Original Article

Effects of atypical antipsychotic drugs on QT interval in patients with mental disorders

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Contributions: (I) Conception and design: All authors; (II) Administrative support: TA Shamliyan; (III) Provision of study materials or patients: TA Shamliyan; (IV) Collection and assembly of data: TA Shamliyan; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Background: Drug-induced QT prolongation is associated with higher risk of cardiac arrhythmias and cardiovascular mortality. We investigated the effects of atypical antipsychotic drugs on QT interval in children and adults with mental disorders.

Methods: We conducted random-effects direct frequentist meta-analyses of aggregate data from randomized controlled trials (RCT) and appraised the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Our search in PubMed, EMBASE, the Cochrane Library, clinicaltrials.gov, and PharmaPendium up to October 2017 identified studies that examined aripiprazole, quetiapine, risperidone, olanzapine, ziprasidone and brexpiprazole.

Results: Low quality evidence suggests that aripiprazole (four meta-analyses and twelve RCTs), brexpiprazole (one systematic review and four RCTs) or olanzapine (five meta-analyses and twenty RCTs) do not increase QT interval. Low quality evidence suggests that ziprasidone (five meta-analyses and 11 RCTs) increases QT interval and the rates of QT prolongation while risperidone (four meta-analyses, 70 RCTs) and quetiapine (two meta-analyses and seven RCTs) are associated with QT prolongation and greater odds of torsades de pointes ventricular tachycardia especially in cases of drug overdose.

Conclusions: The main conclusion of our study is that in people with mental disorders and under treatment with atypical antipsychotic drugs, in order to avoid QT prolongation and reduce the risk of ventricular tachycardia clinicians may recommend aripiprazole, brexpiprazole or olanzapine in licensed doses. Long-term comparative safety needs to be established.

Keywords: Quality of evidence; cardiovascular morbidity; drug-induced QT prolongation; aripiprazole; quetiapine; risperidone; olanzapine; ziprasidone; brexpiprazole

Submitted Nov 24, 2017. Accepted for publication Mar 07, 2018.
doi: 10.21037/atm.2018.03.17
View this article at: http://dx.doi.org/10.21037/atm.2018.03.17

Introduction

Observational studies provide consistent evidence that prolonged QT interval is associated with higher risk of all-cause and cardiovascular mortality (1). Drug-induced prolongation of QT contributes to higher mortality (2,3). The risk of drug-induced prolongation of QT is much higher in older adults and people with multiple chronic conditions (4). Psychotropic drugs including atypical antipsychotic agents are commonly prescribed for licensed and off-label indications and may contribute to the higher risk of drug-induced QT prolongation (5,6). This rapid

review focuses on the effects of atypical antipsychotic drugs on QT interval in children and adults with mental disorders.

Methods

We used a standard recommended methodology in conducting systematic literature reviews and meta-analyses from the Cochrane Collaboration and the Agency for Healthcare Research and Quality (7,8). We developed a priori protocol for a systematic literature review to answer the clinical question about the safety of atypical antipsychotic drugs on QT interval in children and adults with mental disorders.

We defined the target population as people with mental disorders treated with atypical antipsychotic drugs. Eligible interventions included atypical antipsychotics when compared with placebo or other antipsychotic medications. Eligible outcomes included change in QT Interval, clinically important prolongation of QT corrected to RR interval ≥450 msec in men ≥480 msec in women, and QTc ≥500 msec associated with increased risk of life-threatening torsades de pointes ventricular tachycardia (9).

We conducted a comprehensive search in PubMed, EMBASE, the Cochrane Library, www.clinicaltrials.gov and PharmaPendium (www.pharmapendium.com) up to October 2017 to find systematic reviews, published and unpublished RCTs, and nationally represented controlled observational studies that reported adjusted effect estimates (7,8). All of the authors determined the studies' eligibility. All citations found during the searches are stored in a reference database.

The data was extracted from the Clinical Trials Transformation Initiative (CTTI) (https://www.ctti-clinicaltrials.org/aact-database), checked for quality, and stored in the HPCC platform (High-Performance Computing Cluster, https://hpccsystems.com/).

We performed direct frequentist meta-analyses of aggregate data when definitions of the active and control intervention and patient outcomes were deemed similar for pooling (10). We used random effects models to address inevitable differences in patient characteristics across primary RCTs. For each abstracted hypothesis, we calculated absolute risk difference and relative risk with 95% CI. We calculated number needed to treat and number of attributable events per 1,000 treated with 95% CI based on statistically significant differences in absolute risks of the outcomes. We examined consistency in results across studies with chi-square tests and I^2 statistics and concluded statistically significant heterogeneity if I^2 was >50% (7). Statistically significant heterogeneity did not preclude statistical pooling (10). However, we planned exploring heterogeneity with a priori defined patient characteristics, drug doses, and study quality if this information was available in the studies (10).

We used consensus method guidelines for systematic review and meta-analyses that do not recommend conducting post hoc analyses of statistical power (11-14). Instead, we downgraded our confidence in true treatment effects based on calculated optimal information size as the number of patients required for an adequately powered individual trial (15). Since power is more closely related to number of events than to sample size, we concluded imprecision in treatment effects if fewer than 250 patients experienced the event (15).

We used Statistics/Data Analysis, STATA software (StataCorp LP, College Station, Texas). Statistical significance was evaluated at a 95% confidence level.

We evaluated the quality of systematic reviews using the Assessment of Multiple Systematic Reviews (AMSTAR) (16). For primary RCTs, we used the Cochrane risk of bias tool on a 3-point scale: high bias, low bias, and unclear (17,18). A low risk of bias was assumed when RCTs met all the risk-of-bias criteria, a medium risk of bias if at least 1 of the risk-of-bias criteria was not met, and a high risk of bias if two or more risk-of-bias criteria were not met. An unknown risk of bias was assigned for the studies with poorly reported risk-of-bias criteria. We assigned high risk of bias to all observational studies.

The authors assigned the quality of evidence ratings as high, moderate, low, or very low, according to risk of bias in the body of evidence, directness of comparisons, precision and consistency in treatment effects, and the evidence of reporting bias, using Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology (19).

A high quality of evidence was assigned to well-designed RCTs with consistent findings. The quality of evidence was downgraded to moderate if at least 1 of 4 quality of evidence criteria was not met; for example, moderate quality of evidence was assigned if there was a high risk of bias in the body of evidence or if the results were not consistent or precise. The quality of evidence was downgraded to low if two or more criteria were not met. We concluded a high risk of bias in the body of evidence if at least one RCT had high risk of bias. We downgraded the quality of evidence

when we suspected high risk of publication bias due to unavailability of the results in clinicaltrials.gov or journal articles.

A low quality of evidence was assigned to nonrandomized studies, but the rating was upgraded if there was a strong or dose-response association (20). Evidence was defined as insufficient when no studies provided valid information about treatment effects. This approach was applied regardless of whether the results were statistically significant.

Results

Our comprehensive search in PubMed, EMBASE, the Cochrane Library, and clinicaltrials.gov up to May 2017 identified clinical studies that examined aripiprazole, quetiapine, risperidone, olanzapine, ziprasidone or brexpiprazole.

Risperidone was examined in three systematic reviews and meta-analyses, one individual patient data network meta-analysis of 64 RCTs, published and unpublished data from six RCTs and six non-randomized studies (21-40).

Evidence suggests that risperidone is associated with QT prolongation in children and adolescents with mental disorders (*Table 1*).

A single industry-sponsored individual patient meta-analysis of 64 RCTs suggests that risperidone results in QT prolongation when compared with placebo in adults with mental disorders (*Table 1*). The evidence from the FDA Adverse Event Reporting System database suggests that risperidone is associated with greater odds of torsades de pointes ventricular tachycardia in adults with indication for antipsychotics (*Table 1*). Industry—sponsored post-marketing analysis suggests that all cases of ventricular tachycardia have been associated with overdose of risperidone (41).

The direct evidence of comparative safety between risperidone and other antipsychotics is sparse. Risperidone is associated with QT abnormalities when compared with aripiprazole in pediatric patients with mental disorders and concomitant use of stimulants (*Table 2*). Some evidence suggests that there are no differences in QT abnormalities or rates of torsades de pointes between risperidone and atypical antipsychotics or haloperidol in adults with mental disorders (*Table 2*). A single RCT suggests that risperidone decreases QT interval when compared with ziprasidone (*Table 2*).

