Proarrhythmic Risk with Antipsychotic and Antidepressant Drugs
Implications in the Elderly

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Contents

Abstract .......................................................................................................................... 998
1. Basic Cardiac Electrophysiology of Corrected QT (QTc) Interval Prolongation and Polymorphic Ventricular Tachycardia/Torsade de Pointes .......................................................... 999
2. Recent US FDA Concerns: Sertindole and Ziprasidone ........................................... 1000
3. Risk Factors for QT Interval Prolongation in the Elderly .......................................... 1001
   3.1 Age ................................................................................................................. 1001
   3.2 Circadian Variation ......................................................................................... 1002
   3.3 Sex ................................................................................................................. 1002
   3.4 Cardiovascular Disease .................................................................................. 1003
   3.5 Electrolyte Abnormalities .............................................................................. 1003
   3.6 Pharmacodynamic/Pharmacokinetic Factors .................................................. 1003
4. Congenital Long QT Syndrome ............................................................................. 1003
5. Antipsychotic Drugs and Sudden Cardiac Death .................................................... 1003
6. Literature Review .................................................................................................. 1004
   6.1 Methodology ................................................................................................. 1004
   6.2 Findings .......................................................................................................... 1004
   6.3 Discussion ...................................................................................................... 1004
7. Reflections, Conclusions and Recommendations .................................................. 1009
Abstract

The quinidine-like effects of some antidepressant drugs (particularly tricyclic antidepressants) and many antipsychotic drugs (particularly the phenothiazines) confound treatment of psychosis and depression in patients with major mental illness. This is especially true among elderly patients with existing risk factors for corrected QT (QTC) interval prolongation.

We used PubMed, previously reported review articles and the extensive personal files of the authors to identify cases of subjects aged ≥60 years who developed QTC interval prolongation, polymorphic ventricular tachycardia (PVT)/torsade de pointes (TdP) and/or sudden cardiac death while taking antipsychotic or antidepressant drugs or a combination of these medications. We identified 37 patients who had taken, in total, 46 antipsychotic or antidepressant drugs.

Our most striking finding was that almost four-fifths of our cases involved women. When the 14 critically ill subjects receiving haloperidol intravenously were excluded, 91.3% of our subjects were women. Almost three-quarters of our study subjects had cardiovascular disease.

Intravenous administration of haloperidol in the critically ill and profoundly agitated elderly warrants particular comment. Of the 14 subjects in this category identified, six were men and eight were women. In 13 cases, the drug dose far exceeded the 2 mg necessary to produce an antipsychotic effect. These clinicians were using an agent to achieve sedation that usually requires very high doses in the critically ill and profoundly agitated elderly to achieve this effect.

Inclusion criteria for our literature review required antipsychotic and/or antidepressant drug-induced QTc interval prolongation. Even so, our finding that 31 of our 37 subjects developed PVT is sobering. However, the reader should not conclude that drug-induced QTc interval prolongation is highly predictive of PVT or its TdP subtype. All of our study subjects had at least two risk factors for TdP, with age and sex being the most common. We included the rare case of a patient with congenital long QT syndrome who developed further lengthening of the QTc interval and TdP when prescribed an antidepressant drug well known to produce QTc interval prolongation.

We conclude with recommendations for clinicians not expert in the specialty of cardiology to deal with the many questions raised in this review. Specifically, such clinicians treating elderly patients with antipsychotic and antidepressant drugs that may prolong the QTc interval should aggressively obtain a baseline ECG for elderly female patients with additional risk factors such as personal or family history of pre-syncope or syncope, electrolyte disturbances or cardiovascular disease. Elderly male patients are also subject to QTc interval prolongation when such risk factors are present. It is important that the clinicians themselves inspect ECGs. If the QT interval is more than half the RR interval, QTc interval prolongation is likely to be present. In such cases, a cardiology colleague interested in QTc interval issues and TdP should be asked to review the ECG. Finally, nothing in our recommendations replaces meticulous attention to US FDA guidelines in the package insert of each drug.
Our aim was to (i) review the basic cardiac electrophysiology of corrected QT (QTC) interval prolongation and risk factors for such prolongation and (ii) review the literature on antipsychotic and antidepressant drug-induced QTC interval prolongation as it relates to the elderly, who are commonly prescribed these agents and who may have existing risk factors for QTC interval prolongation. Our goal is to enhance care of the elderly with psychiatric problems requiring administration of antipsychotic and antidepressant drugs.

Our group has had a long-standing interest in the effect that psychotropic drugs may have on QT interval prolongation, polymorphic ventricular tachycardia (PVT) and sudden cardiac death.1-6 The best-known form of PVT is called torsade de pointes (Tdp). Tdp is principally found in association with prolongation of the QT interval in sinus rhythm.7-17 Because Tdp is an electrocardiographic subtype of PVT, we will use the general term PVT unless the electrocardiographic manifestations clearly identify Tdp.

1. Basic Cardiac Electrophysiology of Corrected QT (QTC) Interval Prolongation and Polymorphic Ventricular Tachycardia/Torsade de Pointes

Figure 1 shows the standard electrocardiographic intervals as commonly seen in lead II. The summation of the electrical forces generated within the myocardium by the various cardiac cells accounts for these surface findings.

