

# Clinical Management of Cardiovascular Risks During Treatment With Psychotropic Drugs

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The treatment of schizophrenia—as well as dementia, psychotic depression, and bipolar disorder—was greatly improved by the development of new atypical antipsychotic drugs in the past decade. However, cardiovascular and metabolic risks that are associated with some of these agents have become worrisome to clinicians and researchers. In this article, I will review psychotropic and other agents that have been associated with cardiovascular changes during treatment. Screening for cardiac vulnerability at baseline, as well as at regular intervals during treatment if the patient has certain risk factors, is important when treating patients with psychotropic agents.

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Although the treatment of schizophrenia, dementia, psychotic depression, and bipolar disorder was greatly improved by the introduction of new atypical antipsychotic drugs in the past decade, cardiovascular risks that are associated with some of these agents have become worrisome to clinicians and researchers. Because the cardiovascular side effects of antipsychotic drugs and other agents differ, I will review agents that have been associated with cardiovascular changes during treatment and then describe how clinicians can best manage vulnerable patients.

## CARDIOVASCULAR RISKS WITH MEDICATIONS

Different medications produce different types of cardiovascular effects, if they produce them at all. One type of cardiovascular problem currently challenging physicians who treat patients with antipsychotic agents is prolongation of the corrected QT interval (QTc), as measured by an electrocardiogram (ECG). A long QT interval can be congenital or drug-induced and may result in torsades de pointes, a potentially fatal arrhythmia.<sup>1</sup> A “long” QT interval has been defined at various lengths over the years, but recently 440 ms has been considered to be the upper limit of normal, and an interval greater than 500 ms has been considered to be of concern as a marker of an increased risk

for torsades de pointes and sudden death.<sup>2</sup> A QTc of more than 500 ms is a signal to change the treatment method. QTc prolongation is rare in healthy populations, but testing an older patient’s QTc at baseline is helpful. Nagy et al.<sup>3</sup> reported that the QT interval can lengthen by 16 ms to 23 ms after food is eaten. Also, time of day affects the QT interval—the length and variability of the QTc are greatest upon waking, when the risk for heart attacks and sudden death is known to be highest.<sup>4</sup>

The fact that healthy people who are not taking cardiac drugs can experience sudden death from medications has become clear to clinicians over the past decade (although some earlier hints, which will be described, provided a foundation for this realization). Until the early 1990s, torsades de pointes due to a prolonged QTc was thought to be a problem facing only patients with cardiovascular disease who were taking antiarrhythmic medications or patients who had congenital long QT syndrome. Then, some patients who took the newly marketed antihistamines terfenadine and astemizole experienced torsades de pointes.<sup>5</sup> Warnings were placed in the product labeling, and these drugs were eventually removed from the U.S. market in the late 1990s.<sup>6,7</sup> It was discovered that both of these antihistamines relied on the cytochrome P450 (CYP) 3A4 enzyme for their metabolism,<sup>8</sup> and many of the deaths occurred in people who were taking the antihistamines in combination with drugs that inhibit that enzyme, such as the antibiotic erythromycin and the antifungal ketoconazole.<sup>5</sup> Other patients who experienced torsades de pointes had taken overdoses or had serious liver disease, low potassium levels, congestive heart failure, or congenital long QT syndrome.<sup>9–11</sup>

The problem related to these antihistamines is a main reason why evidence of prolonged QTc with new antipsychotic agents has been so worrisome in the last few years.

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However, the current concern with new antipsychotic agents is not the first time that psychotropic agents have been associated with cardiac problems. During the height of the use of the tricyclic antidepressants (TCAs) 20 years ago, TCAs were associated with death when taken in overdose. In fact, tricyclic drugs were involved in more than 1000 deaths by overdose per year during the late 1970s and early 1980s.<sup>12</sup> Because the TCAs are type I antiarrhythmic drugs, they carry a significantly increased mortality rate after myocardial infarction, and they increase the risk of mortality in patients with ischemic heart disease.<sup>13</sup> However, because the fatalities with TCAs were mostly related to overdoses, clinicians did not come away with the same feeling of prescribing uncertainty that was caused later by terfenadine and astemizole. That is, with the TCA deaths, clinicians could pinpoint particular patients with a cardiovascular illness that made them prone to risk, whereas clinicians were surprised by the unpredictability of death in their patients who took usual doses of terfenadine and astemizole for a minor illness like hay fever.