Post-marketing surveillance suggests 43 cases of prolonged QT intervals and 71 cases of torsades de pointes tachycardia in people treated with risperidone among other medications for various mental disorders (*Table S1*).

Ziprasidone was examined in four systematic reviews and meta-analyses, one industry sponsored individual patient data network meta-analysis and published and unpublished data from 11 RCTs and three non-randomized trials (30,35,37,38,42-56).

Evidence suggests that ziprasidone increases QT interval and the rates of QT prolongation by >30 msec when compared with placebo (*Table 3*) or haloperidol (*Table 4*) in people with mental disorders. Ziprasidone also prolongs QT interval when compared with olanzapine and risperidone (*Table 5*). There are no differences in the length of QT interval after treatment with ziprasidone versus aripiprazole (*Table 5*). Chlorpromazine increases the duration of QT interval when compared with ziprasidone (*Table 5*).

Available studies did not report the rates of torsade de pointes ventricular tachycardia in adults treated with ziprasidone. Post-marketing observational study suggested no differences in mortality after 1-year treatments with ziprasidone versus olanzapine in 18,154 adults with schizophrenia (*Table S2*). Post-marketing surveillance identified 202 cases of prolonged QT interval and 83 cases of torsade de pointes in patients treated with ziprasidone among other drugs (*Table S1*).

The evidence is applicable mostly to adults. Pediatric studies reported no events of QT prolongation after higher (160 mg/day) or lower (20 mg/d titrated to between 80 mg/day) doses on ziprasidone (37,42).

Olanzapine was examined in four systematic reviews and meta-analyses and one individual patient data network meta-analysis. (35,37,38,57,58). We also identified published and unpublished data from 20 RCTs and 1 non-randomized trial (30,43,59-79).

Available low-quality evidence suggests that olanzapine has no effect on QT interval when compared with placebo in children and adolescents with mental disorders (*Table 6*). We also found that that oral olanzapine has no effect on QT interval while intramuscular olanzapine decreases QT interval when compared with placebo in adults with mental disorders (*Table 6*).

A single small RCT suggests that there are no differences in QT interval between olanzapine and haloperidol in children and adolescents with autistic disorder (*Table 7*). Moderate quality evidence suggests that there are no differences in QT interval between olanzapine and

Table 1 Risperidone versus placebo on QT interval in people with mental disorders

Outcome	Risk with intervention per 1,000	Risk with comparator per 1,000	Relative measure of association	Number of participants (studies)	Quality (GRADE)	Comments[†]
Risperidone in children and adolescents						
QTc change	NR	NR	MD 0.38 (–1.50, 2.26); SMD 0.02 (–0.06, 0.09)	3,196 (23 studies) (35)	Low	No difference
QT prolongation	0	0	RR Undetermined	335 (1 RCT) (31,32,36,37)	Very low	No difference
QT prolongation	NR	NR	Adjusted OR 1.96 (1.02, 2.90)	3,472,494 [1 observational study of FDA Adverse Event Reporting System (FAERS)] (25)	Very low	Favors control (no risperidone)
QTc prolongation	NR	NR	Adjusted RR 1.19 (0.94, 1.51)	1,006 (1 observational study) (22)	Very low	No difference
Risperidone higher (1.5–6.0 mg/day) versus lower (0.15–0.6 mg/day) dose in adolescents with schizophrenia						
QTcLD >60 msec	0	0	RR undetermined	257 (1 RCT) (31,32,36,37)	Very low	No difference
Risperidone in adults						
Change in QT 30–60 msec	137	118	RR 1.16 (0.98, 1.37)	4,027 (64 RCTs) (21)	Moderate	No difference
Change in QT 30–60 msec; subgroup: age <30 yrs	103	50; attributable events per 1,000 treated 53 [24, 82]	RR 2.07 (1.33, 3.21); NNT 19 (12, 42)	1,215 (64 RCTs) (21)	Low	Favors placebo
Change in QT 30–60 msec; subgroup: age 30–74 yrs	143	152	RR 0.94 (0.75, 1.19)	1,807 (64 RCTs) (21)	Low	No difference
Change in QT 30–60 msec; subgroup: age >74 yrs	162	149	RR 1.09 (0.81, 1.47)	1,005 (64 RCTs) (21)	Low	No difference
Change in > 60 msec	23	22	RR 1.06 (0.70, 1.61)	4,027 (64 RCTs) (21)	Low	No difference
Change in >60 msec; subgroup: age <30 yrs	8	10	RR 0.85 (0.26, 2.77)	1,215 (64 RCTs) (21)	Low	No difference
Change in >60 msec; subgroup: age 30–74 yrs	23	15	RR 1.49 (0.72, 3.06)	1,807 (64 RCTs) (21)	Low	No difference
Change in >60 msec; subgroup: age >74 yrs	42	50	RR 0.84 (0.47, 1.50)	1,005 (64 RCTs) (21)	Low	No difference
Change in > 60 msec and ≥500 msec	1	1	RR 0.62 (0.09, 4.41)	4,027 (64 RCTs) (21)	Low	No difference

Table 1 (*continued*)

Table 1 (*continued*)

Outcome	Risk with intervention per 1,000	Risk with comparator per 1,000	Relative measure of association	Number of participants (studies)	Quality (GRADE)	Comments[†]
Change in >60 msec and ≥500 msec; subgroup: age <30 yrs	0	0	RR undetermined	1,215 (64 RCTs) (21)	Low	No difference
Change in >60 msec and ≥500 msec; subgroup: age 30–74 yrs	0	0	RR undetermined	1,807 (64 RCTs) (21)	Low	No difference
Change in >60 msec and ≥ 500 msec; subgroup: age >74 yrs	3	5	RR 0.62 (0.09, 4.35)	1005 (64 RCTs) (21)	Low	No difference
Torsades/QT prolongation	18	9; attributable events per 1,000 treated 8 [4, 13]	RR 1.90 (1.29, 2.79); NNT 119 (77, 256)	10,029 (64 RCTs) (21)	Low	Favors placebo
QTc prolongation	NR	NR	Adjusted MD 0.07 (−0.47, 0.61)	1,017 (1 observational study) (24)	Very low	No difference
Torsades de Pointes and/or QT interval abnormalities (>4 cases)	NR	NR	Adjusted OR 6.96 (5.55, 8.72)	67,992 [1 observational study of FDA Adverse Event Reporting System (FAERS)] (34)	Very low	Favors control (no risperidone)
Torsades de Pointes to sudden cardiac death, >4 cases	NR	NR	Adjusted OR 1.63 (1.50, 1.77)	67,992 [1 observational study of FDA Adverse Event Reporting System (FAERS)] (34)	Very low	Favors control (no risperidone)

[†], we concluded that there is no difference in outcomes between active and control interventions based on P>0.05 and inability to reject null hypotheses but without post-hoc analysis of the statistical power to detect true differences. 95% confidence interval in ()/[]; GRADE, Grading of Recommendations Assessment, Development and Evaluation; OR, odds ratio; NNT, number needed to treat to achieve an outcome in one patient; NNT is calculated as 1/absolute risk difference; attributable events per 1,000 treated as the number of excessive or avoided events per 1,000 treated that are attributed to active treatment; attributable events per 1,000 treated are calculated as absolute rate difference multiplied by 1,000; RCT, randomized controlled trial; RR, relative risk; MD, mean difference; SMD, standardized mean difference between intervention and comparator where the magnitude of the effect is defined as small (SMD, 0–0.5 standard deviations), moderate (SMD, 0.5–0.8 standard deviations), and large (SMD >0.8 standard deviations); QTcLD, interval corrected for heart rate using the population specified linear derived method; NR, not reported.

