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RESEARCH ARTICLE

The impact of adjunctive aripiprazole on QT interval: A 12-week open label study in patients on olanzapine, clozapine or risperidone

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Abstract

Objective: To evaluate the effect of adjunct aripiprazole on QT of patients clinically stabilized on atypical antipsychotics.

Methods: The dataset was from an open-label 12-week prospective trial that evaluated adjunctive use of 5 mg/day of aripiprazole on metabolic profile in patients with schizophrenia, or schizoaffective disorder stabilized on olanzapine, clozapine, or risperidone. Bazett-corrected QT (QTc) was manually calculated from ECGs measured at baseline (before aripiprazole) and week 12, by two doctors blind to the diagnosis and atypical antipsychotic. The change in QTc (ΔQTc: baseline QTc–week 12 QTc) and the number of participants in normal, borderline, prolonged, and pathological groups after 12 weeks were analyzed.

Results: Fifty-five participants, mean age of 39.3 (SD 8.2) years, were analyzed. The ΔQTc after 12 weeks was 5.9 ms ($p = 0.143$) for the whole sample; 16.4 ms ($p = 0.762$), 3.7 ms ($p = 0.480$) and 0.5 ms ($p = 0.449$), for the clozapine, risperidone and olanzapine group, respectively. There was no significant statistical difference comparing the change in QTc overall, and between atypical antipsychotic groups, when evaluating from baseline to endpoint. However, stratifying the sample based on sex-dependent QTc cut-offs showed a 45% decrease in abnormal QTc readings ($p = 0.049$) after aripiprazole initiation; 20 subjects had abnormal QTc at baseline, while only 11 subjects had abnormal QTc at 12 weeks. 25.5% of participants showed a reduction in at least one QTc severity group, while 65.5% had no change and 9.0% worsened in QTc group, after 12 weeks of adjunct aripiprazole.

Conclusion: Low-dose adjunctive aripiprazole did not prolong QTc in patients stabilized on either olanzapine, risperidone, or clozapine. More controlled studies evaluating the QTc effect of adjunctive aripiprazole should be done to confirm and support these findings.

The study was conducted at the Institute of Mental Health, Singapore.

KEYWORDS
adjunctive antipsychotic, aripiprazole, atypical antipsychotics, QT prolongation, schizoaffective, schizophrenia

1 | INTRODUCTION

Drug-induced QT prolongation is associated with a higher risk of cardiac arrhythmias and cardiovascular mortality. Antipsychotic medications are associated with electrocardiogram (ECG) changes, including prolonging the QT interval (Leucht et al., 2013). This is due to effects on the cardiac human ether-a-go-related (hERG) potassium channels (Chohan et al., 2015; Taylor et al., 2021). The QT interval is the time from the start of the Q wave to the end of the T wave, and represents the period of ventricular depolarization and repolarization. The QT interval is inversely proportional to the heart rate. Therefore, the rate-corrected QT interval (QTc) is of more utility as it allows for comparing QT values across different heart rates and time points. A prolonged QTc, defined as >450 milliseconds (ms) for males and >470 ms for females, is associated with a higher risk of potentially fatal cardiac arrhythmias, including Torsade de Pointes (TdP), especially at QTc values of >500 ms (Nachimuthu et al., 2012; Taylor et al., 2021).

Guidelines for the management of prolonged QT include: (1) repeat the ECG and consider reducing the dose or switching to a drug with a lower QTc effect and referring to a cardiologist, or (2) if QTc >500 ms, to repeat ECG, stop the suspected causative drug(s), switch to a drug with lower QTc effect, and immediately refer to a cardiologist (Lambiase et al., 2019; Taylor et al., 2021). Though these steps are crucial to address the risks due to prolonged QT, they might worsen mental state and increase the risk of relapse, particularly if the previous drug effectively treated the psychosis.

Aripiprazole is an atypical antipsychotic medication with a favorable safety profile and tolerability compared to other antipsychotics (Polcwiartek et al., 2015). It has a high affinity for the D2R and D3R dopamine receptor subtypes and multiple serotonergic receptors but a moderate affinity for adrenergic and histaminergic receptors (de Bartolomeis et al., 2015). It also shows lower weight gain and alterations in metabolic profile compared to other atypical antipsychotics and fewer extrapyramidal side effects than typical antipsychotics (Ribeiro et al., 2018). As an adjunct, it has been found to improve the metabolic profile and weight loss in patients on clozapine and reduce cardiometabolic risk in patients on olanzapine (Gupta et al., 2021).