Welch and Chue<sup>2</sup> published a review that includes a list of medications, including psychotropics, that have been reported to cause QTc prolongation and torsades de pointes. The authors noted that older antipsychotic agents, including phenothiazines and butyrophenones, were associated with long QTc and torsades de pointes. These older antipsychotics, which are discussed in the next section, were used long before the antihistamine-related deaths occurred. However, due to various reasons, these antipsychotics did not stir as much concern about QTc prolongation as the antihistamines or even the TCAs did.

Although Welch and Chue<sup>2</sup> listed the TCAs and lithium as producing long QTc and torsades de pointes, the cardiac problems associated with TCAs and lithium are unlikely to be a result of QTc prolongation or torsades de pointes. Although the TCAs are cardiotoxic drugs, the mechanism of cardiac action differs from that of the antipsychotics. The QTc includes the QRS, which is a measurement of the time elapsed during depolarization of the heart, and the ST segment, which is a measurement of the time elapsed during repolarization of the heart.<sup>1</sup> The majority of the QTc measurement is repolarization, which has a different physiology from depolarization. All the drugs that have caused QTc prolongation and torsades de pointes have been drugs that affect the potassium channel during repolarization (the ST segment).<sup>14</sup> The TCA agents lengthen the QTc but primarily by their effect on sodium channels during depolarization (the QRS segment).<sup>15</sup> Although sodium, calcium, and potassium channels play a role in repolarization, the potassium channel plays the most significant part in drug-induced QT syndromes, torsades de pointes, and sudden death.<sup>11</sup> Lithium affects the electrical activity of the heart, but the problem most consistently documented with lithium is sinus node disease, which is not a lengthening of the QTc<sup>16</sup> but most likely a calcium channel effect on the

sinus node. Therefore, although psychotropic drugs other than antipsychotics can cause cardiovascular problems, there is little evidence that psychotropic drugs other than certain antipsychotics are associated with problems due to QTc prolongation.

In fact, in striking contrast with the TCAs, the antidepressants in the selective serotonin reuptake inhibitor (SSRI) class, as well as bupropion, seem to be safe drugs for cardiac populations. Although systematically collected data are limited with SSRIs, short-term studies suggest that these agents may actually be beneficial in patients with ischemic heart disease.<sup>17,18</sup> A growing body of data<sup>19,20</sup> suggests that the SSRIs decrease the stickiness of platelets.

Like the SSRIs, antiepileptic drugs also appear to be safe in terms of QTc prolongation and torsades de pointes. Sinha and Naritoku<sup>21</sup> recently reported that intravenous valproate was well tolerated in patients who were elderly and had cardiovascular instability; there were no significant changes in blood pressure, pulse, or use of vasopressors. The literature has few reports of cardiovascular problems with the anticonvulsant agents. Of course, it is always prudent to be aware of potential drug interactions.

Since the antihistamine-related deaths occurred, certain drugs have been removed from the market or have had warnings added to the package label after cardiovascular problems have become apparent during clinical use (Table 1).<sup>6,7,22-27</sup> Agents listed in Table 1 were removed from the market or were given a boxed or bolded warning in their package label by the U.S. Food and Drug Administration (FDA) or the drug manufacturer or both, but it is important to remember that other agents may be dangerous. For example, in 1999 the manufacturer of pimozide sent a letter<sup>28</sup> to health care providers about a change in its labeling to reflect the potential for sudden death when high doses are used, especially in patients who take drugs that inhibit the CYP3A enzyme, but pimozide did not receive a bolded or boxed warning in the label or get removed from the market. The FDA operates with extreme caution when approving new drugs in light of the problems with cardiac safety in the recent past, but older drugs may have been approved without this type of scrutiny.

## ANTIPSYCHOTIC AGENTS AND QTc PROLONGATION

As mentioned, certain antipsychotic agents, both old and new, have been found to have the potential to prolong the QTc, and this observation has received much attention recently. Although the cardiovascular risks of the antipsychotics vary, some of these drugs are more dangerous than others, particularly thioridazine, mesoridazine, pimozide, and droperidol (Table 2). Mehtonen et al.<sup>29</sup> tracked sudden death in some 35,000 coroners' cases from Finland over a 3-year period. Of the 189 cases that met the criteria for sudden unexpected death, 49 were related to psychotropic drugs, and 46 of the 49 cases involved antipsy-

