

## Antipsychotic Drugs: Prolonged QTc Interval, Torsade de Pointes, and Sudden Death

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**Objective:** The authors review the mechanisms and establish the risk of torsade de pointes and sudden death with antipsychotic drugs.

**Method:** They present a review of original concepts, the distinction between familial and drug-induced cases of torsade de pointes, and the recognition of the role of noncardiac drugs in torsade de pointes and sudden death. They review the evidence linking QTc interval prolongation, potassium channels, and torsade de pointes from both the long QT syndrome and drugs. They examine the risk for torsade de pointes from antipsychotic drugs and estimate the frequency of sudden death on the basis of epidemiological data in normal and schizophrenic populations.

**Results:** All drugs that cause torsade de pointes prolong the QTc interval and bind to the potassium rectifier channel, but the relationships are not precise. Prediction of torsade de pointes and sudden death can be improved by examining

dose dependency, the percent of QTc intervals higher than 500 msec, and the risk of drug-drug interactions. Although sudden unexpected death occurs almost twice as often in populations treated with antipsychotics as in normal populations, there are still only 10–15 such events in 10,000 person-years of observation.

**Conclusions:** Although pimozide, sertindole, droperidol, and haloperidol have been documented to cause torsade de pointes and sudden death, the most marked risk is with thioridazine. There is no association with olanzapine, quetiapine, or risperidone. Ziprasidone does prolong the QT interval, but there is no evidence to suggest that this leads to torsade de pointes or sudden death. Only widespread use will prove if ziprasidone is entirely safe. To date, all antipsychotic drugs have the potential for serious adverse events. Balancing these risks with the positive effects of treatment poses a challenge for psychiatry.

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In 1996 a new atypical antipsychotic, sertindole, was not registered in the United States because it prolonged the QTc interval and was associated with 12 sudden unexplained deaths (1, 2). In 1998, the Committee on Safety of Medicines in the United Kingdom, which had previously approved the drug, found further evidence associating sertindole with malignant arrhythmia, and the manufacturer voluntarily suspended sale of the drug (3). In July of 2000, psychiatrists received a “Dear Doctor” letter warning that thioridazine prolonged the QTc interval and was associated with cases of torsade de pointes and sudden death. A “black box” was added to the package insert. Two months later, mesoridazine was also given a black box because of a dose-dependent prolongation of the QT interval and three published reports of ventricular tachycardia. For similar reasons, the antipsychotic pimozide was approved for use in Tourette’s syndrome with very restrictive labeling (4, pp. 1108–1110). These recent events present psychiatry with a problem that has been brewing in general medicine for more than a decade.

Torsade de pointes is a malignant ventricular arrhythmia that is associated with syncope and sudden death.

The term literally means a twisting of the points and refers to a characteristic pattern of polymorphic ventricular tachycardia. It was first described in 1966 (5), is associated with long QT intervals (4, pp. 1108–1110), and is generally unresponsive to the usual antiarrhythmic drugs. It occurs in both a primary and secondary form. The primary form is congenital, and cases can be either familial or sporadic. The secondary form is usually drug induced, the classic example being in reaction to quinidine (6). Initially torsade de pointes was seen as a problem limited to cardiac drugs and individuals with a congenitally long QT interval (7). That perception changed in the late 1980s with the experience with terfenadine (8).

### Torsade de Pointes and Noncardiac Drugs

The first-generation antihistamines were very useful but often impaired psychomotor performance and made patients sleepy. Terfenadine was the first of a new generation that minimized these complications because they penetrated the CNS poorly. It was introduced in 1986, and

for several years no serious difficulties were noted (9). In 1990, the first report of torsade de pointes appeared (8), and by 1992 the Food and Drug Administration (FDA) added a “black box” warning to the labeling of both terfenadine and a similar second-generation antihistamine, astemizole. The delay in recognizing this problem stemmed primarily from the low incidence of events and from premarketing trials that preferentially selected patients free of other medications.