Table 2 Risperidone versus active comparators on QT interval in people with mental disorders

Outcome	Risk with intervention per 1,000	Risk with comparator per 1,000	Relative measure of association	Number of participants (studies)	Quality (GRADE)	Comments[†]
Risperidone versus aripiprazole in children and adolescents						
QTc, msec, >18 months	NR	NR	MD –1.20 (–8.94, 6.54); SMD –0.06 (–0.46, 0.33)	99 (prospective analysis registry*) (23)	Very low	No difference
QTc >450 msec, or QTc prolongation >60 msec, or QTc dispersion >100 msec; subgroup: concomitant stimulant	NR	NR	Adjusted OR 4.23 (1.10, 17.00)	99 (prospective registry analysis*) (23)	Very low	Favors aripiprazole
QTc >500 msec	0	0	RR undetermined	99 (prospective analysis registry*) (23)	Very low	No difference
Risperidone long-acting Injection versus oral atypical antipsychotics (olanzapine, quetiapine, aripiprazole or amisulpride) in adults						
QT prolonged	0	11	RR 0.35 (0.01, 8.56)	167 (1 RCT) (39)	Very low	No difference
Risperidone or paliperidone versus active control in adults						
Torsades/QT prolongation	18	19	RR 0.94 (0.59, 1.51)	7,573 (64 RCTs) (21)	Very low	No difference
Risperidone 16 mg/d versus haloperidol 15 mg/d in adults						
QTc >500 msec	0	0	RR Undetermined	52 (1 RCT) (30,38)	Very low	No difference
Risperidone 4 mg versus risperidone, 2 mg/d + Haloperidol, 2 mg/d in adults						
QTc, msec	NR	NR	MD –1.49 (–14.77, 11.79); SMD –0.06 (–0.57, 0.46)	58 (1 RCT) (28,29)	Very low	No difference
Risperidone versus olanzapine in adults						
Torsades de Pointes, sudden cardiac death	NR	NR	Adjusted HR 1.04 (0.88, 1.24)	459,614 (1 observational study of medicaid database) (33)	Very low	No difference
Risperidone versus ziprasidone in adults						
QTc	NR	NR	MD –21.80 (–28.13, –15.47); SMD –2.76 (–3.90, –1.62)	24 (1 RCT) (26,27)	Very low	Favors risperidone

*, SafEty of NeurolepTics in Infancy and Adolescence (SENTIA) registry (https://sentia.es). [†], we concluded that there is no difference in outcomes between active and control interventions based on P value >0.05 and inability to reject null hypotheses but without post-hoc analysis of the statistical power to detect true differences. 95% confidence interval in ( ); GRADE, Grading of Recommendations Assessment, Development and Evaluation; OR, odds ratio; NNT, number needed to treat to achieve an outcome in one patient; NNT is calculated as 1/absolute risk difference; attributable events per 1,000 treated as the number of excessive or avoided events per 1000 treated that are attributed to active treatment; attributable events per 1,000 treated are calculated as absolute rate difference multiplied by 1,000; RCT, randomized controlled trial; RR, relative risk; MD, mean difference; SMD, standardized mean difference between intervention and comparator where the magnitude of the effect is defined as small (SMD, 0–0.5 standard deviations), moderate (SMD, 0.5–0.8 standard deviations), and large (SMD >0.8 standard deviations); QTc, corrected QT interval; NR, not reported.

Table 3 Ziprasidone versus placebo on QT interval in people with mental disorders

Outcome	Risk with intervention per 1,000	Risk with comparator per 1,000	Relative measure of association	Number of participants	Quality (grade)	Comments[†]
Ziprasidone monotherapy versus placebo						
QT change from baseline	NR	NR	MD 3.90 (2.43, 5.37); SMD 0.19 (0.12, 0.26)	5,217 (44)*	Low	Favors placebo
Peak measured QTc ≥450 msec	8	10	RR 0.78 (0.37, 1.62)	5,217 (44)*	Very low	No difference
Peak measured QTc ≥480 msec	0	0	RR 0.64 (0.03, 15.58)	5,217 (44)*	Very low	No difference
Peak measured QTc ≥500 msec	0	0	RR 0.64 (0.03, 15.58)	5,217 (44)*	Very low	No difference
Maximal QTc change from baseline ≥30 msec	90	59; attributable events per 1,000 treated 31 [14, 49]	RR 1.52 (1.16, 2.01); NNT 32 [21, 74]	5,217 (44)*	Low	Favors placebo
Maximal QTc change from baseline ≥60 msec	7	8	RR 0.91 (0.40, 2.06)	5,217 (44)*	Very low	No difference
Maximal QTc change from baseline ≥75 msec	3	1	RR 2.54 (0.33, 19.50)	5,217 (44)*	Very low	No difference
Ziprasidone plus lamotrigine versus placebo plus lamotrigine						
QTc change from baseline	NR	NR	MD 2.00 (–4.53, 8.53); SMD 0.13 (–0.30, 0.57)	82 (44)*	Very low	No difference
Peak measured QTc ≥450 msec	24	24	RR 1.00 (0.06, 15.45)	82 (44)*	Very low	No difference
Peak measured QTc ≥480 msec	0	0	RR undetermined	82 (44)*	Very low	No difference
Peak measured QTc ≥500 msec	0	0	RR Undetermined	82 (44)*	Very low	No difference
Maximal QTc change from baseline ≥30 msec	0	49	RR 0.20 (0.01, 4.04)	82 (44)*	Very low	No difference
Maximal QTc change from baseline ≥60 msec	0	0	RR undetermined	82 (44)*	Very low	No difference
Maximal QTc change from baseline ≥75 msec	0	0	RR undetermined	82 (44)*	Very low	No difference
Ziprasidone plus lithium versus placebo plus lithium						
QTc change from baseline	NR	NR	MD 2.10 (–1.32, 5.52); SMD 0.10 (–0.06, 0.26)	608 (44)*	Low	No difference
Peak measured QTc ≥450 msec	27	19	RR 1.43 (0.48, 4.21)	608 (44)*	Very low	No difference
Peak measured QTc ≥480 msec	3	0	RR 2.38 (0.10, 58.25)	608 (44)*	Very low	No difference
Peak measured QTc ≥500 msec	0	0	RR undetermined	608 (44)*	Very low	No difference

Table 3 (*continued*)

Table 3 (*continued*)

Outcome	Risk with intervention per 1,000	Risk with comparator per 1,000	Relative measure of association	Number of participants	Quality (grade)	Comments[†]
Maximal QTc change from baseline ≥30 msec	112	86	RR 1.31 (0.80, 2.15)	608 (44)*	Very low	No difference
Maximal QTc change from baseline ≥60 msec	12	7	RR 1.59 (0.29, 8.60)	608 (44)*	Very low	No difference
Maximal QTc change from baseline ≥75 msec	3	7	RR 0.40 (0.04, 4.35)	608 (44)*	Very low	No difference
Ziprasidone plus valproate versus placebo plus valproate						
QTc change from baseline	NR	NR	MD 3.40 (0.71, 6.09); SMD 0.20 (0.04, 0.36)	631 (44)*	Low	Favors placebo
Peak measured QTc ≥450 msec	21	0	RR 10.81 (0.63, 186.38)	631 (44)*	Very low	No difference
Peak measured QTc ≥480 msec	0	0	RR undetermined	631 (44)*	Very low	No difference
Peak measured QTc ≥500 msec	0	0	RR undetermined	631 (44)*	Very low	No difference
Maximal QTc change from baseline ≥30 msec	60	37	RR 1.62 (0.76, 3.45)	631 (44)*	Very low	No difference
Maximal QTc change from baseline ≥60 msec	0	0	RR undetermined	631 (44)*	Very low	No difference
Maximal QTc change from baseline ≥75 msec	0	0	RR undetermined	631 (44)*	Very low	No difference

*, individual patient data network meta-analysis of 40 Pfizer-sponsored phase II–IV RCTs in schizophrenia or bipolar disorder patients including 5 pediatric RCTs; [†], we concluded that there is no difference in outcomes between active and control interventions based on P>0.05 and inability to reject null hypotheses but without post-hoc analysis of the statistical power to detect true differences. 95% confidence interval in ( )/[ ]; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NNT, number needed to treat to achieve an outcome in one patient; NNT is calculated as 1/absolute risk difference; attributable events per 1,000 treated as the number of excessive or avoided events per 1,000 treated that are attributed to active treatment; attributable events per 1,000 treated are calculated as absolute rate difference multiplied by 1,000; RCT, randomized controlled trial; RR, relative risk; MD, mean difference; SMD, standardized mean difference between intervention and comparator where the magnitude of the effect is defined as small (SMD, 0–0.5 standard deviations), moderate (SMD, 0.5–0.8 standard deviations), and large (SMD >0.8 standard deviations); QTc, corrected QT interval; NR, not reported.

