Corrected QT Changes During Antipsychotic Treatment of Children and Adolescents: A Systematic Review and Meta-Analysis of Clinical Trials

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Objective: To evaluate the effect of antipsychotics on the corrected QT (QTc) interval in youth.

Method: We searched PubMed (http://www.ncbi.nlm.nih.gov/pubmed) for randomized or open clinical trials of antipsychotics in youth <18 years with QTc data, meta-analyzing the results. Meta-regression analyses evaluated the effect of age, sex, dose, and study duration on QTc. Incidences of study-defined QTc prolongation (>440–470 milliseconds), QTc >500 milliseconds, and QTc change >60 milliseconds were also evaluated.

Results: A total of 55 studies were meta-analyzed, evaluating 108 treatment arms covering 9 antipsychotics and including 5,423 patients with QTc data (mean age = 12.8 ± 3.6 years, female = 32.1%). Treatments included aripiprazole: studies = 14; n = 814; haloperidol: studies = 1; n = 15; molindone: studies = 3; n = 125; olanzapine: studies = 5; n = 212; paliperidone: studies = 3; n = 177; pimozide: studies = 1; n = 25; quetiapine: studies = 5; n = 336; risperidone: studies = 23; n = 2,234; ziprasidone: studies = 10, n = 523; and placebo: studies = 19, n = 962. Within group, from baseline to endpoint, aripiprazole significantly decreased the QTc interval (−1.44 milliseconds, CI = −2.63 to −0.26, p = .017), whereas risperidone (+1.68, CI = +0.67 to +2.70, p = .001) and especially ziprasidone (+8.74, CI = +5.19 to +12.30, p < .001) significantly increased QTc. Compared to pooled placebo arms, aripiprazole decreased QTc (p = .007), whereas ziprasidone increased QTc (p < .001). Compared to placebo, none of the investigated antipsychotics caused a significant increase in the incidence of the 3 studied QTc prolongation measures, but there was significant reporting bias.

Conclusion: Based on these data, the risk of pathological QTc prolongation seems low during treatment with the 9 studied antipsychotics in otherwise healthy youth. Nevertheless, because individual risk factors interact with medication-related QTc effects, both medication and patient factors need to be considered when choosing antipsychotic treatment.

Key Words: adolescents, antipsychotics, children, ECG, QTc

J Am Acad Child Adolesc Psychiatry 2015;54(1):25–36.

The use of antipsychotics for children and adolescents has increased steadily over the past decades,[1-3] although there are still many unanswered questions pertaining to the scope and magnitude of adverse events in this population, particularly regarding potential long-term harm.

Prolongation of the heart rate corrected QT interval (QTc), a condition that may progress to the malignant ventricular arrhythmia torsades de pointes (TdP) in susceptible individuals, is a known side effect associated with antipsychotics.[4] TdP may lead to sudden cardiac death within minutes if not treated appropriately, and although the exact relationship between prolongation of the QTc interval and the risk of TdP remains elusive, QTc prolongation is still the best clinical surrogate marker for TdP risk.[5]

This article is discussed in an editorial by Dr. Kaizad Munshi, Dr. Mark E. Alexander, and Dr. Paul Hammerness on page 9.

This article can be used to obtain continuing medical education (CME) at www.jaacap.org.

Supplemental material cited in this article is available online.

The QT interval on an electrocardiogram (ECG) is the period from the beginning of the Q-wave to the end of the T-wave. The QT interval shortens at higher heart rates, and should therefore be corrected for heart rate.[6,7] Bazett's $\left(\mathrm{QTc} = \frac{\mathrm{QT}}{\sqrt{\mathrm{RR}}}\right)$[8] or Fridericia's $\left(\mathrm{QTc} = \frac{\mathrm{QT}}{\sqrt[3]{\mathrm{RR}}}\right)$[9] correction formula are most frequently used, where RR is the interval between the 2 R-waves preceding the T-wave in question.

Almost all antipsychotic agents have been associated with some degree of QTc prolongation. This happens primarily as a result of blockage of the rapidly activating delayed rectifier channel IKr, whereby the ion current responsible for repolarization is reduced.[10] Other risk factors for QTc prolongation include electrolyte disturbances, drug–drug interactions related to polypharmacy, and structural heart diseases.[10] Cardiovascular disease (CVD), a very common long-term comorbidity in patients with psychotic disorders,[11-14] is an important risk factor for QTc prolongation and TdP.[15,16] Finally, patients with inherited long QT syndrome (LQTS)[17] may have no symptoms except for a higher predilection toward clinically significant QTc prolongation when exposed to other risk factors, including QTc-prolonging medications.[18]

Reviews and clinical trials that focus explicitly on ECG changes in children and adolescents during antipsychotic treatment are scarce.[19-21] Therefore, the effect of individual antipsychotics on the QTc interval in young patients is still uncertain, and clinicians may be concerned when prescribing antipsychotics because of this uncertainty. QTc >450 milliseconds, and/or QTc prolongation >60 milliseconds, are often used as thresholds requiring increased attention in clinical settings,[19] and it is recommended that physicians consider cardiovascular risk factors and status (including QTc interval) when choosing antipsychotic medications in youth and monitor QTc interval depending on patient- and treatment-related risk factors.[22,23] To the best of our knowledge, this is the first systematic review and meta-analysis to focus on QTc changes based on clinical trials of antipsychotic treatment in this age group.

The purpose of this study was to systematically review and meta-analyze the current literature regarding effects of first- and second-generation antipsychotics (FGAs and SGAs) on the QTc interval in children and adolescents, and to use these data to help guide clinicians about the safe use of specific antipsychotics.