Aripiprazole was previously placed in the "no effect" category on the QTc but is currently classified as having "low effect" due to contradictory data (Taylor et al., 2021). Previous studies have shown aripiprazole having no effect on QTc (Beach et al., 2013; Germanò et al., 2014; Kane et al., 2002; Karz et al., 2015; Leucht et al., 2013; Li et al., 2014; Nelson et al., 2009; Nosè et al., 2016; Potkin et al., 2003; Sarin et al., 2004; Stip & Tourjman, 2010), while others demonstrated a decrease in QTc (Jensen et al., 2015; Kasper et al., 2003; Koller et al., 2021; Marder et al., 2003; Polcwiartek et al., 2015). Studies have also suggested a possible risk of QTc prolongation, and even TdP, with low doses of aripiprazole (Belmonte et al., 2016; Hategan & Bourgeois, 2014; Nelson, 2011; Nelson & Leung, 2013). When used as an adjunct to another antipsychotic, few cases document a QTc prolonging effect (Leo et al., 2008; Suzuki et al., 2011). To date, there is a lack of controlled studies investigating the impact of adjunctive aripiprazole on QTc of patients stabilized on another antipsychotic.

This study examines the effect of 5 mg adjunct aripiprazole on the QTc of patients on atypical antipsychotics, olanzapine, clozapine, and risperidone. The QTc at baseline and 12 weeks post-treatment were compared for any significant changes.

2 | METHODS

2.1 | Study design

This analysis is derived from the dataset of a larger open-label 12-week prospective study that evaluated the effect of adjunct aripiprazole on metabolic profile in patients stabilized on atypical antipsychotics (olanzapine, clozapine, or risperidone). The study was conducted between May 2016 and September 2019 at the outpatient clinic at the Institute of Mental Health (IMH), Singapore. Enrolled participants were prescribed 5 mg aripiprazole per day, in addition to their atypical antipsychotic, for 12 weeks. Medication adherence was monitored by pill counts; participants with more than 75% non-adherence were withdrawn from the study. Safety and tolerability were monitored closely throughout the study. The study was approved by the local ethics committee, National Health Group Domain Specific Review Board (DSRB Ref 2016/00106), written informed consent was obtained at the point of recruitment, the study was registered at ClinicalTrials.gov (identifier: NCT02949752; https://clinicaltrials.gov/ct2/show/NCT02949752?cond=NCT02949752&draw=2&rank=1), and follows the CONSORT guidelines.

2.2 | Participants

Outpatients aged 21–65 years old from the IMH, Singapore, were invited to participate in the study if they fulfilled the following inclusion criteria: (i) diagnosis of schizophrenia or schizoaffective disorder as assessed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), (ii) on stable doses of atypical antipsychotics (olanzapine, clozapine or risperidone for at least 1 month), (iii)

not on more than one of the previously listed atypicals in a single prescription, and (iv) current body mass index (BMI) ≧25 kg/m^2 or ≧7% increase in weight from pre-antipsychotic treatment. The exclusion criteria included the following: (i) previous allergy to aripiprazole/contraindication to use aripiprazole, (ii) current substance misuse (including alcohol but excluding tobacco), (iii) non-adherent with current prescribed medications, (iv) diagnosed with intellectual disability, (v) had any major or unstable medical or neurological illness (such as uncontrolled diabetes and hypertension), (vi) diagnosed with an eating disorder, (vii) pose a serious risk of harm to self or to others, (viii) women who are breastfeeding or pregnant, (ix) diagnosed with severe Personality Disorder, (x) diagnosed with thyroid dysfunction as evidenced by serum thyroid function tests (i.e., thyroid stimulating hormone and free thyroxine levels >10% above or below the limits of the normal range), (xi) using any medication for weight loss within the past 1 month to the study entry, (xii) clinically significant abnormalities in physical examinations, ECG or lab assessments, (xiii) baseline BMI <18.5 kg/m^2.

2.3 | Materials

BMI, heart rate (HR; bpm [beats/min]), and ECGs were measured at baseline (before aripiprazole administration) and week 12. All ECGs were 12-lead resting ECG (25 mm/s paper speed, 10 mm/mV amplitude) and recorded using the Philips PageWriter TC50 ECG machine. QT interval was manually calculated independently by two doctors blinded to the diagnosis and atypical antipsychotic group. The QT interval was obtained by measuring the longest QT interval in lead II, V5, or V6 (Burns & Buttner, 2021; Gueta et al., 2020; Lambiase et al., 2019). The QT interval is defined from the start of the Q wave to the end of the T wave. The end of the T wave was determined by the intercept between the isoelectric line with the tangent drawn through the maximum downslope of the T wave. The manually calculated QT interval was inputted into the "Corrected QT Interval" calculator on the MDCalc application (Sagie et al), which adjusts for HR, using the Bazett formula: QT interval/$\sqrt{}$(RR interval).

