# Cardiovascular Effects of Antipsychotics Used in Bipolar Illness

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Many antipsychotics are used to treat disorders other than schizophrenia, such as bipolar disorder. However, some of these agents are associated with cardiovascular side effects that can have serious or fatal implications for the patient. One dangerous side effect is QT prolongation, which can lead to torsades de pointes and ventricular arrhythmia. The group of drugs labeled as antipsychotics is diverse, making it challenging for the clinician to keep track of which agents cause which effects and important for the clinician to learn to identify signs of cardiovascular side effects and manage those events when they occur.

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Many antipsychotics are used to treat disorders other than schizophrenia, including bipolar disorder. However, some of these agents are associated with cardiovascular side effects, such as hypotension and QT prolongation, that can have serious or fatal implications for the patient. The group of drugs labeled as antipsychotics is diverse, with a variety of chemical structures, pharmacologic effects, receptor interactions, and adverse reactions. Therefore, cardiovascular side effects that occur cannot be considered as class effects but rather as effects that may occur with one antipsychotic but not another, or in conjunction with one adjunctive medication but not another. This class diversity makes it challenging for the clinician to keep track of which agents cause which effects and important for the clinician to learn to identify signs of cardiovascular side effects. Syncope and dizziness, for example, are two clues that cardiovascular disease or side effects might be present, and a patient experiencing these symptoms should be examined thoroughly to determine whether or not the cause is cardiovascular in nature.

The prevalence of circulatory disease is high in schizophrenic patients, perhaps because of continued antipsychotic therapy, especially combined therapy with more than one antipsychotic or without adjunctive anticholinergic agents. Waddington and coworkers[1] followed 88 inpatients with schizophrenia for 10 years. Over that time period, 39 died, but none committed suicide. The relative risk of death among these patients compared with the general population was 1.33. Causes of death included circulatory disease, malignant disease, respiratory disease, injury and poisoning, and "other causes," with circulatory disease being the most common. The authors found that treatment with more than one antipsychotic and the lack of adjunctive anticholinergic therapy were associated with reduced survival.

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## $\alpha_1$-ADRENERGIC BLOCKADE

In focusing on cardiovascular adverse actions, a number of physiologic effects are associated with the mechanism of action of antipsychotics. Some of these effects may be due to peripheral actions that the clinician may not be aware of. For example, $\alpha_1$-adrenergic blockade can result in a number of risks, such as syncopal episodes, hypotension, increased risk of fractures, as well as a possibly increased incidence of anginal episodes. A drop in blood pressure would increase cardiac workload, and those patients without adequate perfusion would be most sensitive to that increase.

Some studies have measured the rate of hypotension as a side effect of antipsychotic treatment. Even those that have not measured blood pressure directly but have recorded rates of dizziness can offer a clue into the rate of hypotension. Table 1[2] shows the rate of hypotension and/or dizziness with selected antipsychotics. As the table shows, some agents have been associated with little hypotension but higher rates of dizziness. This area of study clearly merits more attention.

The concern with hypotension is not always mortality, but the risk of long-term disability associated with falls, particularly falls in the elderly population. Kario and colleagues[3] evaluated 266 subjects aged 65 years or older and followed them for 1 year. During the follow-up period, 60 participants (22%) recorded 1 or more falls. Falls were more common in younger subjects and in women and were identified with lower systolic blood pressure. In terms of independent risk factors in this study, lower systolic blood pressure and gender were both significant. Clearly, when blood pressure and the ability to generate appropriate pulse pressure are compromised, the risk of falling increases. Not all falls result in fatal or debilitating injury, but even those falls that result in minor or no injuries can undermine an elderly person's confidence in his or her mobility and independence, possibly limiting that person's activities.

## QT PROLONGATION

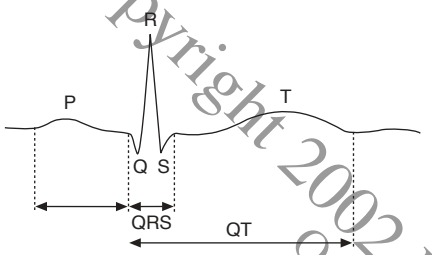
Another cardiovascular side effect of some antipsychotics is QT prolongation. The electrical action of the heart has 2 components: depolarization, or the stage before the peak of the cardiac wave that leads to the contraction of the heart muscle, and repolarization, the

Table 1. Hypotension and Dizziness With Selected Antipsychotic Agents[a]

| Drug | No. of Studies | Daily Dose Range, mg | Duration, wk | % Reporting Hypotension | % Reporting Dizziness |
|---|---|---|---|---|---|
| Clozapine | 7 | 350–543 | 4–52 | 4.8–16.7 | 3.5–50 |
| Haloperidol | 11 | 3–24.8 | 5–52 | NS to 2 | 0–25 |
| Risperidone | 7 | 2–16 | 8–28 | NS to 1 | 11.9–38 |
| Olanzapine | 4 | 5–20 | 6–28 | NS | 7.7–17.4 |
| Quetiapine | 4 | 75–750 | 6–8 | 4–14 | 11 |
| Ziprasidone | 2 | 80–160 | 4 | 1.3 | 2–8 |

[a]Data from Stanniland and Taylor.[2] Abbreviation: NS = only side effects that were significantly different between study groups were reported, and since no significant differences for this category were found, data were not reported.