METHOD

Inclusion and Exclusion Criteria for Literature Search

Trials fulfilling the following characteristics were included: prospective study, randomized or not, with or without a comparator; patients aged <18 years; any antipsychotic treatment, with or without placebo arm; treatment indication was a psychiatric condition; and numerical QTc change data (reported or calculable).

Exclusion criteria were as follows: articles in other languages than English; records with no online abstract; reviews; trials not in children/adolescents; trials not in patients with psychiatric disorders; trials not using antipsychotics; studies that were not clinical trials; no reported/obtainable QTc data. Trials including both children/adolescents and adults were included, if the lower age limit was 16 years of age or below and at least 75% of participants were <18 years of age.

The primary outcome was the change in QTc interval at study endpoint compared to baseline. Key secondary outcomes included the difference between change in QTc in each antipsychotic group compared to placebo in head-to-head trials as well as compared to all placebo groups pooled together. Additional secondary outcomes were number of events of QTc above study-defined threshold value (i.e., >440–470 milliseconds), events of QTc >500 milliseconds, and events of prolongation >60 milliseconds.

Source

Studies were identified by searching the electronic database PubMed (http://www.ncbi.nlm.nih.gov/pubmed) from database inception. The final search (described below) was performed on May 14, 2014.

Search Strategy

Search terms were as follows: (child OR children OR childhood OR adolescent OR adolescence OR youth); and (antipsychotic* OR neuroleptic* OR amisulpride OR aripiprazole OR asenapine OR blonanserin OR chlorpromazine OR clothiapine OR clozapine OR droperidol OR flupenthixol OR fluphenazine OR haloperidol OR iloperidone OR loxapine OR lurasidone OR mesoridazine OR molindone OR mosapramine OR olanzapine OR paliperidone OR perphenazine OR perospirone OR pimozide OR prochlorperazine OR remoxipride OR risperidone OR sertindole OR sulpiride OR thioridazine OR thiothixene OR tiapride OR trifluoperazine OR quetiapine OR ziprasidone OR zuclopenthixol).

The resulting articles were filtered by "English language" and "Abstract available." The asterisk after "antipsychotic" and "neuroleptic" served to produce all iterations of the search term.

Study Selection

Records that could be excluded at the title and abstract level were discarded. The remaining articles were saved. Each article was read through by the first author and discarded if ineligible. Articles that were not available online were requested through the library service at the University of Copenhagen. In articles mentioning that ECG was performed at baseline and follow-up but QTc values or QTc changes were not reported, these data were requested from the authors by e-mail.

Data Extraction

For each article, QTc measurements and other relevant data (see section "Data Items") were entered into a database (Excel 2010, Microsoft, Redmond, USA). Change in QTc value from baseline to

FIGURE 1 Consolidated Standards of Reporting Trials (CONSORT) diagram, displaying the flowchart of the article search and selection process. Note: ECG = electrocardiogram; w/o = without.

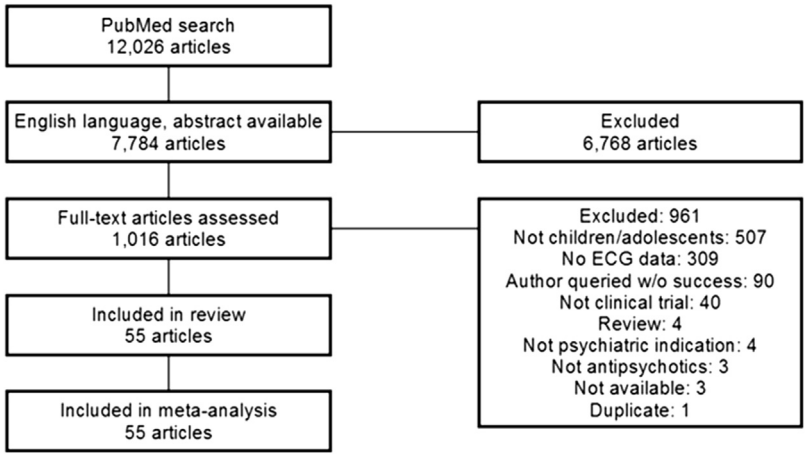

TABLE 1 Study Summary

Antipsychotics	No. of Studies and Patients	Indication, No. of Studies (%)	Design, No. of Studies (%)	Blinding, No. of Studies (%)	Patients per Study	Mean Dose (mg/d)	Duration (wk)	Mean Age (y)	% Female
Aripiprazole (ARI)	14 studies, 862 patients	TS = 3 (21.4) Irritability in AD = 2 (14.3) Any diagnosis = 1 (7.1) Aggression in CD = 1 (7.1) BD = 1 (7.1) BP-I = 1 (7.1) CD = 1 (7.1) PDD-NOS and Asperger = 1 (7.1) SCZ = 1 (7.1) SCZ and acute mania = 1 (7.1) TD = 1 (7.1)	Prospective = 10 (71.4) RCT = 4 (28.6)	OL = 10 (71.4) DB = 4 (38.6)	40.2 ± 41.6	14.0 ± 3.7	15.0 ± 3.9	12.3 ± 3.5	30.2 ± 5.5
Molindone (MOL)	3 studies, 138 patients	E-O SCZ spectrum = 2 (66.7) ADHD = 1 (33.3)	RCT = 2 (66.7) RCT-E = 1 (33.3)	DB = 2 (66.7) OL = 1 (33.3)	23.0 ± 7.6	65.4 ± 8.2	15.5 ± 3.9	8.9 ± 3.0	28.4 ± 5.3
Olanzapine (OLA)	5 studies, 243 patients	E-O SCZ spectrum = 2 (40.0) Acute manic or mixed episode = 1 (20) Psychosis = 1 (20) SCZ = 1 (10)	RCT = 4 (80.0) RCT-E = 1 (10.0)	DB = 5 (100.0)	48.6 ± 36.0	10.2 ± 3.2	7.1 ± 2.7	15.4 ± 3.9	35.2 ± 5.9
Paliperidone (PALI)	3 studies, 179 patients	Autism with irritability = 1 (33.3) PDD-NOS and Asperger's = 1 (33.3) SCZ = 1 (33.3)	Prospective = 2 (66.7) RCT = 1 (33.3)	OL = 2 (66.7) DB = 1 (33.3)	29.8 ± 12.9	5.7 ± 2.4	6.4 ± 2.5	14.9 ± 3.9	31.1 ± 5.6
Placebo	19 studies, 1141 patients	SCZ = 5 (26.3) CD, ODD, DBD NOS = 4 (21.1) Acute manic or mixed episode = 2 (10.5) BD = 2 (10.5) Irritability in AD = 2 (10.5) AD = 1 (5.3) Anorexia nervosa = 1 (5.3) BP-I = 1 (5.3) Overt aggressive behavior + CD, ODD, ADHD + IQ 60-91 = 1 (5.3)	RCT = 19 (100.0)	DB = 19 (100.0)	60.1 ± 34.6		10.8 ± 3.3	12.6 ± 3.5	30.8 ± 5.6
Quetiapine (QUE)	5 studies, 489 patients	Acute manic or mixed episode = 1 (20) ADHD+CD/ODD and aggression = 1 (20)	Prospective = 3 (60.0) RCT = 1 (20.0) RCT-E = 1 (20.0)	OL = 3 (60.0) DB = 1 (20.0) SB = 1 (20.0)	81.5 ± 134.0	529.3 ± 23.0	22.4 ± 4.7	13.6 ± 3.7	38.9 ± 6.2

