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REVIEW

QTc Interval Prolongation with Therapies Used to Treat Patients with Parkinson's Disease Psychosis: A Narrative Review

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Abstract: In addition to the classic motor symptoms of Parkinson's disease (PD), people with PD frequently experience nonmotor symptoms that can include autonomic dysfunction and neuropsychiatric symptoms such as PD psychosis (PDP). Common patient characteristics, including older age, use of multiple medications, and arrhythmias, are associated with increased risk of corrected QT interval (QTc) prolongation, and treatments for PDP (antipsychotics, dementia medications) may further increase this risk. This review evaluates how medications used to treat PDP affect QTc interval from literature indexed in the PubMed and Embase databases. Although not indicated for the treatment of psychosis, dementia therapies such as donepezil, rivastigmine, memantine, and galantamine are often used with or without antipsychotics and have minimal effects on QTc interval. Among the antipsychotics, data suggesting clinically meaningful QTc interval prolongation are limited. However, many antipsychotics have other safety concerns. Aripiprazole, olanzapine, and risperidone negatively affect motor function and are not recommended for PDP. Quetiapine is often sedating, can exacerbate underlying neurogenic orthostatic hypotension, and may prolong the QTc interval. Pimavanserin was approved by the US Food and Drug Administration (FDA) in 2016 and remains the only FDA-approved medication available to treat hallucinations and delusions associated with PDP. However, pimavanserin can increase QTc interval by approximately 5–8 ms. The potential for QTc prolongation should be considered in patients with symptomatic cardiac arrhythmias and those receiving QT-prolonging medications. In choosing a medication to treat PDP, expected efficacy must be balanced with potential safety concerns for individual patients.

Keywords: QTc interval prolongation, antipsychotic agents, clozapine, quetiapine, pimavanserin

Introduction

Parkinson's disease (PD) is classically characterized by motor features related to central nervous system degeneration.[1] Although motor symptoms are central to the diagnosis of PD, it is now recognized as a motor and nonmotor systemic illness with involvement of the autonomic nervous system and multiple major neurotransmitter systems in the brain. Nonmotor manifestations include autonomic dysfunction and neuropsychiatric symptoms (NPS), which may manifest at any stage but are particularly prevalent in advanced PD.[2,3] The causes of both autonomic dysfunction and NPS are multifactorial, include disease-specific neurodegeneration, and can be exacerbated by treatments for PD.[4–7]

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Approximately 70%–80% of people with PD experience central and peripheral autonomic dysfunction, which can affect the cardiac sympathetic and parasympathetic systems.[8–10] Myocardial denervation has been observed in patients early in the course of PD disease and can lead to corrected QT interval (QTc) prolongation.[11] Prolongation occurs regardless of comorbidities or coadministration of QTc-prolonging medications[9,12] and appears to worsen with PD severity and age.[13] QTc prolongation >500 ms is particularly dangerous, as it can lead to arrhythmias, including Torsade de pointes (TdP), which is associated with sudden cardiac death.[14]

PD-related NPS include anxiety, depression, agitation, aggression, and psychosis.[3,5] NPS are caused by alterations to a variety of neurotransmitters such as dopaminergic, serotonergic, noradrenergic, and cholinergic signaling.[5] PD psychosis (PDP) affects more than 20% of all patients with PD and up to 70% of those with advanced PD.[6,15] The hallucinations and delusions that occur with PDP are typically visual, stemming from changes in dopaminergic and serotonergic pathways, including upregulation of 5-HT_{2A} signaling.[16] Auditory, olfactory, and tactile hallucinations may also manifest as the disease progresses.[6,7] PDP symptoms may be experienced as threatening or nonthreatening and add to patient distress and caregiver burden, such that their occurrence is a common reason for nursing home admission.[17–19] Due to the lack of effective treatment options for PDP, symptom management has traditionally involved reducing the dosage of medication used to treat Parkinsonism (eg, levodopa) at the cost of the motor benefits associated with the medication. That, however, is not always practical because of exacerbation of motor symptoms. Therefore, treatment often involves managing cholinergic deficit and serotonergic dysfunction by adding a new medication as needed to alleviate remaining psychotic symptoms.[6,15] Quetiapine has been the drug of choice in the past, despite a paucity of evidence supporting its use.

Although only pimavanserin is currently approved to treat hallucinations and delusions associated with PDP,[20] a variety of antipsychotics (eg, quetiapine, clozapine, and risperidone), acetylcholinesterase inhibitors (eg, donepezil, galantamine, rivastigmine), or the N-methyl-D-aspartate (NMDA) receptor antagonist memantine are commonly used (Table 1).[20–29] Data are inconsistent regarding the effects of antipsychotics on QTc interval prolongation.[30–32] Some studies suggest that antipsychotics and antidementia therapies have no or minimal cardiac effect, others show clinically significant changes in QTc interval, and still others have attributed effects on QTc interval to polypharmacy or cardiac comorbidities.[31,33,34]

A common mechanism by which drugs prolong the QTc interval includes blocking potassium channels encoded by the human ether-A-go-go-related gene (hERG), which drives cardiac and neuronal cell repolarization.[35,36] Antipsychotics, including aripiprazole, clozapine, olanzapine, pimavanserin, quetiapine, and risperidone, have been shown to be able to block or inhibit these channels in vitro.[35,37–39] Acetylcholinesterase inhibitors (eg, donepezil, galantamine, rivastigmine) can affect heart function by increasing acetylcholine levels, thereby activating cardiac acetylcholine receptors, which in turn open voltage-gated calcium channels to increase intracellular calcium, which can prolong the QTc interval.[40,41] Memantine blocks NMDA receptors, which when activated in the heart promote cardiac cell apoptosis and oxidative stress, and promote development of ventricular arrhythmias.[42] Thus, memantine's primary effect on the heart would be expected to be cardioprotective. However, some reports have suggested that memantine treatment could promote adverse cardiovascular events in some patients, though the mechanisms at play are unclear.[43,44] Given these potential mechanisms of QTc prolongation and the risk for QTc interval prolongation in older patients with PD, we reviewed the literature to better understand the relative prolongation induced by therapies commonly used in real-world settings to treat PDP.

Literature Search

PubMed and Embase databases were searched for English-language publications with available full text. No date restrictions were set. A search of titles and abstracts was conducted in December 2019 and January 2020. Both atypical antipsychotics and dementia medications regularly used to treat psychosis in people with PD were included in the search. The search string used the following terms: "QT interval prolongation" AND "aripiprazole OR clozapine OR olanzapine OR pimavanserin OR quetiapine OR risperidone OR donepezil OR galantamine OR memantine OR rivastigmine."

The authors assessed the titles and abstracts of search results for eligibility, and full text was obtained for all potentially relevant articles. Publications were included in the literature review if they described findings related to QTc interval among adults receiving at least 1 antipsychotic or dementia treatment of interest. Systematic

Table 1 Medications Commonly Used to Treat Parkinson's Disease Psychosis (Name, Disease State Studied, Evidence of QT Interval Prolongation >500 ms, Increase in QT Interval from Baseline)

Agent	Monotherapy Indication(s) in Adults	Target Dose in Adults[a]	Mechanism of Action
Aripiprazole[21]	Schizophrenia	10–15 mg/d	Possibly mediated via D_2 and 5-HT_{1A} receptor partial agonism and 5-HT_{2A} receptor antagonism
	Bipolar mania	15 mg/d	
Clozapine[22]	Schizophrenia	300–450 mg/d	Possibly mediated via D_2 and 5-HT_{2A} receptor antagonism
Olanzapine[25]	Schizophrenia	10 mg/d	Possibly mediated via dopamine and 5-HT_2 receptor antagonism
	Bipolar (mania or mixed episodes)	10–15 mg/d	
Pimavanserin[20]	Parkinson's disease psychosis	34 mg/d	Possibly mediated via inverse agonist and antagonist activity at 5-HT_{2A} receptors and to a lesser extent at 5-HT_{2C} receptors
Quetiapine[29]	Schizophrenia	150–750 mg/d	Possibly mediated via D_2 and 5-HT_2 receptor antagonism
	Bipolar mania	400–800 mg/d	
	Bipolar depression	300 mg/d	
Risperidone[24]	Schizophrenia	4–8 mg/d	Possibly mediated via D_2 and 5-HT_2 receptor antagonism
	Bipolar mania	1–6 mg/d	
Donepezil[26]	Alzheimer's dementia	5–23 mg/d	Possibly increases acetylcholine concentration through reversible inhibition of its hydrolysis by cholinesterase
Galantamine[27]	Alzheimer's dementia	16–24 mg/d	
Memantine[28]	Alzheimer's dementia	10 mg twice daily	Possibly mediated via open-channel N-methyl-D-aspartate receptor antagonism
Rivastigmine[23]	Alzheimer's dementia	3–6 mg twice daily	Possibly increases acetylcholine concentration through reversible inhibition of its hydrolysis by cholinesterase
	Parkinson's disease dementia	3–6 mg twice daily	

Notes: [a]Most medications are used off label in Parkinson's disease–related psychosis (PDP). The effective dose for patients with PDP may be lower than that listed in the product label.
Abbreviation: d, day.

reviews and meta-analyses, prospective, retrospective, and observational studies, and case reports were included. Reports or studies in patients <18 years of age were excluded, as were reports of QTc interval prolongation following overdose and congenital long QT syndrome. Narrative review articles, preclinical studies, disease management guidelines, conference abstracts, and correspondence were also excluded. Study results and details from case reports regarding medication effects on QTc interval were extracted from all articles meeting the inclusion criteria.