Figure 2 shows the tangent method of calculating the QT interval.18 Empirically, we know that the QT interval varies inversely with the heart rate: the slower the heart rate, the longer the QT interval. Various group-derived formulas may be used to correct (normalize) the QT interval (QTC interval) for heart rate.19 The Bazett formula20 (QTC=QT interval in seconds divided by the square root of the RR interval in seconds) is the most popular method for correction currently in use. Table I shows recommended Bazett-corrected QTC interval measurements for diagnosing QT interval prolongation in the adult.19

Figure 3 shows the action potential of a single ventricular muscle cell. Shown are sodium (Na+), calcium (Ca2+) and potassium (K+) ionic movements during the ventricular muscle cell action potential. Ions are distributed unevenly between the interstitium and interior of the myocyte because of impermeable, negatively charged proteins inside the myocyte and a cell membrane that selectively limits ionic movement between the cell and interstitium.21 Ion channels consist of specialized proteins and are selective for certain ions. Factors such as membrane potential, neurohormones, adenosine triphosphate supply and drugs may modify ion channel activity.

A net inward flux of sodium and then calcium drives cell depolarization (figure 3). A net outward flux of potassium largely using the rapid delayed rectifier potassium channels (IKr) drives cellular repolarization. Any agent, drug, condition or process reducing outward potassium currents may prolong (lengthen or delay) repolarization, rendering the patient vulnerable to PVT and Tdp.

Figure 4 depicts sequential changes in the ECG and the action potential leading to Tdp.22 QTC interval prolongation occurs when drugs or conditions enhance inward depolarizing sodium or calcium currents or decrease outward potassium.23 Potassium channel blockade is the most
common mechanism of drug-induced PVT and TdP.

Antipsychotic drugs, particularly thioridazine of the phenothiazine family, primarily block the rapid component of the \( I_{Kr} \) (figure 4), yielding inhomogeneous lengthening of the myocyte action potential, QTC interval prolongation, early after depolarizations (EADs) and TdP.\(^{[24]}\) The quinidine-like (ion-blocking) properties of tricyclic antidepressants (TCAs) act primarily on sodium influx during phase 0 (sodium 'fast' channel) of the action potential. TCA-induced widening of the QRS interval occurs most commonly in overdose.\(^{[25]}\) TCAs may secondarily affect calcium influx (calcium 'slow' channel) and potassium efflux during phase 3 of the action potential, thereby lengthening the JT interval component of the QT interval. Thus, TCAs may cause QTc interval prolongation both by widening the QRS interval and by delaying repolarization (lengthening the JT interval). It is the latter rather than the former effect of TCAs that will concern us in this discussion. The secondary effects of TCAs and the primary effects of thioridazine-like drugs may act together to lengthen the QTc interval and stimulate TdP. Drugs that lengthen the JT interval are of greater concern than drugs that widen the QRS complex alone.

Figure 5 shows the typical ECG features of PVT of the TdP type. Tachycardia is present because the ventricular beats appear close together. The arrhythmia is presumed to arise in ventricular tissue because the ventricular complexes are wide. It is important to note that the ventricular complexes vary in configuration. That is, their shape (morphology) varies from beat to beat, consistent with PVT of the TdP type. Cyclic alternation of the QRS electrical axis is characteristic of TdP.

In TdP, both the QT and QTc interval commonly exceed 500 msec.\(^{[26]}\) The most common QT or QTc interval in TdP is 600–649 msec.

2. Recent US FDA Concerns: Sertrindole and Ziprasidone

Beginning early in 1990, clinicians, investigators and regulatory agencies have gained greater understanding of the link between antipsychotic drugs and QTc interval prolongation, PVT and sudden cardiac death.\(^{[27–29]}\) By the mid-1990s, prolongation of the QT interval associated with TdP was the single most common reason for withdrawing or restricting drugs previously approved by the US FDA.\(^{[30]}\) Leading that list of drugs were the two non-sedating antihistamines terfenadine and astemizole, both of which were ultimately withdrawn from the market.

Sertrindole is a new generation antipsychotic drug associated with QTc interval prolongation and TdP.\(^{[30]}\) It was not approved by the FDA in 1996 but was used in the UK in 1996 and other European countries until the manufacturer withdrew it in 1998. Sertrindole continues to be used in various parts of the world.

By the late 1990s, the FDA was highly sensitized to drugs that may prolong the QTc interval. When the manufacturer of ziprasidone sought FDA approval in 1998, the company was asked to conduct an extensive study of this agent along with other older and newer antipsychotic drugs. This led to the Pfizer 054 study (see section 3.6).\(^{[31]}\) Ziprasidone was approved by the FDA in 2000.

