# Schizophrenia, Antipsychotic Drugs, and Cardiovascular Disease

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Since the early 1980s, concern within the psychiatric community about whether antipsychotics are associated with adverse cardiovascular events has grown. In the early 1990s, it became clear that mesoridazine could cause torsades de pointes. More recently, concern has focused on the propensity that some atypical antipsychotics have to prolong corrected QT (QTc) interval and whether this can result in torsades de pointes and sudden death. Unfortunately, it has been difficult to accurately determine what role, if any, that atypical antipsychotics may have in contributing to these events, in part because of the rarity of the events and the lack of a sound, predictable marker. The best currently available markers, QTc interval and binding to the rapid delayed rectifier potassium current, are imprecise and cannot be relied upon to accurately predict torsades de pointes. Current evidence suggests that although atypical antipsychotics may increase the QTc interval, prolongation does not result in torsades de pointes, as observed with many conventional antipsychotics. Among the marketed atypical drugs, there was considerable concern about QTc prolongation with ziprasidone, but currently available data do not support the occurrence of torsades de pointes with any of the available atypical antipsychotic drugs. However, identifying when QTc prolongation carries a risk of torsades de pointes remains a problem in developing new drugs. Psychiatric populations are at high risk for cardiovascular disease, and emerging data indicate that some atypical antipsychotics may be associated with cardiovascular adverse events unrelated to QT prolongation. Thus, it is prudent for the psychiatric community to be aware of psychiatric patients' baseline medical condition and their risk status for cardiovascular disease.
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Cardiovascular disease is the top cause of death among both men and women, accounting for approximately 30% of all deaths in the United States.[1,2] An estimated 340,000 cases per year are due to ventricular fibrillation.[3] Patients with schizophrenia have a higher prevalence of cardiovascular disease than the general population,[4–6] and the risk of atherosclerosis and sudden death in these patients has been reported to exist unrelated to the effect of antipsychotic drugs.[4]

For the past several years, the psychiatric community has been concerned about the cardiac effects some atypical antipsychotics may have, especially corrected QT (QTc) interval prolongation and the risk of sudden death. Current information suggests that concerns regarding the risk of QTc prolongation with the atypical antipsychotics now marketed are minimal.

This article reviews the issue of QTc prolongation and the implications of using atypical antipsychotics in light of new data. The physiology and markers of QTc prolongation and a review of the controversy surrounding antipsychotics will be presented. Other cardiovascular complications (metabolic effects, orthostatic hypotension, and myocarditis) also are briefly addressed.

## OVERVIEW OF TORSADES DE POINTES

Torsades de pointes (TdP), French for "twisting of the points," is a polymorphic ventricular tachycardia in which the morphology of the QRS complexes differs from beat to beat. Two forms of the arrhythmia exist: primary (congenital) and secondary (drug induced). TdP always occurs in the setting of QT prolongation and is often associated with syncope and sudden death.[7]

A basic knowledge of cardiovascular physiology is useful to fully understand the development of TdP. Muscle contraction of the heart involves an action potential, which is characterized by transmembranal movement of sodium, potassium, calcium, and a variety of ion channel subtypes in the cardiac cells.[8] Normal contraction of

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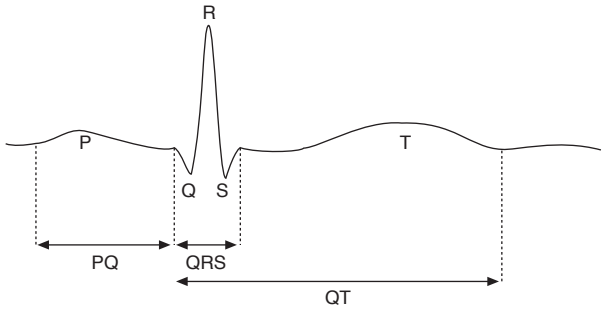
Figure 1. Normal Electrocardiogram[a,b]