**Table 1. Medications No Longer Marketed or Given Warnings Due to Cardiac Safety Concerns<sup>a</sup>**

Not marketed in US and removed from European market
Sertindole (antipsychotic)
Removed from market
Astemizole (antihistamine)
Terfenadine (antihistamine)
Grepafloxacin (antibiotic)
Cisapride (gastrointestinal prokinetic agent)
Black box warning
Droperidol (antipsychotic)
Thioridazine (antipsychotic)
Mesoridazine (antipsychotic)
Bolded warning
Ziprasidone (antipsychotic)
Dalfopristin-quinupristin (antibacterial)
Gatifloxacin (antibacterial)
Moxifloxacin (antibacterial)
Sotalol (antiarrhythmic)
Dofetilide (antiarrhythmic)

<sup>a</sup>Data from Seldane press release,<sup>6</sup> astemizole press release,<sup>7</sup> Rawlins,<sup>22</sup> Raxar press release,<sup>23</sup> cisapride press release,<sup>24</sup> PDR,<sup>25</sup> Novartis,<sup>26</sup> and droperidol press release.<sup>27</sup>

chotic drugs. Of those 46 deaths, 28 involved thioridazine, an older phenothiazine antipsychotic. Thioridazine was introduced in 1959, and high doses were initially used. Cardiovascular problems and sudden death were noted with thioridazine during the early 1960s, but actually retinopathy caused the doses to be restricted to lower levels in the mid-1960s. This restriction also limited the cardiac effects. Other antipsychotic agents—mesoridazine and pimozide (phenothiazines) and droperidol (a butyrophenone)—also were linked to prolonged QTc, torsades de pointes, and sudden death, but they were not used to the extent that thioridazine was.<sup>30</sup> Reilly et al.<sup>31</sup> recently examined ECGs from 101 healthy people and 495 psychiatric patients in various settings, and they found that the risk for abnormally long QTc (which they defined as more than 456 ms) was substantially higher in patients who took thioridazine, droperidol, or TCAs, as well as in patients who were older than 65 years.

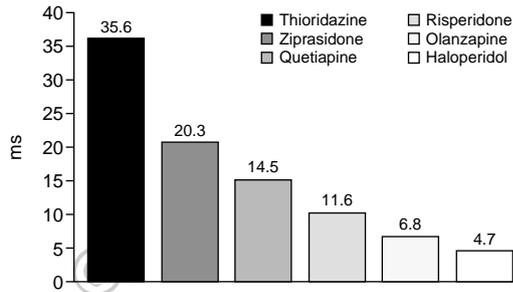
The most widely used antipsychotic agents in the 1980s and early 1990s (before the introduction of the new atypical antipsychotics) were haloperidol and fluphenazine.<sup>30</sup> Haloperidol has been the standard against which the new atypical agents have all been compared. Although haloperidol has been associated with QTc prolongation, torsades de pointes, and sudden death, these adverse effects occurred in a very different setting than other antipsychotic deaths. Because haloperidol has a reputation as a safe cardiovascular drug, it has been used extensively in intensive care settings, where it is frequently used parenterally for agitation in medical and surgical patients. When these patients receive haloperidol, they are usually monitored. Sudden death or serious cardiac arrhythmias, when they occur, are therefore likely to be documented. On the other hand, in psychiatric outpatients, sudden death is rarely accompanied by ECG monitoring.

**Table 2. Antipsychotic Agents and Relative Risk of QTc Prolongation or Torsades de Pointes**

Drugs (Year of FDA Approval)	Risk
Low-potency phenothiazines	
Chlorpromazine (1954)	Rare or uncertain
Thioridazine (1959)	Worst
Mesoridazine (1970)	Problematic
High-potency phenothiazines	
Perphenazine (1957)	Rare or uncertain
Trifluoperazine (1958)	Rare or uncertain
Fluphenazine (1959)	Rare or uncertain
Pimozide (1984)	Worst
Butyrophenones	
Haloperidol (1967)	Rare or uncertain
Droperidol (1970)	Worst
Atypical antipsychotics	
Clozapine (1990)	Rare or uncertain for QTc (other cardiac problems exist)
Risperidone (1993)	Rare or uncertain
Olanzapine (1996)	Rare or uncertain
Quetiapine (1997)	Rare or uncertain
Ziprasidone (2001)	Rare or uncertain but limited use to date

At the time of the antihistamine-related deaths in the early 1990s, the new antipsychotic sertindole was introduced in Europe, but because initial tests had found prolonged QTc in a dose-dependent fashion, sertindole was not marketed in the United States. In 1998, the use of sertindole was suspended in Europe because sudden deaths and serious arrhythmias had occurred.<sup>22</sup> Although it was never introduced for use in the United States, sertindole had a major impact by creating an awareness of cardiac effects with atypical antipsychotic agents. The current hyper-concern about the risks of QTc prolongation, torsades de pointes, and sudden death with the atypical antipsychotic agents has grown out of this history of cardiac problems with the older antipsychotics, compounded by the antihistamine-related deaths and the sertindole scrutiny of the 1990s.

