finally, as shown in Table 3, initial covariates selected for a binary logistic model included disorganized speech, negative symptoms, amisulpride, clozapine, rigidity, hypercholesterolemia, and sedation, whereas QTc prolongation was defined as a dependent variable. In addition, the potential effects of age, sex, region group, income group, inpatient/outpatient status, and duration of illness on the binary logistic model were controlled. All study participants were included in the binary logistic model. The binary logistic model was validated by the Hosmer–Lemeshow goodness-of-fit test ($\chi^2 = 6.885$, $df = 8$, $P = .549$). As a result of forward selection to avoid multicolinearity, the model explained a 27.9% (Nagelkerke's R^2) variability in QTc prolongation and showed that use of amisulpride (aOR = 5.355, $P = .010$) and clozapine (aOR = 4.652, $P = .004$), rigidity (aOR = 4.926, $P = .004$), and hypercholesterolemia (aOR = 6.000, $P = .001$) were distinctive correlates for QTc prolongation. By contrast, disorganized speech, negative symptoms, and sedation were not significantly related to QTc prolongation.

4 | DISCUSSION

In this study, we report that the prevalence of QTc prolongation in Asian patients with schizophrenia is 1.1% and hypothesize that this prevalence may indicate the necessity of extra clinical attention for patients with schizophrenia, especially those treated with antipsychotics and other psychotropic drugs, and are thus at risk of QTc prolongation. A prospective observational study by Ali et al showed that out of 405 patients who used psychotropic medications for seven or more days and were over 18 years, 23 (5.7%) patients presented with QTc prolongation.[12] A one sample t test of our results and Ali et al's results showed no significant difference in the prevalence rates of the two studies[12] ($t = 1.478$, $P = .379$). In addition, a study by Rettenbacher et al[13] reported no significant differences in QTc intervals or QTc variability between 61 schizophrenia patients and 31

TABLE 2 Clinical characteristics of schizophrenia patients with and without QTc prolongation (n = 2553)