As it turned out, both terfenadine and astemizole are very dependent on CYP3A4, and most of the fatalities resulted from coadministration of substances that inhibit that enzyme (10). The most frequent offenders were azole antifungals like ketoconazole or the macrolide antibiotics such as erythromycin. Torsade de pointes also occurred when these drugs were administered to individuals with serious liver disease, congestive heart failure, hypokalemia, and congenital long QT syndrome as well as in overdoses. Thus, a drug administered for a minor illness like hay fever could cause a fatal arrhythmia under circumstances that were difficult to predict (7). By 1997 it was apparent that the 1992 “black box” warning did not eliminate these deaths, and the FDA removed both antihistamines from the U.S. market.

Until the “Seldane [terfenadine] episode,” noncardiac drugs were not appreciated as potential causes of arrhythmia in patients without cardiac disease. It is now clear that arrhythmia can occur not only with antihistamines but also with antimalarial drugs (quinine and halofantrine), antifungals (sparofloxin and grepafloxen), macrolide antibiotics (erythromycin and clarithromycin), the gastric motility enhancer cisapride, and, most germane to this discussion, the psychotropic drugs (11, 12).

## Physiology of the QT Interval

The length of the QTc interval has been associated with the risk of sudden death after myocardial infarction and the long QT syndrome in several epidemiological studies (13, 14). Although it is not proven that drug-induced QTc interval prolongation behaves in the same manner, increasingly the underlying pathology seems to be the same, and QTc interval prolongation is a flag that warns of the possibility of torsade de pointes and sudden death. However, it is important to realize that QTc interval prolongation is a warning, not the risk itself. Not all drugs that prolong the QTc interval produce torsade de pointes and sudden death. Amiodarone, a class III antiarrhythmic drug, produces substantial prolongation of the QTc interval but very rarely produces torsade de pointes. Conversely, quinidine, with less severe prolongation, is more often a cause of torsade de pointes.

The QT interval is an ECG measure that includes both depolarization and repolarization. It begins with the onset of ventricular depolarization (Q wave) and ends with completion of repolarization (T wave). Because the QT interval

shortens with increasing heart rates, it is usually corrected for heart rate (QTc). Although cardiologists disagree about how best to accomplish this correction (15), there is no evidence that any particular method is a better predictor of sudden death (14).

Depolarization of ventricular cells is the result of a rapid influx of sodium ions through selective sodium channels, and its duration is measured by the QRS interval. Tricyclic antidepressants block this sodium channel, and, as a result, slow depolarization and widen both the QRS and the QTc intervals. However, QT lengthening with tricyclic antidepressants is primarily the result of the QRS change and not primarily related to a delay in repolarization (end of the S to the end of the T).

Repolarization involves calcium, sodium, and several potassium channels, but potassium channels play the pivotal role in drug-induced torsade de pointes. The potassium channel most often involved in drug-induced QT syndromes is the potassium rectifier ( $I_{Kr}$ ) channel (16). Drugs blocking the  $I_{Kr}$  channel can induce torsade de pointes and sudden death in apparently healthy adults (17). This is in sharp contrast to sodium (depolarizing) channel blockade, in which modest drug-induced prolongation of the QRS is not associated with sudden death in individuals without preexisting cardiac disease. This understanding supplies a rationale for why thioridazine, a drug that blocks  $I_{Kr}$  channel, is more often associated with sudden death in otherwise healthy individuals than the tricyclic antidepressants even though both slow cardiac conduction. Although drugs that block the  $I_{Kr}$  channel can cause arrhythmia in healthy individuals, such events are much more likely in patients with heart disease. That is why torsade de pointes originally appeared limited to cardiac drugs.

It has also become clear that drugs with minimal QTc interval prolongation by themselves can interact with other compounds with fatal consequences. Astemizole alone prolongs the QTc interval an average of only 7 msec, yet there are convincing cases of torsade de pointes and sudden death when it is combined with drugs that inhibit CYP3A4. Cetirizine is another second-generation antihistamine that produces slightly longer QTc interval prolongations than astemizole under baseline conditions (13). Astemizole is solely dependent on CYP3A4, but cetirizine has multiple metabolic pathways available and as a result is not vulnerable to drug-drug interactions; torsade de pointes has not been reported with cetirizine.