The mean Bazett-corrected QT interval (QTc) was obtained between the two independent raters. The change in QTc (ΔQTc) was calculated by subtracting the mean QTc from week 12 from baseline. Additionally, participants were stratified into the following QTc cutoff groups based on several studies (Aman et al., 2002; Croonenberghs et al., 2005; Findling et al., 2008, 2009, 2013; Haas, Delbello et al., 2009; Haas, Eerdekens et al., 2009; Haas, Unis et al., 2009; Jensen et al., 2015; Kent et al., 2013; Reyes, Buitelaar et al., 2006; Reyes, Croonenberghs et al., 2006; Reyes, Olah et al., 2006; Shea et al., 2004; Snyder et al., 2002; Turgay et al., 2002):

- Normal: females: <450 ms, males: <430 ms
- Borderline: females: 451–470 ms, males: 431–450 ms
- Prolonged: females: >470–500 ms, males: >450–500 ms
- Pathological: >500 ms (females and males).

2.4 | Statistical analyses

Descriptive statistics and analyses were conducted using SPSS Version 24.0 (IBM). Intra-class correlation coefficient (ICC) estimates and their 95% confident intervals were calculated based on a mean-rating (k = 2), absolute-agreement, 2-way mixed-effects model. Paired t-test and repeated measures ANOVA with Bonferroni and Tukey correction were used to analyze the change in mean QTc between baseline to week 12 of the whole sample and atypical antipsychotic groups while correcting for age and sex.

McNemar's test was used to analyze the significance between the change in the number of patients in the "Normal" and "Abnormal" QTc group from baseline to week 12. The "Normal" QTc group comprised participants in the normal QTc cutoff group, and the "Abnormal" QTc group comprised participants in the borderline, prolonged and pathological QTc cutoff groups. Analyses were two-tailed, and a p-value <0.05 was considered significant.

3 | RESULTS

The final sample consisted of 55 participants, as demonstrated in Figure 1. Sixty-seven patients were screened; 55 were included in the final analyses. 18 were on olanzapine, 23 were on risperidone, and 14 were on clozapine.

The clinical and demographic characteristics of participants are shown in Table 1. The participants ranged from 25 to 54 years old, with a mean (SD) age of 39.3 (8.2). The mean (SD, range) dosage of risperidone was 3.2 mg/day (1.6 mg, 0.5–6.0 mg). The mean (SD, range) dosage of olanzapine was 11.9 mg/day (5.7 mg, 5.0–20.0 mg). The mean (SD, range) dosage of clozapine was 292.9 mg/day (115.8 mg, 125.0–500.0 mg).

The ICC for the QT interval between the two raters was 0.951 (confidence interval [CI] 0.931–0.966), indicating excellent inter-rater reliability. At baseline, the mean (SD) HR was 76 (13), and QTc was 427.3 (32.7). At week 12, the mean (SD) HR was 77 (15), and QTc was 421.4 (29.3). The ΔQTc was 5.9 (p = 0.143 corrected for age and sex). Table 2 illustrates the mean QTc at baseline and week 12, and change in QTc between males and females.

At baseline, the mean (SD) QTc and HR of those in the olanzapine group were 418.9 (28.1) and 70 (9), respectively. At week 12, the mean (SD) QTc and HR was 418.3 (26.1) and 70 (10), respectively, and ΔQTc was 0.5 (p = 0.449). At baseline, the mean (SD) QTc and HR of those in the risperidone group was 428.8 (31.3) and 72 (8), respectively. At week 12, the mean (SD) QTc and HR was 425.0 (33.5) and 77 (14), and ΔQTc was 3.7 (p = 0.480). At baseline, the mean (SD) QTc and HR of those in the clozapine group was 435.8 (39.6) and 72 (8), respectively. At week 12, the mean (SD) QTc and HR was 419.5 (27.4) and 77 (13), respectively, and ΔQTc was 16.4 (p = 0.762). There was no significant statistical difference comparing the change in QTc from baseline to 12 between atypical antipsychotic groups.