TABLE 1 Continued

Antipsychotics	No. of Studies and Patients	Indication, No. of Studies (%)	Design, No. of Studies (%)	Blinding, No. of Studies (%)	Patients per Study	Mean Dose (mg/d)	Duration (wk)	Mean Age (y)	% Female
		Bipolar spectrum disorders = 1 (20) Mood symptoms other than BP-I = 1 (20) SCZ or BP-I = 1 (20)							
Risperidone (RIS)	23 studies, 2,445 patients	AD = 2 (8.7) Any = 2 (8.7) BD = 1 (4.3) BP-I = 1 (4.3) CD, ODD, DBD NOS = 9 (39.1) SCZ = 3 (13.0) E-O SCZ spectrum disorders = 2 (8.7) Behavioral problems in autism = 1 (4.3) Psychosis = 1 (4.3) Overt aggressive behavior + CD, ODD, ADHD + IQ 60-90 = 1 (4.3)	RCT = 13 (56.5) RCT-E = 6 (26.1) Prospective = 4 (17.4)	DB = 14 (60.9) OL = 9 (39.1)	78.9 ± 95.6	2.1 ± 1.5	29.0 ± 5.4	12.2 ± 3.5	30.0 ± 5.5
Ziprasidone (ZIP)	10 studies, 897 patients	BD = 3 (30.0) AD = 1 (10.0) SCZ = 2 (20.0) BPM, SCZ or schizoaffective disorder = 1 (10.0) Any diagnosis = 1 (10.0) TS, OCD, PDD = 1 (10.0) TS or chronic TD = 1 (10.0)	Prospective = 5 (50.0) RCT = 2 (20.0) RCT-E = 2 (20.0) PK = 1 (10.0)	OL = 8 (80.0) DB = 2 (20.0)	69.0 ± 76.9	62.7 ± 8.0	16.1 ± 4.0	14.4 ± 3.8	41.1 ± 6.4
Pimozide	1 study, 25 patients	TS	Prospective	OL	25	4.4	104.0	9.1	12.0
Haloperidol	1 study, 15 patients	Psychosis	RCT	DB	15	5.0	8.0	15.4	47.0
All trials	55 trials, 108 treatment arms, 6,434 patients	Disruptive behavior spectrum: 11 (20.0) Bipolar disorder spectrum: 10 (18.2) Schizophrenia spectrum: 10 (18.2) Autism spectrum: 7 (12.7) Tic disorder spectrum: 5 (9.1) SCZ and BD: 3 (5.5)	RCTs:24 (43.6) Prospective trials: 21 (38.2) RCT-Es: 9 (16.3) PKs:1 (1.8)	OL = 30 (54.5) DB = 24 (43.6) SB = 1 (1.8)	59.6 ± 72.0	ARI: 14.0 ± 3.7 MOL: 65.4 ± 8.2 OLA: 10.2 ± 3.2 PALI: 5.7 ± 2.4 QUE: 529.3 ± 23.0 RIS: 2.1 ± 1.5 ZIP: 62.7 ± 8.0	20.1 ± 4.5	12.8 ± 3.6	32.1 ± 5.7

TABLE 1 Continued

Antipsychotics	No. of Studies and Patients	Indication, No. of Studies (%)	Design, No. of Studies (%)	Blinding, No. of Studies (%)	Patients per Study	Mean Dose (mg/d)	Duration (wk)	Mean Age (y)	% Female
		Any diagnosis: 3 (5.5) Aggression in ADHD/DB: 2 (3.6) Mood disorders other than BD: 1 (1.8) Anorexia nervosa: 1 (1.8) ADHD: 1 (1.8) TS/OCD/Autism: 1 (1.8)							

Note: AD = autistic disorder; ADHD = attention-deficit/hyperactivity disorder; BP-I = bipolar-I disorder; BD = bipolar disorder; BPM = bipolar mania; CD = conduct disorder; DB = double-blinded; DBD NOS = disruptive behavior disorder not otherwise specified; E-O = early onset; N/A = not applicable [i.e. could not be summarized from table]; OCD = obsessive-compulsive disorder; ODD = oppositional defiant disorder; OL = open label; PK = pharmacokinetic; RCT = randomized controlled trial; RCTE = RCT extension; SB = single-blinded; SCZ = schizophrenia; TD = tic disorder; TS = Tourette syndrome.

last follow-up (ΔQTc) was entered directly where possible; if only baseline and follow-up data were reported, ΔQTc was calculated by subtracting the baseline value from the follow-up value. When standard deviations (SDs) were missing, they were imputed using the pooled SDs from studies reporting on the same antipsychotic or placebo.