<table>
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<tr>
<th>Rating</th>
<th>Adult men (msec)</th>
<th>Adult women (msec)</th>
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<tr>
<td>Normal</td>
<td>&lt;430</td>
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</tr>
<tr>
<td>Borderline</td>
<td>430–450</td>
<td>450–470</td>
</tr>
<tr>
<td>Prolonged</td>
<td>&gt;450</td>
<td>&gt;470</td>
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3. Risk Factors for QT Interval Prolongation in the Elderly

3.1 Age

Su et al. described aging trends of the QT interval in healthy elderly subjects. In this study, subjects from the Taiwanese community provided a medical history and underwent a physical examination and laboratory studies, including blood tests, a resting ECG and an echocardiogram. Exclusion criteria included diabetes mellitus, hypertension or other chronic diseases by history, haemoglobin <11 mg/dL or serum creatinine >1.5 mg/dL, echocardiographic evidence of significant valvular disease, depressed left ventricular ejection fraction or segmental wall motion abnormalities, electrocardiographic evidence of left ventricular hypertrophy with strain, advanced atrioventricular block, right or left bundle branch block, myocardial ischaemia or cardiac rhythm other than sinus rhythm. The investigators manually measured the QT interval from the beginning of the QRS complex to the end of the T wave.

The study group comprised 115 persons (90 men and 25 women). The mean ± SD maximum serial QT interval measurements at baseline (mean ± SD age 73 ± 4 years), 2 years (75 ± 4 years) and 4 years (77 ± 4 years) were 396 ± 25, 397 ± 25 and 399 ± 25 msec, respectively. The mean ± SD maximum serial QTc interval measurements at baseline, 2 years and 4 years were 422 ± 20, 425 ± 21 and 429 ± 27 msec, respectively. The mean maximum QTc interval increased significantly during the 4-year follow-up period (p = 0.001). The investigators concluded that the QTc interval increases progressively with age.

However, judgements about drug-induced QTc interval prolongation in studies and clinical practice are based on periods of weeks and months, not years. Although the FDA requires drug-induced group mean QTc interval lengthening of no more than 5 msec before it will approve a
3.2 Circadian Variation

The QTc interval varies throughout the 24-hour cycle. Night-time values are about 20 msec longer than daytime measurements because of differences in sympathetic and parasympathetic (autonomic) tone.\textsuperscript{35,36} In 20 normal subjects, the daily mean ± SD QTc interval variation was 76 ± 19 msec (range 35–108 msec). Cardiovascular disease may increase this variation.\textsuperscript{36}

3.3 Sex

The QTc interval does not vary by sex at birth.\textsuperscript{37} The male QTc interval shortens by about 20 msec at puberty compared with adolescent girls. This shortening appears to be androgen driven. The sex difference in QTc interval remains until age 50–55 years, when declining male testosterone levels narrow the difference. However, a sex-related difference in QTc interval may persist even into old age (table I). Based on
the usual cardiovascular risk factors, we would expect about 45% of cases of TdP to occur in women; however, about 70% of cases of TdP occur in women, including older women.\cite{37}

3.4 Cardiovascular Disease

Elderly men and women tend to have longer QTc intervals than their non-elderly counterparts even when both groups are free of cardiovascular disease.\cite{40} Age-matched subjects with cardiovascular disease tend to have longer QTc intervals than subjects without cardiovascular disease.\cite{40}

3.5 Electrolyte Abnormalities

Electrolyte abnormalities, particularly hypokalaemia and hypomagnesaemia, may contribute to or even cause QTc interval prolongation.\cite{38-40} Hypokalaemia prolongs the cardiac action potential and may cause EADs leading to TdP (figure 4). Diuretics are the most common cause of hypokalaemia. Other causes include excessive vomiting and diarrhoea. Postprandial states may lower serum potassium levels, as may exercise and agitation.

3.6 Pharmacodynamic/Pharmacokinetic Factors

Drugs may alter phase 3 (figure 3) potassium flow (pharmacodynamic factor) and disrupt the synchronous action of individual cardiac cells during the latter part of repolarization.\cite{23} This may induce EADs and TdP. Five to ten percent of European Americans are ‘poor metabolizers’ (pharmacokinetic factor) of certain drugs.\cite{23} The cytochrome P450 (CYP) isoenzyme 2D6 most commonly explains these differences in metabolism. The Pfizer 054 study extended our understanding of ‘poor metabolizers’ and others by evaluating the potential for metabolic inhibitors such as paroxetine to induce QTc interval prolongation by increasing antipsychotic drug concentrations.\cite{41} The metabolic pathways inhibited in the Pfizer 054 study were CYP2D6 (paroxetine) for thioridazine, risperidone and haloperidol; CYP3A4 (ketoconazole) for ziprasidone, quetiapine and haloperidol; and CYP1A2 (fluvoxamine) for olanzapine. Only quetiapine and haloperidol were associated with drug-induced QTc interval prolongation exacerbated by a metabolic inhibitor. Aripiprazole was not included in this study but is metabolized by both CYP2D6 and CYP3A4 pathways.

4. Congenital Long QT Syndrome

The congenital long QT syndrome (LQTS) occurs in about one in 5000 births and accounts for about 3000–4000 deaths per year in the US (mostly children and young adults).\cite{42} Schwartz and colleagues\cite{43,44} reported that treatment with β-adrenoceptor antagonists or left cardiac sympathetic denervation reduced the 10-year mortality from 71% to 6%. With treatment, many LQTS patients will live into old age and provide a patient set particularly vulnerable to drugs that may prolong the QTc interval and lead to TdP.