Table 4 Ziprasidone versus haloperidol on QT interval in people with mental disorders

Outcome	Risk with intervention per 1,000	Risk with comparator per 1,000	Relative measure of association	Number of participants (studies)	Quality (GRADE)	Comments[†]
Ziprasidone oral						
QTc interval ≥450 msec	28	11	RR 1.86 (0.57, 6.04)	569 (4 RCTs) (47)	Low	
450 msec ≤ QTc interval <480 msec	24	0	RR 4.12 (0.89, 19.09)	569 (4 RCTs) (47)	Low	
QTc interval ≥480 msec	4	12	RR 0.61 (0.03, 11.80)	509 (3 RCTs) (38,47)	Low	
QTc prolongation	NR	NR	MD 15.30 (6.22, 24.38); SMD 0.92 (0.34, 1.49)	52 (1 RCT) (38,43)	Very low	Favors haloperidol
QT change from baseline	NR	NR	MD 4.70 (3.30, 6.10); SMD 0.23 (0.16, 0.29)	5,339(44)*	Very low	Favors haloperidol
Peak measured QTc ≥450 msec	8	3	RR 2.64 (0.81, 8.59)	5,339 (44)*	Very low	No difference
Peak measured QTc ≥480 msec	0	0	RR 0.72 (0.03, 17.67)	5,339 (44)*	Very low	No difference
Peak measured QTc ≥500 msec	0	0	RR 0.72 (0.03, 17.67)	5,339 (44)*	Very low	No difference
Maximal QTc change from baseline ≥30 msec	90	60 attributable events per 1,000 treated 30 [13, 47]	RR 1.51 (1.16, 1.95); NNT 33 (21, 74)	5,339 (44)*	Low	Favors haloperidol
Maximal QTc change from baseline ≥60 msec	7	3	RR 2.40 (0.73, 7.85)	5,339 (44)*	Very low	No difference
Maximal QTc change from baseline ≥75 msec	3	1	RR 2.88 (0.37, 22.11)	5,339 (44)*	Very low	No difference
Ziprasidone, intramuscular						
QTc change from baseline	NR	NR	MD 1.10 (–2.59, 4.79); SMD 0.04 (–0.09, 0.18)	960 (44)*	Low	No difference
Peak measured QTc ≥450 msec	8	17	RR 0.46 (0.13, 1.57)	960 (44)*	Very low	No difference
Peak measured QTc ≥480 msec	2	7	RR 0.23 (0.02, 2.52)	960 (44)*	Very low	No difference
Peak measured QTc ≥500 msec	0	3	RR 0.15 (0.01, 3.75)	960 (44)*	Very low	No difference
Maximal QTc change from baseline ≥30 msec	81	70	RR 1.16 (0.71, 1.88)	960 (44)*	Very low	No difference
Maximal QTc change from baseline ≥60 msec	14	23	RR 0.59 (0.22, 1.57)	960 (44)*	Very low	No difference
Maximal QTc change from baseline ≥75 msec	5	17	RR 0.28 (0.07, 1.14)	960 (44)*	Very low	No difference

*, individual patient data network meta-analysis of 40 Pfizer-sponsored phase II–IV RCTs in schizophrenia or bipolar disorder patients including 5 pediatric RCTs. [†], We concluded that there is no difference in outcomes between active and control interventions based on P value>0.05 and inability to reject null hypotheses but without post-hoc analysis of the statistical power to detect true differences. 95% confidence interval in ( )/[ ]; GRADE, Grading of Recommendations Assessment, Development and Evaluation; NNT, number needed to treat to achieve an outcome in one patient; NNT is calculated as 1/absolute risk difference; attributable events per 1,000 treated as the number of excessive or avoided events per 1,000 treated that are attributed to active treatment; attributable events per 1,000 treated are calculated as absolute rate difference multiplied by 1,000; RCT, randomized controlled trial; RR, relative risk; MD, mean difference; SMD, standardized mean difference between intervention and comparator where the magnitude of the effect is defined as small (SMD, 0–0.5 standard deviations), moderate (SMD, 0.5–0.8 standard deviations), and large (SMD >0.8 standard deviations); QTc, corrected QT interval; NR, not reported;

Table 5 Ziprasidone versus other antipsychotic drugs on QT interval in people with mental disorders

Outcome	Risk with intervention per 1,000	Risk with comparator per 1,000	Relative measure of association	Number of participants (studies)	Quality (GRADE)	Comments[†]
Ziprasidone versus aripiprazole						
QT change from baseline	NR	NR	MD 3.50 (–0.03, 7.03); SMD 0.17 (–0.02, 0.35)	4,423 (44)*	Low	No difference
Peak measured QTc ≥450 msec	8	9	RR 0.90 (0.12, 6.50)	4,423 (44)*	Very low	No difference
Peak measured QTc ≥480 msec	0	0	RR 0.08 (0.00, 2.01)	4,423 (44)*	Very low	No difference
Peak measured QTc ≥500 msec	0	0	RR 0.08 (0.00, 2.01)	4,423 (44)*	Very low	No difference
Maximal QTc change from baseline ≥30 msec	90	51	RR 1.76 (0.80, 3.86)	4,423 (44)*	Low	No difference
Maximal QTc change from baseline ≥60 msec	7	0	RR 1.67 (0.10, 27.17)	4,423 (44)*	Very low	No difference
Maximal QTc change from baseline ≥75 msec	3	0	RR 0.68 (0.04, 11.50)	4,423 (44)*	Very low	No difference
Ziprasidone versus chlorpromazine						
QT change from baseline	NR	NR	MD –9.10 (–13.88, –4.32); SMD –0.43 (–0.61, –0.25)	4,430 (44)*	Low	Favors ziprasidone
Peak measured QTc ≥450 msec	8	16	RR 0.48 (0.12, 1.96)	4,430 (44)*	Very low	No difference
Peak measured QTc ≥480 msec	0	0	RR 0.09 (0.00, 2.13)	4,430 (44)*	Very low	No difference
Peak measured QTc ≥500 msec	0	0	RR 0.09 (0.00, 2.13)	4,430 (44)*	Very low	No difference
Maximal QTc change from baseline ≥30 msec	90	226	RR 0.40 (0.28, 0.56)	4,430 (44)*	Low	Favors ziprasidone
Maximal QTc change from baseline ≥60 msec	7	24	RR 0.29 (0.09, 0.93)	4,430 (44)*	Very low	Favors ziprasidone
Maximal QTc change from baseline ≥75 msec	3	8	RR 0.35 (0.05, 2.64)	4,430 (44)*	Very low	No difference
Ziprasidone versus olanzapine						
QT change from baseline	NR	NR	MD 5.30 (3.04, 7.56); SMD 0.26 (0.14, 0.37)	4,640 (44)*	Low	Favors olanzapine
Peak measured QTc ≥450 msec	8	0	RR 5.21 (0.32, 84.86)	4,640 (44)*	Very low	No difference
Peak measured QTc ≥480 msec	0	0	RR 0.23 (0.01, 5.72)	4,640 (44)*	Very low	No difference
Peak measured QTc ≥500 msec	0	0	RR 0.23 (0.01, 5.72)	4,640 (44)*	Very low	No difference
Maximal QTc change from baseline ≥30 msec	90	66	RR 1.37 (0.91, 2.08)	4,640 (44)*	Low	No difference
Maximal QTc change from baseline ≥60 msec	7	0	RR 4.74 (0.29, 77.42)	4,640 (44)*	Very low	No difference
Maximal QTc change from baseline ≥75 msec	3	0	RR 1.94 (0.12, 32.77)	4,640 (44)*	Very low	No difference

Table 5 (*continued*)

Table 5 (*continued*)

Outcome	Risk with intervention per 1,000	Risk with comparator per 1,000	Relative measure of association	Number of participants (studies)	Quality (GRADE)	Comments[†]
Ziprasidone versus risperidone						
QT change from baseline	NR	NR	MD 2.80 (0.35, 5.25); SMD 0.13 (0.03, 0.24)	4,703 (44)*	Low	Favors risperidone
Peak measured QTc ≥450 msec	8	3	RR 3.04 (0.42, 22.19)	4,703 (44)*	Very low	No difference
Peak measured QTc ≥480 msec	0	0	RR 0.28 (0.01, 6.79)	4,703 (44)*	Very low	No difference
Peak measured QTc ≥500 msec	0	0	RR 0.28 (0.01, 6.79)	4,703 (44)*	Very low	No difference
Maximal QTc change from baseline ≥30 msec	90	108	RR 0.83 (0.62, 1.12)	4,703 (44)*	Low	No difference
Maximal QTc change from baseline ≥60 msec	7	10	RR 0.69 (0.24, 1.95)	4,703 (44)*	Very low	No difference
Maximal QTc change from baseline ≥75 msec	3	5	RR 0.55 (0.12, 2.46)	4,703 (44)*	Very low	No difference

*, individual patient data network meta-analysis of 40 Pfizer-sponsored phase II–IV RCTs in schizophrenia or bipolar disorder patients including 5 pediatric RCTs. [†], we concluded that there is no difference in outcomes between active and control interventions based on P value>0.05 and inability to reject null hypotheses but without post-hoc analysis of the statistical power to detect true differences. 95% confidence interval in ( ); GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial; RR, relative risk; MD, mean difference; SMD, standardized mean difference between intervention and comparator where the magnitude of the effect is defined as small (SMD, 0–0.5 standard deviations), moderate (SMD, 0.5–0.8 standard deviations), and large (SMD >0.8 standard deviations); QTc, corrected QT interval; NR, not reported.