The extraction process was performed by the first author (K.G.J.) and repeated by a second author (A.K.P.) to minimize errors. In case of disagreement, a consensus was reached. If needed, a third author (C.U.C.) was involved.

Where multiple follow-up data were noted, only the last (endpoint) value was entered into the database. For articles containing data on both an acute trial and an extension trial, these data were treated as separate treatment arms. For trials reporting data for different time points pre- and post-dose (i.e., pharmacokinetic trials), pre-dose ECG at follow-up was chosen. Where QTc values using several correction formulae were reported, Bazett's formula was chosen to minimize differences between comparisons, as this correction formula is most frequently used.

There was 1 case of duplicate publication, in which the ECG results from 1 study[24] were re-evaluated more thoroughly in a second study.[25] In this case, after corresponding with the authors, we chose to include the more thorough analyses.

Different studies used different cut-off values for the term "QTc prolongation." Most studies used a cut-off value of 450 milliseconds, a few used 440 milliseconds, and even fewer used 460 or 470 milliseconds. To analyze as many events as possible, we accepted this difference and abstracted events for these slightly heterogeneously defined thresholds. However, as a number of studies by Janssen pharmaceuticals used cut-off values of QTc that were not comparable to those in the other studies (i.e., normal: females: ≤450 milliseconds, males: ≤430 milliseconds; borderline: females: 451–470 milliseconds, males: 431–450 milliseconds; prolonged: females: >470–500 milliseconds, males: >450–500 milliseconds; pathological: >500 milliseconds [females and males]),[26-40] we excluded the categorical outcomes from these trials.

For 1 trial,[41] QTc was calculated using Bazett's formula for children with a heart rate of <60 beats per minute (beats/min) and Fridericia's for children with heart rate ≥60 beats/min. As the number of patients was not provided for each of these categories, mean change in QTc and SD were merged per treatment arm based on the proportion of patients with heart rate of <60 and ≥60, respectively.

Data Items

For each trial, the following data were extracted where available. Trial settings: Authors, year, type of trial, study settings, blinding procedures, duration of intervention, number of patients, whether or not missing data were handled by methods such as last observation carried forward (LOCF), method of QT assessment, QTc correction formula used, and affiliations to or contributions from the pharmaceutical industry. Intervention: antipsychotics evaluated, indication, target dose range, and mean dose (±SD). Patient characteristics: age range, mean age (±SD), number of patients with follow-up ECG, use of concomitant medication, and sex distribution. Outcome measures: manual versus machine reading of QTc, baseline and endpoint QTc data (±SD), ΔQTc (±SD) and statistics/p value of QTc change, number of patients with study-defined QTc prolongation, number of patients with QTc >500 milliseconds, and number of patients with QTc change >60 milliseconds.

Risk of Bias in Individual Studies

Risk of bias was examined for blinded randomized studies using the Cochrane bias method as described in the Cochrane Handbook,[42]

where the following dimensions are evaluated: sequence generation, allocation concealment, blinding participants and personnel, blinding of outcome assessment, incomplete data, selective outcome reporting, and other sources of bias.

For the non-randomized studies, we assessed risk of bias based on the dimensions outlined by the Cochrane Collaboration.[42] For the purpose of this review, each non-RCT was assessed using the following questions: Selection bias: Were inclusion criteria clearly defined? Was the study sample size adequate (low risk n >20, unclear ≥15–20, high risk <15)? Performance bias: Were health care providers blinded? Detection bias: Was ECG assessed by non-blinded raters (high risk) or by machine (low risk) or unknown (unclear risk)? Were the methods for ECG acquisition clearly defined and identical (morning ECG, at rest, supine)? Attrition bias: Were statistical methods applied for losses to follow-up (for instance, LOCF)? Reporting bias (concerning publication biases and selective reporting of results): Was there indication of selective reporting (i.e., missing data on QTc or on number of patients with prolonged QTc)? and other sources of bias.

The purpose of this risk of bias assessment was to provide full transparency to allow readers to estimate the overall quality of the included trials; however, we chose not to exclude any trials based on this assessment.

Data Analysis

Demographic population, illness, and treatment data were analyzed using descriptive statistics. QTc data were entered into and meta-analyzed using Comprehensive Meta-Analysis Version 3.0 (http://www.meta-analysis.com/), Biostat, Englewood, USA.

To pool and compare change in QTc from baseline to last assessment across treatment groups, weighted mean difference (WMD) ± 95% CI was used. For comparison across categorical outcomes, odds ratios (ORs) with 95% CIs were used. Categorical outcomes included number of patients with the following: study-defined QTc prolongation (i.e., >440, >450, >460, >470 milliseconds); QTc >500 milliseconds; and QTc change from baseline to last assessment >60 milliseconds. We performed analyses using 2 different sets of studies: single group analyses of all available study arms with a given treatment arm, namely, specific antipsychotic or placebo; and pairwise analyses of antipsychotic–placebo comparisons in placebo-controlled trials. There were too few active controlled trials to run antipsychotic versus antipsychotic treatment analyses. In the study arm–based data set, all outcomes were compared both within treatment group and comparing individually pooled antipsychotic groups against the pooled placebo arms. In addition, exploratory meta-regression analyses were performed, assessing the following moderator variables: study duration, mean age, percentage of females, and medication dose.