[a]Reprinted with permission from Haddad and Anderson.[8]
[b]P wave = atrial depolarization, PR interval = delay, QRS complex = ventricular depolarization, T wave = ventricular repolarization, and QT interval = beginning of ventricular depolarization to end of ventricular repolarization.

the heart, as observed on an electrocardiogram, consists of atrial depolarization and ventricular depolarization and repolarization. Depolarization results primarily from the influx of sodium, whereas repolarization results from the influx of calcium and efflux of potassium ions.[8,9] The QT interval represents the period from the beginning of ventricular depolarization to the end of ventricular repolarization (Figure 1). The QT interval is typically reported as QTc, which is the QT interval corrected for variations in heart rate.[8] At present, more than 20 different types of ion channels have been identified in the human heart.[10] Of these, the rapid delayed rectifier potassium current ($I_{Kr}$), the L-type calcium current ($I_{Ca,L}$), the late sodium channel current ($I_{Na}$), and the slowly activating delayed rectifier potassium current ($I_{Ks}$) appear to contribute to the QT-prolonging effects of many drugs.[10]

## Markers of Torsades de Pointes

Unfortunately, the ability to predict TdP is difficult, in part because of the lack of any reliable marker of its occurrence and the rarity of the event.[10] At present, the best marker is QT prolongation, determined by measurement of the QTc interval, with an increase to > 500 msec or an increase from baseline of 60 msec considered a risk for the development of TdP.[8] However, the QTc interval is a very crude indicator due to a lack of consensus regarding at what degree prolongation becomes clinically significant.[8,9,11] For example, amiodarone and pentobarbital have been shown to cause dose-dependent prolongation of the QT interval and action potential[12,13]; however, the risk of TdP with these agents is minimal.

Recent investigations suggest that prolongation of the action potential primarily occurs in endocardial and epicardial cells, rather than the M cells (cells located in the deep layers of the ventricular myocardium).[12,13] Some investigators have suggested that this prolongation results in reducing transmural dispersion repolarization, thereby reducing the likelihood of TdP. In contrast, preferential prolongation of the action potential within the M cells leads to prolongation of the QT interval and subsequent increase in transmural dispersion repolarization, which increases the risk for TdP.[14] Examples of drugs that increase transmural dispersion repolarization and have resulted in the development of TdP in humans include terfenadine, sotalol, erythromycin, and cisapride.[10] In addition to a lack of a direct relationship between the QTc interval and the potential for developing the arrhythmia, the imprecision of the formulas (Bazett, Fridericia, Framingham, etc.) used to correct the QT for variation in cardiac rate and intraindividual variability (e.g., variations in diurnal and prandial patterns, weight, and sex) to some extent also contributes to the poor ability of QT prolongation to predict TdP.[8,9,15] As a result, more optimal alternatives are needed to better predict TdP. Potential candidates include $I_{Kr}$, calcium handling, and magnesium.

So far, all drugs that cause TdP bind to the $I_{Kr}$ potassium channel, which is an ion channel encoded by the human ether-a-go-go–related gene and has been used as a model for testing arrhythmic potential. The advantage of the cloned human channel is that it allows in vitro identification of compounds early in drug development that have the potential to bind to this channel without obtaining human safety data. It is measurable by isolating ventricular monocytes from species such as the guinea pig, rabbit, and dog or preferably noncardiac mammalian cells made to express human ion channels. Because interference from other ion currents (e.g., sodium, calcium) can confound the measurement, the latter method is preferred.[10]

Current knowledge suggests that drugs causing TdP are blockers of this ion current.[8] Although it is reasonable to speculate that the degree of $I_{Kr}$ blockade would predict an increased risk of developing TdP, like QT prolongation, $I_{Kr}$ blockade alone is not sufficient evidence of a genuine risk.[10] This is because it is a nonspecific marker, failing to distinguish drugs that have the potential to place patients at risk for the arrhythmia. For example, verapamil, an inhibitor of $I_{Kr}$,[16] would be expected to cause QT prolongation, increasing the risk for TdP. However, verapamil also blocks $I_{Ca,L}$, which is believed to ultimately reduce the proarrhythmic risk associated with QT prolongation.[17,18] Thus, the development of many potentially useful drugs is at risk of being prematurely halted if $I_{Kr}$ alone is relied on as a predictor of tachyarrhythmias.