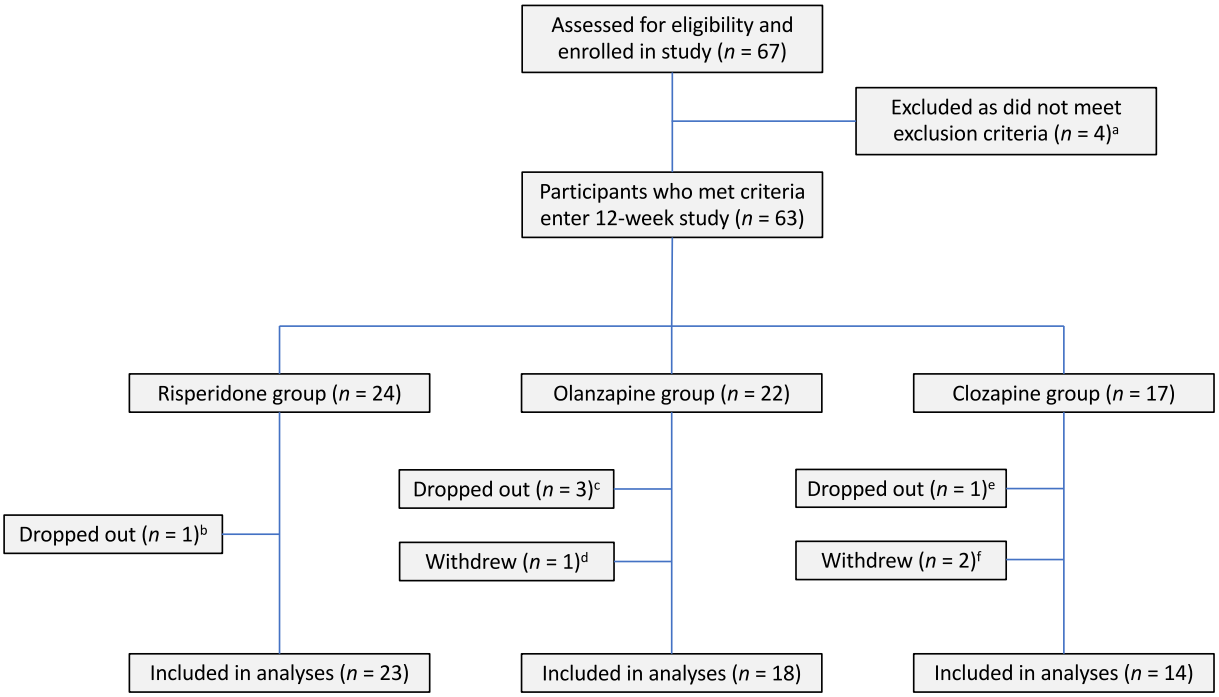

FIGURE 1 Flow of participants. [a]Excluded due to abnormal baseline blood results; [b]Dropped out due to increased anxiety; [c]Dropped out due to loss to follow up ($n = 1$) and at request ($n = 2$); [d]Withdrawn due to mental state deterioration; [e]Dropped out at request; [f]Withdrawn due to inpatient admission ($n = 1$) and social issues ($n = 1$).

There was a significant difference in the frequency of patients in the "normal" and "abnormal" QTc groups at week 12 versus baseline ($p = 0.049$), as demonstrated in Table 3 and Figure 2. Figure 3 indicates that while 14 patients improved, five patients worsened, and 36 patients had no change within QTc cutoff grouping after 12 weeks of adjunctive aripiprazole. None of the participants developed an increase in QTc up to 60 ms or ≥25% increase in QTc from baseline to post-treatment.

4 | DISCUSSION

The present study examined the impact of adjunctive aripiprazole on QTc. There was a non-significant trend toward a reduction in the QTc after 12 weeks of adjunctive aripiprazole when evaluating the QTc from baseline to endpoint. However, stratifying the sample based on sex-dependent QTc cutoffs showed a 45% decrease in abnormal QTc readings ($p = 0.049$); 20 subjects had abnormal QTc at baseline, while only 11 subjects had abnormal QTc at 12 weeks (Figure 2). Interestingly, 25.5% of participants showed a reduction in at least one severity group after aripiprazole initiation, that is, prolonged to borderline or borderline to normal, while 65.5% had no change and 9.0% worsened in QTc group (Figure 3). This discrepancy from the initial analysis could be because sex-dependent QTc cutoffs were used to stratify participants into normal, borderline, and prolonged QTc groups (Takeuchi et al., 2015)—this dataset dimension was not applicable to the paired *t*-test or repeated measures ANOVA.

The improvement in QTc in several patients from our study warrants further exploration of the pharmacokinetics between aripiprazole and atypical antipsychotics and how these combinations may, directly and indirectly, affect QTc, and, more specifically, the hERG potassium channels. We hypothesize three possibilities for the reduction in QTc: (1) aripiprazole's overall hERG-blocking properties causes a QTc reduction, (2) aripiprazole outcompetes another existing atypical antipsychotic in binding to hERG potassium channels, leading to a relatively less "QTc prolonging effect" than if the atypical antipsychotic was present alone. Aripiprazole has been found to have a relatively lower selectivity for (Kongsamut et al., 2002; Otsuka Pharmaceutical, 2014) and lower potency inhibitory effects on (Huang et al., 2010) the hERG potassium channel compared to other antipsychotics. (3) the presence of aripiprazole in the serum leads to a reduction in the concentration of another atypical antipsychotic—although there is a lack of pharmacokinetic studies to support this currently, there is an overlap in metabolic pathways and interaction between aripiprazole and atypical antipsychotics (Jiang et al., 2021; Waade et al., 2009); unfortunately, the study designs did not include measuring serum levels of the atypical antipsychotics when co-medicated with aripiprazole. In a study identifying clinically relevant cytochrome P450-mediated drug-drug interactions involving antipsychotics among 10,001 elderly patients with behavioral and psychological symptoms of dementia, aripiprazole (high-affinity substrate) was found to cause higher rates of CYP2D6-mediated drug interactions (perpetrator drug 94.6% of the time) compared to risperidone (moderate-affinity substrate; perpetrator