Heterogeneity of outcomes was studied using the I^2 statistic, with $I^2 \geq 50\%$ indicating significant heterogeneity, as well as the χ^2 test for heterogeneity. All tests used random effects models[43] and were 2-sided, and α was set at 0.05. We used funnel graphs (trial effect against trial size) to investigate the likelihood of publication bias.[44]

RESULTS

Search Results

The electronic search yielded 12,026 hits. After filtering for English language and abstract availability, a total of 7,784 abstracts were downloaded. Altogether, 6,768 articles were excluded at the title/abstract level. The resulting 1,016 articles were further evaluated by the first author, of which 961 met the exclusion criteria listed above. Figure 1 is the Consolidated Standards of Reporting Trials (CONSORT) diagram showing the overall search process. In total, 55 articles contained sufficient QTc data and were included. For 19 studies, authors/pharmaceutical companies shared previously unpublished data upon request.

Study, Patient, and Treatment Characteristics

A total of 55 studies[25-41,45-82] were reviewed, evaluating 108 treatment arms including 6,434 patients on 9 different antipsychotics or placebo, of which 5,423 had QTc data (weighted mean age = 12.8 ± 3.6 years, 32.1% female). Only 4 studies examined the effect of antipsychotic treatment on cardiac conduction as their primary aim[47,49,59,78]; in the remaining trials, ECG changes were a secondary safety assessment. Table 1 summarizes the included studies and basic characteristics across treatment arms. Details for each included study can be found in Table S1 (available online).

TABLE 2 Meta-Analysis of Corrected QT Interval (QTc) Change With Individual Antipsychotics and Placebo (All Designs)

Treatment	No. of Treatment Arms	No. of Patients	Mean ΔQTc (milliseconds)	95% CI		*p* vs. 0, Within Group	*p* Each Group vs. Placebo	Heterogeneity Within Group	
				Lower	Upper			*p*	I^2 (%)
Placebo	19	962	1.30	−0.28	2.88	.108		.027*	42.30
Aripiprazole	20	814	−1.44	−2.63	−0.26	.017*	.007**	.504	0.00
Molindone	6	125	−2.20	−5.84	1.44	.237	.084	.147	38.85
Olanzapine	5	212	0.29	−4.92	5.50	.913	.716	<.0001***	83.08
Paliperidone	6	177	0.83	−3.22	4.88	.689	.832	.074	50.17
Quetiapine	6	336	1.92	−2.58	6.42	.403	.799	.014*	65.01
Risperidone	31	2,234	1.68	0.67	2.70	.001**	.689	.271	12.41
Ziprasidone	13	523	8.74	5.19	12.30	<.001***	<.0001***	<.0001***	75.69
Total	106[a]	5,383[a]							

Note: ΔQTc = change in corrected QT interval from baseline to last follow-up.

[a]*One study with haloperidol and one with pimozide were not able to be meta-analyzed.*

*p < .05; **p < .01; ***p < .001.

Altogether, 24 studies (43.6%) were blinded randomized controlled trials (RCTs); 19 (34.5%) were placebo controlled. Treatments included aripiprazole: studies = 14, n = 814; haloperidol: studies = 1, n = 15; molindone: studies = 3, n = 125; olanzapine: studies = 5, n = 212; paliperidone: studies = 3, n = 177; pimozide: studies = 1, n = 25; quetiapine: studies = 5, n = 336; risperidone: studies = 23, n = 2,234; ziprasidone: studies = 10, n = 523; and placebo: studies = 19, n = 962. Weighted mean doses were as follows: aripiprazole: 14.0 ± 3.7 mg/d; haloperidol: 5.0 mg/d; molindone: 65.4 ± 8.2 mg/d; olanzapine: 10.2 ± 3.2 mg/d; paliperidone: 5.7 ± 2.4 mg/d; pimozide: 4.4 mg/d; quetiapine: 529.3 ± 23.0 mg/d; risperidone: 2.1 ± 1.5 mg/d; ziprasidone: 62.7 ± 8.0 mg/d. The mean trial duration was 16.3 weeks (<12 weeks: 33 trials [60.0%]; ≥12 to <24 weeks: 7 trials [12.7%]; ≥24 weeks: 15 trials [27.3%]).

The most frequent indications were a diagnosis of disruptive behavior disorders (conduct disorder [CD], oppositional defiant disorder [ODD], and disruptive behavior disorder not otherwise specified [DBD-NOS]: 11 studies, 20.0%), schizophrenia spectrum disorders (10 studies, 18.2%), or bipolar spectrum disorders (10 studies, 18.2%).

Meta-Analysis of QTc Change

Pooling all study arms of individual antipsychotics or placebo together (Table 2, Figure 2, and Figure S1, available online), aripiprazole was associated with a significant decrease in the QTc interval (−1.44 milliseconds, CI = −2.63 to −0.26, $p = .017$). A significant increase in the QTc duration was found with risperidone (+1.68 milliseconds, CI = +0.67 to +2.70, $p = .001$) and, especially, ziprasidone (+8.74 milliseconds, CI = +5.19 to +12.30, $p < .001$). None of the other antipsychotics or placebo were associated with a QTc change that was significantly different from 0. QTc change results were significantly heterogeneous for olanzapine ($I^2 = 83.1\%$, $p < .0001$), ziprasidone ($I^2 = 76\%$, $p < .0001$), quetiapine ($I^2 = 65.0\%$, $p = .014$), and placebo ($I^2 = 42.3\%$, $p = .027$).

The single studies with pimozide or haloperidol could not be meta-analyzed. In 1 study of pimozide versus aripiprazole,[59] the mean QTc change for pimozide was 25.20 milliseconds (n = 25). In 1 haloperidol study,[74] the mean QTc change was 8 milliseconds (n = 15).