As suggested by the work done with verapamil,[17,18] blockade of $I_{Ca,L}$ appears to have a role in reducing proarrhythmic risk associated with QT prolongation. Wehrens et al.[19] suggest that ventricular arrhythmias may be precipitated by impairment in calcium handling. In their study,[19] leakage of intracellular calcium was caused by the depletion of the channel-stabilizing protein calstabin2 from the ryanodine receptor–calcium release channel complex, increasing the risk for cardiac arrhyth-

mias. It is unclear whether these effects apply to the development of TdP and how leakage of intracellular calcium relates to measurements of dispersion; further evidence is needed. However, calcium appears to be an important determinant and may ultimately improve evaluation of drugs predictive of causing TdP.

Along with sodium, potassium, and calcium, magnesium also is important in muscle contraction and is often used in conditions (e.g., hypertensive crisis, premature labor) in which the contractility of muscles needs to be altered.[20,21] Hypomagnesemia is a known risk factor for TdP, arising with and contributing to the persistence of hypokalemia and hypocalcemia. As a result, administration of magnesium sulfate often is used in the management of the arrhythmia.[22] Whether magnesium has any value as a marker in predicting TdP has yet to be determined.

## HISTORY OF CARDIOVASCULAR DISEASE WITH SCHIZOPHRENIA AND ANTIPSYCHOTICS

In 1963, a report of sudden arrhythmic death with features similar to TdP was described in 2 patients receiving thioridazine.[23] However, TdP would not be officially described and recognized until 1966, when Dessertenne[24] reported a case of ventricular tachycardia with 2 variable foci in a patient receiving quinidine. For more than a decade, TdP was believed to be a concern only in patients with underlying cardiovascular disease. This belief changed in the early 1990s, when the antihistamine terfenadine was reported to cause TdP induced by a drug interaction with ketoconazole.[25] By 1992, the labeling for terfenadine and a related drug, astemizole, had a black box warning, and by 1997, the medications were removed from the U.S. market. From this point on, arrhythmias were recognized as an adverse event that could occur in noncardiac patients and could be induced by a variety of medications, including antimalarials, antifungals, macrolide antibiotics, and psychotropics.[26,27]

In the late 1980s, a task force was convened by the American Psychiatric Association to discuss the issue of sudden death associated with conventional antipsychotics.[28] Although the panel agreed that thioridazine was linked to ventricular arrhythmia and sudden death, no agreement was reached about whether other antipsychotics caused these events.[28] Factors contributing to this dispute included the rarity of the event, a background incidence of sudden death in patients with schizophrenia that was present before the use of antipsychotic drugs, and heavy smoking seen in these patients.[7,28] However, a Finnish study[29] made it clear that thioridazine was associated with sudden death. During the 3-year study period, Mehtonen et al.[29] examined 24,158 coroners' cases in which both autopsy and toxicology reports were available. Of these cases, 49 deaths were identified as sudden death among otherwise healthy adults receiving psychotropic medications. A phenothiazine was considered responsible for 46 of the 49 cases, with 28 of the 46 being associated with thioridazine.[29] Despite this indisputable evidence that thioridazine caused TdP, concern about TdP faded among mental health care professionals with the availability of the atypical antipsychotics, which did not appear to carry this risk.