In addition to drug interactions, vulnerability to arrhythmia is affected by gender (females are at higher risk), potassium depletion, and ejection fraction. This makes predicting the risk of serious arrhythmia difficult. The QT interval is at best only modestly associated with torsade de pointes, but despite its difficulties it is the best predictor available.

QTc intervals are usually around 400 msec in duration, and values lower than 440 are considered normal. The

greater the duration, the more likely torsade de pointes becomes, but 500 msec has frequently been used as a cut-off because longer QTc interval measures are associated with substantially higher risk. However, other factors can influence this risk. It would be safest to find a drug that has no effect on the QTc interval, but that alternative does not always exist. The biggest problem comes when a useful new drug shows a small or modest prolongation. The first question is whether the prolongation is dose dependent, because some patients will undoubtedly be either slow metabolizers or given unusually high doses. In addition, psychiatric patients will take overdoses. Next, it is necessary to know the metabolic pathway and enzyme dependence of the compound in order to predict the potential for interactions. Even when these factors are known, it remains to be seen how frequently syncope, torsade de pointes, and sudden death actually occur.

### Torsade de Pointes and Antipsychotic Drugs

The first report of sudden arrhythmic death with an antipsychotic drug appeared in 1963, 2 years before the first description of torsade de pointes (18). It described two patients who died while receiving 1500 and 3600 mg/day of thioridazine, respectively, plus 26 cases of patients with T wave changes who were receiving doses as low as 200 mg/day. In both fatal cases, terminal ECGs were reported to show heart block alternating with episodes of ventricular tachycardia. However, the implications were not appreciated for a number of years. Since its introduction in 1959, thioridazine had gained wide acceptance because it was less likely to cause extrapyramidal reactions than other antipsychotics then available. Initially, high doses were used; however, in the mid-1960s, this was found to cause retinopathy, and the maximum allowable dose was severely restricted (19, 20). That restriction not only avoided the retinal complications but undoubtedly limited the number of sudden cardiac deaths and made the connection of thioridazine to torsade de pointes less obvious. Nevertheless, questions about the cardiovascular effects of thioridazine persisted, and case reports of arrhythmia and sudden death continued to accumulate (21).

Another circumstance that clouded the picture was that the tricyclic antidepressants that came into use about the same time also had cardiac effects, and the differences between the effects of the two types of drugs were not well understood. In the 1960s, it was evident that the tricyclics were fatal in overdose and that the cause of these deaths was most often cardiovascular. What remained in dispute was whether cardiac risks existed at normal therapeutic levels. By the end of the 1970s, it was clear that tricyclic antidepressants either at or just above therapeutic levels prolonged intraventricular conduction and had a quinidine-like antiarrhythmic action (22). For a decade it appeared that the only patients at major risk from therapeutic levels

of tricyclic antidepressants were those with preexisting intraventricular conduction disease (bundle branch block, etc.) (23).

This remained the impression until the late 1980s, when the Cardiac Arrhythmia Suppression Trial demonstrated that class I antiarrhythmics (sodium channel blockers) actually increased mortality in patients with ischemic heart disease. For more than a decade now, it has been recognized that tricyclic antidepressants are potentially dangerous drugs in patients with bundle branch disease or substantial ischemic heart disease as well as in overdose (24). Tricyclic antidepressants have proven safe in medically healthy adults at usual doses, although rare reports of death in children are worrisome (25).

Up until 1980, the major distinction in cardiac effects between the antidepressant and antipsychotic drugs was that the tricyclic antidepressants were more likely to cause adverse events. During the late 1970s and early 1980s tricyclic antidepressants caused more than a thousand overdose deaths each year (26). Thioridazine was associated with ventricular arrhythmia and sudden death more often than the other phenothiazines, but thioridazine-related sudden deaths were uncommon, and whether the other antipsychotics caused sudden death at all was in dispute (27, 28). Both thioridazine and tricyclic antidepressants were regularly described as "quinidine-like" in references to their action on the heart (29).