Comparing antipsychotics to pooled placebo, the change with risperidone was no longer significant, but aripiprazole was still associated with a significantly shorter QTc ($p = .007$), whereas ziprasidone was associated with a significantly longer QTc ($p < .001$).

Across the placebo-controlled studies, only the QTc increase associated with ziprasidone ($p = .020$) was significant compared to placebo; all other antipsychotics had p values ranging from .359 to .856. Table 3 and Figure S2, available online, show the outcomes from the meta-analysis for individual medications versus placebo.

Meta-Regression Analysis of QTc Change

In meta-regression analyses, we investigated the effect of age, sex, duration of treatment, and antipsychotic dose on the relationship between individual antipsychotics and QTc (Table S2, available online). For quetiapine, we found a significant inverse dose relationship ($p < .001$) and also an inverse relationship to age ($p < .001$) and percentage of females ($p = .001$). We also found a significant association between duration of treatment and QTc increase for risperidone ($p = .012$), and there was a trend toward an inverse dose-dependency for aripiprazole ($p = .059$), indicating that higher doses were associated with greater QTc decrease.

Meta-Analysis of QTc Prolongation Outcomes

Compared to placebo, none of the investigated antipsychotics caused a significant increase in the incidence of the 3 studied QTc prolongation measures (Table 4). However, the number of events was numerically higher for ziprasidone than for any of the other antipsychotics. In particular, the percentage of patients with an increase from baseline to endpoint >60 milliseconds was 3.14% for ziprasidone, 1.02% for placebo, and 0.45% for risperidone.

FIGURE 2 Forest plot of pooled corrected QT (QTc) changes. Note: Pooled QTc changes (milliseconds ± 95% CI) are shown for each antipsychotic with data from ≥2 studies and placebo.

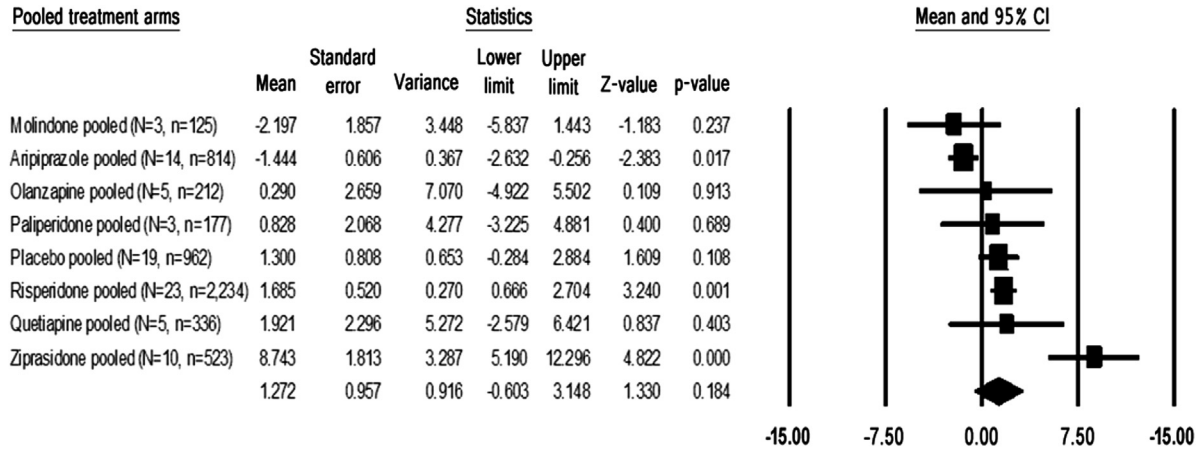

TABLE 3 Effect Size of Corrected QT Interval (QTc) Change With Antipsychotics Versus Placebo in Placebo-Controlled Trials

Treatment	No. of Treatment Arms	No. of Patients	Effect Size, Cohen's d	95% CI		p vs. Placebo	Heterogeneity Within Group	
				Lower	Upper		p	I^2(%)
Aripiprazole	8	571	−0.07	−0.21	0.08	.359	.942	0.00
Olanzapine	2	148	−0.04	−0.33	0.25	.783	.530	0.00
Paliperidone	4	139	0.03	−0.31	0.37	.850	.554	0.00
Quetiapine	1	15	−0.30	−1.02	0.42	.410	1.000	0.00
Risperidone	12	573	−0.01	−0.14	0.11	.856	.426	1.90
Ziprasidone	2	218	0.50	0.08	0.92	.020*	.083	66.78

*$p < .05$.

Risk of Bias Across and Within Trials

Although lack of blinding should have little or no effect on ECG-based QT interval assessments, in open trials in which QTc measurements were made manually, assessors may have been partial toward or against the investigated drug. As 78% of included studies did not describe how QTc measurements were made, it is difficult to assess the impact of this confounding effect, but most likely automated QTc measurements were used. The potential risk of bias was assessed separately for blinded RCTs (Table S3 and Figure S3, available online) and remaining open trials (Table S4 and Figure S4, available online).

Across the 24 randomized trials, we found the following risk of bias characteristics, as outlined in the Cochrane Handbook, chapter 13[42] (see Risk of Bias in Individual Studies section in this article): sequence generation: low risk: 14 trials (58.3%), unclear: 10 (41.7%), high risk: 0 (0%); allocation concealment: low risk: 8 trials (33.3%), unclear: 15 (62.5%), high risk: 1 (4.2%); blinding participants and personnel: low risk: 6 trials (25%), unclear: 17 (70.8%), high risk: 1 (4.2%); blinding of outcome assessment: low risk: 8 trials (33.3%), unclear: 16 (66.7%), high risk: 0 (0%); incomplete data: low risk: 15 trials (62.5%), unclear: 9 (37.5%), high risk: 0 (0%); Selective outcome reporting: low risk 5 trials (20.8%), unclear: 7 (29.2%), high risk: 12 (50%, high risk mostly being due to the fact that many trials did not report all 3 relevant categorical outcomes of QTc prolongation); other sources of bias: low risk: 23 trials (95.8%), unclear: 1 (4.2%), and high risk: 0 (0%).