Ziprasidone, an atypical antipsychotic, was approved by the FDA in 2001 for the treatment of psychosis, but evidence of modest QTc prolongation in initial trials with this agent delayed its approval in 1998 and prompted additional testing. When it was approved, bolded warnings were added to the package label. One additional study<sup>32</sup> that the FDA requested after the initial review was a comparison of the QTc prolongation of ziprasidone against that of thioridazine, haloperidol, risperidone, olanzapine, and quetiapine in patients who were drug free at baseline. All drugs were given at the highest possible dose allowed by the package label except thioridazine, which was given at less than half the recommended highest dose. The researchers found that thioridazine lengthened patients' QTc the most (despite the low dose having been used) and haloperidol did the least, with the atypical antipsychotics falling in between (Figure 1). One finding of this study is that risperidone showed a QTc lengthening more than twice that of haloperidol. The literature shows only 1 report<sup>33</sup> of

Figure 1. Mean Change in QTc from Baseline to Steady State<sup>a</sup>

<sup>a</sup>Data from Pfizer Advisory Committee Meeting Briefing Document, page 78.<sup>32</sup>

sudden death with risperidone, and the patient did not experience torsades de pointes. By comparison, haloperidol, with a smaller QTc prolongation, has been associated with 2 dozen documented torsades deaths.<sup>30</sup> Among the atypical agents, ziprasidone prolonged QTc more than the others did, although there were no sudden deaths. A point that the makers of ziprasidone made in this report was that although ziprasidone had an effect on the QTc similar to that of terfenadine with no inhibitor present, ziprasidone did not further increase the QTc in the presence of a metabolic inhibitor, as did terfenadine. The existence of this segment in the briefing document for the FDA illustrates the impact that the antihistamine-related deaths had on the approval process for new drugs. Further acknowledging previous cardiac safety issues, the makers of ziprasidone also noted that the incidence of QTc surpassing the 500 ms mark was more than 100 times greater with the nonapproved antipsychotic sertindole than with ziprasidone. The labeling for ziprasidone has bolded warnings that discourage use in patients with hypokalemia, hypomagnesemia, congenital prolonged QT syndrome, a history of cardiac arrhythmias or myocardial infarction, or concurrent use of other medications that prolong the QTc.<sup>34</sup>

Clozapine was the original atypical antipsychotic, but it was not used in the comparison with ziprasidone conducted for the FDA. It is approved only as second-line treatment due to the possibility of agranulocytosis and the need for regular blood monitoring. However, clozapine is associated with clinically significant weight gain<sup>35</sup> and other types of cardiac toxicity. Risperidone, which poses little direct risk on cardiac function, was the second atypical antipsychotic; it is associated with a moderate amount of weight gain,<sup>36</sup> although less so than clozapine or olanzapine. Olanzapine also seems to pose little direct risk on cardiac function; its drawbacks are related to weight gain, lipid abnormalities, and treatment-emergent diabetes.<sup>36-38</sup> Although ziprasidone may have a greater effect on cardiac function than olanzapine, it has a negligible effect on weight—in premarketing studies,<sup>34</sup> only 10% of ziprasidone-treated patients gained  $\geq 7\%$  of their body weight compared with 4% of placebo-

treated patients. Quetiapine, the other atypical antipsychotic, is associated with moderate weight gain. In premarketing studies,<sup>39</sup> significantly more quetiapine-treated patients (23%) gained  $\geq 7\%$  of their body weight compared with placebo-treated patients (6%). The quetiapine prescribing information<sup>39</sup> recommends caution when treating patients with known cardiac disease.