5. Antipsychotic Drugs and Sudden Cardiac Death

Compelling findings link antipsychotic drugs and sudden cardiac death.\cite{45-47} Ray et al.\cite{47} recently reported that both typical (older) and atypical (newer or new generation) antipsychotic drugs are associated with similar, dose-related risks of sudden cardiac death and that, overall, users of antipsychotic drugs have about twice the risk of sudden cardiac death as nonusers. Although the mechanism underlying this link has
not been defined, drug-induced blockade of potassium channels resulting in cardiac repolarization (JTI interval) prolongation is most suspect.\textsuperscript{47}

6. Literature Review

The purpose of our literature review was to gather a series of cases demonstrating antipsychotic and antidepressant drug-induced QTc interval prolongation and the complications that may follow in elderly subjects. Imbedded in this series is a compilation of risk factors that may place elderly patients at increased risk of drug-induced QTc interval prolongation.

6.1 Methodology

The following tools were used to gather information reported in this paper. First, PubMed was searched up to December 2008 using the terms ‘QT interval AND antipsychotic drugs’ and ‘QT interval AND antidepressant drugs’. Secondly, references were reviewed from recent review articles describing antipsychotic drugs and antidepressant drugs and the QT interval. Thirdly, the first author’s files on the QT interval gathered over the past 20 years were reviewed for articles about antipsychotic drugs and antidepressant drugs and the QT interval. This compilation of case reports was not exhaustive. Rather, we sought to gather a sufficient number of cases to develop useful commentary.

6.2 Findings

Table II documents 37 cases (8 [21.6\%] men and 29 [78.4\%] women) of subjects aged $\geq 60$ years who experienced QTc interval prolongation, PVT/TdP and/or sudden cardiac death while taking antipsychotic or antidepressant drugs or a combination of those medications. The subjects’ ages ranged between 60 and 92 years with two subjects being reported only as ‘elderly’. Drugs, risk factors and complications for each subject are listed in table II.

Table III shows psychotropic drug class and frequency of use. Among the 37 patients, 46 antipsychotic or antidepressant drug treatments involving 20 different drugs (haloperidol was given both orally and intravenously) were taken.

6.3 Discussion

The most striking finding in our literature review of QTc interval prolongation and antipsychotic and antidepressant drugs in the elderly was that almost four-fifths of the 37 cases we found involved women. If we exclude the 14 critically ill subjects receiving haloperidol intravenously, 21 (91.3\%) of the remaining 23 subjects were women. In an earlier review of new generation antipsychotic drugs and QTc interval prolongation in all age groups, we found that six cases involved male subjects and three cases involved female subjects.\textsuperscript{12} In an earlier review of TCAs, QTc interval prolongation and TdP in all age groups, we found that one case involved male subjects and 12 cases involved female subjects.\textsuperscript{13}

In a general review of sex and TdP, Woosley and Sketch\textsuperscript{[37]} reported that about 70\% of cases of TdP occur in women. In an autopsy review of 49 cases of sudden death associated with antipsychotic and antidepressant drug use in Finland, Mehtonen et al.\textsuperscript{[75]} reported on 18 men (36.7\%) and 31 women (63.3\%).

Twenty-seven (72.0\%) of our 37 cases (table II) had some aspect of cardiovascular disease or its equivalent (hypertension or diabetes mellitus). Age alone may explain this finding. Previously, we reported that cardiovascular disease itself may be a greater risk factor for QTc interval prolongation than psychotropic drug administration.\textsuperscript{14}

Intravenous administration of haloperidol in critically ill elderly patients warrants particular comment. Of the 14 subjects identified in our review who received this treatment, 6 (42.9\%) were men and 8 (57.1\%) were women (table II). In each case, the drug was given to manage severe agitation. In every case but patient 35, who was given 0.5 mg of haloperidol intravenously, the dose of this drug far exceeded the 2 mg necessary to produce an antipsychotic effect.\textsuperscript{[76]} Thus, clinicians were seeking the sedating effect of the drug, and this effect occurs at doses considerably greater than 2 mg. Complications found among these 14 patients included nine subjects who developed