Of the 463 publications returned by the database searches, 90 had available full text, met the eligibility criteria, and were included in the literature review. Due to the stringency of our search criteria, some publications that reported QTc prolongation may have been missed. In particular, the authors were aware of 2 additional relevant articles not included in the search results that presented sufficient value to be included in this review. These articles described cardiac safety (including effects on QTc interval) in patients receiving clozapine[45] and donepezil.[46] The literature review, therefore, included 12 systematic reviews or meta-analyses (Table 2), 54 prospective or retrospective studies (Table 3), and 26 case reports (Table 4).

The definition of QTc prolongation varied across publications. Some studies and case reports considered prolongation to occur at ≥500 ms, whereas others used lower limits (eg, >450–470 ms), and still others referred to the magnitude of increase from baseline (eg, >60 ms).

Table 2 Systematic Reviews and Meta-Analyses

Reference	Patient Population	Effect on QTc Interval	Risk of QTc Prolongation
Multiple medications			
Huhn et al 2019[31]	Schizophrenia	Mean difference (95% CI) vs placebo: Aripiprazole: −0.43 ms (−3.62 to 2.77) Olanzapine: 4.29 ms (1.91–6.68) Quetiapine: 3.43 ms (0.94–6.00) Risperidone: 4.77 ms (2.68–6.87)	NR
Aronow et al 2018[30]	Mental disorders	SMD (95% CI) vs placebo: Aripiprazole: NR Olanzapine: −0.14 (−0.29 to 0.01) Quetiapine: 0.67 (0.14–1.19) Risperidone: NR	RR (95% CI) vs placebo: Aripiprazole: 0.89 (0.08–9.81) Olanzapine: 0.34 (0.16–0.70) to 0.46 (0.04–4.96) Quetiapine: 2.87 (0.12–70.08) Risperidone: 0.62 (0.09–4.41) to 1.90 (1.29–2.79)
Takeuchi et al 2015[59]	Schizophrenia or schizoaffective disorder concurrently using ≥2 APs	Mean change from baseline: Clozapine + risperidone: −11 to −10 ms Clozapine + aripiprazole: 4 ms Clozapine + placebo: −3 to 13 ms Risperidone alone: −8 ms	NR
Asmal et al 2013[87]	Schizophrenia	Mean difference (95% CI): Quetiapine vs olanzapine: 4.81 (0.34–9.28) Quetiapine vs risperidone: 2.21 (−5.05 to 9.48)	RR (95% CI) vs active comparator: Quetiapine vs aripiprazole: 3.21 (0.13–76.74) Quetiapine vs olanzapine: 12.96 (0.73–229.17) Quetiapine vs risperidone: 1.34 (0.36–5.04)
Leucht et al 2013[57]	Schizophrenia or related disorders	SMD (95% CI): Aripiprazole vs placebo: 0.01 (−0.13 to 0.15) Aripiprazole vs quetiapine: −0.17 (−0.33 to 0.01) Aripiprazole vs risperidone: −0.25 (−0.40 to −0.10) Aripiprazole vs olanzapine: −0.21 (−0.37 to −0.05) Olanzapine vs placebo: −0.22 (−0.31 to −0.11) Olanzapine vs risperidone: −0.04 (−0.16 to 0.09) Quetiapine vs placebo: 0.17 (0.06–0.29) Quetiapine vs olanzapine: −0.04 (−0.18 to 0.11) Quetiapine vs risperidone: −0.08 (−0.22 to 0.06) Risperidone vs placebo: −0.25 (−0.36 to −0.15)	OR (95% CI): Aripiprazole: 0.01 (−0.13 to 0.15) Olanzapine: 0.22 (0.11–0.31) Quetiapine: 0.17 (0.06–0.29) Risperidone: 0.25 (0.15–0.36)
Chung et al 2011[56]	Schizophrenia	Mean difference (95% CI) vs placebo or other APs: Aripiprazole: −2.49 (−6.87 to 1.88; $P = 0.26$) Olanzapine: 0.38 (−3.05 to 3.81) Risperidone: 2.51 (−0.10 to 5.11)	RR (95% CI): Aripiprazole: 0.33 (0.12–0.93) Olanzapine: 0.84 (0.44–1.58) Risperidone: not available
Aripiprazole			
Polcwiartek et al 2015[58]	Patients with risk factors for TdP	Mean difference (95% CI) vs placebo: −0.73 (−0.87 to −0.6; $P < 0.001$)	RR (95% CI) vs placebo: 0.85 (0.51–1.43; $P = 0.54$) RR (95% CI) vs other antipsychotics: 0.53 (0.32–0.88; $P = 0.01$)
Olanzapine			
Kishi et al 2015[88]	Agitation	SMD (95% CI) vs placebo: −0.14 (−0.29 to 0.01; $P = 0.08$)	RR (95% CI) vs placebo: 0.34 (0.16–0.70; $P = 0.003$)

(*Continued*)

Table 2 (Continued).

Reference	Patient Population	Effect on QTc Interval	Risk of QTc Prolongation
Risperidone			
Rabkin, 2014[122]	Patients across multiple age decades	Little effect on QTc, but a trend of increasing QTc with age: person in mid-70s beginning risperidone with QTc of 1 SD greater than mean would have treatment response 1 SD greater than average response to risperidone	NR
Cartwright et al 2013[120]	People receiving risperidone	0.6 to 13.9 ms increase from baseline	0–50% of patients with QTc >420 ms or changes ≥30 ms; higher proportion in patients with poor risperidone metabolism, ie, higher plasma concentration
Gopal et al 2013[121]	Patients in registration studies of risperidone	NR	QTcF >60 ms and ≥500 ms in 0.1% of patients receiving risperidone and 0.1% receiving placebo; all of these patients >74 years old
Rattehalli et al 2016[123]	Schizophrenia	NR	RR (95% CI): 8.46 (1.07–67.07)

Abbreviations: AP, antipsychotic; CI, confidence interval; OR, odds ratio; NR, not reported; QTc, corrected QT interval; QTcF, Fridericia-corrected QT interval; RR, risk ratio; SD, standard deviation; SMD, standardized mean difference; TdP, Torsades de pointes.

Antipsychotics

Most publications reported on multiple antipsychotics rather than assessing the effects of a single drug and evaluated treatments in people with schizophrenia, not PDP. The magnitude of effect on QTc interval and risk of prolongation >500 ms varied across antipsychotics and between studies. Analyses reported a 0.4-ms reduction in QTc interval with aripiprazole and a 3- to 6-ms increase with quetiapine, olanzapine, and risperidone,[31] with quetiapine and olanzapine associated with increases greater than those with risperidone ($P < 0.01$).[47] In contrast, 1 study found no QTc prolongation with olanzapine, quetiapine, or risperidone,[48] with similar rates of change in QTc interval among these 3 medications (−0.0099 to 0.0030 ms/day).[49]

Many factors can affect a patient's QTc intervals, including cardiac and hepatic comorbidities, use of QTc-prolonging medications, older age, female sex, and time of day.[50–52] The choice of antipsychotic may contribute to 17%–55% of a patient's response, with 10%–12% of this variation attributed to genetic expression.[53]

In general, QTc prolongation appears to occur infrequently with atypical antipsychotics. A search of the World Health Organization pharmacovigilance database found that, as of January 2010, 489 reports exist on QT prolongation, TdP, and/or cardiac arrest related to olanzapine, and 520 reports exist on QT prolongation, TdP, and/or cardiac arrest related to quetiapine since the medication approvals in 1996 and 1995, respectively.[54] Analysis of a database encompassing Austria, Germany, and Switzerland reported a QTc prolongation frequency of 0.006% among patients treated with clozapine or quetiapine and 0% with aripiprazole, olanzapine, and risperidone.[55]

Aripiprazole

Aripiprazole was mentioned in 6 systematic reviews and meta-analyses,[30,31,56–59] 13 prospective or observational studies,[33,47,55,60–69] and 4 case reports.[70–73] The literature consistently showed that aripiprazole is associated with small reductions in QTc interval. Four meta-analyses of aripiprazole described reduced mean QTc intervals (−0.43 to −3.38 ms) and reduced risk of prolongation with aripiprazole when compared with placebo (risk ratios [RR], 0.33 [95% confidence interval (CI), 0.12–0.93] to 7.58 [0.40–143.03]; Table 2).[30,31,56,58]

Six studies of 1351 patients with psychiatric disorders reported no clinically significant QTc interval prolongation with aripiprazole (Table 3).[60,62,63,65,66,74] These findings were supported by a cross-sectional study that controlled for patient age, sex, diagnosis, length of illness, setting (inpatient vs outpatient), use of mood stabilizers or antidepressants, number of antipsychotics, and antipsychotic dose.[33] In that study, aripiprazole was associated with a