In 1991, Mehtonen et al. (30) examined all medicolegal autopsies (coroner's cases) in Finland over a 3-year period. Among 24,158 cases, they found 49 sudden unexpected deaths among apparently healthy adults taking psychotropic medication. Forty-six of these 49 deaths involved a phenothiazine, primarily thioridazine (28 of the 46 cases). Mehtonen et al. concluded that sudden unexpected death in apparently healthy adults was associated with low-potency phenothiazines, especially thioridazine, but not tricyclic antidepressants. Although their finding is interesting, there was at the time no theoretical basis to explain why, when both tricyclic antidepressants and phenothiazines lengthen the QTc interval, only phenothiazines produced torsade de pointes. Studies of the long QT syndrome and the terfenadine story in the early 1990s have increased our understanding of the underlying mechanisms and created a rational explanation for these early observations.

It is difficult with rare events such as sudden death to be sure that a drug is at fault. This is particularly true with antipsychotics because these drugs are administered to a patient population more likely to experience sudden death. Comparing rates of sudden death in patients with schizophrenia who are taking phenothiazines with rates among normal comparison populations confounds receiving a drug with having schizophrenia, and both issues are confounded by heavy smoking (31, 32). These confounds are controlled when all subjects involved have schizophrenia (30).

The most compelling evidence exists with thioridazine (33). It prolongs the QT interval, blocks the  $I_{Kr}$  channel (34), and is associated with numerous cases of torsade de pointes and causes an excess number of sudden death, even when compared with other antipsychotics (30). Pimozide, sulpiride, and droperidol (a butyrophenone) also prolong the QTc interval and have clearly been associated with torsade de pointes and sudden death (35, 36). However, these drugs were never as widely used as thioridazine, and as a result far fewer data are available and direct comparisons of risk are not possible. Although not as strong, the data also suggest that torsade de pointes can occur with any low-potency phenothiazine, particularly at high doses (37). The high-potency antipsychotics fluphenazine and haloperidol were the most widely used drugs in the 1980s and early 1990s (Table 1) and were considered safe drugs, although there were reports of torsade de pointes with haloperidol (38).

Haloperidol is an interesting compound. Available since 1958, it has been very widely used not only in psychiatric patients but also in medical and surgical patients for the control of severe agitation. Both individual case reports and small series document that it can prolong the QTc interval, cause torsade de pointes, and result in sudden death. These events can occur at normal therapeutic doses with either oral (38, 39) or intravenous (40) use and in overdose (41). Most psychiatric use is in outpatient settings. If sudden death occurs in that setting, there is almost never an ECG to document either the QTc interval or torsade de pointes. In contrast, the use of haloperidol to control severe agitation in medical patients usually occurs in hospitals, often in an intensive care unit. As a result, ECGs are frequently available before, during, and after an episode of drug-induced torsade de pointes. There are at least two dozen such well-documented cases (42).

In spite of the fact that there is no question that haloperidol can induce torsade de pointes and sudden death, the frequency with which this occurs is substantially less than with thioridazine. In the examination of sudden deaths in Finland during the mid-1980s by Mehtonen et al. (30), thioridazine was involved in 28 (61%) of the 46 sudden antipsychotic deaths; in 15 of these cases thioridazine was the only drug ingested. Even though haloperidol was used with equal frequency during that period in Finland, it was involved in only six (13%) of the 46 deaths and was never the only drug involved.