	Total sample (n = 2553)	QTc prolongation		Statistical coefficients	Unadjusted *P*-value	Adjusted *P*-value[a]
		Presence (n = 27)	Absence (n = 2526)			
Baseline characteristics						
Age, mean (SD) years	39.7 (13.1)	51.3 (14.5)	39.6 (13.5)	$t = 4.191$	<.0001	–
Female, n (%)	1070 (41.9)	20 (74.1)	1050 (41.6)	$\chi^2 = 11.595$	.001	–
Body mass index, mean (SD) kg/m^2	23.8 (4.7)	24.9 (3.7)	23.8 (4.6)	$t = 1.148$	.251	.415
Regional group[b]				$\chi^2 = 22.517$	<.0001	–
Eastern Asia, n (%)	826 (32.4)	20 (74.1)	806 (31.9)			
Southeastern Asia, n (%)	1014 (39.7)	6 (22.2)	1008 (39.9)			
Southern Asia, n (%)	713 (27.9)	1 (3.7)	712 (28.2)			
Income group[c]				$\chi^2 = 26.752$	<.0001	–
High income, n (%)	773 (30.3)	20 (74.1)	753 (29.8)			
Upper middle income, n (%)	385 (15.1)	4 (14.8)	281 (15.1)			
Lower middle income, n (%)	1395 (54.6)	3 (11.1)	1392 (55.1)			
Inpatient, n (%)	1539 (60.3)	25 (92.6)	1514 (59.9)	$\chi^2 = 11.899$	.001	–
Duration of illness				$\chi^2 = 33.269$	<.0001	–
<3 months, n (%)	136 (5.3)	0 (0.0)	136 (5.4)			
3-6 months, n (%)	98 (3.8)	1 (3.7)	97 (3.8)			
6-12 months, n (%)	139 (5.4)	0 (0.0)	139 (5.5)			
1-5 years, n (%)	496 (19.4)	1 (3.7)	495 (19.6)			
5-10 years, n (%)	492 (19.3)	2 (7.4)	490 (19.4)			
10-20 years, n (%)	627 (24.6)	5 (18.5)	622 (24.6)			
>20 years, n (%)	565 (22.1)	18 (66.7)	547 (21.7)			
Psychopathological characteristics						
Delusions, n (%)	1207 (47.3)	14 (51.9)	1193 (47.2)	$\chi^2 = 0.229$	0.632	.661
Hallucinations, n (%)	1271 (49.8)	19 (70.4)	1252 (49.6)	$\chi^2 = 4.626$	.031	.160
Disorganized speech, n (%)	824 (32.3)	4 (14.8)	820 (32.5)	$\chi^2 = 3.806$	.051	.029
Catatonic behavior, n (%)	485 (19.0)	3 (11.1)	482 (19.1)	$\chi^2 = 1.103$	.294	.636
Negative symptoms, n (%)	977 (38.3)	7 (25.9)	970 (38.4)	$\chi^2 = 1.760$	.185	.025
Verbal aggression, n (%)	722 (28.3)	4 (14.8)	718 (28.4)	$\chi^2 = 2.440$	.118	.640
Physical aggression, n (%)	609 (23.9)	1 (3.7)	608 (24.1)	$\chi^2 = 6.100$	.014	.155
Psychotropic drug using patterns[d]						
Amisulpride, n (%)	119 (4.7)	5 (23.8)	114 (4.5)	$\chi^2 = 11.792$	.001	.005
Clozapine, n (%)	416 (16.3)	11 (40.7)	405 (16.0)	$\chi^2 = 11.957$	.001	.010
Olanzapine, n (%)	598 (23.4)	5 (18.5)	593 (23.5)	$\chi^2 = 0.366$	.545	.582
Risperidone, n (%)	923 (36.2)	4 (14.8)	919 (36.4)	$\chi^2 = 5.383$	.020	.108
Antipsychotic polypharmacy, n (%)	1023 (40.1)	6 (22.2)	1017 (40.3)	$\chi^2 = 3.620$	.057	.014
Anticonvulsant, n (%)	396 (15.5)	5 (18.5)	396 (15.5)	$\chi^2 = 0.188$	.664	.620
Antidepressant, n (%)	284 (11.1)	4 (14.8)	280 (11.1)	$\chi^2 = 0.376$	.540	.720
Anxiolytic, n (%)	881 (34.5)	11 (40.7)	870 (34.4)	$\chi^2 = 0.469$	.493	.610
Antiparkinson drugs, n (%)	868 (34.0)	13 (48.1)	855 (33.8)	$\chi^2 = 2.435$	.119	.325
Chlorpromazine equivalent, mean (SD)	594.7 (562.6)	579.7 (259.9)	594.9 (625.4)	$t = -0.126$	.900	.445
Imipramine equivalent, mean (SD)	18.5 (89.6)	19.1 (49.8)	18.5 (107.4)	$t = 0.029$	.977	.981
Diazepam equivalent, mean (SD)	10.1 (43.4)	10.8 (18.5)	10.1 (51.0)	$t = 0.072$	.942	.826
Levodopa equivalent, mean (SD)	36.4 (83.8)	56.1 (91.2)	36.2 (71.2)	$t = 1.299$	.194	.694

TABLE 2 (Continued)

	Total sample (n = 2553)	QTc prolongation		Statistical coefficients	Unadjusted *P*-value	Adjusted *P*-value[a]
		Presence (n = 27)	Absence (n = 2526)			
Drug-induced adverse events						
Rigidity, n (%)	322 (12.8)	9 (39.1)	313 (12.5)	$\chi^2 = 14.443$	<.0001	.001
Akinesia, n (%)	182 (7.2)	1 (4.5)	181 (7.3)	$\chi^2 = 0.240$	.624	.989
Tremor, n (%)	469 (18.6)	7 (30.4)	462 (18.5)	$\chi^2 = 2.159$	.142	.679
Akathisia, n (%)	210 (8.3)	3 (13.6)	207 (8.3)	$\chi^2 = 0.814$	.367	.351
Dystonia, n (%)	68 (2.7)	1 (4.5)	67 (2.7)	$\chi^2 = 0.287$	.592	.332
Constipation, n (%)	588 (23.3)	15 (60.0)	573 (23.0)	$\chi^2 = 18.977$	<.0001	.135
Excessive salivation, n (%)	342 (13.6)	4 (16.0)	338 (13.5)	$\chi^2 = 0.129$	.720	.925
Dry mouth, n (%)	400 (15.8)	3 (12.0)	397 (15.9)	$\chi^2 = 0.280$	.596	.651
Postural hypotension, n (%)	109 (4.3)	2 (8.0)	107 (4.3)	$\chi^2 = 0.821$	.365	.392
Dysuria, n (%)	78 (3.1)	2 (8.3)	76 (3.1)	$\chi^2 = 2.196$	.138	.111
Blurred vision, n (%)	149 (5.9)	3 (12.0)	146 (5.9)	$\chi^2 = 1.665$	.197	.374
Sexual dysfunction, n (%)	130 (5.5)	1 (4.2)	129 (5.5)	$\chi^2 = 0.081$	.776	.992
Impaired glucose tolerance, n (%)	138 (5.6)	4 (16.7)	134 (5.5)	$\chi^2 = 5.649$	.017	.783
Hypercholesterolemia, n (%)	192 (7.8)	9 (36.0)	183 (7.5)	$\chi^2 = 27.754$	<.0001	.005
Weight gain, n (%)	280 (11.5)	3 (13.0)	277 (11.5)	$\chi^2 = 0.057$	.812	.222
Sedation, n (%)	255 (10.1)	5 (20.8)	250 (10.0)	$\chi^2 = 3.099$	.078	.005