The concern returned when sertindole was submitted to the U.S. Food and Drug Administration for approval. In premarketing trials, sertindole was found to cause dose-dependent increases in the QTc interval, with 7% to 8% of patients having QTc values ≥ 500 msec.[30] In addition, sertindole was found to be associated with 12 cases of sudden death and 23 cases of syncope among 1446 patients.[7] As a result, sertindole was not approved for use in the United States and, following evidence of additional cases, was initially suspended from the European market in 1998[31] but then was reinstated with a restrictive label.[32]

The issue of cardiovascular adverse events resurfaced with ziprasidone, which was shown to prolong the QT interval but to a lesser degree than sertindole and thioridazine.[30,33] Ziprasidone was approved for use in the United States in 2001, and with usage in over 1 million patients (I. Lombardo, M.D., written communication, Pfizer Inc, New York, N.Y., June 24, 2005) has not been associated with an increased risk of TdP. However, the risk of TdP with ziprasidone remains a concern among some mental health care professionals, for whom the issue is difficult to understand.

## CURRENT AND FUTURE IMPLICATIONS OF ATYPICAL ANTIPSYCHOTICS

Difficulty in identifying patients at risk for cardiovascular complications has been a long-standing problem. Safety evaluation of drugs during premarketing trials often is insufficient to detect the occurrence of TdP and sudden death. In addition, risks may become apparent only when the drug is used in populations not routinely assessed in premarketing studies. For example, in the Cardiac Arrhythmia Suppression Trial,[34] class I antiarrhythmics (encainide and flecainide) were determined to increase mortality in patients with heart attacks, despite being effective in suppressing ventricular arrhythmias in nonischemic cardiac patients.

In the case of the atypical antipsychotics, several factors contribute to the difficulty in identifying patients with psychiatric disorders at risk for cardiovascular complications. In general, patients with disorders such as schizophrenia have an underlying predisposition for cardiovascular disease, including atherosclerosis and sudden death.[4] The increased risk for cardiovascular disease may be related, in part, to abnormalities in metabolic effects (e.g., weight, glucose) and poor lifestyle choices (e.g., smoking, sedentary lifestyle) observed in these patients, regardless

**Table 1. Common Examples of Cytochrome P450 3A4 Inhibitors[a]**

| Example |
|---|
| Antidepressants |
| Nefazodone |
| Fluvoxamine |
| Fluoxetine[b] |
| Sertraline[b] |
| Paroxetine[b] |
| Venlafaxine[b] |
| Antifungals |
| Ketoconazole |
| Itraconazole |
| Fluconazole |
| Macrolide antibiotics |
| Clarithromycin |
| Erythromycin |
| Miscellaneous |
| Cimetidine |
| Diltiazem |
| Protease inhibitors |

[a]Based on Cupp and Tracy.[40]
[b]Weak inhibitors (fluoxetine > sertraline > paroxetine or venlafaxine).

of antipsychotic therapy.[4,32,35,36] In a retrospective analysis of claims data from April 1995 to March 1999 obtained from a large managed care database, Enger et al.[37] suggested that cardiovascular risk among patients with schizophrenia may not be the result of direct effects of antipsychotic use. Additionally, patients with underlying cardiovascular disease are at increased risk for developing ventricular tachyarrhythmias or sudden death[3]; however, little is known about the cardiovascular risk of administering atypical antipsychotics to such patients because they are usually excluded from premarketing clinical trials. In a retrospective examination of Tennessee Medicaid enrollees from January 1988 to December 1993, Ray et al.[38] found an increased risk of sudden death in patients taking moderate doses of conventional antipsychotics (2.4 times greater than nonusers; $p < .001$). However, in the presence of severe cardiovascular disease, this risk was 3.5 times greater than in nonusers ($p < .001$).

Assessment of the potential for a new drug to cause TdP is hindered by the lack of a clinically useful marker. Even when accurately measured, QTc does not necessarily predict TdP or sudden death. Studies assessing the QT-prolonging effects should be designed to evaluate the full dosage range of the agents under all relevant conditions, including metabolic interference.[10] The latter is especially important because changes in the QTc interval may occur when drug plasma levels are increased by concomitant administration of known cytochrome P450 (CYP) inhibitors, especially CYP3A4 inhibitors.[15,25,39] Examples of common inhibitors of CYP3A4 are listed in Table 1.[40] Although these assessments are helpful in identifying drugs with potential risk of causing TdP, a clinically useful marker is needed to definitively determine the risk associated with new drugs.