Table 3 Prospective, Retrospective, Observational Studies

Reference	Medications	Study Design	Patient Population	N	Mean Age, Years	Effect on QT Interval
Multiple medications						
Friedrich et al 2020[55]	Aripiprazole Clozapine Olanzapine Quetiapine Risperidone	Observational	Psychiatric inpatients	291,510	NR	• Proportions of patients with long QTc: o Aripiprazole: 0.00% o Clozapine: 0.006% o Olanzapine: 0.00% o Quetiapine: 0.006% o Risperidone: 0.00%
Hatta et al 2019[61]	Aripiprazole Clozapine Olanzapine Risperidone	Naturalistic (real world)	Acute-phase schizophrenia and related disorders	1543	47.1	• Overall, 1.7% rate of QTc ≥450 and 0% QTc ≥500 ms at discharge or 3 months after hospitalization
San-Juan-Rodriguez et al 2019[131]	Donepezil Galantamine Memantine Rivastigmine	Retrospective cohort	Alzheimer's disease	73,475	81.8	• Proportions of patients with prolongation: o Donepezil: 0.1% o Galantamine: 0.2% o Memantine: 0.1% o Rivastigmine: 0.01% • Combination therapy with memantine plus acetylcholinesterase inhibitor: 0.1%
Tümüklü et al 2019[81]	Clozapine Olanzapine Quetiapine Risperidone	Pilot	Treatment-naïve schizophrenia	60	40.0	• Mean ± SD QTc: o Clozapine: 443.5 ± 30.1 o Olanzapine: 427.5 ± 24.2 o Quetiapine: 427.4 ± 30.1 o Risperidone: 422.5 ± 14.0
Spellmann et al 2018[68]	Aripiprazole Olanzapine Quetiapine Risperidone	Retrospective	Schizophrenia	199	33.3	• Significantly greater QTc prolongation in women than men ($P = 0.02$) and in older vs younger patients ($P = 0.010$) • Change in mean QTc vs baseline: o Aripiprazole: 4.6 ms (P = NS) o Olanzapine: 3.6 ms (P = NS) o Quetiapine: 14.4 ms ($P = 0.001$) o Risperidone: 2.0 ms (P = NS)

Khan et al 2017[92]	Olanzapine Quetiapine Risperidone	Retrospective, cross-sectional	Psychiatry inpatients	600	25[a]	• 51.7% of patients experienced QT-related DDIs • DDIs were more common among women (31.3%) than men (20.3%) and associated with taking ≥6 concomitant medications and ≥2 QT-prolonging medications • APs implicated in QT-related DDIs were o Olanzapine plus: escitalopram (8%), zuclopenthixol (5%), fluoxetine (4.2%), metronidazole (1.6%), quetiapine (1.4%) o Quetiapine plus: haloperidol (3%), risperidone (2%), fluoxetine (2%), escitalopram (1.9%), paroxetine (1.1%) o Risperidone plus: haloperidol (4%), fluoxetine (2.3%), escitalopram (2.3%), zuclopenthixol (1.4%), domperidone (1.3%)
Rodríguez-Leal et al 2017[80]	Clozapine Olanzapine Quetiapine Risperidone	Naturalistic (real world)	Psychiatric inpatients	225	54.6	• 4% annual rate of QTc prolongation • Drugs implicated in prolongation: olanzapine (44.4%), clozapine (22.2%), quetiapine (22.2%), risperidone (22.2%) • Multiple drugs implicated in prolongation in 55.6% of cases
Viscogliosi et al 2017[96]	Olanzapine Quetiapine	Prospective	Alzheimer's disease agitation	50[b]	NR	• 30.4% of patients receiving olanzapine and 26.0% receiving quetiapine had QT prolongation >10%
Barbui et al 2016[33]	Aripiprazole Clozapine Olanzapine Quetiapine Risperidone	Cross-sectional survey	Psychiatric illness	725	NR	• Mean QTc interval 5.3 ms longer in women than men • QTc interval 7.44 ms longer in patients receiving ≥2 APs ($P = 0.006$), but AP dose had a greater effect on QTc interval than did polypharmacy • People receiving aripiprazole had significantly less risk of QTc prolongation ($P = 0.013$)
Olsen et al 2016[49]	Olanzapine Quetiapine Risperidone	Pragmatic, randomized	Inpatients with psychosis	173	34.1	• Rate of QTc interval change per day: o Olanzapine: −0.0099 ms o Quetiapine: −0.0027 ms o Risperidone: −0.0030 ms

(*Continued*)

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Table 3 (Continued).

Reference	Medications	Study Design	Patient Population	N	Mean Age, Years	Effect on QT Interval
Sasaoka et al 2016[67]	Aripiprazole Clozapine Donepezil Galantamine Olanzapine Quetiapine Risperidone	Time-to-onset analysis	Adverse events reported to the JADER database			• Reporting odds ratios (95% CI) of long QT syndrome: o Aripiprazole: 2.0 (1.3–3.2) o Clozapine: 2.5 (1.4–4.3) o Donepezil: 10.3 (8.2–13.0) o Galantamine: 2.5 (1.1–5.7) o Olanzapine: 3.1 (2.1–4.5) o Quetiapine: 1.8 (1.1–3.0) o Risperidone: 2.4 (1.7–3.5) • Median 14.0 days to onset of long QT syndrome with donepezil
Kram et al 2015[64]	Aripiprazole Olanzapine Quetiapine Risperidone	Retrospective cohort	Critically ill with delirium	156	61.5	• QTc prolongation >470 (men) or >480 ms (women) in 31.4% of patients • QTc prolongation >500 ms in 19.2% of patients
Suzuki et al 2014[32]	Olanzapine Risperidone	Prospective, single arm	Schizophrenia	21	26.9	• Females, but not males, had a significant decrease in QTc interval (−18.2 ms) after switching from olanzapine to risperidone ($P = 0.008$)
Suzuki et al 2013[47]	Aripiprazole Olanzapine Quetiapine Risperidone	Prospective, single arm	Schizophrenia	222	35.2	• Mean QTc interval significantly longer for quetiapine than for aripiprazole or risperidone ($P < 0.05$), and for olanzapine or risperidone ($P = 0.006$) • Sex difference in QTc response was observed only with olanzapine, with significantly longer mean QTc for females (419.5 ms) than males (402.8 ms; $P = 0.007$) • Female sex, olanzapine, and quetiapine contributed to prolonged QTc interval; body mass index contributed to shortened QTc interval
Suzuki et al 2013[69]	Aripiprazole Olanzapine Quetiapine Risperidone	Prospective	Psychiatric inpatients	20	36.2	• Change in QTc after switching AP: o Aripiprazole → quetiapine: 16.0 ms ($P = 0.004$) o Olanzapine → quetiapine: 9.3 ms (P = NS) o Risperidone → quetiapine: 8.7 ms (P = NS)

Aberg et al 2012[53]	Olanzapine Quetiapine Risperidone	Genome-wide association	Schizophrenia	738	40.4	• Only quetiapine significantly affected QTc interval; effects on QTc prolongation were mediated by *SLC22A23* gene ($P < 0.001$) • Mixed-model estimate of AP effects on QTc interval: o Olanzapine: −10% o Quetiapine: 19% o Risperidone: −14%
Watanabe et al 2012[52]	Olanzapine Risperidone	Prospective, controlled	Schizophrenia	106	35.9[b]	• Mean QTcF was higher for patients than healthy volunteers during daytime (11.8 ms; $P = 0.002$) and nighttime (14 ms; $P = 0.002$) • Mean ± SD differences between nighttime and daytime QTcF: o Risperidone: 13.9 ± 15.0 ms ($P < 0.001$ for night vs day; $P = 0.003$ for difference vs olanzapine) o Olanzapine: 3.5 ± 11.7 ms o Healthy controls: 5.2 ± 10.5 ms
Meyer-Massetti et al 2011[54]	Olanzapine Quetiapine	Retrospective database	People with adverse drug reactions	1009[b]	45–47	• Absolute numbers of QT prolongation, Torsade de pointes, or cardiac arrest: o Olanzapine: n = 489 o Quetiapine: n = 520
Yang et al 2011[51]	Clozapine Risperidone	Cross-sectional, naturalistic	Psychiatric inpatients	549	50.2	• QTc interval was higher with clozapine vs risperidone ($P < 0.009$), and clozapine was associated with increased risk of QTc prolongation • Adjusted relative risk (95% CI) of QTc prolongation: o Clozapine: 3.77 (1.22–11.21) o Risperidone: 1.19 (0.94–1.51) • Sex and age were risk factors for increased QTc ($P < 0.01$)
Ozeki et al 2010[48]	Olanzapine Quetiapine Risperidone	Retrospective	Schizophrenia inpatients	412[b]	NR	• Incidence of QTc >470 ms (males) or >480 ms (females) o Olanzapine: 0.0% o Quetiapine: 0.0% o Risperidone: 1.6%
Correll et al 2009[78]	Clozapine Olanzapine Quetiapine	Retrospective case control	Psychiatric inpatients receiving 2 APs (cases) or 1 AP (controls)	111	43.3	• Mean QTc duration and dispersion were similar between cases and controls • QTc prolongation occurred in patients receiving olanzapine + quetiapine (n = 2), olanzapine + clozapine (n = 1), olanzapine (n = 3), quetiapine (n = 2), and clozapine (n = 1) • Clozapine treatment and age ≥44 years were associated with QTc interval ($P < 0.01$)

(*Continued*)

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Table 3 (Continued).