Abbreviation: QTc, QT interval.
[a]Adjusted for the effects of age, sex, regional group, income group, inpatient, and duration of illness.
[b]Defined by the United Nations classification: Eastern Asia (China, Hong Kong, Japan, Korea, and Taiwan); Southern Asia (Bangladesh, India, Pakistan, and Sri Lanka); and Southeastern Asia (Indonesia, Malaysia, Myanmar, Singapore, Thailand, and Vietnam).
[c]Defined by the World Bank list of economies: high income (Hong Kong, Japan, Korea, Singapore, and Taiwan); upper middle income (China, Malaysia, and Thailand); and lower middle income (Bangladesh, India, Indonesia, Myanmar, Pakistan, Sri Lanka, and Vietnam).
[d]Defined by the Anatomical Therapeutic Chemical (ATC) classification system: antipsychotics (N05A), mood stabilizers (N03A), antidepressants (N06A), anxiolytics (N05B and N05C), and antiparkinsonian drugs (N04).

TABLE 3 Binary logistic model for the distinctive clinical correlates of QTc prolongation (n = 2553)

	B	SE	Wald	Adjusted *P*-value[a]	Adjusted odds ratio[a]	95% confidence interval
Amisulpride	1.676	0.650	6.666	.010	5.355	1.498-19.138
Clozapine	1.537	0.530	8.400	.004	4.652	1.645-13.157
Rigidity	1.595	0.549	8.437	.004	4.926	1.680-14.448
Hypercholesterolemia	1.792	0.522	11.797	.001	6.000	2.158-16.680

Abbreviation: QTc, QT interval.
[a]Adjusted for the effects of age, sex, regional group, income group, inpatient, and duration of illness.

sex- and age- matched healthy controls. It is hypothesized that the prevalence of QTc prolongation may be affected by previously established risk factors, such as the use of certain antipsychotics and newer antidepressants, rather than the psychiatric diagnoses themselves. The known risk factors for torsade de pointes are in line with our findings regarding the increased risk of QTc prolongation due to significantly older age, being female, and increased duration of illness in patients with schizophrenia.[14] In addition, we found that the majority of patients with QTc prolongation were from countries classified as high income. This finding may at first seem counter-intuitive; however, the demographics of participants from high-income countries consisted mainly of elderly, female patients, who were taking amisulpride and clozapine, sometimes in combination with newer antidepressants. The aforementioned clinical characteristics are all known risk factors of QTc prolongation. As such, we hypothesize that these demographic and clinical characteristics influenced the increased incidence of QTc prolongation in participants from high-income countries.

With regard to the psychopathological characteristics, we found that patients with schizophrenia without QTc prolongation are more likely to present with disorganized speech and negative symptoms than those with QTc prolongation. The findings cannot be simply

explained. We hypothesize that this is because of the difference in pharmacological antipsychotic treatment between these two groups. In additional statistical analyses, patients with disorganized speech had significantly higher prescription rates of haloperidol (χ^2 = 39.574; P < .0001) and levopromazine (χ^2 = 28.224; P < .0001), than those without disorganized speech. Meanwhile, those with negative symptoms had significantly higher prescription rates of blonanserin (χ^2 = 16.169; P < .0001), and levopromazine (χ^2 = 11.199; P = .001) than those without negative symptoms. It has been reported that haloperidol, levopromazine, blonaserin, and levopromazine are associated with QTc prolongation.[15] Thus, our hypothesis is that these prescription patterns for antipsychotics may play the role of an intervening variable that results in an inverse correlation between QTc prolongation and disorganized speech/negative symptoms.