Although most of the atypical antipsychotics have the potential to prolong the QTc interval,[7,41,42] there have been no reports of TdP resulting from QTc prolongation with these agents. Clozapine is known to be associated with various cardiovascular risks, unrelated to QTc prolongation (see next section).

Data published by Harrigan et al.[33] further suggest that atypical antipsychotics are not associated with clinically detrimental effects on the QTc interval. This open-label fixed-sequence study evaluated the effect of 6 antipsychotics (thioridazine, haloperidol, olanzapine, risperidone, quetiapine, and ziprasidone) on the QTc interval, alone and in the presence of metabolic inhibition. All of the treatment groups showed an increase in the mean baseline QTc interval; however, this increase did not exceed 500 msec in any treatment group during the course of the study. Although thioridazine was administered at the lower end of its dosage range (300 mg/day), whereas all other agents were given at their highest recommended dosage, thioridazine was still associated with the greatest change in mean baseline QTc (30.1 msec) (Figure 2). The mean change in baseline QTc for the atypical antipsychotics ranged from 15.9 msec with ziprasidone to 1.7 msec with olanzapine. Similar results were observed with the coadministration of a metabolic inhibitor.[33]

In summary, current evidence suggests that prolongation of the QTc interval by atypical antipsychotics does not appear to be associated with TdP or sudden death. Controlled data are needed in patients with cardiovascular disease to determine if these patients are at higher risk of developing TdP or sudden death when treated with atypical antipsychotics. It remains prudent to screen patients for a family history of long QTc syndrome, other drugs that produce TdP, or serious overt heart disease. Mental health professionals should not hesitate to prescribe atypical antipsychotics for appropriate patients.

## OTHER CARDIAC COMPLICATIONS

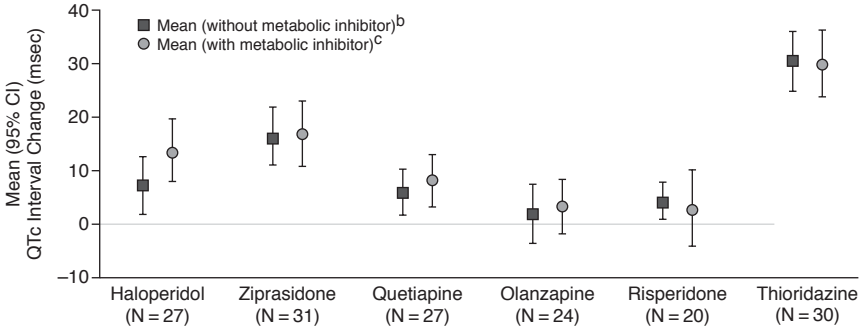
### Metabolic Effects

A review by Ryan and Thakore[6] indicates that schizophrenia and/or antipsychotic agents are associated with metabolic abnormalities, including weight gain, diabetes mellitus, and increased triglyceride levels, known to be associated with increased cardiovascular risk.[3] To what extent these abnormalities are the result of the illness and/or the drug treatments is beyond the scope of this article but are thoroughly reviewed by Henderson[43] in this supplement.