Reference	Medications	Study Design	Patient Population	N	Mean Age, Years	Effect on QT Interval
Chan et al 2007[60]	Aripiprazole Risperidone	Randomized, double blind, parallel group	Schizophrenia	83	35	• No clinically significant increases in QTc interval with aripiprazole or risperidone • Mean ± SD change in QTcB: −1 ± 39 ms (aripiprazole) and 8 ± 34 ms (risperidone; *P* = NS between groups)
Harrigan et al 2004[91]	Olanzapine Quetiapine Risperidone	Prospective, randomized, open-label, parallel group	Chronic treatment for psychotic disorder	85[b]	38–39[b]	• Mean change from baseline QTc: o Olanzapine: 1.7 ms o Quetiapine: 5.7 ms o Risperidone: 3.6–3.9 ms • For all drugs, mean change from baseline QTc was similar in the presence vs absence of a metabolic inhibitor
Lin et al 2004[50]	Clozapine Risperidone	Observational	Schizophrenia inpatients	412	43.3	• 14.3% incidence of QTc prolongation (>421 ms) in patients, including those receiving clozapine (n = 64) and risperidone (n = 75) • Factors associated with QTc prolongation: clozapine dose, female gender, increased age
Cohen et al 2001[77]	Clozapine Olanzapine	Observational	Schizophrenia	38[b]	32.8–34.0[b]	• Incidence of prolonged QTcB interval: o Clozapine: 71.4% o Olanzapine: 64.7%
Aripiprazole						
Madhusoodanan et al 2004[65]	Aripiprazole	Naturalistic (real world), observational	Inpatients age >60 years with schizophrenia/schizoaffective disorder and comorbidities	10	70.3	• Mean −13.3-ms QTc interval change with aripiprazole • QTc increased in 2 patients (5–22 ms) and decreased in 8 patients (7–47 ms)
Keck et al 2003[63]	Aripiprazole	Randomized, double blind, placebo controlled	Inpatients with bipolar I disorder	262	40.5	• 1 (0.4%) placebo patient with QTcB ≥450 ms and ≥10% increase from baseline, which normalized with QTcFDA calculation • No clinically significant increases in QTc interval with aripiprazole
Pigott et al 2003[66]	Aripiprazole	Randomized, double blind, placebo controlled	Schizophrenia	310	42.0	• Mean QTc changes from baseline to endpoint, aripiprazole vs placebo: o QTcB: −6.94 vs −0.01 ms o QTcFDA: −5.51 vs −0.86 ms
Kane et al 2002[62]	Aripiprazole	Randomized, double blind, placebo controlled	Inpatients with schizophrenia or schizoaffective disorder	414	38.6	• Change from baseline QTcB interval was statistically similar between aripiprazole and placebo

Clozapine						
Xiang et al 2015[82]	Clozapine	Observational	Schizophrenia inpatients	3482	45.5	• Overall 2.4% incidence of QTc prolongation (men, 2.5%; women, 2.1%; P = NS) • Odds ratio (95% CI) for QTc prolongation: o Clozapine: 2.4 (1.4–4.2) o Olanzapine: 0.3 (0.1–0.9) o Quetiapine: 0.2 (0.05–1.02) o Risperidone: 0.5 (0.3–1.01)
Grande et al 2011[79]	Clozapine	Retrospective	Psychiatric outpatients	82	31.2	• No statistically significant increase in QTc interval or prevalence of QTc prolongation with clozapine
Kang et al 2000[45]	Clozapine	Retrospective	Schizophrenia inpatients	61	31	• 24.5% incidence of new-onset ECG abnormalities after clozapine use • 15.8% incidence of new abnormalities among patients receiving another AP at baseline, 46.7% incidence among treatment-naïve patients • Abnormalities included 1 case of transient QTc prolongation (533 ms), which reverted to normal (430 ms) within 1 month despite increased clozapine dose • Significant positive relationship between clozapine dose and change in QTc interval ($P < 0.05$)
Donepezil						
Isik et al 2012[46]	Donepezil	Prospective, single arm	Alzheimer's disease	52	74.9	• No changes to ECG parameters in comparison with baseline
Memantine						
Zhou et al 2019[140]	Memantine	Randomized, controlled	Alzheimer's disease	80	71	• Prolongation reported for 2 patients receiving memantine plus citalopram and 0 patients receiving memantine only
Olanzapine						
Petersen et al 2014[95]	Olanzapine	Observational case series	Psychiatric inpatients	91	39[a]	• 1% incidence of QTc prolongation (1 patient receiving 90 mg/d olanzapine)
Kwon et al 2012[93]	Olanzapine	Randomized, double blind, parallel group	Schizophrenia	193	34.9	• Mean 3.5 ms increase from baseline in QTc interval with olanzapine
Brown et al 2005[89]	Olanzapine	Retrospective cohort	Psychiatric inpatients with psychosis	23[b]	53.9[b]	• QTc interval increased from 406 ms to 422 ms after olanzapine (95% CI, 410–433 ms)

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Table 3 (Continued).

Reference	Medications	Study Design	Patient Population	N	Mean Age, Years	Effect on QT Interval
Lindborg et al 2003[94]	Olanzapine, intramuscular	Pooled data from randomized, double-blind trials	Psychiatric inpatients with agitation	1054	36.3–77.6	• No differences in interpretation of results when using QTcB vs QTcF formulas • Incidence of QT prolongation statistically similar between olanzapine and placebo • Mean QTc interval change from baseline statistically similar between olanzapine and placebo 2-hr post dose • Older patients with dementia had decreased QTc interval vs placebo 24-hr post dose (6.8 ms; $P = 0.01$)
Czekalla et al 2001[90]	Olanzapine	Pooled data from randomized, double-blind, controlled trials	Schizophrenia and schizoaffective disorders	1342[b]	38	• 17.9% incidence of clinically significant increase (≥30 ms) in maximum QTcB value • Mean change in QTcB interval ranged from −7.83 ± 23.09 ms to 8.44 ± 27.12 ms; all changes statistically nonsignificant for 5–10 mg/day; only the 15 mg/day group in 1 study had a significant increase (8.44 ms; $P = 0.038$)
Quetiapine						
Lee et al 2019[109]	Quetiapine	Prospective, observational cohort	Critically ill with delirium	95	58.6[b]	• Mean difference vs baseline: 2.7 ms ($P = 0.50$)
Dube et al 2018[106]	Quetiapine	Prospective, observational cohort	Critically ill with delirium	103	59.5	• 13.6% incidence of QTc interval prolongation >60 ms from baseline • 13.6% incidence of QTc interval >500 ms • Median change from baseline 20.5 ms
Fox et al 2020[107]	Quetiapine	Prospective, observational cohort	Critically ill with delirium	40	66.6	• 10.0% incidence of QTc prolongation, with both patients receiving 0–1 concomitant QTc-prolonging medication
Mangan et al 2018[110]	Quetiapine	Retrospective	Critically ill with delirium	154	50	• QTc change from baseline: 2 (interquartile range, −16 to 21) • 13% rate of QTc >500 ms • Patients with QTc prolongation were significantly older (mean ± SD, 54 ± 11 vs 45 ± 17 years; $P = 0.002$) and had higher baseline QTc (454 ± 33 vs 442 ± 30 ms; $P = 0.045$)
Kim et al 2016[108]	Quetiapine	Randomized, open label, crossover	Healthy volunteers	33	NR	• 2.9% incidence of QTc prolongation of 30–60 ms • Greatest increase in QTc interval (10.2 ms) occurred by 1 hr post dose ($P < 0.001$)

Nielsen et al 2015[111]	Quetiapine	Randomized, double blind	Schizophrenia	114[b]	NR	• (Mean ± SD) change from baseline: o QT: −15.5 ± 27.5 ($P < 0.001$) o QTcB: 7.9 ± 21.9 ($P = 0.001$) o QTcF: −0.5 ± 17.9 ($P = 0.76$) • 9.6% incidence of QTcF increase >20 ms
Potkin et al 2013[112]	Quetiapine	Randomized, open label	Schizophrenia or schizoaffective disorder	33[b]	NR	• Mean ± SD change from baseline with quetiapine: o QTcF: 1.3 ± 11.1 ms o QTcB: 12.6 ± 14.2 ms • No significant effect of increasing plasma concentration on QTc change
Devlin et al 2010[105]	Quetiapine	Randomized, double-blind, placebo-controlled pilot	Critically ill with delirium	36	62.4[b]	• 39% incidence of QTc prolongation >60 ms from baseline with quetiapine • 22% incidence of QTc >500 ms with quetiapine
Risperidone						
Suzuki et al 2014[128]	Risperidone	Prospective, single arm	Schizophrenia	66	37.4	• QTc interval was longer in patients with *ABCB1 3435CT + TT* genotype, low weight, and elderly ($P < 0.05$ for all)
Ranjbar et al 2012[126]	Risperidone	Case-controlled cohort	Inpatients with psychosis	60[b]	39.6[b]	• QTcB increment was statistically significant over time in the risperidone but not in the placebo group • Risk ratio of QTcB >450 ms at discharge for risperidone vs placebo ranged from 1.08 to 1.2
Suzuki et al 2012[127]	Risperidone	Prospective, single arm	Psychiatric illness, primarily schizophrenia	61	32.4	• Significant, positive correlation between plasma paliperidone (main risperidone metabolite) and QTc interval ($r = 0.361$; $P = 0.004$); no correlation between QTc interval and risperidone dose or patient age
Azorin et al 2006[124]	Risperidone	Randomized, double blind, parallel group, flexible dose	Schizophrenia	89[b]	35	• 26% incidence of borderline prolonged QTcB interval (QTcB 431–450 [males] and 451–470 ms [females]) with risperidone • 4.5% incidence of QTcB prolongation (QTcB >450 [males] and >470 ms [females]) with risperidone

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Table 3 (Continued).