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<table>
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<tr>
<th>Patient number</th>
<th>Study and year</th>
<th>Age (y), sex</th>
<th>Drugs</th>
<th>Risk factors</th>
<th>Complications</th>
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<tbody>
<tr>
<td>1</td>
<td>Fowler et al.,[48] 1976</td>
<td>64, female</td>
<td>Thoridazine, mesoridazine</td>
<td>Female sex</td>
<td>Syncope, sinus arrest, ventricular bigeminy, ventricular fibrillation, multifocal ventricular tachycardia</td>
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<td>2</td>
<td>Fowler et al.,[48] 1976</td>
<td>73, female</td>
<td>Chlorpromazine, nontriptoline and then amitriptyline</td>
<td>Female sex, hypertensive cardiovascular disease, congestive heart failure, diuretic use</td>
<td>Ventricular fibrillation, multifocal ventricular tachycardia, LBBB</td>
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<td>3</td>
<td>Fowler et al.,[48] 1976</td>
<td>71, female</td>
<td>Thoridazine, mesoridazine</td>
<td>Female sex</td>
<td>Syncope, cardiac arrest, multifocal ventricular beats and bigeminy</td>
</tr>
<tr>
<td>4</td>
<td>Ko et al.,[49] 1982</td>
<td>71, male</td>
<td>Doxepin (40 mg daily), trifluoperazine (4 mg daily), thoridazine (100 mg daily)</td>
<td>Seizures, hypertension</td>
<td>QTC prolongation to 620 msec, syncope, TdP, cardioversion on one occasion for TdP, temporary transvenous catheter placement to treat recurrent TdP</td>
</tr>
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<td>5</td>
<td>Flugelman et al.,[50] 1982</td>
<td>71, female</td>
<td>Clomipramine (200 mg daily)</td>
<td>Female sex, three generations of a family with congenital long QT syndrome</td>
<td>QTC interval prolongation to 580 msec, presented with runs of PVT treated with lidocaine (lignocaine), resulting in TdP progressing to ventricular fibrillation successfully reversed with electroversion, on discharge from the hospital while free of medications, QTC interval remained prolonged at 480 msec</td>
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<td>6</td>
<td>Herrmann et al.,[51] 1983</td>
<td>81, female</td>
<td>Maprotiline</td>
<td>Female sex, hypothyroidism, diabetes mellitus</td>
<td>QTC interval prolongation to 710 msec, syncope, TdP</td>
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<td>7</td>
<td>Davison,[52] 1985</td>
<td>71, female</td>
<td>Amitriptyline</td>
<td>Female sex, QRS duration 120 msec</td>
<td>QTC interval prolongation to 570 msec, TdP</td>
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<td>Jerjes Sanchez Diaz et al.,[53] 1985</td>
<td>65, female</td>
<td>Amitriptyline</td>
<td>Female sex, serum potassium 3.2 mmol/L</td>
<td>QTC interval prolongation to 520 msec, syncope, TdP</td>
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<td>Zee-Cheng et al.,[54] 1985</td>
<td>63, female</td>
<td>Haloperidol overdose (420 mg)</td>
<td>Female sex, hypocalcaemia</td>
<td>QTC interval prolongation to 680 msec, recurrent TdP requiring ventricular overdrive pacing</td>
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<td>Zee-Cheng et al.,[54] 1985</td>
<td>60, female</td>
<td>Haloperidol overdose (1000 mg)</td>
<td>Female sex, hypocalcaemia</td>
<td>QTC interval prolongation to 480 msec, recurrent TdP requiring ventricular overdrive pacing</td>
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<td>11</td>
<td>Casazza et al.,[55] 1986</td>
<td>60, female</td>
<td>Desipramine, dothiepin (dosulepin)</td>
<td>Female sex</td>
<td>QTC interval prolongation to 540 msec, syncope, TdP</td>
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<td>12</td>
<td>Fayer,[56] 1986</td>
<td>Elderly female</td>
<td>Haloperidol (up to 15 mg daily)</td>
<td>Female sex, hypertension, sick sinus syndrome with bradycardia of 30 beats/min</td>
<td>QTC interval prolongation to 600 msec, TdP, recurrent bradycardia requiring permanent ventricular pacemaker placement</td>
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<td>13</td>
<td>Wilt et al.,[57] 1993</td>
<td>63, female</td>
<td>Haloperidol (IV 489 mg over 36 hours)</td>
<td>Female sex</td>
<td>QTC interval prolongation to 670 msec, TdP</td>
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<th>Drugs</th>
<th>Risk factors</th>
<th>Complications</th>
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<td>Metzger and Friedman, 1993</td>
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<td>Haloperidol (IV 96 mg over the preceding 24 hours)</td>
<td>Respiratory failure secondary to chronic obstructive pulmonary disease requiring intubation, bacterial pneumonia, dilated and hypokinetic right ventricle and decreased systolic contraction, hypocalcaemia, hypotension</td>
<td>QTc interval prolongation to 500 msec, sudden cardiac death</td>
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<td>15</td>
<td>Hunt and Stern, 1995</td>
<td>76, female</td>
<td>Haloperidol (IV 44.5 mg over 10 hours)</td>
<td>Female sex, coronary artery disease, congestive heart failure, hypomagnesaemia, hypocalcaemia, severe anaemia, hypoxaemia</td>
<td>QTc interval prolongation to 670 msec, TdP</td>
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<td>16</td>
<td>Hunt and Stern, 1995</td>
<td>65, female</td>
<td>Haloperidol (IV 65 mg on post-operative day 1, 300 mg on post-operative day 2, 600 mg on post-operative day 3)</td>
<td>Female sex, coronary artery disease, rheumatic heart disease, congestive heart failure, hypomagnesaemia, atrial flutter and fibrillation</td>
<td>Received 30 mg of haloperidol IV before onset of ventricular tachycardia on post-operative day 2, QTc interval prolongation to 628 msec, TdP occurred four times with one occasion requiring defibrillation</td>
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<td>17</td>
<td>Di Salvo and O’Gara, 1995</td>
<td>65, male</td>
<td>Haloperidol (IV more than 300 mg over 3 days preceding TdP)</td>
<td>Baseline QTc interval prolongation to 496 msec, RBBB, ventricular trigeminy</td>
<td>QTc interval prolongation to 594 msec, TdP followed by ventricular fibrillation requiring defibrillation</td>
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<td>Di Salvo and O’Gara, 1995</td>
<td>65, female</td>
<td>Haloperidol (IV more than 400 mg over 4 days preceding TdP)</td>
<td>Female sex, rheumatic heart disease treated surgically, atrial flutter</td>
<td>QTc interval prolongation to 628 msec, TdP requiring cardioversion followed by several more episodes of TdP</td>
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<td>76, female</td>
<td>Haloperidol (IV more than 40 mg over 2 days preceding TdP)</td>
<td>Female sex, coronary artery disease, left ventricular hypertrophy, pulmonary oedema, marked hypertension, baseline QTc interval of 450 msec, hypocalcaemia</td>
<td>QTc interval prolongation to 670 msec, TdP</td>
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<td>20</td>
<td>Mazur et al., 1995</td>
<td>74, female</td>
<td>Trazodone (150 mg daily)</td>
<td>Female sex, co-administration of amiodarone, hypertension, coronary artery disease, diastolic heart failure, ventricular demand (VVI) pacemaker</td>
<td>Dizziness following addition of trazodone, paced ventricular rhythm of 70 beats/min with markedly prolonged QTc interval to 777 msec, TdP</td>
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<td>21</td>
<td>Appleby et al., 1996</td>
<td>74, female</td>
<td>Fluoxetine (20 mg daily) for 3 weeks after long-term treatment with amisulpride</td>
<td>Female sex, mild hypertension</td>
<td>QTc interval prolongation to 600 msec, syncope, TdP</td>
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<td>Rialan et al., 1995</td>
<td>67, female</td>
<td>Maprotiline</td>
<td>Female sex, QRS duration of 120 msec</td>
<td>QTc interval prolongation to 582 msec, syncope, TdP</td>
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<th>Patient number</th>
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<th>Risk factors</th>
<th>Complications</th>
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<td>Sharma et al.,[94] 1998</td>
<td>64, female</td>
<td>Haloperidol (IV 115 mg over 10 hours)</td>
<td>Female sex, critically ill</td>
<td>QTc interval prolongation to 605 msec, TdP</td>
</tr>
<tr>
<td>24</td>
<td>Sharma et al.,[94] 1998</td>
<td>75, female</td>
<td>Haloperidol (IV 85 mg over 27.3 hours)</td>
<td>Female sex, critically ill</td>
<td>QTc interval prolongation to 567 msec, TdP</td>
</tr>
<tr>
<td>25</td>
<td>Sharma et al.,[94] 1998</td>
<td>71, male</td>
<td>Haloperidol (IV 70 mg over 2.5 hours)</td>
<td>Critically ill</td>
<td>QTc interval prolongation to 521 msec, TdP</td>
</tr>
<tr>
<td>26</td>
<td>Iglesias et al.,[60] 2000</td>
<td>76, male</td>
<td>Tiapride (300 mg daily)</td>
<td>Mild congestive heart failure, atrial fibrillation</td>
<td>QTc interval prolongation to 600 msec, TdP</td>
</tr>
<tr>
<td>27</td>
<td>Douglas and Block,[66] 2000</td>
<td>75, male</td>
<td>Haloperidol (IV at a rate of up to 20 mg in 6 hours)</td>
<td>Advanced coronary artery disease, myocardial infarction, acute coronary artery angioplasty</td>
<td>QTc interval prolongation to 615 msec, ventricular fibrillation, cardioversion to normal sinus rhythm</td>
</tr>
<tr>
<td>28</td>
<td>Douglas and Block,[66] 2000</td>
<td>68, male</td>
<td>Haloperidol (IV 2 mg/hour with 1 mg bolus to a maximum of 5 mg/hour)</td>
<td>Unstable angina complicated by pulmonary oedema requiring tracheal intubation and mechanical ventilation</td>
<td>QTc interval prolongation to 648 msec</td>
</tr>
<tr>
<td>29</td>
<td>Douglas and Block,[66] 2000</td>
<td>77, male</td>
<td>Haloperidol (IV 2 mg) on day 8, haloperidol (IV 2 mg) on day 9, haloperidol (IV 2 mg on two occasions) on day 13</td>
<td>Unstable angina requiring coronary artery angioplasty and stent placement complicated by ventricular fibrillation, left ventricular ejection fraction of 20%, tracheal intubation and intra-aortic balloon pump</td>
<td>QTc interval prolongation to 554 msec on day 8, 508 msec on day 9 and 508 msec on day 13</td>
</tr>
<tr>
<td>30</td>
<td>Lantini et al.,[87] 2001</td>
<td>69, female</td>
<td>Maprotiline</td>
<td>Female sex, advanced heart failure with peripheral oedema, coronary artery disease</td>
<td>QTc interval prolongation to 700 msec, TdP</td>
</tr>
<tr>
<td>31</td>
<td>Kang et al.,[69] 2004</td>
<td>87, female</td>
<td>Risperidone followed by olanzapine</td>
<td>Female sex, hypertension, hypokalaemia (3.1 mmol/L), thiazide diuretic</td>
<td>QTc interval prolongation to 494 msec taking first risperidone and then olanzapine</td>
</tr>
<tr>
<td>32</td>
<td>Wilting et al.,[98] 2006</td>
<td>83, female</td>
<td>Fluoxetine (20 mg daily)</td>
<td>Female sex, LBBB</td>
<td>QTc interval prolongation to 478 msec corrected for LBBB, syncope, TdP</td>
</tr>
<tr>
<td>33</td>
<td>Letsas et al.,[70] 2006</td>
<td>60, female</td>
<td>Venlafaxine (150 mg daily)</td>
<td>Female sex, hypertension, mild left ventricular hypertrophy</td>
<td>QTc interval prolongation to 562 msec</td>
</tr>
<tr>
<td>34</td>
<td>Klein-Schwartz et al.,[71] 2007</td>
<td>75, female</td>
<td>Ziprasidone (480 mg)</td>
<td>Female sex</td>
<td>QTc interval prolongation to 470 msec</td>
</tr>
<tr>
<td>35</td>
<td>Katajärvi et al.,[72] 2007</td>
<td>92, female</td>
<td>Haloperidol (0.5 mg IV)</td>
<td>Female sex</td>
<td>QTc interval prolongation to 468 msec</td>
</tr>
<tr>
<td>36</td>
<td>Huang et al.,[73] 2007</td>
<td>69, female</td>
<td>Sulpiride</td>
<td>Female sex, coronary artery disease</td>
<td>QTc interval prolongation to 660 msec, syncope, TdP</td>
</tr>
<tr>
<td>37</td>
<td>Ravina et al.,[74] 2007</td>
<td>Elderly female</td>
<td>Risperidone</td>
<td>Female sex</td>
<td>QTc interval prolongation to 760 msec, TdP, asystole, death</td>
</tr>
</tbody>
</table>