### Effects on Blood Pressure

Antipsychotics frequently have effects on blood pressure and heart rate, among which orthostatic hypotension is common.[44] These effects are probably related primarily to the α-adrenergic properties of these agents.[44–46] Because

**Figure 2. Mean (95% confidence interval) Changes From Baseline in the QTc Interval at Steady-State Maximum-Plasma Concentration and in the Presence of the Metabolic Inhibitors (completers)[a]**




[a]Reprinted with permission from Harrigan et al.[33]
[b]Data for risperidone monotherapy at 6 to 8 mg/d.
[c]Data for risperidone at 16 mg/d with metabolic inhibitor.

orthostatic hypotension is correlated with the antagonistic effects of antipsychotics at $\alpha_1$-adrenergic receptors, low-potency agents (e.g., chlorpromazine, thioridazine, clozapine) are more likely to produce orthostatic hypotension than high-potency agents (e.g., haloperidol, risperidone, olanzapine).[44] All of the atypical antipsychotics have the propensity to cause hypotension. In a review of the safety and tolerability of atypical antipsychotics, Tandon[47] indicates that the risk of orthostatic hypotension is greatest with clozapine and least with olanzapine and ziprasidone. Both risperidone and quetiapine were noted to have a mild to low risk of producing orthostatic hypotension. In general, hypotension is prominent during the initial oral or parenteral administration of these agents but subsides with continued use. The risk of orthostatic hypotension, with or without syncope, is of sufficient concern with clozapine that a box warning is contained in the product labeling.[48]

### Myocarditis

Myocarditis appears to be a rare but serious adverse event reported with clozapine.[49] Postmarketing data for clozapine indicate that the risk of myocarditis appears to be of significant concern during, but not limited to, the first month of therapy.[48] The package insert for clozapine contains a black box warning for myocarditis, and the manufacturer recommends that clozapine be promptly discontinued in patients in whom myocarditis is suspected.[48] In an analysis of an international database on adverse drug reactions maintained by the World Health Organization, Coulter et al.[50] examined the relationship between antipsychotics and myocarditis and cardiomyopathy using Bayesian statistics. Results indicate that compared with other antipsychotics, myocarditis and cardiomyopathy are strongly associated with clozapine use. Conventional antipsychotics (e.g., chlorpromazine, fluphenazine) were also reported to be significantly associated with these adverse events. Of the other atypical antipsychotics evaluated, risperidone was significantly associated with cardiomyopathy but not myocarditis, and there were few reports of either adverse event with olanzapine and quetiapine. Further research is needed to determine if the association between antipsychotics and myocarditis and cardiomyopathy is causally related.

## CONCLUSION

Prediction of TdP will improve as we gain a better understanding of the physiology involved in the development of this rare adverse effect. Atypical antipsychotics undoubtedly represent a significant advance in the treatment of schizophrenia, offering many positive benefits (e.g., reduced risk of extrapyramidal symptoms, positive effects on mood, cognition, and negative symptoms) not possible with conventional antipsychotics. Current literature suggests that although the atypical antipsychotics may prolong the QT interval, these agents are not associated with TdP. If TdP occurs at all, it is extremely rare and most likely would occur in patients with a family history of long QTc syndrome, other drugs that produce TdP, or serious overt heart disease. No class of agents is without associated adverse events. As such, it is prudent for the mental health community to be aware of their patients' baseline medical condition and risk status for cardiovascular disease. Good treatment involves monitoring both the medical as well as the psychiatric condition of the patient.

*Drug names:* amiodarone (Cordarone, Pacerone, and others), chlorpromazine (Sonazine, Thorazine, and others), cimetidine (Tagamet and others), clarithromycin (Biaxin and others), clozapine (Clozaril, FazaClo, and others), diltiazem (Cartia, Taztia, and others), erythromycin (Eryc, E-Glades, and others), flecainide (Tambocor and others),

fluconazole (Diflucan and others), fluoxetine (Prozac and others), fluphenazine (Prolixin and others), haloperidol (Haldol and others), itraconazole (Sporanox and others), ketoconazole (Ketozole, Nizoral, and others), nefazodone (Serzone and others), olanzapine (Zyprexa), paroxetine (Paxil and others), pentobarbital (Nembutal), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft), sotalol (Betapace, Sorine, and others), venlafaxine (Effexor), verapamil (Isoptin, Verelan, and others), ziprasidone (Geodon).

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