## Atypical Antipsychotics

Clozapine brought to psychiatry the promise of antipsychotic drugs that were both free of tardive dyskinesia and more effective than the older, typical dopamine blockers. However, clozapine came with serious side effects, including agranulocytosis, and pharmaceutical manufacturers raced to develop safer analogs. The first three compounds, risperidone, olanzapine, and quetiapine, all claimed to be

TABLE 1. Types of Antipsychotics

Type and Generic Name	Trade Name	Year of FDA Approval
Low-potency phenothiazines		
Chlorpromazine	Thorazine	1954
Thioridazine	Mellaril	1959
Mesoridazine	Serentil	1970
High-potency phenothiazines		
Perphenazine	Trilafon	1957
Trifluoperazine	Stelazine	1958
Fluphenazine	Prolixin	1959
Pimozide	Orap	1984
Butyrophenones		
Haloperidol	Haldol	1967
Droperidol	Inapsine	1970
Atypical neuroleptics		
Clozapine	Clozaril	1990
Risperidone	Risperdal	1993
Olanzapine	Zyprexa	1996
Quetiapine	Seroquel	1997
Ziprasidone	Geodon	2001

similar but safer drugs. All proved to be free of agranulocytosis and less likely to produce extrapyramidal reactions than the typical antipsychotics. However, some question whether their therapeutic efficacy is equal to clozapine, and, to varying degrees, they have been associated with weight gain, increased lipids, and diabetes.

In the early 1990s, a new drug application for sertindole, an antipsychotic that seemed similar to olanzapine and quetiapine, showed a dose-dependent increase in the QTc interval that averaged 22 msec at usual therapeutic doses. In addition, 12 unexplained sudden deaths and 23 cases of syncope occurred among 1,446 patients during sertindole's premarketing trials (2). Although the drug was not approved for marketing in the United States in 1996, it was in Europe. However, in 1998 the Committee on Safety of Medicines in the United Kingdom found evidence of 36 unexplained deaths and 13 serious but nonfatal arrhythmias and suspended sales of sertindole (43).

The problem with sertindole was a surprise to most psychiatrists in that, except for clozapine, cardiac difficulties had not been seen with the atypical antipsychotics. However, it probably should not have been so surprising. Minor effects on the  $I_{Kr}$  channel or the QT interval or both had been reported with the original atypical drugs (44). Although neither olanzapine nor quetiapine had been implicated in cases of torsade de pointes or sudden death, clozapine had been linked to serious cardiac problems (45), and reports suggested that risperidone could cause sudden death (46). In addition, it was clear from experience with antihistamines, antibiotics, and the older phenothiazines that members of the same pharmacological class can vary dramatically in their effect on the potassium channel and their ability to prolong the QT interval (47).

Although there is no question that syncope, torsade de pointes, and sudden death are associated with drugs that prolong repolarization by blocking the  $I_{Kr}$  channel, the pharmacology is complex and only partially understood (44). There are several potassium, sodium, and calcium

**TABLE 2. Effect of Six Antipsychotic Drugs on QTc Interval (Bazett Correction) Reported in a Study by Pfizer for the Food and Drug Administration**

Drug <sup>a</sup>	QTc Interval (msec)					
	Baseline	Change at Steady State		Change With Inhibitor Present		Inhibitor
	Mean	Mean	95% CI	Mean	95% CI	
Ziprasidone (N=31)	402.1	20.3	14.2 to 26.4	20.0	13.7 to 26.2	Ketoconazole
Risperidone (N=20)	396.3	11.6	7.4 to 15.8	3.2	-4.7 to 11.1	Paroxetine
Olanzapine (N=24)	397.9	6.8	0.8 to 12.7	5.3	-0.1 to 10.7	Fluvoxamine
Quetiapine (N=27)	398.0	14.5	9.5 to 19.5	19.7	14.3 to 25.0	Ketoconazole
Thioridazine (N=30)	395.9	35.6	30.5 to 40.7	28.0	21.6 to 34.5	Paroxetine
Haloperidol (N=20)	394.7	4.7	-2.0 to 11.3	8.9	1.9 to 15.9	Paroxetine/ketoconazole

<sup>a</sup> For all drugs except risperidone and haloperidol, N is the number of patients who began and completed the study for whom data were available on measures at steady state and with inhibitor present; 25 patients taking risperidone and 27 patients taking haloperidol began the study.

channels involved in repolarization. The long QT syndrome arises from several different mutations, and there are slight phenotypic differences between them. To date, drug-induced torsade de pointes has consistently involved blockade at the  $I_{Kr}$ , a channel expressed by the HERG gene (11). The relationship among the potassium, sodium, and calcium channels, other pharmacological effects of antipsychotics, and nondrug issues influencing risk is unclear and beyond the scope of this article. Nevertheless, the complexity of the QT interval is now an issue for psychiatry with the introduction of ziprasidone.

