Which psychotropics carry the greatest risk of QTc prolongation?

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Series Editor

Mrs. A, age 68, has a 40-year history of schizoaffective disorder with comorbid anxiety disorder not otherwise specified, type 2 diabetes mellitus, and hypertension. She takes furosemide, 40 mg/d, lisinopril, 20 mg/d, and metformin, 2,000 mg/d, for hypertension and diabetes; lorazepam, 1.5 mg/d, and paroxetine, 40 mg/d, for anxiety; and quetiapine extended release, 800 mg/d, for psychotic features and mood dysregulation with schizoaffective disorder. Mrs. A's husband died 5 years ago and she lives alone in a senior care facility. Mrs. A uses a weekly pill reminder box because her residential facility does not monitor medication adherence. She sees her psychiatrist once a month and her primary care provider every 3 months. She has no history of illicit drug, alcohol, or tobacco use.

Two weeks ago, Mrs. A was found leaning against the wall in a hallway, complaining of dizziness and disorientation, and unable to find her way back to her apartment. In the emergency department, her serum potassium is low (3.0 mEq/L; normal range: 3.5 to 5.0), fasting glucose is elevated (110 mg/dL; range: 65 to 99), and ECG reveals a prolonged QTc interval of 530 milliseconds. Before this episode, Mrs. A had been medically stable without mood or psychotic symptoms, although her daughter reported medication self-administration was becoming difficult.

Exposure to psychotropics carries a risk of QTc prolongation. The QT interval is an ECG measure of ventricular depolarization and repolarization. The QTc designation indicates a correction for heart rate with increasing heart rate correlating with a shorter QT interval. Readings of 440 milliseconds are considered normal.[1] QTc prolongation is defined as >450 milliseconds for men and >470 milliseconds for women.[2] An increase in the QT interval is a predictor of serious cardiac events.[3]

Antidepressants and antipsychotics have been associated with QTc prolongation. When identifying agents that could disrupt cardiac conduction, clinicians need to consider whether the drug's molecular structure, receptor affinity, or pharmacologic effects are most critical.[2] Although these may be important, patient-specific variables that increase the risk of QTc prolongation may have greater impact. These include:

- age >65
- female sex

Practice Points

- **Screen patients for risk factors for prolonged QTc interval**, such as congenital long QT syndrome, family history of cardiac conduction abnormalities, and previous occurrences of medication-mediated QTc prolongation.
- **Obtain baseline and steady state ECG** when initiating high-risk agents, particularly when administering combination therapy.
- **Use the lowest effective dose** of antidepressants and antipsychotics and monitor symptoms closely.

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- electrolyte imbalances (specifically low serum potassium and magnesium levels)
- high or toxic serum levels of the suspected drug
- preexisting cardiovascular impairment, such as bradycardia.[4,5]

Other risk factors include concurrent use of an agent with similar cardiovascular effects or one that competes for metabolism (either enzymatic or at the binding site), physiologic limitations such as renal insufficiency, and medication changes that may increase or decrease psychotropic clearance.[4,6] Geriatric patients with dementia have an increased risk for cardiovascular-related death.[7,8]

Antidepressants

Among tricyclic antidepressants, most reports of QTc prolongation involve amitriptyline and maprotiline.[9] Risk factors include demographics (eg, female sex, age), personal or family history (congenital long QT syndrome, cardiovascular disease), and concurrent conditions or drug use, particularly those associated with QTc prolongation.[3] Desipramine and nortriptyline also have been identified as high-risk agents.[10]

QTc prolongation has been reported with all selective serotonin reuptake inhibitors at plasma concentrations above the therapeutic level.[11] Fluoxetine-associated QTc prolongation was limited to cases of overdose or when additional risk factors were reported.[4] QTc prolongation from psychotropics could increase the risk of torsades de pointes, according to an analysis of the FDA Adverse Event Reporting System.[12] In 2011, the FDA reported an increased risk of abnormal heart rhythms—including QTc prolongation—with citalopram doses >40 mg/d.[13] Although cases of QTc prolongation with paroxetine have not been reported,[11] the Arizona Center for Education and Research on Therapeutics lists paroxetine with other agents that may increase the risk for QTc prolongation with concurrent use of medications that may prolong QTc interval.[14] Venlafaxine doses >300 mg/d may require additional cardiac monitoring.[5,12] Data from venlafaxine poisoning case reports found a positive correlation between dose and QTc prolongation.[15] In a review of toxicology database information, Wenzel-Seifert et al[4] found extended QT interval with citalopram, fluoxetine, and venlafaxine at toxic doses or in the presence of additional risk factors such as sex, older age, or personal or family history of congenital long QT syndrome or cardiovascular disease.