**Note:** IV = intravenous; LBBB = left bundle branch block; RBBB = right bundle branch block.
Table III. Antipsychotic and antidepressant drugs and patient number (see Table II) taking each drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patient number*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antipsychotic drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>2</td>
</tr>
<tr>
<td>Haloperidol IV</td>
<td>13, 14, 15, 16, 17, 18, 19, 23, 24, 25, 27, 28, 29, 35</td>
</tr>
<tr>
<td>Haloperidol oral</td>
<td>9, 10, 12</td>
</tr>
<tr>
<td>Mesocondazaine</td>
<td>1, 3</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>31</td>
</tr>
<tr>
<td>Risperidone</td>
<td>31, 37</td>
</tr>
<tr>
<td>Sulpiride</td>
<td>36</td>
</tr>
<tr>
<td>Thoridazine</td>
<td>1, 3, 4</td>
</tr>
<tr>
<td>Tiapride</td>
<td>26</td>
</tr>
<tr>
<td>Trifluoperazine</td>
<td>4</td>
</tr>
<tr>
<td><strong>Antidepressant drugs</strong></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline</td>
<td>2, 7, 8, 21</td>
</tr>
<tr>
<td>Clomipramine</td>
<td>5</td>
</tr>
<tr>
<td>Desipramine</td>
<td>11</td>
</tr>
<tr>
<td>Dothiepin (dosulepin)</td>
<td>11</td>
</tr>
<tr>
<td>Doxepin</td>
<td>4</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>21, 32</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>6, 22, 30</td>
</tr>
<tr>
<td>Nortriptyline</td>
<td>2</td>
</tr>
<tr>
<td>Trazodone</td>
<td>20</td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>33</td>
</tr>
</tbody>
</table>