Table 6 Olanzapine versus placebo on QT interval in people with mental disorders

Outcome	Risk with intervention per 1,000	Risk with comparator per 1,000	Relative measure of association	Number of participants (studies)	Quality (GRADE)	Comments[†]
Olanzapine versus placebo in children and adolescents						
Change in QTc	NR	NR	MD −1.01 (−6.45, 4.43); SMD −0.04 (−0.18, 0.11)	1,174 (5 studies) (35,60-62)	Very low	No difference
Oral olanzapine versus placebo in adults						
QT prolonged	NR	NR	RR 0.34 (0.16, 0.70)	869 (6 RCTs) (58,63-69)	Low	No difference*
QT prolonged	9	20	RR 0.46 (0.04, 4.96)	201(1 RCT) (74,75)	Very low	No difference
Change in QTc	NR	NR	SMD −0.14 (−0.29, 0.01)	724 (7 RCTs) (58,63-69)	Moderate	No difference
Intramuscular olanzapine versus placebo in adults						
QTc prolongation >30 msec, 2 hours	15	21	RR 0.73 (0.18, 2.86)	556 (4 RCTs) (57,63,66,78,79)	Very low	No difference
QTc prolongation >60 msec, 2 hours	5	7	RR 0.73 (0.07, 7.94)	556 (4 RCTs) (57,63,66,78,79)	Very low	No difference
QTc prolongation >500 msec, 2 hours	0	0	RR Undetermined	556 (4 RCTs) (57,63,66,78,79)	Very low	No difference
Change in QT, 2 hours after olanzapine 2.5 mg in agitated adults with schizophrenia	NR	NR	MD −5.90 (−10.61, −1.19); SMD −0.30 (−0.54, −0.06)	270 (4 RCTs) (57,63,66,78,79)	Very low	Favors olanzapine
Change in QT, 2 hours after olanzapine 5 mg in agitated adults with schizophrenia	NR	NR	MD −6.30 (−11.56, −1.04); SMD −0.29 (−0.53, −0.05)	270 (4 RCTs) (57,63,66,78,79)	Very low	Favors olanzapine
Change in QT, 2 hours after olanzapine 7.5 mg in agitated adults with schizophrenia	NR	NR	MD −5.30 (−10.54, −0.06); SMD −0.24 (−0.48, 0.00)	270 (4 RCTs) (57,63,66,78,79)	Very low	Favors olanzapine
Change in QT, 2 hours after olanzapine 10 mg in agitated adults with schizophrenia	NR	NR	MD −2.70 (−7.92, 2.52); SMD −0.12 (−0.36, 0.12)	270 (4 RCTs) (57,63,66,78,79)	Very low	No difference
Change in QT, 2 hours after olanzapine 2.5 mg in adults with dementia	NR	NR	MD −7.80 (−12.92, −2.68); SMD −0.36 (−0.60, −0.12)	272 (4 RCTs) (57,63,66,78,79)	Very low	Favors olanzapine
Change in QT, 2 hours after olanzapine 5 mg in adults with dementia	NR	NR	MD −0.20 (−5.65, 5.25); SMD −0.01 (−0.25, 0.23)	272 (4 RCTs) (57,63,66,78,79)	Very low	No difference

[†], we concluded that there is no difference in outcomes between active and control interventions based on P value >0.05 and inability to reject null hypotheses but without post-hoc analysis of the statistical power to detect true differences. *, no statistically significant differences in absolute risk. 95% confidence interval in ( ); GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial; RR, relative risk; MD, mean difference; SMD, standardized mean difference between intervention and comparator where the magnitude of the effect is defined as small (SMD, 0–0.5 standard deviations), moderate (SMD, 0.5–0.8 standard deviations), and large (SMD >0.8 standard deviations); QTc, corrected QT interval; NR, not reported.

Table 7 Olanzapine versus acive comparators on QT interval in people with mental disorders

Outcome	Risk with intervention per 1,000	Risk with comparator per 1,000	Relative measure of association	Number of participants (studies)	Quality (GRADE)	Comments[†]
Olanzapine versus haloperidol in children and adolescents with autistic disorder						
QT prolonged	0	0	RR Undetermined	12 (1 RCT) (37,70)	Very low	No difference
Olanzapine versus haloperidol in adults with various mental disorders						
QT prolonged	NR	NR	RR 0.37 (0.13, 1.05)	433 (3 RCTs) (58,63-69)	Low	No difference
Change in QTc	NR	NR	SMD −0.13 (−0.34, 0.08)	343 (2 RCTs) (58,63-69)	Moderate	No difference
QTc >500 milliseconds	0	0	RR Undetermined	51 (1 RCT) (30)	Very low	No difference
Olanzapine versus haloperidol in adults with bipolar disorder						
QT prolonged	9	0	RR 0.57 (0.02, 13.53)	125(1 RCT) (74,75)	Very low	No difference
Intramuscular olanzapine versus haloperidol in agitated adults with schizophrenia						
Change in QT, 2 hours after olanzapine 2.5 mg	NR	NR	MD −9.00 (−14.26, −3.74); SMD −0.41 (−0.65, −0.17)	270 (4 RCTs) (57,63,66,78,79)	Very low	Favors olanzapine
Change in QT, 2 hours after olanzapine 5 mg	NR	NR	MD −9.40 (−15.16, −3.64); SMD −0.39 (−0.63, −0.15)	270 (4 RCTs) (57,63,66,78,79)	Very low	Favors olanzapine
Change in QT, 2 hours after olanzapine 7.5 mg	NR	NR	MD −8.40 (−14.14, −2.66); SMD −0.35 (−0.59, −0.11)	270 (4 RCTs) (57,63,66,78,79)	Very low	Favors olanzapine
Change in QT, 2 hours after olanzapine 10 mg	NR	NR	MD −5.80 (−11.53, −0.07); SMD −0.24 (−0.48, 0.00)	270 (4 RCTs) (57,63,66,78,79)	Very low	Favors olanzapine
QTc prolongation >30 msec, 2 hours	13	38	RR 0.35 (0.10, 1.22)	476 (4 RCTs) (57,63,66,78,79)	Very low	No difference
QTc prolongation >60 msec, 2 hours	6	0	RR 2.64 (0.13, 54.58)	476 (4 RCTs) (57,63,66,78,79)	Very low	No difference
QTc prolongation >500 msec, 2 hours	0	6	RR 0.18 (0.01, 4.29)	476 (4 RCTs) (57,63,66,78,79)	Very low	No difference
Change in QT, 2 hours	NR	NR	MD −3.70 (−8.25, 0.85); SMD −0.16 (−0.35, 0.03)	476 (4 RCTs) (57,63,66,78,79)	Very low	No difference

Table 7 (*continued*)

Table 7 (*continued*)

Outcome	Risk with intervention per 1,000	Risk with comparator per 1,000	Relative measure of association	Number of participants (studies)	Quality (GRADE)	Comments[†]
Olanzapine versus asenapine in adults with schizophrenia						
QTc ≥500 msec	0	0	RR undetermined; SMD	1,225 (1 RCT) (71)	Very low	No difference
QTcF prolonged	13	24	RR 0.53 (0.18, 1.53)	1,225 (1 RCT) (71)	Very low	No difference
Olanzapine versus lorazepam in agitated patients						
Change in QTc	NR	NR	SMD −0.12 (−0.36, 0.12)	276 (2 RCTs) (58,63-69)	Moderate	No difference
Olanzapine combined with fluoxetine versus fluoxetine in stabilized adults with treatment-resistant depression						
Change in QTcF	NR	NR	MD −1.57 (−5.84, 2.70); SMD −0.07 (−0.27, 0.12)	329 (1 RCT) (73)	Low	No difference
QTcF ≥500 msec	0	0	RR undetermined	429 (1 RCT) (73)	Very low	No difference
Olanzapine versus olanzapine combined with lithium, valproate or carbamazepine						
QTcF ≥450 msec for men or ≥470 msec for women	0	0	RR undetermined	137 (1 RCT) (59)	Very low	No difference