Reference	Medications	Study Design	Patient Population	N	Mean Age, Years	Effect on QT Interval
Sala et al 2005[34]	Risperidone	Naturalistic, observational	Female psychiatric inpatients	38	45	• Mean ± SD QTc interval after treatment: o Antipsychotic only (including risperidone): 421 ± 20 ms o Antipsychotic plus antidepressant or lithium: 438 ± 30 ms ($P < 0.05$ vs monotherapy) • Borderline QTc prolongation in 1 monotherapy and 7 polytherapy patients ($P < 0.05$) • Two patients receiving risperidone (combination with escitalopram or clomipramine) had QTc prolongation of 55 and 66 ms
Llerena et al 2004[125]	Risperidone	Genotype analysis	Schizophrenia inpatients	35	43	• Higher QTc intervals in patients with 1 *CYP2D6* active gene vs 2 ($P < 0.05$) • Number of *CYP2D6* active genes was related ($P < 0.05$) to dose-corrected plasma risperidone, active moiety (risperidone + 9-OH-risperidone), and risperidone/9-OH-risperidone ratio
Yerrabolu et al 2000[129]	Risperidone	Retrospective	Psychiatric illness receiving risperidone maintenance therapy	20	70	• QTcB significantly increased with risperidone • No patients experienced symptomatic ventricular arrhythmia

Notes: [a]Median age. [b]Data are for subjects receiving 1 of the medications included in this review and do not reflect subjects receiving other medications.

Abbreviations: AP, antipsychotic; CI, confidence interval; DDI, drug–drug interaction; ECG, electrocardiogram; JADER, Japanese Adverse Drug Event Report; NR, not reported; NS, not specified; QTc, corrected QT interval; QTcB, Bazett's corrected QT interval; QTcF, Fridericia corrected QT interval; QTcFDA, FDA Neuropharmacological division–corrected QT interval; SD, standard deviation.

Table 4 Case Reports and Case Series

Reference	Patient Age, Years	Patient Sex	Psychiatric Condition	Medications Taken at Admission	Effect on QT Interval
Multiple medications					
Nordin et al 2018[73]	30	Male	Schizophrenia	Clozapine 100 mg/d	QTc was 504 ms with clozapine, reduced to 460–494 ms after switching to aripiprazole 15 mg/d + ECT
Nelson et al 2013[72]	42	Male	Schizophrenia	Quetiapine 400 mg/d	Quetiapine discontinued after hospitalization (QTc 528 ms) for sepsis, reinitiated to treat psychotic symptoms, and discontinued after 1 dose when QTc interval measured 644 ms. QTc returned to 414 ms 23 days later. Aripiprazole 2.5 mg/d initiated, but TdP and QTc 624 ms occurred 5 days later. Aripiprazole discontinued and QTc normalized (450 ms) after 14 days
Vieweg et al 2013[130]	28–87	Male (n = 4)/ female (n = 9)	Various	Various	All cases had QTc prolongation with APs in the absence of overdose. Risk factors for QTc prolongation: risperidone, female sex, older age, heart disease, hypokalemia, bradycardia, liver disease, QTc-prolonging drugs (other than risperidone), and metabolic inhibitors
Lazarczyk et al 2012[71]	37	Female	Schizophrenia	Aripiprazole: 20 mg/d Haloperidol: 3 mg/d Escitalopram: 20 mg/d Benzodiazepines: dose NR	Addition of risperidone 1–2 mg/d increased QTc interval from 458 to 508 ms. Prolongation remained despite discontinuation of potential QTc-prolonging drugs. Administration of other APs, including clozapine, did not affect QTc
Cohen et al 2001[83]	30	Male	Schizophrenia	Clozapine: 500 mg/d	QTc with clozapine 500 mg/d (monotherapy): 624 ms. QTc with olanzapine 10 mg/d + valproic acid 1800 mg/d: 504 ms
Aripiprazole					
Karz et al 2015[70]	80	Female	Schizoaffective disorder, bipolar type	Aripiprazole: 10 mg/d Fluoxetine: 20 mg/d Lisinopril: 5 mg/d Simvastatin: 10 mg/d Aspirin: 81 mg/d	Aripiprazole was discontinued post-MI. QTc interval increased (475 to 568 ms), remained elevated for 2 weeks, and decreased to 444 ms after reinitiating aripiprazole, titrated to 15 mg/d

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Table 4 (Continued).

Reference	Patient Age, Years	Patient Sex	Psychiatric Condition	Medications Taken at Admission	Effect on QT Interval
Clozapine					
Kim et al 2018[85]	45	Male	Schizophrenia	Clozapine: 400 mg/d	QTcB: 508 ms QTcF: 484 ms QTc Framingham: 479 ms QTc Hodges: 475 ms
Dewan et al 2004[84]	45	Male	Schizophrenia	Clozapine: 150 mg/d Quetiapine: 800 mg/d	QTc interval increased from 428 ms to 472 ms within 2 weeks of initiating clozapine; QTc returned to 428 ms ≤3 days of switching to quetiapine
Tanner et al 2003[86]	31	Male	Schizophrenia	Clozapine: 400 mg/d	QTc 479 and tachycardia (HR 110 bpm) with clozapine; normal QTc interval and HR after switching to olanzapine 10 mg/d and antihypertensive drugs (beta blocker, loop diuretic, angiotensin-converting enzyme)
Donepezil					
Vogel et al 2019[119]	26	Female	Major depressive disorder	Quetiapine (100 mg in the morning, 200 mg midday, 300 mg before bed), divalproex sodium ER 500 mg BID, metoprolol ER 25 mg/d, montelukast 10 mg/d, polyethylene glycol-3350 17 g/d, calcium + vitamin D, pantoprazole 40 mg/d, cephalexin 500 mg QID	QTc 425–438 ms and tachycardia (112 bpm) on admission. Reducing quetiapine dose and adding donepezil 10 mg BID increased QTc to 496 ms. QTc 416 ms after discontinuing donepezil (quetiapine 50 mg TID and pantoprazole 40 mg/d continued)
Gurbuz et al 2016[132]	84	Female	Alzheimer's disease	Admission: donepezil 10 mg/d, ramipril 5 mg/d, acetylsalicylic acid 100 mg/d	QTcB 624 ms on admission, which developed to TdP. QTc 450 ms 3 days after discontinuing donepezil
Kitt et al 2015[134]	80	Female	Alzheimer's disease	Donepezil 10 mg/d, bumetanide 2 mg/d, perindopril 8 mg/d, lansoprazole 30 mg/d, atorvastatin 20 mg/d, diltiazem M/R 60 mg/d, fluoxetine 60 mg/d	Donepezil dose increased from 5 mg/d 2 weeks before admission. QTc 490 ms on admission developed to TdP with QTc 550 ms
Hadano et al 2013[133]	86	Female	Alzheimer's disease	Donepezil 5 mg/d, amlodipine 5 mg/d	QTc 436 ms on admission with atrial fibrillation, developed to 5 episodes of TdP (QTc 433 ms). No TdP after discontinuing both amlodipine and donepezil