## MANAGING CARDIOVASCULAR RISKS OF MEDICATIONS

Risks for cardiovascular problems and populations who are at risk have been identified in various studies. Ruschena et al.<sup>40</sup> investigated cases of sudden death that were reported to the State Coroner of Victoria, Canada, during the year 1995 and matched those records to a psychiatric database to determine who had received psychiatric treatment. Their results were consistent with the literature, i.e., people with schizophrenic and affective disorders have an increased mortality rate compared with the general population. In their study, besides sudden death from suicide, homicide, and substance abuse, sudden death was primarily due to ischemic heart disease. In a similar investigation, Chute et al.<sup>41</sup> reviewed 66 cases of sudden death among people with schizophrenia that were reported to the medical examiner of the state of Maryland during the 3 years from 1994 through 1996. Besides the incidence of suicide, accidents, and homicide, the majority of cases of sudden death were mainly a result of atherosclerotic cardiovascular disease.

Ruschena and colleagues<sup>40</sup> noted that the risk factors for sudden death due to cardiovascular disease are prevalent in people with mental disorders, including a disregard for health in general (e.g., substance abuse, smoking, and poor diet), financial hardship, side effects of medications, and poor access to health care. In addition, these people may not be able to articulate physical problems or comply with treatment recommendations, or they may not seek treatment at all. In fact, people with schizophrenia have been reported to have a high tolerance for pain.<sup>42</sup>

When assessing patients for cardiovascular vulnerability, an important question to ask is whether anyone in their family has ever suddenly died or been subject to the episodes of sudden unconsciousness known as syncope. Syncope is associated with episodes of torsades de pointes and can be a symptom of long QT syndrome. During every evaluation of a patient who is going to take an antipsychotic drug, it is important to obtain a medical history, including a family history, of cardiovascular disease, diabetes, hypertension, syncope, or sudden death. If there is some question about the reliability of the psychotic patient's testimony regarding family history, a family member should provide the information.

For older patients or those with a worrisome set of risk factors, the general principle should be for the psychiatrist

to request a baseline ECG from a cardiologist or internist. Any patient with a QTc greater than 450 ms, significant cardiovascular disease, or family history of a long QT syndrome should not receive ziprasidone unless there is a compelling reason (e.g., the patient has failed to respond to other drugs). If there is evidence of a long QTc, ziprasidone should be avoided. If there are already problems associated with lipid levels, weight gain, or diabetes, olanzapine and clozapine should be avoided. However, after a careful risk-benefit analysis, clinicians may find that the therapeutic efficacy of a drug will in some cases override cardiovascular or metabolic concerns. Combinations of drugs are always a potential risk, and an ECG could be helpful when deciding whether to combine antipsychotic drugs.

### CONCLUSION

The approval of a new psychotropic agent that is effective but prolongs the QT interval creates a challenge for clinicians. However, as always, the goal in deciding on a treatment is to weigh the patient's risk factors with the potential benefits and side effects of the drugs available. Initial assessments of cardiovascular risks are useful when beginning a patient on antipsychotic treatment. I am not convinced that ziprasidone causes severe enough QTc prolongation that regular monitoring is necessary in any patients except those with overt cardiovascular disease. However, clinical experience will prove its level of safety.

Clinicians need to take into account not only the safety profile of the drug, but also the risk profile of the patient. For example, a patient with preexisting heart disease should not be given ziprasidone until further information is gathered about this agent. There would be different concerns with a patient who is obese or has high lipid levels or a family history of diabetes (see Davidson,<sup>43</sup> this supplement). Psychiatrists face complicated issues in selecting safe treatments for patients with schizophrenia, dementia, and other psychotic illnesses. Internists, cardiologists, and family doctors can help psychiatrists manage these cases. As always, good care is a matter of balancing risks and benefits. None of the present antipsychotic medications is ideal.

*Drug names:* bupropion (Wellbutrin and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), dalfopristin-quinupristin (Synercid), dofetilide (Tikosyn), droperidol (Inapsine and others), erythromycin (Ery-Tab, Eryc, and others), fluphenazine (Prolixin, Permitil, and others), gatifloxacin (Tequin), grepafloxacin (Raxar), haloperidol (Haldol and others), ketoconazole (Nizoral and others), mesoridazine (Serenal), moxifloxacin (Avelox), olanzapine (Zyprexa), perphenazine (Trilafon and others), pimozide (Orap), quetiapine (Seroquel), risperidone (Risperdal), sotalol (Betapace, Sorine, and others), thioridazine (Mellaril and others), trifluoperazine (Stelazine and others), 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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