TABLE 1 Clinical and demographic characteristics of participants.

	Overall sample ($n = 55$) n (%)	Olanzapine ($n = 18$) n (%)	Risperidone ($n = 23$) n (%)	Clozapine ($n = 14$) n (%)
Age, mean [SD]	39.3 [8.2]	37.7 [6.8]	43.8 [7.7]	33.9 [6.6]
Sex				
Female	28 (50.9)	11 (61.1)	11 (47.8)	6 (42.9)
Male	27 (49.1)	7 (38.9)	12 (52.2)	8 (57.1)
Ethnicity				
Chinese	39 (70.9)	13 (72.2)	13 (56.5)	13 (92.9)
Malay	11 (20.0)	3 (16.7)	8 (34.8)	0 (0.0)
Indian	4 (7.3)	1 (5.6)	2 (8.7)	1 (7.1)
Others	1 (1.8)	1 (5.6)	0 (0.0)	0 (0.0)
BMI (kg/m^2), mean [SD]	31.2 [4.2]	30.2 [4.2]	32.1 [4.7]	31.0 [3.1]
Metabolic comorbidities				
Diabetes mellitus	4 (7.3)	0 (0.0)	4 (17.4)	0 (0.0)
Dyslipidemia	34 (6.8)	11 (61.1)	14 (60.9)	9 (64.3)
Diagnosis				
Schizophrenia	45 (81.8)	13 (72.2)	19 (82.6)	14 (100.0)
Schizoaffective disorder	9 (16.4)	5 (27.8)	4 (17.4)	0 (0.0)
Dosage (mg/day), mean [SD]	-	11.9 [5.7]	3.2 [1.6]	292.9 [115.8]
Relevant chronic medications				
Cardiovascular agents	5 (9.1)	1 (5.6)	3 (23.0)	1 (7.1)
Atenolol	1 (1.8)	0 (0.0)	0 (0.0)	1 (7.1)
Propanolol	3 (5.5)	1 (5.6)	2 (8.7)	0 (0.0)
Amlodipine	1 (1.8)	0 (0.0)	1 (4.3)	0 (0.0)
Sodium valproate	9 (16.4)	3 (16.7)	3 (13)	3 (21.4)
SSRI/TCA/SNRI	30 (54.5)	10 (55.6)	20 (43.5)	10 (71.4)
Fluoxetine	9 (16.4)	2 (11.1)	1 (4.3)	6 (42.9)
Escitalopram	5 (9.1)	3 (16.7)	2 (8.7)	0 (0.0)
Fluvoxamine	12 (21.8)	5 (27.8)	6 (26.1)	1 (7.1)
Setraline	1 (1.8)	0 (0.0)	0 (0.0)	1 (7.1)
Dothiepin and Fluoxetine	1 (1.8)	0 (0.0)	1 (4.3)	0 (0.0)
Clomipramine	1 (1.8)	0 (0.0)	0 (0.0)	1 (7.1)
Venlafaxine	1 (1.8)	0 (0.0)	0 (0.0)	1 (7.1)
Antipsychotic depot	21 (38.4)	8 (44.4)	13 (56.5)	0 (0.0)
Flupenthixol decanoate	19 (34.5)	7 (38.9)	12 (52.2)	0 (0.0)
Clopixol	2 (3.6)	1 (5.6)	1 (4.3)	0 (0.0)
Baseline QTc				
Normal	35 (63.6)	14 (77.8)	14 (60.9)	7 (50.0)
Borderline	10 (18.2)	3 (16.7)	4 (17.4)	3 (21.4)
Prolonged	10 (18.2)	1 (5.6)	5 (21.7)	4 (28.6)
Pathological	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: BMI, body mass index; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, serotonin reuptake inhibitors; TCA, tricyclic antidepressant.

TABLE 2 Mean QTc at baseline and week 12 and paired *t*-test for change in mean QTc for males ($n = 27$) and females ($n = 28$), corrected for age.