For the 31 nonrandomized trials, clinicians were not blinded in all studies. Except for 1 trial (3.2%), in which the exclusion criteria included baseline QTc value <425,[65] none of the studies had clearly identifiable sources of bias in the inclusion criteria. Sample size was adequate in 22 trials (71.0%). Risk of bias due to unblinded ECG assessments was low in 4 trials (12.9%), unclear in 23 (74.2%), and high in 4 (12.9%). Differences in ECG procedures: low risk in 5 trials (16.1%), unclear in 26 (83.9%), and high risk in 0 (0%). Inadequate handling of losses to follow-up: low risk: 15 trials (48.4%), unclear: 4 (12.9%), and high risk: 12 (38.7%). Selective reporting: low risk: 11 trials (35.5%), unclear: 0 (0%), and high: 20 (64.5%, high risk mostly being due to the fact that many trials did not report all 3 relevant categorical outcomes of QTc prolongation). Finally, low risk of bias by other sources of bias was identified in 27 (87.1%) trials, unclear in 3 (9.7%), and high in 1 (3.2%).

Publication Bias

There was no discernible publication bias regarding QTc change, either by treatment group or in the head-to-head trials against placebo (data not shown). Although for risperidone and ziprasidone there were asymmetrical funnel plots, the bias was in the direction of reporting larger QTc changes (data not shown). However, regarding each of the 3 categorical outcomes relating to prolongation of the QTc, which were reported only in subgroups of the studies, there was significant publication bias indicating missing reports of QTc prolongation (data not shown). Notably, this publication bias applied to the antipsychotics and to placebo to the same degree.

DISCUSSION

In this meta-analysis, we found that ziprasidone was associated with a significant increase in the QTc interval both within drug comparisons and also when compared to pooled placebo or compared directly in placebo-controlled trials. This finding is consistent with findings in adults.[16,83-85] Although the magnitude of change (+8.74 milliseconds, CI = +5.19 to +12.30 milliseconds) seemed higher in youth than in a recent review of ziprasidone in 4,306 adults (+3.6 milliseconds, CI = −37.2 to +44.4 milliseconds),[86] the upper bound of the 95% CI, which indicates risk for individuals with especially large QTc increases, was almost 4 times higher in the adult population. Although the incidence of QTc prolongation across the 3 categorical outcomes was highest for ziprasidone, incidences were very low and not different from pooled placebo. Nevertheless, in the largest randomized active-controlled trial that compared ziprasidone with olanzapine in more than 18,000 adults, there was no difference in cardiac mortality or all-cause mortality over a 1-year duration,[87] calling into question the clinical relevance of QTc prolongation even with ziprasidone. However, these results should be interpreted in light of the fact that participants in safety studies are usually free of many other, clinically encountered risk factors, and often a baseline QTc value exceeding 450 milliseconds is an exclusion criterion.

TABLE 4 Incidence of Corrected QT Interval (QTc) Prolongation Across Drugs

Drug	Patients With QTc > Cut-Off, n	Total n	%	Patients With QTc > 500 ms, n	Total n	%	Patients With ΔQTc >60 ms, n	Total n	%
Placebo	5	265	1.89	0	425	0.00	3	295	1.02
Aripiprazole	5	232	2.16	0	257	0.00	0	97	0.00
Haloperidol	ND								
Molindone	0	65	0.00	0	65	0.00	0	65	0.00
Olanzapine	ND								
Paliperidone	0	154	0.00	0	154	0.00	0	154	0.00
Pimozide	ND			0	25	0.00	ND		
Quetiapine	1	64	1.56	0	64	0.00	0	49	0.00
Risperidone	9	711	1.27	0	1,402	0.00	6	1,348	0.45
Ziprasidone	16	500	3.20	1	500	0.20	12	382	3.14
Total	36	1,991	1.81	1	2,892	0.03	21	2,390	0.88

Note: ΔQTc = change in corrected QT interval from baseline to last follow-up; ms = miliseconds; ND = no data.

Across the included antipsychotics, aripiprazole significantly shortened the QTc interval, also compared to placebo, with a trend toward dose dependency. This is comparable to results in adults. In a meta-analysis of 828 adults treated with aripiprazole, aripiprazole decreased QTc compared to baseline, but not compared to placebo (−4.16 versus −3.56 milliseconds).[88]

Risperidone also increased the duration of the QTc interval, but this effect could not be differentiated from placebo, either using the pooled placebo arms or in head-to-head trials. None of the other antipsychotics assessed in this meta-analysis were significantly associated with increased QTc interval; however, the substantial QTc increase for pimozide seen in 1 single study[59] suggests that, as is the case for adults,[4,16] pimozide should very likely be avoided in youth with relevant risk factors for cardiac conduction abnormalities.

Of note, in a large multiple treatments meta-analysis,[83] the effect on QTc in adults by aripiprazole was not significantly different from placebo (OR = 0.01; CI = −0.13 to 0.15), whereas risperidone (OR = 0.25; CI = 0.15−0.36) and ziprasidone (OR = 0.41; CI = 0.31−0.51) increased QTc significantly compared to placebo.

Several limitations of our study require consideration. A more comprehensive list of trials may have been achieved by searching other databases as well, such as the Cochrane Database and Medline. However, PubMed also receives data from these sources, and an extensive overlap would be suspected. Also, including only generic names and not brand names might have limited the number of trials, but it is common practice to use generic names for reports of clinical trials.