Table

Examples of QTc prolongation associated with select antipsychotics[a]

Antipsychotic	Approximate QTc interval prolongation in milliseconds[b]
Aripiprazole[4,17]	-1 to -4
Clozapine[4]	10
Haloperidol[1,2]	7 to 15
Mesoridazine[16]	39 to 53
Olanzapine[1]	2 to 6.5
Paliperidone[4]	2 to 4
Pimozide[2]	19
Quetiapine[1,2]	6 to 15
Risperidone[1,2]	3.5 to 10
Sertindole[1]	30
Thioridazine[2,16]	33 to 41
Ziprasidone[1,2]	16 to 21

[a]List is not comprehensive. Other antipsychotics may be associated with QTc prolongation

[b]QTc prolongation interval may depend on the route of administration

Antipsychotics

Case reports, case series, and research trials have evaluated the risk of QTc prolongation with antipsychotics (***Table***).[1,2,4,16,17] The first-generation antipsychotics thioridazine,[4,16,18] mesoridazine,[16,18] chlorpromazine,[19] and haloperidol[3] warrant cardiac monitoring. The QTc prolongation effects of thioridazine and its active metabolite

Clinical Point

QTc prolongation has been reported with all SSRIs at plasma concentrations above the therapeutic level

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Clinical Point

QTc prolongation has been associated with long-term ziprasidone use more often than with risperidone, olanzapine, or quetiapine

Related Resources

- De Hert M, Detraux J, van Winkel R, et al. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. Nat Rev Endocrinol. 2011;8(2):114-126.
- Vieweg WV, Wood MA, Fernandez A, et al. Proarrhythmic risk with antipsychotic and antidepressant drugs: implications in the elderly. Drugs Aging. 2009;26(12):997-1012.
- Sandson NB, Armstrong SC, Cozza KL. An overview of psychotropic drug-drug interactions. Psychosomatics. 2005;46(5):464-494.

Drug Brand Names

Amantadine • Symmetrel
Amitriptyline • Elavil
Aripiprazole • Abilify
Asenapine • Saphris
Chlorpromazine • Thorazine
Citalopram • Celexa
Clozapine • Clozaril
Desipramine • Norpramin
Fluoxetine • Prozac
Furosemide • Lasix
Haloperidol • Haldol
Hydroxyzine • Atarax, Vistaril
Iloperidone • Fanapt
Lisinopril • Prinivil, Zestril
Lorazepam • Ativan
Lurasidone • Latuda
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Quetiapine • Seroquel
Risperidone • Risperdal
Tamoxifen • Nolvadex, Soltamox
Thioridazine • Mellaril
Venlafaxine • Effexor
Ziprasidone • Geodon

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mesoridazine are well-documented and thioridazine-mediated QTc prolongation increases are dose-dependent.[4,18] ECG monitoring is recommended with IV haloperidol, which is used for delirium in adults.[20] QTc prolongation has been associated with long-term ziprasidone use more often than with risperidone, olanzapine, or quetiapine.[19] Ziprasidone prolongs the QTc interval an average of 20 milliseconds,[21] which could represent a clinically significant change. QTc prolongation for iloperidone is comparable to ziprasidone and haloperidol.[22] There is some evidence that aripiprazole may shorten, rather than prolong, the QTc interval.[4,17]

Cardiovascular adverse effects associated with clozapine—including QTc prolongation—are dose-dependent.[3] Olanzapine prolongs QTc interval, although the mean change is less than with other agents unless other variables were present, such as:

- concomitant use of medications that may prolong QTc interval (ie, amantadine, hydroxyzine, or tamoxifen[2])
- preexisting cardiovascular conduction disorders
- higher doses (>40 mg/d).[3,23]

In 17 case reports of cardiac changes associated with quetiapine use, doses ranged from 100 mg/d[24] to an overdose of 36 g/d.[25] Only 1 patient death was reported secondary to overdose and preexisting dysrhythmia and hypertension.[26] QTc prolongation associated with risperidone was minor[1] based on oral doses in the normal therapeutic range and incidences of overdose.[10] Paliperidone[27] and lurasidone[28] are associated with clinically insignificant QTc prolongation. Changes in QTc interval were positively correlated with asenapine dose, although at the highest dose of 40 mg/d, the increase was <5 milliseconds.[29]

Mrs. A presents with a number of risk factors for QTc prolongation, including older age, female sex, and psychiatric and medical comorbidities that require medication. A pill count revealed that she was taking more than the prescribed daily doses of her medications. During the interview, Mrs. A said that if she missed her medication time, she would take them when she remembered. If she could not remember if she took her pills, she would take them again. Her physicians will explore strategies to increase medication adherence.

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Clinical Point

Paliperidone and lurasidone are associated with clinically insignificant QTc prolongation