					95% CI				
		HR (SD)	Mean QTc (SD)	SE	Upper	Lower	*t*	*df*	*p*-Value
Males ($n = 27$)	Baseline	76 (12)	420 (28.1)	5.4	-	-	-	-	-
	Week 12	76 (13)	408.3 (23.4)	4.5	-	-	-	-	-
	ΔQTc	-	11.6 (26.7)	5.1	1.1	22.2	2.264	26	0.245
Females ($n = 28$)	Baseline	77 (15)	434.4 (35.6)	6.7	-	-	-	-	-
	Week 12	79 (18)	434.1 (29.3)	5.5	-	-	-	-	-
	ΔQTc	-	0.4 (30.2)	5.7	−11.4	12.1	0.063	27	0.968

Abbreviations: ΔQTc, change in QTc; 95% CI, 95% confidence interval; df, degrees of freedom; HR, heart rate; SD, standard deviation; SE, standard error; t, t-statistic.

TABLE 3 Frequency of patients in different QTc cutoff groups at baseline and week 12 ($n = 55$).

QTc group	Baseline *n* (%)	Week 12 *n* (%)
Normal	35 (63.6)	44 (80.0)
Borderline	10 (18.2)	9 (16.4)
Prolonged	10 (18.2)	1 (1.8)
Pathological	0 (0)	1 (1.8)

drug 78.8% of time) (Matos et al., 2020). If taken concomitantly, aripiprazole would be expected to competitively inhibit risperidone's metabolism by preferentially binding to CYP2D6, possibly leading to increased plasma concentration of risperidone. More studies analyzing the pharmacokinetic interaction between aripiprazole and atypical antipsychotics is needed to confirm such hypotheses.

A possible reason for the non-significant QTc effect when evaluating the QTc from baseline to endpoint is that an adjunctive dose of 5 mg might be too small to demonstrate significant observable differences. Aripiprazole significantly decreased QTc, compared to placebo in a dose-dependent manner, in a meta-analysis investigating QTc changes of antipsychotic treatment in 5423 youth <18 years (Jensen et al., 2015). Another meta-analysis of randomized multicenter placebo-controlled trials investigating the effect of aripiprazole in 932 adults with schizophrenia found that up to 30 mg/day of aripiprazole significantly decreased QTc compared to baseline (Marder et al., 2003). A 52-week double-blind, multicenter randomized controlled trial (RCT) evaluating the long-term efficacy and safety of 30 mg/day of aripiprazole in 1294 adult patients with chronic schizophrenia showed a significant decrease in QTc as well (Kasper et al., 2003). An RCT evaluating the safety and cardiovascular effects of aripiprazole versus olanzapine showed that 10 mg of aripiprazole significantly decreased QTc over 5 days (Koller et al., 2021). However, some studies showed no significant difference in QTc when aripiprazole was used as monotherapy (Beach et al., 2013; Germanò et al., 2014; Kane et al., 2002; Karz et al., 2015; Leucht et al., 2013; Li et al., 2014; Nosè et al., 2016; Potkin et al., 2003; Sarin et al., 2004; Stip & Tourjman, 2010). A large multicenter 6-week RCT using up to 20 mg/day of aripiprazole adjunctive to antidepressants for adults with major depressive disorder found no significant QTc effect (Nelson et al., 2009). Thus, future studies evaluating the effect of adjunctive aripiprazole on QTc should aim to increase the study duration and the adjunctive dose to maximize potential observable differences.

One participant in our study had an increase in QTc from 479 ms at baseline to 507 ms at week 12. Upon examining the case, it was concluded that the increase in QTc was likely due to the concomitant prescription of antibiotics and an increase in other potential QT-prolonging medications. Nonetheless, she was urgently referred to an acute care hospital, where her subsequent QTc readings reduced to normal range. A QTc-prolonging effect of aripiprazole monotherapy has been demonstrated in a study of healthy volunteers (Belmonte et al., 2016) and a few case studies (Hategan & Bourgeois, 2014; Nelson, 2011). In both case studies, the patients were taking non-psychotropic medications that may have confounded the etiology of QTc prolongation (Lee et al., 2004), admitted for intensive care, or had medical comorbidities that could predispose QTc effects. Similarly, in a case study of a 30-year-old male on 6 mg/day risperidone cross-titrating to aripiprazole, increasing aripiprazole from 18 mg/day up to 30 mg/day increased QTc in a dose-dependent manner (Suzuki et al., 2011). Few case reports document a QTc prolonging effect of aripiprazole when co-administered with another antipsychotic—when aripiprazole was added onto risperidone (Suzuki et al., 2011) and haloperidol was added to aripiprazole (Leo et al., 2008). There is a lack of controlled studies evaluating QTc in the co-administration of aripiprazole with another antipsychotic. Further research to evaluate the pharmacodynamics and pharmacokinetics of aripiprazole with different antipsychotics will help optimize therapeutic efficacy and safety when prescribing adjunctive antipsychotic treatment.