[†], we concluded that there is no difference in outcomes between active and control interventions based on P>0.05 and inability to reject null hypotheses but without post-hoc analysis of the statistical power to detect true differences. 95% confidence interval in ( ); GRADE, Grading of Recommendations Assessment, Development and Evaluation; NNT, number needed to treat to achieve an outcome in one patient; NNT is calculated as 1/absolute risk difference; attributable events per 1,000 treated as the number of excessive or avoided events per 1,000 treated that are attributed to active treatment; attributable events per 1,000 treated are calculated as absolute rate difference multiplied by 1,000; RCT, randomized controlled trial; RR, relative risk; MD, mean difference; SMD, standardized mean difference between intervention and comparator where the magnitude of the effect is defined as small (SMD, 0–0.5 standard deviations), moderate (SMD, 0.5–0.8 standard deviations), and large (SMD >0.8 standard deviations); QTc, corrected QT interval; QTcF, Fridericia's corrected QT interval; NR, not reported.

haloperidol, asenapine, or lorazepam in adults with mental disorders (*Table 7*). Intramuscular olanzapine decreases QT interval when compared with haloperidol in agitated adults (*Table 7*).

Post-marketing surveillance suggests 84 cases of prolonged QT intervals and 53 cases of torsades de pointes tachycardia in people treated with olanzapine among other medications for various mental disorders (*Table S1*).

Quetiapine was examined in two systematic reviews and meta-analyses (38,80). We also identified published and unpublished data from 7 RCTs and 4 non-randomized studies (21-40,81-86).

When compared with placebo or no active treatment, evidence suggests that quetiapine is not associated with the risk of QT prolongation in children and adolescents (*Table 8*). In contrast, quetiapine is associated with higher odds of torsade's de pointes or QT interval abnormalities in adult patients with mental disorders (*Table 8*).

When compared with other antipsychotics, sparse evidence suggests that there are no differences in QT interval between quetiapine and haloperidol or risperidone (*Table 9*). Sparse data from a single RCT suggests that quetiapine decreases QT interval when compared with ziprasidone in adults with mental disorders (*Table 9*). Observational analysis of Medicaid database demonstrates that quetiapine is associated with the lower risk of torsade's de pointes or sudden cardiac death when compared with olanzapine (*Table 9*).

Post-marketing surveillance suggests 56 cases of prolonged QT intervals and 90 cases of torsade's de pointes tachycardia in people treated with olanzapine among other medications for various mental disorders (*Table S1*).

Aripiprazole was examined in four systematic reviews and meta-analyses and published and unpublished data from 12 RCTs and three non-randomized trials (35-37,60-62,87-97).

Evidence suggests that there are no differences in QT interval changes or rates of prolonged QT interval between aripiprazole and placebo, risperidone or haloperidol in adults with mental disorders (*Table 10*). Higher dose of aripiprazole does not increase QT interval when compared with the lower dose (*Table 10*). Available studies did not report the rates of torsade de pointes ventricular tachycardia in adults treated with aripiprazole. Post-marketing surveillance identified 15 cases of prolonged QT interval and 21 cases of torsade de pointes in patients treated with aripiprazole among other drugs (*Table S1*).

Sparse evidence suggests that aripiprazole is associated with reduction in QT interval in pediatric patients with mental disorders (*Table 11*). Sparse evidence suggests that there are no differences in the rates of prolonged QT interval between aripiprazole, placebo, risperidone or pimozide in children and adolescents with mental disorders (*Table 11*).

The evidence regarding the role of chronic inflammation or genetic polymorphism on QT interval in patients taking aripiprazole is insufficient (98-100).

Aripiprazole may present a safer choice in patients who need antipsychotic drugs and have no cardiac disorders associated with higher risk of cardiac death (101).

Brexpiprazole was examined in one systematic review and unpublished data from four RCTs (102-105).

Evidence suggests that there are no differences in the rates of the prolonged (>500 msec or increase by >60 msec) QT interval between brexpiprazole and placebo in adults with mental disorders (*Table 12*). Sparse evidence from a single unpublished RCT suggests that the lower (4 mg) but not higher (12 mg) dose of brexpiprazole prolongs QT interval when compared with placebo (*Table 12*). The evidence regarding effects of brexpiprazole on QT interval in children is insufficient. The evidence regarding comparative safety between brexpiprazole and other antipsychotics on QT interval or the risk of ventricular tachycardia is insufficient.

Post-marketing surveillance does not detect cases of prolonged QT intervals or torsades de pointes tachycardia in people treated with brexpiprazole among other medications for various mental disorders (*Table S1*).

Discussion

Our review of clinical trials, observational studies and post-marketing surveillance found mostly low quality of evidence concerning higher risk of antipsychotic drugs induced QT prolongation. In people with mental disorders referred for treatment with atypical antipsychotic drugs, in order to avoid QT prolongation and reduce the risk of ventricular tachycardia clinicians may recommend aripiprazole, brexpiprazole or olanzapine in licensed doses.

Our findings are in concordance with previously published observational studies that reported a positive association between antipsychotic drugs and the increased risk of cardiac arrest (106-108).

We downgraded the quality of evidence due to the high risk of bias and small number of events in the RCTs. The majority of clinical studies did not have statistical

Table 8 Quetiapine versus placebo on QT interval in people with mental disorders

Outcome	Risk with intervention per 1,000	Risk with comparator per 1,000	Relative measure of association	Number of participants (studies)	Quality (GRADE)	Comments[†]
Quetiapine in children and adolescents						
Corrected QT (QTc) changes	NR	NR	MD 0.62 (–4.15, 5.39); SMD 0.02 (–0.10, 0.14)	1,298 (5 studies) (35)	Very low	No difference
QT prolongation	NR	NR	Adjusted OR 1.39 (0.45, 2.33)	3,472,494 [1 observational study of FDA Adverse Event Reporting System (FAERS)] (25)	Very low	No difference
Quetiapine in adults						
QT prolongation	3	0	RR 2.87 (0.12, 70.08)	546 (3 RCTs) (80,81,86)	Low	No difference
QTc prolongation	NR	NR	MD 9.90 (2.10, 17.80)	72 (1 RCT) (80)	Very low	Favors control, no quetiapine
QTcLD >60 msec	0	0	RR 0.00 (0.00, 0.00)	65 (1 RCT) (81)	Very low	No difference
QTcLD increase 30–60 msec	47	45	RR 1.02 (0.10, 10.67)	65 (1 RCT) (81)	Very low	No difference
QTc changes	NR	NR	MD 8.10 (1.64, 14.56); SMD 0.67 (0.14, 1.19)	65 (1 RCT) (81)	Very low	Favors control, no quetiapine
QTc prolongation	NR	NR	Adjusted MD 0.11 (–0.87, 1.09)	1,017 (1 observational study) (24)	Very low	No difference
Torsade's de Pointes and/or QT interval abnormalities (>4 cases)	NR	NR	Adjusted OR 4.78 (3.91, 5.85)	67,992 [1 observational study of FDA Adverse Event Reporting System (FAERS)] (34)	Very low	Favors control, no quetiapine
Torsade's de Pointes to sudden cardiac death, >4 cases	NR	NR	Adjusted OR 1.31 (1.23, 1.39)	67,992 [1 observational study of FDA Adverse Event Reporting System (FAERS)] (34)	Very low	Favors control, no quetiapine

[†], we concluded that there is no difference in outcomes between active and control interventions based on P value >0.05 and inability to reject null hypotheses but without post-hoc analysis of the statistical power to detect true differences. 95% confidence interval in ( ); GRADE, Grading of Recommendations Assessment, Development and Evaluation; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk; MD, mean difference; SMD, standardized mean difference between intervention and comparator where the magnitude of the effect is defined as small (SMD, 0–0.5 standard deviations), moderate (SMD, 0.5–0.8 standard deviations), and large (SMD >0.8 standard deviations); QTcLD, interval corrected for heart rate using the population specified linear derived method; NR, not reported.