Figure 1. The QT Interval[a]




[a]The QT interval is the length of time it takes the electrical system in the heart to repolarize.

stage in which the heart recharges for the next beat and the heart muscle relaxes. The QT interval is the time during which the electrical system in the heart repolarizes (Figure 1). Since this interval varies dependent on heart rate, it is normally measured and reported as the corrected QT interval, or QTc. The formula that is usually used clinically is called the Bazett formula, which works very well in most clinical situations. Other formulae have evolved over the years to compensate for very high heart rates, but most reference points for QT risk are based on the Bazett formula.[4]

Reference points for normal, borderline, and prolonged QTc are shown in Table 2.[4,5] If a patient has a borderline QTc, he or she bears close monitoring. If a patient presents with a QTc longer than 500 msec, he or she would need treatment to shorten that interval.[5] In addition, any patient whose QTc has increased by 60 msec during antipsychotic treatment would also need to be monitored closely.[4]

The electrocardiogram (ECG) measures the surface electrical activity of the heart and is a composite of numerous action potentials. A number of ion fluxes occur during the action potential, one of the most significant being the extrusion of potassium from inside the cell to outside the cell. If that flux of potassium is compromised, the risk for arrhythmias increases because phase 3 of the action potential, that in which the heart is in its relative refractory period, is prolonged. The more time spent in phase 3, the longer the QTc and the greater the risk for an asynchronous potential that might lead to an arrhythmia called torsades de pointes. One of the most common arrhythmias is torsades de pointes.

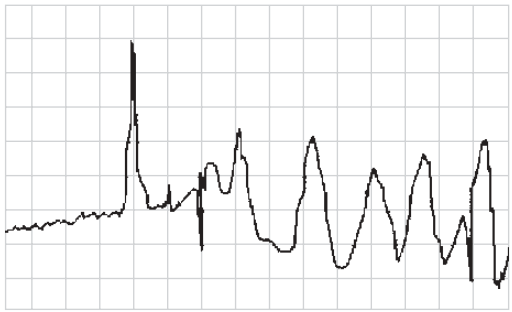
Figure 2 shows an ECG of torsades de pointes—the regularity of a normal heartbeat is clearly lost. The outcome of a torsades de pointes arrhythmia can be reversion to normal sinus rhythm. That

Table 2. QTc Reference Ranges (msec)[a]

| Range | Men | Women |
|---|---|---|
| Normal | < 430 | < 450 |
| Borderline | 431–450 | 451–470 |
| Prolonged | > 450 | > 470 |

[a]Data from Moss[4] and the Committee for Proprietary Medicinal Products.[5]

Figure 2. Ventricular Arrhythmia: Torsades de Pointes[a]



[a]Note that the synchrony of individual cells is lost.

outcome is ideal because the patient merely experiences a brief interruption in consciousness, such as a dizziness episode or a fainting spell. However, that torsades rhythm can evolve into ventricular tachycardia, which also can revert to normal sinus rhythm or can continue into ventricular fibrillation, wherein lies the risk of sudden death associated with these drugs that lengthen the QTc by prolonging the action potential and affecting potassium reflux.

## RISK FACTORS FOR TORSADES DE POINTES

Many risk factors can lead to the development of torsades de pointes (Figure 3). Among those unrelated to pharmacotherapy, hypokalemia has special relevance to psychiatry since serum potassium concentrations in severely agitated patients are significantly lower than in patients with mild agitation. Hatta and colleagues[6] measured serum potassium levels and level of agitation in 313 men with schizophrenia who were admitted to the hospital because of a psychiatric emergency over a 24-month period. Potassium levels were lower in men who were severely agitated compared with those who were mildly agitated, and levels stabilized after 8 hours in those patients who were sedated. In another study, Hatta and coworkers[7] measured QTc in 67 acute, drug-free psychotic patients and compared it with that in outpatients. The mean QTc in outpatients was 405 msec, well within the normal range, but the mean QTc in inpatients was 453 msec, which is a prolonged interval (see Table 2). In acute, inpatient situations, there is an inherent risk of lower potassium levels that is not associated with drug therapy and, therefore, a greater risk for QTc prolongation and torsades de pointes.