Although statistically non-significant, it is interesting to note that the study's clozapine group had the largest reduction in QTc (ΔQTc = 16.4 ms), followed by risperidone (ΔQTc = 3.7 ms) and olanzapine (ΔQTc = 0.5 ms). Differences in the magnitude of ΔQTc between antipsychotic groups are possibly due to pharmacokinetic

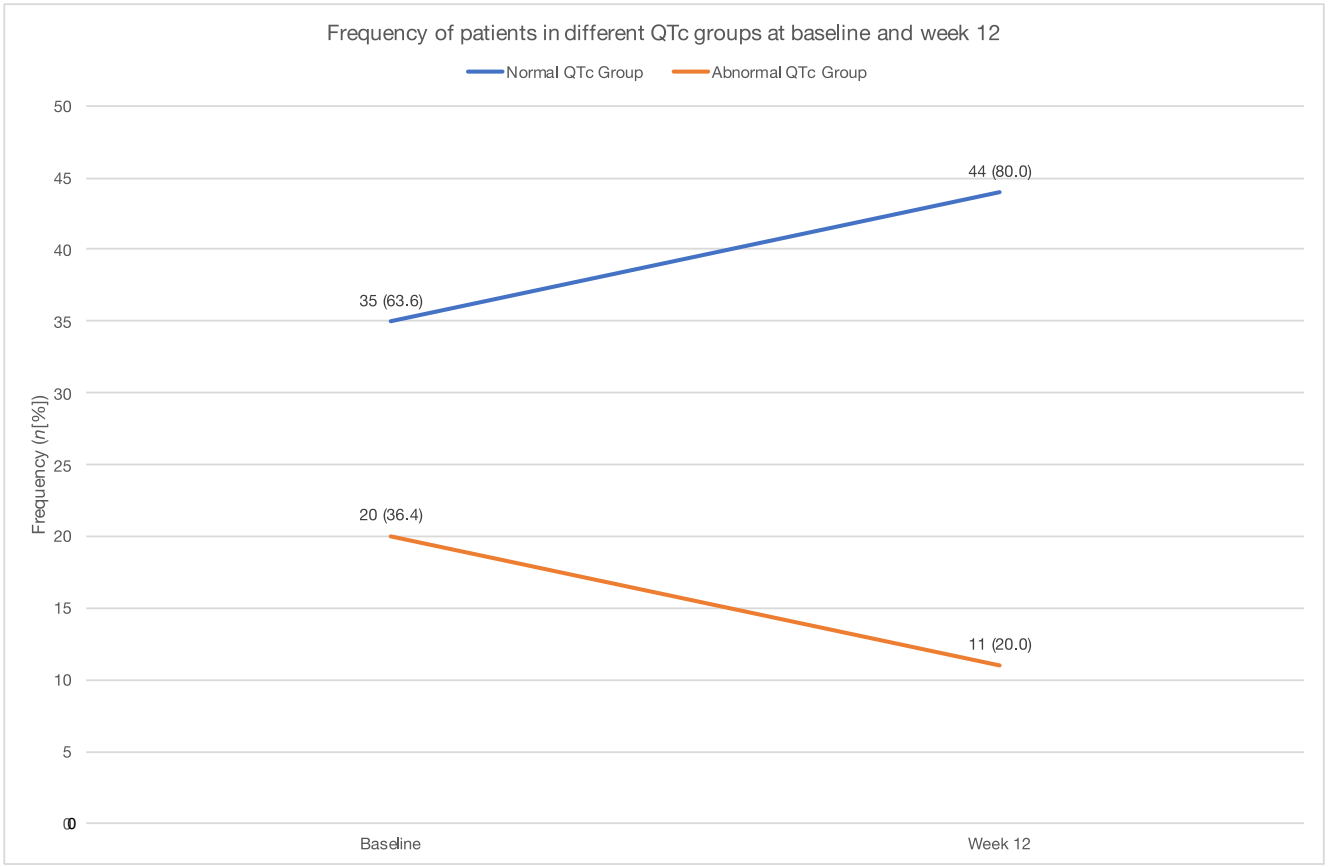

FIGURE 2 Frequency of patients in different QTc groups at baseline and week 12 ($n = 55$; $p = 0.049$, corrected for age and sex). Normal QTc group: females <450 ms, males <430 ms; Abnormal QTc group: females 451 ms and above, males 431 ms and above.