Takaya et al 2009[136]	83	Female	Alzheimer's disease	Donepezil 5 mg/d, bisoprolol 5 mg/d	QTc 645 with atrial fibrillation on admission developed to 2 episodes of TdP. QTc decreased to 485 ms ≤2 weeks after discontinuing donepezil
Tanaka et al 2009[137]	Case 1: 90 Case 2: 87	Case 1: male Case 2: female	Case 1: Alzheimer's disease Case 2: NR	Case 1: donepezil 10 mg/d Case 2: amlodipine 5 mg/d, spironolactone 25 mg/d, warfarin 1 mg/d, donepezil 5 mg/d	Case 1: QT interval 514 ms with A/V block 3 days after increasing donepezil dose from 5 mg/d. QTc 456 ms 5 days after switching donepezil to orciprenaline 30 mg/d Case 2: QTc 461 with atrial fibrillation on first admission, QTc 594 on second admission developed to TdP. QTc 446 ms after switching donepezil to orciprenaline 30 mg/d
Leitch et al 2007[135]	76	Female	Alzheimer's disease, depression	Donepezil 10 mg/d, omeprazole 20 mg/d, escitalopram 10 mg/d, propranolol 80 mg/d	QTc 590–777 ms on admission with TdP. QTc 436 ms after discontinuing donepezil, escitalopram, and propranolol and initiating mirtazapine
Galantamine					
Fisher et al 2008[139]	85	Male	Alzheimer's disease, vascular dementia	Galantamine ER 8 mg/d, irbesartan 75 mg/d, clopidogrel 75 mg/d, simvastatin 20 mg/d, pantoprazole 40 mg/d, ergocalciferol 1000 IU/d, calcium carbonate 600 mg BID, acetaminophen 1 g BID	Syncopal episodes after initiating galantamine 8 mg/d. Galantamine was discontinued, then restarted 1.5 years later. QTcB 421 and QTcF 423 ms while off galantamine increased to 503 and 477 ms, respectively, after reinitiating treatment. QTcB 443 and QTcF 452 ms after discontinuing galantamine and irbesartan
Olanzapine					
Lorenzo et al 2020[99]	70	Male	Agitated delirium while hospitalized	Tamsulosin, terazosin, ibuprofen	QTc 447 ms on admission, increased to 485 ms during hospitalization and treatment with haloperidol, ziprasidone, lorazepam, diazepam, and/or dexmedetomidine. QTc normalized after switching to olanzapine IV 2.5–5 mg every 4 hr
Jeon et al 2011[97]	42	Female	Psychosis	Olanzapine 2.5 mg/d, warfarin 3 mg/d, diazepam 4 mg/d, valproic acid 300 mg BID, topiramate 100 mg BID	QTc 591 ms on admission with dysrhythmia and intermittent TdP in a patient with a history of open-heart surgery. QTc prolongation and TdP persisted after discontinuing olanzapine. Pacemaker implanted. Patient discharged with a prescription for warfarin 3 mg/d only

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Table 4 (Continued).

Reference	Patient Age, Years	Patient Sex	Psychiatric Condition	Medications Taken at Admission	Effect on QT Interval
Kaufman et al 2011[98]	43	Male	Obsessive-compulsive disorder, panic disorder with agoraphobia, generalized anxiety disorder, bipolar not otherwise specified	Fluvoxamine 100 mg/d, alprazolam 0.5 mg BID, lorazepam, fluconazole, chemotherapy with arsenic trioxide 0.15 mg/kg IV	QTc 500 ms during chemotherapy. Fluvoxamine and fluconazole discontinued. Olanzapine 2.5 mg BID initiated without affecting QTc value
Quetiapine					
Gupta et al 2015[116]	48	Female	Bipolar disorder	Lisinopril, quetiapine	QTc 507 ms on admission developed to TdP and cardiac arrest after administration of moxifloxacin
Hasnain et al 2014[117]	14–77	Male (n = 3)/ female (n = 9)	NR	NR	Twelve case reports of quetiapine-associated QTc prolongation.[a] Analysis found no correlation between QTc interval and quetiapine dose
Aghaienia et al 2011[113]	63	Female	Schizoaffective disorder, anxiety	Atorvastatin 10 mg/d, estropipate 0.75 mg/d, famotidine 40 mg/d, lorazepam 1 mg/d, medroxyprogesterone 2.5 mg/d, montelukast 10 mg/d, omeprazole 20 mg/d, paroxetine 40 mg/d, quetiapine ER 800 mg/d, sitagliptin 100 mg/d, trihexyphenidyl 7.5 mg/d, vitamin D 2000 IU	QTc 525 on admission. Quetiapine replaced with paliperidone and QT normalized. Quetiapine reinitiated after discharge, patient was rehospitalized, and quetiapine switched again to paliperidone
Digby et al 2010[114]	58	Female	NR	Quetiapine 50 mg TID and 200 mg/d, citalopram 60 mg/d, hydrochlorothiazide 25 mg/d, clonazepam 1 mg TID, acamprosate 333 mg TID, atenolol 25 mg BID, ranitidine 150 mg/d, mirtazapine 30 mg/d, rosuvastatin 10 mg/d	QTc 720 ms on admission with TdP. QTc normalized with temporary pacemaker and discontinuation of all medications potentially associated with QT prolongation. Follow-up QTc 410 ms
Vieweg et al 2005[118]	45	Female	Depression	Quetiapine 100 mg/d, escitalopram 20 mg/d	QTc 548 ms with TdP and hypomagnesemia on admission
Furst et al 2002[115]	46	Female	Schizophrenia	Quetiapine 800 mg/d, sertraline 100 mg/d, lovastatin 10 mg/d	QTc 569 ms 2 months after initiating lovastatin. Patient took 20 mg lovastatin on day of ECG. Lovastatin dose decreased (5 mg/d), with follow-up QTc 424 ms

Notes: [a]Includes case reports published by Aghaienia et al,[113] Digby et al,[114] Furst et al,[115] Gupta et al[116] and Vieweg et al[118].

Abbreviations: AP, antipsychotic; A/V, atrioventricular; BID, twice daily; bpm, beats per minute; d, day; ECG, electrocardiogram; ECT, electroconvulsive therapy; ER, extended release; HR, heart rate; IV, intravenous; MI, myocardial infarction; NR, not reported; QID, 4 times daily; QTc, corrected QT interval; QTcB, Bazett's corrected QT interval; QTcF, Fridericia corrected QT interval; TdP, Torsade de pointes; TID, 3 times daily.

reduced risk of QTc interval prolongation in contrast to other drugs ($P = 0.013$), whereas no significant effect was observed with clozapine, olanzapine, quetiapine, or risperidone. Case reports of patients receiving aripiprazole were consistent with findings from the meta-analyses and clinical studies (Table 4).[70,73]

The product label for aripiprazole lists QT prolongation as a rare event, occurring in fewer than 1 in 1000 patients.[21] The evidence for QTc interval reduction with aripiprazole, plus its mechanism of action as a dopamine receptor blocker and agonist, would count in its favor as a treatment for PDP. However, aripiprazole is associated with worsened motor function in PD and, therefore, is not recommended for PDP.[75,76]

Clozapine

The effect of clozapine on QTc interval was described in 1 systematic review,[59] 13 studies,[33,45,50,51,55,61,67,77–82] and 6 case reports.[71,73,83–86] One study found no significant change from baseline in mean QTc interval or the incidence of QTc prolongation,[79] but this is inconsistent with findings from other researchers. Four studies of 4951 psychiatric inpatients have reported an increased risk of QTc prolongation with clozapine (odds ratios, 1.006 [95% CI, 1.003–1.008] and 2.4 [95% CI, 1.4–4.2]), with the magnitude of effect being dose dependent (Table 3).[45,50,51,82]

Case reports also reported heterogeneous effects of clozapine. A 37-year-old woman who experienced QTc prolongation (an increase from 458 to 508 ms) with risperidone 1–2 mg/day had no such response with clozapine (dose not specified; Table 4).[71] On the other hand, QTc intervals of 472–504 ms have been reported in men ages 30–45 years taking clozapine 100–400 mg/day.[73,84,86] In each case, QTc returned to baseline after switching to aripiprazole, quetiapine, or olanzapine.

The label for clozapine warns about the risk of QTc prolongation,[22] but the risk appears to be dose dependent,[45,50] and patients with PDP require doses 10-fold lower (6.25–50 mg/day) than those used to treat schizophrenia.[6,75] However, it is important to keep in mind that because the effect is dose-dependent, even a dose that would on its own not cause a significant effect could interact with other QTc-modifying factors (eg, concomitant medication with QTc prolongation effects, age, comorbidities) to cause clinically significant QTc prolongation.[50–52]

Because clozapine does not worsen motor function, it has been used to treat PDP. Long-term treatment with clozapine, however, can cause autonomic dysfunction, including increased heart rate and reduced heart rate variability. Autonomic dysfunction is already a concern in PD, and it further increases the risk of QTc prolongation.[77] Also, clozapine is associated with agranulocytosis, though the risk is dose dependent and usually avoided in patients with PD if low doses are used. Finally, severe neutropenia (neutrophil count $<0.5 \times 103/\mu L$) has been reported in 0.91% of patients treated with clozapine.[6,75] As a result, weekly blood count monitoring is required during the first year of treatment, which increases the burden for patients and caregivers.[6,75]

Olanzapine

Olanzapine was mentioned in 6 systematic reviews and meta-analyses,[30,31,56,57,87,88] 26 studies,[32,33,47–49,52–55,61,64,67–69,77,78,80,81,89–96] and 4 case reports.[83,97–99] Multiple meta-analyses and clinical studies reported no or minimal effect of oral olanzapine on QTc interval,[88,89,91] with a placebo-adjusted standardized mean difference of −0.14 ms[30] and 1.7-ms increases from baseline.[91] Intramuscular olanzapine reduced QT interval by approximately 3 ms during the 24 hours post injection.[30,88,89,94] Any QTc effects may be sex-specific: in a study by Suzuki et al,[47] women who received olanzapine experienced longer mean QTc intervals than men ($P = 0.007$), whereas such differences were not observed with other antipsychotics (Table 3).