We found that a significantly higher of amisulpride was linked to an increased incidence of QTc. This is supported by a meta-analysis by Smith et al,[16] which showed that amisulpride has a greater effect on QTc prolongation than other commonly used antipsychotics. Conversely, Merill et al[17] reported that clozapine cannot be independently associated with QTc prolongation, but rather the combined effects of clozapine and other QTc prolongation-associated risk factors are what may contribute to QTc prolongation. With regard to the patterns of psychotropic drug treatment, we found no significant difference between patients in the QTc prolongation and without QTc prolongation groups. Patients with QTc prolongation tended to use less antipsychotic polypharmacy compared to those without QTc prolongation. However, a systematic review by Takeuchi et al[18] showed that it remains unclear whether antipsychotic polypharmacy worsens QTc prolongation. Thus, despite that, our results between groups are not statistically significant, it indicates that the effect of antipsychotic polypharmacy on QTc requires more research. It is currently hypothesized that the relationship between QTc prolongation and antipsychotic polypharmacy might be affected by combining its effects with other risk factors (ie, psychotropic prescription patterns and other side effects). We found no specific differences between other psychotropic medications and QTc prolongation.

Furthermore, our binary logistic model showed that amisulpride, clozapine, rigidity, and hypercholesterolemia have distinctive correlations with QTc prolongation. A relationship between QTc prolongation and hypercholesterolemia can be partly supported by the following findings: A study by Szabo et al,[19] showed that patients with hyperlipidemia have greater levels of the longest QT interval and QT dispersion. As mentioned earlier, amisulpride is characterized by its greater effects on QTc prolongation compared to other commonly used antipsychotics.[15] Lin et al,[20] reported that clozapine may be one of predictive factors for QTc prolongation in schizophrenia patients treated with antipsychotics. Studies by Merrill et al[17] and Warner et al,[21] reported that the potential effects of clozapine on QTc prolongation may be due to the combined effects of all the possible risk factors associated with clozapine rather than an independent effect on QTc prolongation. Thus, based on our binary logistic model, we hypothesize that clozapine may be distinctively associated with QTc prolongation in terms of its interaction with other psychotropic medications and other adverse effects.

Furthermore, our findings here indicate a possible relationship between QTc prolongation and rigidity. This relationship may be partly explained by the dose–response effects of olanzapine on QT intervals and prolactin levels reported by Suzuki et al.[22]

This study has several limitations. First, the REAP-AP survey was not an epidemiological study in the strictest sense. This is a limitation with respect to the possible generalization or extrapolation of our findings. Second, there was a significant size difference between the two groups—those who presented with QTc prolongation and those who did not present with QTc prolongation—which were compared. This means that the statistical analysis was not robust as it was based on the small number of cases with QTc prolongation (n = 27) and the large sample size of the comparison group (n = 2526) comprising patients who did not show QTc prolongation. Third, although a consensus meeting was held prior to the initiation of our study, the inter-rater reliability for recording of the psychopathological characteristics and the adverse effects were not evaluated. Fourth, in our findings, although the prescribing patterns of psychotropic medications were reported, prescribing periods of psychotropic medications were not evaluated. Thus, it cannot be guaranteed that a potential effect of psychotropic medications on the QTc interval has been incompletely estimated. Fifth, physical diseases of the study subjects were thoroughly evaluated. Thus, the potential effects of the physical disease on QTc prolongation were not evaluated in our study. Further studies on antipsychotics-induced QTc prolongation may be warranted using the detailed information of both prescribing patterns and periods.

In conclusion, despite the limitations, our study revealed that QTc prolongation was prevalent in 1.1% of Asian patients with schizophrenia. The clinical profile of patients with schizophrenia with QTc prolongation was characterized by old age, higher incidence among women, high blood cholesterol levels, lower proportions of disorganized speech and negative symptoms, increased usage of amisulpride and clozapine, and higher proportions of rigidity, and hypercholesterolemia than those without QTc prolongation. Moreover, our binary logistic regression model suggests that amisulpride, clozapine, rigidity, and hypercholesterolemia might be the greatest potential risk factors for QTc prolongation in Asian patients with schizophrenia.

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