There were a number of methodological issues in the included trials on which we based our meta-analysis and conclusions. First, most studies (78.2%) lacked a description of the specific method for correcting the QT interval based on heart rate, which may explain the large heterogeneity observed, and only 12 studies (21.8%) used manual readings. Second, authors used different and often inconsistent cut-off values when reporting QTc prolongation outcomes considered clinically relevant. Third, reporting of QTc outcomes was generally sparse. Only 6 studies (10.9%) reported the method for QT correction, baseline, endpoint, and change in QTc, each with SD, and the number of patients with prolongation events. Fourth, most studies were short-term, yet most of the QTc effect likely occurs early, as we did not find a trial duration effect on QTc change in our meta-regression analyses, except for risperidone, although these analyses may have lacked power.

Furthermore, there was generally little focus on possible ECG changes in efficacy and even in tolerability studies. Despite the widespread use of antipsychotics in youth and hundreds of prospective studies, only 55 studies had analyzable data. In fact, only 36 studies (65.5%) had published numerically reported data, and only 18 studies (32.7%) provided all 3 relevant categorical outcome data on the number of patients with QTc prolongation. The dearth of QTc data is particularly notable regarding randomized and active controlled antipsychotic trials. We were able to obtain data from 19 studies for which specific data were not reported in the published article, often simply stating that ECG findings were "normal." The number of articles missing data on some or all categorical QTc prolongation indices may indicate a potential reporting bias, particularly when authors did not define broadly used terms, such as "no abnormality," "no clinically significant ECG changes," or "possible mild conduction anomaly."[37]

Regarding study quality, we generally found very few instances of high risk of bias in any of the domains outlined by the Cochrane Handbook.[42] The RCTs identified by our search were generally of high standard; however, details of randomization, blinding, and allocation concealment were not always provided systematically.

Finally, the majority of RCTs on antipsychotics in children and adolescents are conducted by pharmaceutical companies, which could lead to reporting biases[89]; yet, without data from these industry-sponsored trials, we would be left with only 17 studies (30.9%). Thus, investigator-initiated, randomized, and long-term controlled studies should be encouraged.

Even though sudden death is extremely rare in children and adolescents,[90] it is important that clinicians are aware of the potential of antipsychotics to prolong QTc. Risk

factors for developing QTc prolongation, as well as for the probability that QTc prolongation has clinical implications, accumulate during life and do so more rapidly in individuals with psychotic disorders who often acquire cardiovascular risk factors.[91] Indeed, a very recent study of 61 youths with type 1 diabetes mellitus showed that, compared to healthy controls, patients with diabetes had a longer mean QTc duration and higher incidence of QTc prolongation.[92] However, the association between duration of QTc interval and the risk of TdP is by no means linear, and more research is needed to shed light on the connection between the biomarker and the clinical endpoint.[93]

Based on our findings and with respect to the impact on cardiac repolarization, first- and second-generation antipsychotics appear to confer little risk of QTc prolongation in otherwise healthy children and adolescents. Nevertheless, because individual risk factors interact with medication-related QTc effects, both medication and patient factors need to be considered when making antipsychotic medication choices. Consideration of these factors is especially relevant in clinical scenarios that may indicate higher patient-related risk factors, such as family history of long QT syndrome or sudden death, prior ECG with a QTc >450 milliseconds, palpitations at rest without anxiety, and dizziness or, especially, syncope upon exertion.[49] &

Accepted October 13, 2014.

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This work was supported by external doctoral research funding for Karsten Gjessing Jensen, MD, by the Dr. Sofus Carl Emil Friis and Hustru Olga Friis Scholarship and by the Educational Fund of the Danish Society of Psychiatry. This work was partially supported by the National Institute of Mental Health (NIMH) Advanced Center for Services and Intervention Research, The Zucker Hillside Hospital (P30MH090590).

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Dr. Correll served as the statistical expert for this research.

The authors thank the following authors and other individuals for sharing unpublished data with them that were included in this meta-analysis: Danielle Coppola, MD, Senior Director, Janssen Research and Development, LLC; Andy Forbes, PhD, Senior Director, Otsuka Pharmaceutical Development and Commercialization (OPDC); Paul J. Perry, PhD, Emeritus Professor of Pharmacy and Psychiatry, University of Iowa; Adam J. Savitz, MD, PhD, Janssen Research and Development, LLC; and Jennifer Stocks, MS, Director, Clinical Research, Supernus Pharmaceuticals.

Disclosure: Dr. Fink-Jensen has conducted an independent investigator- and university-initiated study supported by an unrestricted grant from Novo Nordisk. Dr. Correll has received grant or research support from NIMH, the American Academy of Child and Adolescent Psychiatry, Bristol-Myers Squibb, Janssen/Johnson and Johnson, Novo Nordisk A/S, Otsuka, and the Thrasher Foundation. He has served as a consultant to Actelion, Alexza Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly and Co., Genentech, the Gerson Lehrman Group, IntraCellular Therapies, Janssen/Johnson and Johnson, Lundbeck, Medavante, Medscape, Merck, NIMH, Otsuka, Pfizer, ProPhase, Roche, Sunovion, Supernus, Takeda, and Vanda. He has served on the speakers' bureau of Merck (non-promotional lectures only). He has presented expert testimony for Janssen. He has served as a member of the data safety monitoring boards for Cephalon, Eli Lilly and Co., Janssen, Lundbeck, Pfizer, Takeda, and Teva. Drs. Jensen, Juul, and Pagsberg report no biomedical financial interests or potential conflicts of interest.

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0890-8567/$36.00/©2015 American Academy of Child and Adolescent Psychiatry

http://dx.doi.org/10.1016/j.jaac.2014.10.002

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