Ziprasidone has a modest but unequivocal effect on repolarization that does not appear to be particularly dose dependent. Ziprasidone prolongs the QT interval more than haloperidol, olanzapine, quetiapine, and risperidone but less than sertindole and thioridazine (48). Although it is reassuring that ziprasidone was not associated with cardiac events during premarketing trials, that is not sufficient to guarantee that uncommon but life-threatening arrhythmias will not occur once the drug is in widespread use. Fifteen years ago, terfenadine showed very modest QT prolongations, and sudden deaths were not noted for several years (9). However, when terfenadine was given with ketoconazole, a potent inhibitor of CYP3A4, the average QTc interval jumped by 60 msec. In contrast, the addition of ketoconazole does not change the QTc interval with ziprasidone (48). Though it has a 3A4 pathway, ziprasidone has a major aldehyde oxidase pathway, and this pathway is not known to be subject to either induction or inhibition.

At therapeutic doses, ziprasidone prolongs the QTc interval by 6–10 msec in ECGs obtained at random intervals throughout the dosing interval. Measured in the same way, sertindole increases the QTc interval 20–22 msec (depending on dose), and thioridazine increases it about 30 msec, but comparisons across trials are not accurate. ECG recordings should be made at or near the maximum daily blood level rather than at random intervals. Because the QT interval can be difficult to measure, readings should be made by a core laboratory. These conditions are almost never achieved in psychiatric studies. In addition, trials almost always recruit patients who were switched from another antipsychotic drug and seldom if ever specify what

drug the patients had received or for how long they were withdrawn from the previous before the study drug was administered. Most often the dose of one antipsychotic is lowered as the other is raised, and so-called baseline ECGs are far from drug-free (49). As a result, we do not have accurate estimates of the QT prolongation with any new antipsychotic, and the comparison of prolongation across studies is unreliable.

The best available data come from a study that Pfizer did at the FDA's request comparing the effect of ziprasidone, risperidone, olanzapine, quetiapine, thioridazine, and haloperidol on the QT interval (48). Previous medication was tapered over a 7-day period. Patients received placebo for 5 days before baseline ECGs were obtained. They were then randomly assigned to receive one of the six drugs. For each drug, except thioridazine, the highest dose recommended in the package insert was administered. Blood levels were obtained, and repeat ECGs were recorded at the time of maximum drug blood level. In the final portion of the experiment, an inhibitor specific to the metabolic pathway of that drug was coadministered and repeat ECGs obtained. The results are displayed in Table 2. Even though it was the only drug administered at less than half its recommended maximal dose, thioridazine produced the most prolongation. However, it is interesting to note that risperidone prolonged the QTc interval by almost 12 msec, even though there is no convincing evidence in the literature that it has ever caused torsade de pointes or sudden death, but haloperidol, a drug that can clearly cause torsade de pointes and sudden death, prolonged the QTc interval by less than 5 msec.

Another approach to estimating the risk of torsade de pointes that to some degree circumvents this problem is to measure the percentage of outliers rather than looking at the mean QTc interval change. The FDA has used QTc intervals greater than 500 msec as a clinically significant cutoff. Ziprasidone's new drug application contained 7,876 ECGs collected on 3,095 patients. Two patients in the ziprasidone group had QTc intervals in excess of 500 msec, and one patient in the placebo group exceeded 500 msec. The incidence of QTc intervals exceeding 500 msec in the sertindole new drug application was reported to be 7.8%,

more than 100 times the 0.06% (two of 3,095) seen with ziprasidone (48).