* Patient numbers are bolded if the patient was taking more than one drug.

**IV** = intravenous.

TdP, one patient who developed ventricular fibrillation and one patient who experienced sudden cardiac death. Thus, intravenous administration of haloperidol in the critically ill with severe agitation requires meticulous cardiac monitoring.

If we assume that all of the cases reported by Fowler et al. in 1976[48] manifested PVT, then 31 (83.8%) of our 37 cases (table II) demonstrated some variant of this arrhythmia. Cases that reach the literature must pass several thresholds. By definition, all of our cases manifested QTc interval prolongation. This electrocardiographic measurement is the best predictor of PVT but is still a very poor one. That is, QTc interval prolongation itself is unlikely to predict PVT. All of our 37 cases had at least two risk factors for TdP, with sex and age being the most common of these.[77]

Sixteen (43.2%) of our 37 cases (table III) received an antidepressant drug, with TCAs (12 of the 16) being the most common form of antidepressant drug. Of the TCAs, amitriptyline appeared four times and maprotiline appeared three times. Of the antipsychotic drugs, haloperidol appeared 17 times, with 14 of those appearances due to intravenous administration. Thoridazine appeared three times. In the autopsy survey of sudden death associated with antipsychotic and antidepressant drugs in Finland,[75] thoridazine was involved in more than half of the deaths, with other antipsychotic drugs being involved in the remaining deaths. In only one of the 49 cases did an antidepressant drug appear without co-administration of an antipsychotic drug.

We included the case report of Mazur et al.[61] (table II) involving trazodone even though this profoundly ill 74-year-old woman had a permanent ventricular demand (VVI) pacemaker in place for treatment of sick sinus syndrome. The authors assumed that QTc interval prolongation had largely the same meaning in a patient with paced ventricular beats as in a patient with QTc interval prolongation with an intact cardiac conduction system. All the normative data we have about the QTc interval and its prolongation involve patients with intact cardiac conduction systems. Several months before presentation, this patient received a stable dose of amiodarone (which is well known to induce QTc interval prolongation and, rarely, TdP[78]) followed by addition of trazodone and subsequently reported new-onset dizziness without loss of consciousness. At hospital admission, amiodarone and trazodone were stopped. Shortly thereafter, this patient developed TdP that responded to increased ventricular pacing rate.