Another risk factor for torsades de pointes is long QT syndrome, which can occur in 2 different forms. Inherited long QT syndrome is genetically transmitted, and its frequency may be as high as 1 in 5000 individuals.[8] Cardiac ion channels are defective, which predisposes the individual to torsades de pointes. Long

Figure 3. Risk Factors for Torsades de Pointes

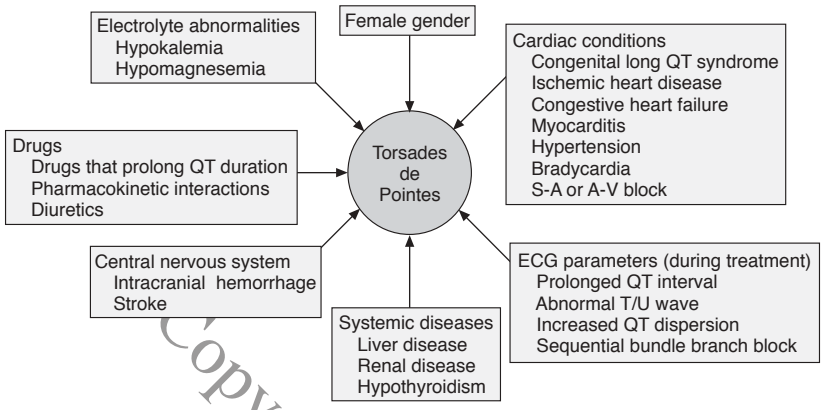



Table 3. Risk Factors for Prolonged QTc in Psychiatric Patients[a]

| Risk Factor | Adjusted Odds Ratio | 95% Confidence Interval |
|---|---|---|
| Age > 65 y | 3.0 | 1.1 to 8.3 |
| Tricyclic antidepressants | 4.4 | 1.6 to 12.1 |
| Droperidol | 6.7 | 1.8 to 24.8 |
| Thioridazine | 5.4 | 2.0 to 13.7 |
| High dose antipsychotic[b] | 5.3 | 1.2 to 24.4 |
| Very high dose antipsychotic[c] | 8.2 | 1.5 to 43.6 |

[a]Data from Reilly et al.[9]
[b]High dose defined as 1001–2000 mg/day of chlorpromazine equivalents.
[c]Very high dose defined as > 2000 mg/day of chlorpromazine equivalents.

QT syndrome is believed to be responsible for 3000 to 4000 deaths per year in children and young adults who have not had ECGs or been diagnosed.[8] Syncopal episodes are a common presentation. Acquired long QT syndrome is associated with medications known to prolong QTc by affecting the potassium rectifier channel in a dose-dependent manner.

Reilly and coworkers[9] studied the ECGs of 101 healthy volunteers and 495 psychiatric patients, including both inpatients and outpatients. Prolonged QTc was defined as longer than 456 msec and was found in 8% of patients. Four variables were significant predictors of prolonged QTc in psychiatric patients: age over 65 years and use of tricyclic antidepressants, droperidol, or thioridazine. High or very high doses of antipsychotics in general also increased the risk for lengthened QTc in psychiatric patients (Table 3). From this, one can deduce that the prevalence of acquired long QT syndrome induced by antipsychotics may increase as the use of antipsychotics widens to include the treatment of other mental disorders.

A number of antipsychotic agents have led to concern about QT changes. One of them—sertindole—was never marketed in the United States in spite of receiving an "approvable" letter from the U.S. Food and Drug Administration (FDA). Thioridazine and mesoridazine are marketed in the United States but carry a "black box" warning advising clinicians about dose-related QTc prolongation and associated risk of torsades de pointes and sudden death. Ziprasidone is also marketed in the United States, but its introduction was delayed because of concerns about QTc lengthening; it was recently approved by the FDA with 9 paragraphs of boldfaced warning in its package insert related to QT prolongation. Although they are all antipsychotics, these drugs have different mechanisms of action, again emphasizing the diversity of this "class" of drugs and the difficulty in making generalizations about them.