Case reports of patients receiving polypharmacy who had prolonged QTc intervals described no cardiac effects of olanzapine (Table 4).[83,97–99] To our knowledge, the only exception reported is that of an elderly woman with a QTc prolongation triggered by the addition of the CYP450 inhibitor ciprofloxacin to an established regimen of olanzapine, valsartan, and azathioprine.[100]

The product label for olanzapine does not warn of QTc effects and reports no significant differences in comparison with placebo in the proportions of patients experiencing clinically important QT changes.[25] Despite the reported cardiac safety of olanzapine, the medication is ineffective in treating psychotic symptoms in PDP and affects motor function;[6,75,76] it therefore is not recommended in this patient population.

Pimavanserin

No studies of pimavanserin were identified in our literature search. However, the product label for pimavanserin advises that the medication prolongs the QT interval.[20] Although clinical trials for pimavanserin were not

identified in the literature search, QT interval prolongation was mentioned in the publications of these trials.[101–104] In a Phase 3 study of patients with PDP, pimavanserin was associated with a mean 7.3-ms increase in Bazett's-corrected QTc interval over 6 weeks, in comparison with no change for placebo.[102] During the open-label extension (OLE) of this study, 12 (2.6%) patients experienced individual events of a Fridericia-corrected QTc interval >500 msec, and 6 (1.3%) patients experienced an adverse event of prolonged QT interval.[104] In the 12-week Phase 2 trial of pimavanserin in patients with Alzheimer's disease, those who received pimavanserin had a mean 9.4-ms increase in Fridericia-corrected QTc interval from baseline, in comparison with a decrease of 2.0 ms for placebo.-[101] One patient in each treatment group had a change from baseline of ≥60 ms, recorded at day 15 for both. In the 12-week open-label period of a Phase 3 trial of pimavanserin in patients with dementia-related psychosis, including patients with Parkinson's disease dementia, pimavanserin was associated with a mean Fridericia-corrected QTc prolongation of 5.4 msec, with 1 (0.3%) patient experiencing an increase in QTc of ≥60 ms.[103] In all studies, the effect of pimavanserin on QTc interval was not associated with related adverse events.[101–104] In 2019, the authors performed a retrospective review of medical records for 48 patients treated with pimavanserin in their movement disorders clinic, with the goal of determining whether their electrocardiograms showed any evidence of QTc abnormalities. No QTc prolongation was identified for any of the 48 patients (data on file).

Pimavanserin is currently the only antipsychotic approved by the US Food and Drug Administration (FDA) for the treatment of hallucinations and delusions associated with PDP.[20] The product label warns about the increased risk of QTc prolongation.[20] Pimavanserin is recommended for patients with PDP who do not have preexistent QTc prolongation and are not taking QTc-prolonging medications.[20] A recent OLE safety study demonstrated the long-term safety and tolerability of pimavanserin specifically in patients with PDP, showing that types of adverse events reported in an OLE study were comparable to the 6-week placebo-controlled studies.[104] Patients were excluded if they received other medications known to prolong the QT interval, or had a baseline Bazett-corrected QT interval of >460 for males or >470 for females.[104]

Quetiapine

Quetiapine was mentioned in 4 systematic reviews and meta-analyses,[30,31,57,87] 25 studies,[33,47–49,53–55,64,67–69,78,80,81,91,92,96,105–112] and 8 publications describing case reports.[72,113–119] A Cochrane meta-analysis reported no significant difference in risk of QTc prolongation between quetiapine and comparator antipsychotics, but RRs (95% CIs) favored comparator drugs: aripiprazole, 3.21 (95% CI, 0.13–76.74); olanzapine, 12.96 (95% CI, 0.73–229.17); and risperidone, 1.34 (95% CI, 0.36–5.04) (Table 2).[87] Quetiapine was associated with a 4.81-ms (95% CI, 0.34–9.28) greater increase in QTc interval than was olanzapine, with similar QTc effects as for risperidone.[87] The results from individual studies were heterogeneous, with some studies[48,111,112] showing minimal or no effect on QTc interval and others[91,106,108] suggesting that quetiapine is associated with mean or median changes from baseline of −5 to +20 ms (Table 3). A mean change in QTc interval of −0.5 ± 17.9 ms was observed with quetiapine doses of 400–600 mg/day, but in the same study, 9.6% of patients had increases in QTc interval >20 ms in relation to baseline.[111] In other studies of psychiatric patients, quetiapine was associated with QTc prolongation of 1.3–5.7 ms in relation to baseline.[69,91,112] In healthy volunteers, quetiapine elicited mean QTc interval increases of 10.2 ms, with prolongation occurring in a dose-dependent manner.[108]

The product label for quetiapine states that QTc effects were not observed in clinical trials but postmarketing reports suggest that prolongation can occur in the context of overdose, comorbidity, and coadministration of QTc-prolonging medications.[29] Quetiapine does not appear to worsen extrapyramidal symptoms. However, orthostatic hypotension and somnolence are commonly reported adverse events and may lead to falls because of its properties as an alpha-1 adrenergic and histamine H1 antagonist.[29] In addition, randomized controlled trials have not consistently shown efficacy in reducing psychosis symptoms in this patient population.[6,75,76]

Risperidone

Risperidone was mentioned in 10 systematic reviews and meta-analyses,[30,31,56,57,59,87,120–123] 28 studies,[32–34,47–53,55,60,61,64,67–69,80–82,91,92,124–129] and 2 case reports.[71,130] Risperidone generally elicited minimal changes in QTc interval, although interpatient and interstudy variability were observed (Tables 2 and 3). Whereas 1 study

identified QTc increases from baseline of up to 12 ms with 3–8 mg/day risperidone,[126] other studies found no significant effect on QTc interval.[32,129] A Cochrane meta-analysis reported a greater risk of prolonged QTc intervals in patients receiving risperidone versus placebo.[123]

In healthy individuals, the QTc interval follows a circadian pattern, being slightly prolonged (approximately 5 ms) at night in relation to daytime. Risperidone appears to exaggerate this pattern (approximately 14 ms prolongation), whereas olanzapine does not.[52]

As with olanzapine, the product label for risperidone does not warn of QTc effects and reports no significant differences in comparison with placebo in the proportions of patients experiencing clinically important QT changes.[24,25] However, risperidone should be avoided for PDP because of the increased risk of extrapyramidal symptoms.[6,75,76]

Dementia Therapies

A retrospective cohort study of Medicare claims between 2006 and 2014 examined cardiovascular events for patients treated with memantine monotherapy, acetylcholinesterase inhibitor monotherapy (ie, donepezil, rivastigmine, galantamine), or a combination of memantine and acetylcholinesterase inhibitor.[131] QTc interval prolongation was reported for 0.1%−0.2% of all patients, with no difference between monotherapy and combination therapy. The risk of QTc interval prolongation was also similar between acetylcholinesterase inhibitor and memantine monotherapies and between combination therapy and memantine monotherapy.

Donepezil

The effect of donepezil on QTc interval was mentioned in 3 studies[46,67,131] and 7 case reports of 8 patients.[119,132–137] The prospective studies identified no significant changes from baseline in the QTc intervals of elderly individuals with Alzheimer's disease receiving donepezil 5–10 mg (Table 3).[46,131] In contrast, a database analysis reported that donepezil, but not antipsychotics or galantamine, was associated with greater odds of long QT syndrome (LQTS) in comparison with other adverse events, with a median 14 days to onset of LQTS.[67] Seven case reports (n = 8) published between 2007 and 2019 described QTc intervals of 463 to 777 ms,[119,132–137] including 4 cases of TdP and 1 instance of TdP without QTc prolongation (433 ms) (Table 4).[132,133,135,136] The product label for donepezil does not mention QTc effects in the context of normal (ie, non-overdose) use.[6,138]

Galantamine

Two studies[67,131] and 1 case report[139] described QTc prolongation during galantamine treatment (Table 3). One study identified a 0.2% rate of QTc prolongation.[131] In the case report, QTc prolongation (503 ms) occurred in an elderly man who restarted galantamine after a 2-week interruption.[139] QTc interval had shortened to 443 ms within 4 days of discontinuing the second round of galantamine (Table 4). Similar to the donepezil label, the galantamine label does not mention effects on QTc during normal use.[27]

Memantine

Two studies[131,140] mentioned the effects of memantine on QT interval (Table 3). In the first, 2 (5%) patients with Alzheimer's disease who received memantine 20 mg/day plus citalopram 30 mg/day experienced QTc interval prolongation, whereas no prolongation was observed in patients who received memantine alone.[140] The second study showed that 0.1% of Medicare patients who received memantine experienced QTc interval prolongation.[131]

Rivastigmine

Only 1 study assessed the effects of rivastigmine on QTc interval, reporting a 0.01% incidence of QTc prolongation with rivastigmine in patients with Alzheimer's disease (Table 3).[131] As with other dementia therapies, the product label for rivastigmine does not mention the drug's effects on QTc in the context of normal use.[23] However, the FDA did not specifically examine QTc prolongation at the time of approval.