There is considerable evidence in the literature that populations with schizophrenia are at higher risk for sudden death independent of drug treatment (50). Sudden death could be the result of schizophrenic illness itself or illnesses related to the very high rate of smoking among such patients or a combination of the two. In spite of this, it seems clear that haloperidol, pimozide, sulpiride, droperidol, and thioridazine increase the risk of sudden death. On the other hand, even with widespread use, neither torsade de pointes nor sudden death has been reported with olanzapine and quetiapine in the literature.

Risperidone can prolong the QTc interval. Evidence comes from both usual oral doses and overdose (51, 52). However, we know of no unequivocal case of risperidone-induced torsade de pointes. There is a single report of sudden death involving a young woman with schizophrenia who was receiving 2 mg/day of risperidone and 100 mg/day of amantadine (46). Following a seizure, her heart arrested twice and she died. During both arrests, ECGs showed evidence of mechanical/electrical dissociation (pulseless electrical activity). Although her QTc interval prolonged significantly, she did not experience torsade de pointes or ventricular tachycardia. Risperidone does lengthen the QTc interval, but the only reported case of sudden death was not due to torsade de pointes.

Before marketing, 4,571 patients received ziprasidone for a total of 1,733 patient-years, and there were 1.6 deaths per 100 patient-years. According to FDA data on olanzapine, there were 1.8 deaths per 100 patients years. However, these rates are based on counting all deaths, including suicide, not just sudden death. Ziprasidone was associated with only 10 sudden deaths (death in less than 24 hours), or 0.56 deaths per 100 patient-years. This is a much lower rate than the 12 sudden deaths that were observed during 476 person-years (2.5 deaths per 100 patient-years) during the sertindole trials.

Another predictor of adverse cardiovascular events is overdose. During the new drug application trials of ziprasidone, 10 individuals ingested doses up to 4,600 mg, but there were no serious cardiac events and no deaths. However, ECG recordings were obtained in only two of the 10 overdoses. One of the two patients ingested 1,880 mg of drug (about 11 times the usual therapeutic dose), and 2.5 hours after the ingestion there was no change from the patient's original baseline ECG intervals. The second patient ingested 3,240 mg (20 times the usual therapeutic dose), and ECGs obtained 4, 6, and 9 hours after ingestion revealed a maximum QTc interval prolongation of 20 msec (48).

## Frequency of Sudden Death

Estimating the risk-benefit ratio involves knowing not only if a drug can cause torsade de pointes and sudden

death but also how often that event is likely to occur. There are several data sets that allow some estimates to be made. One of the best is the examination of Tennessee Medicaid enrollees by Ray and his colleagues (53). They followed approximately half a million enrollees for an average of 2.5 years from January 1988 to December 1993. They found 1,487 sudden unexpected cardiac deaths, or 11.6 per 10,000 person-years of observation. The risk of sudden death for individuals receiving antipsychotic drugs was 2.39 times greater than for nonusers (95% CI=1.77–3.22).

Similar to findings in other studies of sudden unexpected death, rates are strongly influenced by age, gender, and particularly cardiac disease. Among individuals free of cardiac disease, there were 11 sudden cardiac deaths in those receiving antipsychotic drugs compared with seven sudden cardiac deaths over 10,000 person-years of observation.

The figure of 7.0 deaths/10,000 person-years among apparently healthy individuals in this indigent Tennessee population is almost identical to the 7.4 deaths/10,000 person-years seen in the Paris Prospective Study, which followed more than 7,000 healthy civil service workers for 23 years (54), and the 5.5 deaths/10,000 person-years seen among 21,000 middle-aged, healthy physicians in the United States followed for 12 years (55). The risk increased significantly with increasing degrees of heart disease. Obviously, heart disease is much more likely to occur among older individuals. The data suggest that over a decade of exposure there would be four extra deaths among 1,000 apparently healthy young or middle-aged patients with schizophrenia who were treated with antipsychotic drugs. Part of this increase would be attributable to the antipsychotics, but part would be attributable to having schizophrenia and part to both the extraordinary frequency and intensity of smoking among patients with schizophrenia (56).