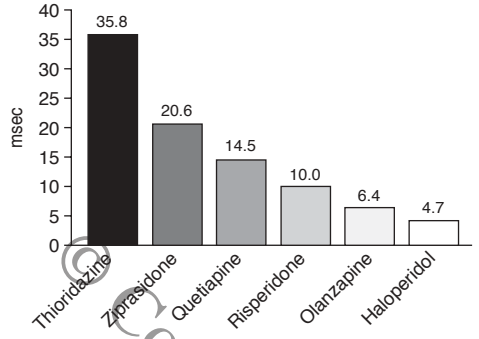
### Study 054

During the approval process for ziprasidone, the FDA requested that the manufacturer compare the effect of ziprasidone on QTc with that of other antipsychotics. Study 054 used oral preparations of thioridazine, quetiapine, risperidone, olanzapine, and haloperidol as comparators.[10,11] A low-risk patient group participated consisting mainly of relatively young men with QTc values in the normal range; 164 patients completed the study. Subjects were titrated to the highest tolerated dose of each drug, and ECGs were conducted at baseline and within 60 minutes of maximum blood drug levels, during dose escalation, at steady state with a metabolic inhibitor, and at steady state without a metabolic inhibitor. Dose escalation and duration were unique for each drug, taking into account tolerability, pharmacokinetics, and time to steady state. QTc was calculated using the Bazett formula as well as the Fridericia formula. The Bazett-corrected QT intervals will be reported here since most reference points for QTc are based on that formula.

Normally in studies like Study 054, in which mean data are reported, a change of 10 msec or more should spur a careful examination of that drug. As Figure 4 shows, 4 of 6 drugs studied had a mean change of 10 msec or greater. Thioridazine had the greatest mean change by far, at 35.8 msec,[12] which is one reason why this drug received a black box after being on the market for many years. However, sudden death associated with thioridazine has been reported in the literature since the 1960s.[13–15] In a more recent study of 49 cases of sudden death associated with antipsychotics or antidepressants, Mehtonen and colleagues[16] found that thioridazine was the only antipsychotic drug in 15 of those cases. Thioridazine use, alone or in combination, was reported in 28 of 49 cases. The thioridazine results of Study 054 simply confirm these earlier reports.

Study 054 also calculated the percentage of patients who experienced an increase in QTc longer than 30, 60, or 75 msec compared with steady state. Almost 30% of patients taking thioridazine had a change of 60 msec or longer in their QTc, and 21% of patients taking ziprasidone had that magnitude of change. Eleven percent of quetiapine-treated patients saw this level of change, and only 4% of patients taking risperidone, olanzapine, or haloperidol experienced a change of 60 msec or more. If that cutoff is raised slightly, only 2 drugs—thioridazine and ziprasidone—were associated with a prolongation of 75 msec or greater. The diversity of this class of drugs is again apparent. However,

Figure 4. Study 054: Mean Change in QTc From Baseline to Steady State[a]




[a]Data from the FDA Psychopharmacological Drugs Advisory Committee.[12]

the standard warning sign that should prompt careful monitoring of a patient is a drug-associated QTc increase of 60 msec or more, and many of the patients in this study were in that group.

## PATIENT MANAGEMENT

It is important to identify patients at risk for cardiovascular side effects. Syncopal episodes are certainly a strong clue that a cardiovascular event or hypotension is occurring in a patient. It is important to caution patients who are taking agents known to lengthen the QT interval to report any symptoms that might be associated with QT prolongation, such as fainting spells, dizziness, palpitations, nausea, and vomiting. If a patient reports nausea and vomiting, electrolyte levels can be affected and put that patient at greater risk. Because of the effects of alcohol on electrolytes, patients should certainly avoid excessive use of alcohol when they are taking long-QT medications, and because of the potential for drug interactions, the clinician needs to know what other agents the patient is taking. Patients with bipolar disorder may be at particular risk since there is a problem with alcohol and substance abuse in that population. In addition, these patients are often on treatment with more than one agent at a time.

For at-risk patients, clinicians should do ECGs and measure serum potassium and magnesium levels before the patient begins treatment with a QT-prolonging drug. If electrolyte levels are abnormal, they should be corrected before treatment is started, and if the baseline QTc is longer than 500 msec, that patient should not be started on treatment with a long-QT drug.

Syncope due to hypotension can be treated in a number of ways, both nonpharmacologic and pharmacologic. The clinician can make sure that patients have adequate volume and are avoiding sympatholytic agents. Patients can also use physical measures such as tensing the legs, changing positions slowly, flexing the feet or doing hand grips before changing positions, and wearing elastic stockings to limit venous pooling. If these measures do not work, pharmacologic measures might. Some of these include fludrocortisone plus a high-salt diet, $\alpha_1$-agonists, nonsteroidal anti-inflammatory agents, caffeine, and possibly some of the selective serotonin reuptake inhibitors.

## CONCLUSION

Although antipsychotics should not be prescribed lightly, the benefits of these drugs often outweigh the risks. Since as a class the antipsychotics are so diverse, if a drug like thioridazine or ziprasidone does cause QT prolongation in a patient, there are still many other antipsychotic agents that may be selected to avoid this effect.

*Drug names:* chlorpromazine (Thorazine and others), fludrocortisone (Florinef), haloperidol (Haldol and others), mesoridazine (Serentil), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

*Disclosure of off-label usage:* The author has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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