Discussion

Psychosis can occur at any stage of PD and is often treated with antipsychotics or dementia medications. Given the motor and nonmotor features of PD, general patient characteristics (eg, older, with comorbidities), and heterogeneous effects of antipsychotics and dementia therapies, the optimal PDP medication has been unclear.[6] Dementia therapies are generally preferred for treating cognitive impairment, despite a lack of studies supporting their efficacy for treating hallucinations and delusions associated with PDP. Antipsychotics such as aripiprazole, olanzapine, and risperidone affect motor function and should be avoided in people with PD.

Clinicians must balance the expected benefits with the potential harms when selecting the appropriate medication

from the remaining options, clozapine, pimavanserin, and quetiapine. For example, clozapine can reduce PDP symptoms but is associated with dose-dependent QTc interval prolongation[45,50,51,82] and autonomic dysfunction, which is already a concern in PD and further increases the risk of QTc prolongation.[77] Furthermore, the requirement for ongoing weekly blood draws to monitor for neutropenia and agranulocytosis adds substantial patient and caregiver burden.[6,75] Quetiapine has not shown efficacy in treating PDP[6,75,76] and is not recommended for patients with comorbidities or who receive concomitant QT-prolonging drugs owing to possible prolongation.[29,91,106,108] Quetiapine can also exacerbate underlying fatigue and cause sedation and orthostatic hypotension, all of which may potentially increase the risk of falling.[29] Pimavanserin was approved by the FDA in April 2016 and is the only medication approved to treat hallucinations and delusions associated with PDP, but it should be avoided in patients with risk factors for prolonged QT interval or who receive QT-prolonging medications.[20] Pimavanserin has been shown to increase QTc interval by approximately 5–8 ms.[20,102]

As PD progresses, therapeutic options may become increasingly limited due to comorbidities and other medications the patient requires; this may coincide with further development of non-motor symptoms that require treatment. Patients with advanced PD frequently present with multiple risk factors for QTc prolongation or the need for medications that cause QTc prolongation that may interact, such as older age and cardiac comorbidities. In such patients, treatments may include an antipsychotic for psychosis, an acetylcholinesterase inhibitor for apathy, domperidone for orthostatic hypotension, or citalopram for depression. The Movement Disorder Society's (MDS) treatment guidelines caution that citalopram poses a risk for QTc prolongation in older adults, especially at higher doses, and domperidone requires electrocardiogram (ECG) monitoring due to its known association with ventricular tachyarrhythmia and sudden cardiac death in PD patients.[141] While MDS guidelines state that acetylcholinesterase inhibitors do not require specialized monitoring, they do acknowledge that these medications could affect the patient's ECG,[141] and the American Geriatrics Society advises caution when combining acetylcholinesterase inhibitors with antipsychotics that affect blood pressure.[142] It is critical that the physician considers these effects before prescribing these medications to avoid an interaction that produces clinically significant QTc prolongation.

While we pursued a broad review of the literature, some reports may have been excluded due to restrictions that we placed on the search. In particular, conference abstracts can report current analyses that could include data of QTc prolongation with the medications that we examined. Due to the inconsistent and limited availability of conference abstracts and lack of peer review, we considered these abstracts outside of the scope of this review. Additionally, our search terms required mention of "QT interval prolongation," which could have excluded some publications that reported QTc prolongation using alternative terms or phrases such as "QT prolongation" or "arrhythmia."

The magnitudes of QT interval prolongation in the studies included in this review were relatively small (often 5–10 ms), and the clinical importance of small changes in the QT interval has not been determined. QTc prolongation >500 ms, which has been associated with a risk of TdP, is generally rare with antipsychotics and dementia treatments.[54,55] The risk of QTc prolongation is increased with the presence of autonomic dysfunction, comorbidities (eg, heart disease, congestive heart failure, myocardial infarction, left ventricular dysfunction, arrhythmia, liver disease, septic shock, thyroid disease), electrolyte imbalance, polypharmacy, increased age, female sex, and genetic variation.[12,51,53,117,122,130,143,144] Symptomatic cardiac arrhythmias, congenital QT interval prolongation, hypomagnesemia, and hypokalemia are particular risk factors for further QT prolongation. In the PD population, autonomic dysfunction, comorbidities (eg, heart, liver, or endocrine conditions), polypharmacy, and older age are common,[12,145–147] and PD occurs at a slightly higher frequency in males than females (1.6:1).[148]

Potential therapies to treat PDP should be considered in the context of other drugs that a patient is receiving for comorbidities to avoid the potential for additive effects of multiple QT-prolonging medications. Drug classes associated with QT interval prolongation include Class 1A or Class 3 antiarrhythmics (eg, quinidine, procainamide, amiodarone, sotalol); antibiotics such as gatifloxacin and moxifloxacin; the antipsychotics ziprasidone, chlorpromazine, and thioridazine; and others (eg, pentamidine, levomethadyl acetate, methadone).[20,29] Also, because most medications included in this review are metabolized by the CYP450 system, coadministration with CYP450 metabolic inhibitors can theoretically increase plasma concentrations of 1 or more of these agents, increasing the risk for cardiotoxicity.[91,100,117,130] In clinical studies, metabolic

inhibitors appear not to influence QTc interval in patients receiving olanzapine, quetiapine, or risperidone,[91,112] but they can interact with clozapine.[22] Some authors have also suggested that dose, which is often elevated in patients who require polypharmacy, may play a larger role than polypharmacy in QTc prolongation.[33,45,50,51,78] Most QTc data from this review were from patients with schizophrenia, who require higher antipsychotic doses than do patients with PDP to alleviate symptoms of psychosis. The use of lower doses for PDP might, therefore, be associated with a reduced risk of QTc prolongation in this patient population.

Clinicians should take care when evaluating QT intervals, to avoid unnecessarily discontinuing useful medications. Although Bazett's formula is commonly used to calculate QTc, it can lead to overcorrection and misunderstanding of the true cardiac effects of medications.[149] This was demonstrated in a case in which a patient receiving clozapine 400 mg/day had a resting heart rate of 80 beats per minute and QTc values of 508 ms (Bazett's), 484 ms (Fridericia), 479 ms (Framingham), and 475 ms (Hodges).[85] Many publications in our review did not report the formula used, and of those that did, Bazett's was more common than Fridericia. In the study by Nielsen et al,[111] QT intervals were corrected with both Fridericia's and Bazett's formulas. Whereas the Fridericia formula showed a mean QTc change from baseline of −0.5 ms ± 17.9 ms with quetiapine, Bazett's formula suggested that QTc interval increased by 7.9 ms ± 21.9 ms. Because of the tendency to overcorrect the QT interval, Bazett's formula is not recommended by the American Heart Association for electrocardiogram calculations.[149]

The risk of QT interval prolongation should be evaluated for an individual patient with PD in the context of selecting an appropriate therapy but should not prevent initiating a treatment for hallucinations and delusions. The presence of psychosis in patients with PD has been associated with increased caregiver burden,[19] nursing home placement,[18] and mortality,[17] indicating a need for timely implementation of an effective treatment strategy.

Importantly, none of the publications described in this review were specifically conducted in patients with PDP. Most studies of antipsychotics were done in patients with schizophrenia or other psychiatric disorders, and most studies of antidementia treatments were done in patients with Alzheimer's disease. Though some characteristics may overlap between patients with PDP and patient populations in these studies, risk factors for medication-related cardiac effects may be more common in certain patient populations than in others. For example, increased age and polypharmacy might increase the risk of QTc prolongation in patients with PDP, and these factors may influence treatment decisions. Clinical trials are therefore needed to determine the QTc-prolonging effects of each drug in this unique patient population. Despite the recent requirements set forth by some insurance companies, mandating electrodiagnostic testing before starting a single drug may not be necessary because there is not a clear consensus on the effect of most of these medications on QTc prolongation.

Conclusions

In general, second-generation antipsychotics are associated with small changes in QTc interval, and pathological QTc prolongation and TdP are rare. The potential for QTc prolongation, however, is important to consider in patients with symptomatic cardiac arrhythmias and those receiving QT-prolonging medications. In choosing a medication to treat PDP, the expected efficacy must be balanced by possible safety concerns for individual patients.

Symptoms of PDP need to be treated and a patient's risk of QT interval prolongation should factor into treatment choice with what is known about medication efficacy and other safety concerns. Pimavanserin is the only FDA-approved treatment for hallucinations and delusions associated with PDP. Clozapine is also effective but can cause (or exacerbate) autonomic dysfunction and requires frequent blood monitoring throughout treatment. The efficacy of quetiapine has not yet been proven in PDP, and other antipsychotics are generally ineffective in PDP or negatively affect motor function. Although clinicians may prescribe acetylcholinesterase inhibitors in the setting of PDP with cognitive impairment, to date, clinical trials have not demonstrated their efficacy in treating specific symptoms of psychosis. Studies are needed that compare the effects of antipsychotics on QT interval in patients with PDP.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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