Table 9 Quetiapine versus other antipsychotics on QT interval in adults with mental disorders

Outcome	Risk with intervention per 1,000	Risk with comparator per 1,000	Relative measure of association	Number of participants (studies)	Quality (GRADE)	Comments[†]
Quetiapine versus haloperidol						
QTc >500 milliseconds	0	0	RR undetermined	54 (1 RCT) (30,38)	Very low	No difference
Quetiapine versus olanzapine						
Torsade's de Pointes, sudden cardiac death	NR	NR	Adjusted HR 0.73 (0.57, 0.93)	459,614 (1 observational study of Medicaid programs) (33)	Very low	Favors quetiapine
Quetiapine versus risperidone						
Electrocardiogram QT Prolonged	1	0	RR 2.54 (0.10, 62.20)	1,082 (1 RCT) (83)	Very low	No difference
Quetiapine versus ziprasidone						
QTc >60 msec	0	0	RR undetermined	70 (1 RCT) (82)	Very low	No difference
Change in QTcF	NR	NR	MD −8.30 (−13.48, −3.12); SMD −0.75 (−1.24, −0.27)	70 (1 RCT) (82)	Very low	Favors quetiapine
Change in QTc	NR	NR	MD −8.20 (−13.38, −3.02); SMD −0.74 (−1.23, −0.26)	70 (1 RCT) (82)	Very low	Favors quetiapine
Change in QTc (FDA)	NR	NR	MD −7.00 (−12.25, −1.75); SMD −0.62 (−1.11, −0.14)	70 (1 RCT) (82)	Very low	Favors quetiapine
Change in QTc (Bazett)	NR	NR	MD −2.10 (−8.43, 4.23); SMD −0.16 (−0.62, 0.31)	70 (1 RCT) (82)	Very low	No difference

[†], we concluded that there is no difference in outcomes between active and control interventions based on P value >0.05 and inability to reject null hypotheses but without post-hoc analysis of the statistical power to detect true differences. 95% confidence interval in ( ); GRADE, Grading of Recommendations Assessment, Development and Evaluation; HR, hazard ratio; RCT, randomized controlled trial; RR, relative risk; MD, mean difference; SMD, standardized mean difference between intervention and comparator where the magnitude of the effect is defined as small (SMD, 0–0.5 standard deviations), moderate (SMD, 0.5–0.8 standard deviations), and large (SMD >0.8 standard deviations); QTc, corrected QT interval; QTcF , Fridericia's corrected QT interval; NR, not reported.

Table 10 Aripiprazole on QT interval in adults with mental disorders

Outcome	Risk with intervention per 1,000	Risk with comparator per 1,000	Relative measure of association	Number of participants (studies)	Quality (GRADE)	Comments[†]
Aripiprazole versus placebo						
Prolongation of QT interval during the study	0	0	RR undetermined	135 (1 RCT) (90)	Very low	No difference
Prolongation of QT interval >30 msec	43	56	RR 0.78 (0.47, 1.28)	1,339 (5 RCTs) (89)	Low	No difference
Prolongation of QTc interval >450 msec	2	2	RR 0.89 (0.08, 9.81)	1,339 (5 RCTs) (89)	Low	No difference
QTc Bazett >450 msec	142	58	RR 2.43 (0.28, 21.29)	38 (1 RCT) (94)	Very low	No difference
QTc Bazett Change from Baseline >30 msec	238	176	RR 1.35 (0.37, 4.86)	38 (1 RCT) (94)	Very low	No difference
QTc Bazett Change from Baseline >60 msec	0	58	RR 0.27 (0.01, 6.25)	39 (1 RCT) (94)	Very low	No difference
QTcF >450 msec	47	58	RR 0.81 (0.05, 12.01)	38 (1 RCT) (94)	Very low	No difference
QTcF change from baseline >30 msec	142	235	RR 0.61 (0.16, 2.35)	38 (1 RCT) (94)	Very low	No difference
QTcF change from baseline >60 msec	0	58	RR 0.27 (0.01, 6.25)	39 (1 RCT) (94)	Very low	No difference
200 versus 300 mg aripiprazole IM Depot						
Electrocardiogram QT corrected interval prolonged	100	133	RR 0.75 (0.08, 7.21)	25 (1 RCT) (96)	Very low	No difference
200 versus 400 mg aripiprazole IM Depot						
Electrocardiogram QT corrected interval prolonged	100	0	RR 4.20 (0.19, 92.87)	24 (1 RCT) (96)	Very low	No difference
300 versus 400 mg aripiprazole IM Depot						
Electrocardiogram QT corrected interval prolonged	133	0	RR 4.67 (0.24, 88.96)	29 (1 RCT) (96)	Very low	No difference
Aripiprazole versus risperidone						
Prolongation of QT interval	0	30	RR 0.07 (0.00, 1.36)	300 (1 RCT) (91)	Very low	No difference
Aripiprazole versus haloperidol						
Prolongation of QT interval	0	0	RR undetermined	424 (1 RCT) (92)	Very low	No difference
Prolongation of QT interval >30 msec	43	80	RR 0.54 (0.31, 0.94)	1,126 (5 RCTs) (89)	Low	No difference

[†], we concluded that there is no difference in outcomes between active and control interventions based on P value >0.05 and inability to reject null hypotheses but without post-hoc analysis of the statistical power to detect true differences. 95% confidence interval in ( ); GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial; RR, relative risk; MD, mean difference; SMD, standardized mean difference between intervention and comparator where the magnitude of the effect is defined as small (SMD, 0–0.5 standard deviations), moderate (SMD, 0.5–0.8 standard deviations), and large (SMD >0.8 standard deviations); QTc, corrected QT interval; QTcF , Fridericia's corrected QT interval; NR, not reported.

Table 11 Aripiprazole on QT interval in children and adolescents with mental disorders

Outcome	Risk with intervention per 1,000	Risk with comparator per 1,000	Relative measure of association	Number of participants (studies)	Quality (GRADE)	Comments[†]
Aripiprazole versus placebo						
Prolongation of QT interval	64	0	RR 7.58 (0.40, 143.03)	98 (1 RCT) (37,88)	Very low	No difference
Corrected QT (QTc) changes	NR	NR	MD –2.74 (–4.71, –0.77); SMD –0.13 (–0.22, –0.03)	1,776 (4 RCTs and 10 non-RCTs) (35,60-62,88)	Low	Favors aripiprazole
Electrocardiogram QT prolonged at the end of the study	62	35	RR 1.75 (0.17, 18.28)	60 (1 RCT) (95)	Very low	No difference
Aripiprazole, high dose 30 mg/d versus low dose 10 mg/d						
Prolongation of QT interval	20	10	RR 1.98 (0.18, 21.48)	197 (1 RCT) (37,93)	Very low	No difference
Aripiprazole versus risperidone						
Prolongation of QT interval	0	0	RR undetermined	60 (1CT) (36,37)	Very low	No difference
QT dispersion (QTd)	NR	NR	MD 1.60 (–1.66, 4.86); SMD 0.25 (–0.26, 0.76)	60 (1CT) (36,37)	Very low	No difference
Aripiprazole versus pimozide						
Prolongation of QT interval	0	40	RR 0.33 (0.01, 7.81)	50 (1CT) (37,87)	Very low	No difference

[†], we concluded that there is no difference in outcomes between active and control interventions based on P value>0.05 and inability to reject null hypotheses but without post-hoc analysis of the statistical power to detect true differences. 95% confidence interval in ( ); GRADE, Grading of Recommendations Assessment, Development and Evaluation; RCT, randomized controlled trial; RR, relative risk; MD, mean difference; SMD, standardized mean difference between intervention and comparator where the magnitude of the effect is defined as small (SMD, 0–0.5 standard deviations), moderate (SMD, 0.5–0.8 standard deviations), and large (SMD >0.8 standard deviations); QTc, corrected QT interval; NR, not reported.