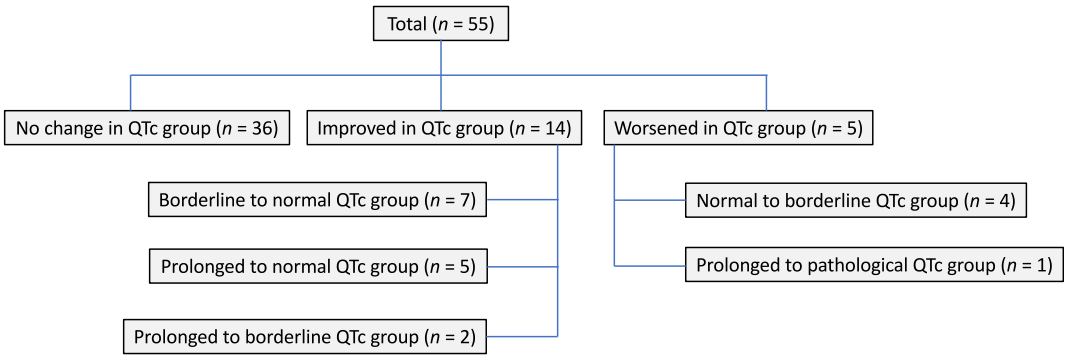

FIGURE 3 Frequency of patients with improved, worsened, or no change in QTc cutoff group after 12 weeks of adjunctive aripiprazole.

interactions (Baumgartner et al., 1996; Nosè et al., 2016; Spina & de Leon, 2007; Taylor et al., 2021). Clozapine is known to prolong the QTc via direct and indirect inhibition of hERG potassium channels in a dose-dependent fashion (Kim et al., 2018; Lee et al., 2006). Serotonin Reuptake Inhibitors (SSRIs), such as fluoxetine, increase serum aripiprazole by 45% via inhibition of its major metabolizers, CYP2D6 and CYP3A4 (Aripiprazole, 2016; Singh et al., 2015; Spina & de Leon, 2014). Comparatively greater ΔQTc in the clozapine group could be due to relatively more patients (71.4%) taking concurrent SSRIs/Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)/Tricyclic Antidepressants (TCA), which increase serum aripiprazole via metabolic inhibition, than in the olanzapine (55.6%) and risperidone (43.5%) group. The higher levels of serum aripiprazole from reduced clearance could possibly outcompete and displace serum clozapine, in a dose-dependent manner, from binding to hERG potassium channels, leading to less QTc prolonging effects overall in the clozapine group.

Polypharmacy is not recommended by current treatment guidelines, however it is commonplace in clinical practice. A systematic review (Takeuchi et al., 2015), examining the increased risk of QTc prolongation with use of polypharmacy, concluded that current evidence fails to confirm that polypharmacy leads to worsening

of QTc prolongation. The review advises exercising caution in the use of polypharmacy, specifically pointing that a combination of QTc prolonging antipsychotics may prolong QTc. Based on the findings of this review, and our own study finding, we can cautiously conclude that adding low dose aripiprazole to atypical antipsychotics, is probably safe from a QTc prolongation perspective.

A limitation of the study is that we did not correct for other confounding factors, such as polypharmacy, pre-existing cardiac/renal disease, or substance abuse. Many of our patients had concurrent medications of varied drug classes (cardiovascular agents, mood stabilizers, antidepressants, first generation antipsychotics, oral hyperglycemic agents). It is unlikely that the concurrent medications, including coexisting psychotropics, directly impacted the QTc change as the doses remained the same throughout the study.

Electrolyte derangements (hypokalemia, hypocalcemia, and hypomagnesemia) and genetic polymorphisms of cardiac ion channels, which can resemble congenital long QT syndromes (Hommers et al., 2021; Spellmann et al., 2018), can also affect cardiac ion channel conductance and QTc. Ideally, studies that impose stringent exclusion criteria may be best to address possible confounders, such as concurrent medications, pre-existing cardiac and renal disease, electrolyte disturbances, and genetic polymorphisms involved in cardiac ion channel conductance; however, stratification and statistically correcting for these factors in a larger sample size may be more feasible.

5 | CONCLUSION

Aripiprazole is known to be one of the least QTc-interfering antipsychotics. Although the primary study was carried out to evaluate the impact of adjunctive aripiprazole on weight and metabolic side effects of atypical antipsychotics (Gupta et al., 2021), this study shows that adjunctive aripiprazole did not result in an increase of QTc in patients stabilized on atypical antipsychotics (olanzapine, risperidone, and clozapine). In fact, we note, interestingly, an improvement in QTc in several patients, which warrants further studies. Hence, more controlled studies evaluating the QTc effect of adjunctive aripiprazole in patients on different antipsychotics should be done to confirm and support these findings. This could also help determine the optimal combination of antipsychotics with a favorable safety and tolerability profile.

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CONFLICT OF INTEREST STATEMENT

No conflicts of interest have been declared.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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