There are clearly differences in the risk of torsade de pointes and sudden death among currently marketed antipsychotic drugs. Thioridazine carries the best-documented and most severe risk. It is many times more likely to cause death than haloperidol. Nevertheless, haloperidol causes QTc interval prolongation and, on occasion, torsade de pointes and death. Although olanzapine, quetiapine, and risperidone bind to the  $I_{Kr}$  channel and can prolong the QTc interval, it is not clear that they have caused torsade de pointes or ventricular fibrillation. These calculations suggest that of the four extra sudden deaths per 1,000 patients per decade of observation in medically healthy patients with schizophrenia compared with matched subjects, only one or two would be accounted for by the difference between the best and the worst antipsychotic drug. In older patients with substantial heart disease or in patients with a prolonged QTc interval when they are not taking drugs, it could be a different story.

## Summary

Torsade de pointes was originally seen as either congenital or induced by cardiac drugs. However, over the last decade it has become clear that noncardiac drugs have the potential to induce torsade de pointes. Among psychotropic drugs, the low-potency phenothiazines have most often been implicated, particularly thioridazine. At the same time that our understanding of torsade de pointes with noncardiac drugs grew, the use of low-potency drugs became less common. They were replaced first by the high-potency phenothiazines and butyrophenones and more recently by the atypical antipsychotics risperidone, olanzapine, and quetiapine, which rarely, if ever, have been associated with torsade de pointes or sudden death. The QTc interval problem in psychiatry seemed to be waning until sertindole showed evidence of QT prolongation, syncope, and sudden death. Recently, the issue of QTc interval prolongation has again surfaced in the FDA evaluation of ziprasidone. The atypical antipsychotics all carry dramatically less risk of extrapyramidal symptoms and are more broadly effective than the classical antipsychotics. However, all bring with them some reasons for concern.

The most common concern with atypical antipsychotics has been weight gain (4, pp. 1108–1110, 1453–1457, 1649–1653, 2008–2012; 57, 58). Patients taking clozapine (4, pp. 2008–2012) and olanzapine (4, pp. 1649–1653) show an average gain of more than 10 lb at 6 months compared with about 5 lb for those taking risperidone (4, pp. 1453–1457). More recently, hyperlipidemia and diabetes have been reported with disturbing frequency (59–62). Although there are contradictory reports about its effect on weight, quetiapine is said to increase cholesterol as well as triglyceride levels (4, pp. 562–566; 63). New-onset diabetes has been seen with both clozapine (64, 65) and olanzapine (65), and there are reports of increased plasma glucose in patients with preexisting diabetes following treatment with clozapine, olanzapine, and quetiapine (66, 67). Although risperidone does increase weight, it has not been associated with lipid abnormalities or new-onset diabetes. Although well-controlled data are still limited, these issues need to be taken into consideration in estimating the risk-benefit ratio of antipsychotic drugs.

Ziprasidone does not appear to cause weight gain, hyperlipidemia, or hyperglycemia but does prolong repolarization more than olanzapine, quetiapine, or risperidone. The low rate of QTc interval prolongation beyond 500 msec, the absence of dose-dependent QTc interval increases or significant drug-drug interactions, and the absence of cardiac events in the few overdoses that have been recorded all suggest that torsade de pointes is not likely to be a serious problem with ziprasidone. If a problem does exist, the frail elderly or patients with preexisting cardiovascular disease would be at the highest risk, and the number of such patients in new drug application trials is very limited. Predictors do not substitute for clinical

data, and only careful postmarketing surveillance after widespread use will settle these issues.

Until we have more experience, it is prudent to ask apparently healthy patients if they have had syncope, if they have relatives with long QT syndrome, or if they have relatives who died suddenly at a young age. Among older patients, especially those with known heart disease or taking drugs that can prolong QT, a pretreatment ECG would be appropriate. At this point in time, an atypical antipsychotic without concern does not exist. In order to balance the risks and benefits of these drugs, the psychiatrist will have to add torsade de pointes, QTc interval, potassium rectifier current, hypertriglyceridemia, serum insulin, and person-years of observation to his or her vocabulary.

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