Table 12 Brexpiprazole versus placebo on QT interval in adults with mental disorders

Outcome	Risk with intervention per 1,000	Risk with comparator per 1,000	Relative measure of association	Number of participants (studies)	Quality (GRADE)	Comments[†]
QTc >500 msec	0	1	RR 0.43 (0.04, 4.71)	3,642 (4 RCTS) (103-105)	Low	No difference
QTcB change >60 msec	7	7	RR 1.04 (0.44, 2.45)	3,625 (3 RCTS) (103,105)	Low	No difference
Increase in QTcB	333	400	RR 0.83 (0.22, 3.18)	17 (1 RCT) (104)	Very low	No difference
Increase in QTcF	250	400	RR 0.63 (0.15, 2.67)	17 (1 RCT) (104)	Very low	No difference
QTc (>450 msec), brexpiprazole 4 mg	81	0; attributable events per 1,000 treated 81 [8, 154]	RR 11.00 (0.62, 194.77); NNT 12 [7, 132]	124 (1 RCT) (103)	Very low	Favors placebo in absolute scale
QTc (>480 msec), brexpiprazole 4 mg	0	0	RR undetermined	124 (1 RCT) (103)	Very low	No difference
QTc (>450 msec), brexpiprazole 12 mg	75	0	RR 10.50 (0.58, 190.65)	115 (1 RCT) (103)	Very low	No difference
QTc (>480 msec), brexpiprazole 12 mg	19	0	RR 3.50 (0.15, 84.16)	115 (1 RCT) (103)	Very low	No difference
Change in maximum QTc, brexpiprazole 4 mg	NR	NR	MD 1.60 (–1.42, 4.62); SMD 0.19 (–0.17, 0.54)	124 (1 RCT) (103)	Very low	No difference
Change in summary of maximum minus mean QTc, brexpiprazole 4 mg	NR	NR	MD 12.70 (8.95, 16.45); SMD 1.20 (0.81, 1.58)	124 (1 RCT) (103)	Very low	Favors placebo
Change in maximum QTc, brexpiprazole 12 mg	NR	NR	MD 2.10 (–1.45, 5.65); SMD 0.22 (–0.15, 0.59)	115 (1 RCT) (103)	Very low	No difference
Change in summary of maximum minus mean QTc, brexpiprazole 12 mg	NR	NR	MD 13.50 (9.20, 17.80); SMD 1.13 (0.74, 1.53)	115 (1 RCT) (103)	Very low	Favors placebo

[†], we concluded that there is no difference in outcomes between active and control interventions based on P value >0.05 and inability to reject null hypotheses but without post-hoc analysis of the statistical power to detect true differences. 95% confidence interval in ( ); GRADE, Grading of Recommendations Assessment, Development and Evaluation; NNT, number needed to treat to achieve an outcome in one patient; NNT is calculated as 1/absolute risk difference; attributable events per 1,000 treated as the number of excessive or avoided events per 1,000 treated that are attributed to active treatment; attributable events per 1,000 treated are calculated as absolute rate difference multiplied by 1,000; RCT, randomized controlled trial; RR, relative risk; MD, mean difference; SMD, standardized mean difference between intervention and comparator where the magnitude of the effect is defined as small (SMD, 0–0.5 standard deviations), moderate (SMD, 0.5–0.8 standard deviations), and large (SMD >0.8 standard deviations); QTc, corrected QT interval; NR, not reported.

power to detect higher risk of ventricular tachycardia. We further downgraded the quality of evidence due to reporting bias because very small proportion of primary studies that examined benefits of atypical antipsychotics also examined drug-induced QT prolongation. Retrospective post-marketing case reports collection is biased because the reporting depends on clinician opinion regarding the association between ventricular tachycardia and administration of antipsychotic drugs (109).

Available industry guidelines recommend intensive ECG monitoring of QT intervals in clinical trials of non-antiarrhythmic drugs with suspected pro-arrhythmic potential but do not require proactive post-marketing monitoring in real-life settings (110). Some clinical guidelines recommend careful consideration of individual benefits and harms including drug-induced QT prolongation in people with mental disorders and indication for antipsychotic drugs (111-113). Only two British guidelines and one US guideline meet 2013 Institute of Medicine criteria for trustworthy guidelines (111-113). Drug labels recommend against administration of quetiapine or ziprasidone in combination with other drugs that are known to prolong QT interval and in people with bradycardia, hypokalemia or hypomagnesemia, congenital prolongation of the QT interval (114,115). Despite these recommendations, prevalence of polypharmacy with multiple pro-arrhythmic drugs is high (2,4,101).

Our review has implications for clinical practice. Clinicians should evaluate baseline risk for cardiac arrhythmias before offering atypical antipsychotic drugs (116). Routine ECG monitoring for the prolongation of QT interval should be recommended for all patients under the treatment with atypical antipsychotic drugs (117). Multidisciplinary coordinated care should be practiced to avoid polypharmacy with multiple pro-arrhythmic drugs (116,118). Patients should be proactively examined for clinical symptoms indicating the occurrence of cardiac arrhythmias, e.g., dizziness, palpitations, or syncope (119). Our review has policy implications. Prescribing quality in compliance with licensed drug use should be routinely evaluated with electronic decision support systems. (114,115,120). Proactive technologically advanced pharmacovigilance applications should be implemented to decrease the risk of drug-induced QT prolongation and cardiac arrhythmias (109,121-124).

Our review has research implications. Future proactive post-marketing surveillance should examine long-term comparative safety of atypical antipsychotic drugs in patients with different age, primary diagnosis and multiple comorbidities and concomitant drugs. Novel technology applications and adequate statistical methods should be used for routine analysis of antipsychotic-induced QT prolongation and cardiac arrhythmias.

Acknowledgements

This work is supported by Elsevier Evidence-based Medicine Center.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Aronow WS, Shamliyan TA. Effects of atypical antipsychotic drugs on QT interval in patients with mental disorders. Ann Transl Med 2018;6(8):147 doi: 10.21037/atm.2018.03.17

Supplementary

Table S1 Post-marketing reports of adverse effects associated with antipsychotics (from PharmaPendium.com)

Drug	Adverse effects [case]	Gender [case]	Age [case]
Risperidone	Torsade de pointes [71]	Female [38], Male [26]	20+ [49], <20 [2]
Risperidone	Electrocardiogram QT corrected interval prolonged [43]	Female [23], Male [20]	20+ [26], <20 [4]
Ziprasidone Hydrochloride	Torsade de pointes [83]	Female [61], Male [19]	20+ [57]
Ziprasidone Hydrochloride	Electrocardiogram QT corrected interval prolonged [202]	Female [117], Male [63]	20+ [129], <20 [22]
Olanzapine	Torsade de pointes [54]	Female [32], Male [19]	20+ [51]
Olanzapine	Electrocardiogram QT corrected interval prolonged [84]	Female [48], Male [26]	20+ [61], <20 [6]
Quetiapine	Torsade de pointes [90]	Female [68], Male [14]	20+ [79], <20 [1]
Quetiapine_	Electrocardiogram QT corrected interval prolonged [56]	Female [28], Male [24]	20+ [39], <20 [9]
Aripiprazole	Torsade de pointes [21 cases]	Female [12], Male [6]	20+ [15], <20 [2]
Aripiprazole	Electrocardiogram QT corrected interval prolonged [15 cases]	Female [6], Male [6]	20+ [6], <20 [4]

Table S2 Mortality and hospitalization in 18,154 adults with schizophrenia treated with ziprasidone or olanzapine [crude results from the Ziprasidone Observational Study of Cardiac Outcomes (ZODIAC)]

Outcome	Risk with intervention per 1,000	Risk with comparator per 1,000	Relative measure of association	Quality (GRADE)	Comments
Non-suicide mortality, 1 year	9	9	RR 1.02 (0.76, 1.39)	Very low	No difference
All-cause mortality, 1 year	11	11	RR 1.01 (0.77, 1.33)	Very low	No difference
Cardiovascular mortality, 1 year	0	1	RR 0.38 (0.10, 1.41)	Very low	No difference
Mortality due to suicide, 1 year	2	2	RR 1.19 (0.61, 2.31)	Very low	No difference
Sudden death, 1 year	0	0	RR 0.67 (0.11, 3.99)	Very low	No difference
Hospitalization, all-cause, 1 year	151	109	RR 1.39 (1.29, 1.50)	Low	Favors olanzapine
Hospitalization, arrhythmia, 1 year	1	0	RR 1.75 (0.51, 5.98)	Very low	No difference
Hospitalization, myocardial infarction, 1 year	1	1	RR 1.18 (0.53, 2.64)	Very low	No difference
Hospitalization, diabetic ketoacidosis, 1 year	1	1	RR 1.00 (0.29, 3.45)	Very low	No difference