We also included the case report of Wilting et al.[69] which involved fluoxetine, even though this 83-year-old woman had a left bundle branch block. The authors reported a 'corrected' QT interval of 478 msec. As noted in the previous paragraph, all the normative data we have about the QTc interval and its prolongation involves patients with intact cardiac conduction systems. Left bundle branch block appears in patients who have some conduction system delay in part of the
left bundle of His. Darpo\textsuperscript{[79]} documented the 20 drugs most commonly reported to be associated with TdP between 1983 and 1999 and found that fluoxetine was listed immediately after haloperidol. However, the market share of fluoxetine far exceeded that of all the remaining psychotropic agents added together. Therefore, fluoxetine was far less likely than haloperidol to induce TdP.

As recorded in Table III, seven subjects (patients 1, 2, 3, 4, 11, 21 and 31) received two or more psychotropic drugs associated with QTc interval prolongation. We do not know if a combination of such drugs (possible interactive effect) is more likely to produce QTc interval prolongation than a higher dose of a single agent. Given this uncertainty, we recommend using a single agent unless there is a compelling reason to administer two or more psychotropic drugs that may prolong the QTc interval.

In a study comparing monotherapy versus polytherapy with psychotropic drugs, Sala et al.\textsuperscript{[80]} reported that no significant QTc interval prolongation appeared during monotherapy with an antipsychotic drug. However, combining antipsychotic drugs with an antidepressant drug yielded significant QTc interval prolongation. These authors recommended careful electrocardiographic monitoring of patients taking combinations of antipsychotic and antidepressant drugs.

The new generation (atypical) antipsychotic drugs appearing in Table III are olanzapine, risperidone and ziprasidone. The absence of quetiapine, currently the most commercially successful atypical antipsychotic drug in the US, does not imply that this drug is less likely to induce QTc interval prolongation and TdP. We recently published a case report of a middle-aged woman taking quetiapine who developed QTc interval prolongation and TdP and we reviewed the literature, finding no cases that have not been included in this review.\textsuperscript{[14]} Also, we did not find any examples of aripiprazole-associated QTc interval prolongation complications. The relative newness of this drug may account for its absence from our review.

The combination of congenital and acquired QTc interval prolongation reported by Flugelman et al.\textsuperscript{[50]} warrants particular attention (Table II, patient 5). When the patient was free of medication, her baseline QTc interval was prolonged at 480 msec. Addition of therapeutic doses of clomipramine in the absence of any known risk factors other than age and sex provoked symptomatic PVT. Thus, a personal and family history that includes information on pre-syncpe, syncope, seizures and unexpected death should be carefully taken before psychotropic drugs known to prolong the QTc interval are prescribed. Any information suggestive of congenital LQTS justifies a baseline ECG.

7. Reflections, Conclusions and Recommendations

This review has raised many more questions than it has answered. Al-Khatib et al.\textsuperscript{[81]} in a thoughtful review of what clinicians should know about the QT interval, acknowledge that lack of information prevents clinicians from minimizing the risk of TdP. Further complicating this problem is the report by Viskin et al.\textsuperscript{[82]} that most physicians, including many cardiologists, fail to accurately calculate a QTc interval or correctly identify a prolonged QT interval. Bai and Yan\textsuperscript{[83]} extend this lament in an editorial appearing in the same premier journal dedicated to cardiac electrophysiology.

Hongo and Goldschlager\textsuperscript{[84]} have chided clinicians for their over-reliance on computerized interpretations of the ECG. Recently, cardiac electrophysiologists debated whether QT interval prolongation is a reliable predictor of ventricular arrhythmias.\textsuperscript{[85,86]} Malik\textsuperscript{[87]} described the most popular formula for calculating the QTc interval (Bazett, see section I) as "clearly one of the worst options." Recently, Malik et al.\textsuperscript{[88]} used the Fredericia formula (QTc = QT/cube root of the RR interval) modified by individually optimized curvature correction to offer an accurate measurement of the QTc interval throughout the 24-hour cycle. In an editorial comment, Franz\textsuperscript{[89]} noted that in the best of circumstances, QTc interval prolongation is a poor predictor of TdP unless it is very long. The method of measuring the QTc interval described by Malik et al.\textsuperscript{[88]} is
labour intensive and unlikely to be adopted on a large scale in the near future.

Phoon proposed that as long as the heart rate is 70 beats/minute or more, the QTc interval will be normal if the QT interval is less than half of the RR interval. QT intervals that are half or more of the RR interval bear careful scrutiny. Based on our observations and review of the literature, the non-cardiologist prescribing anti-psychotic and antidepressant drugs that may prolong the QTc interval in elderly patients should aggressively obtain a baseline ECG for female patients with additional risk factors such as personal or family history of pre-syncpe or syncope, electrolyte disturbance or cardiovascular disease. Elderly male patients are also subject to QTc interval prolongation and TdP if those risk factors are present. It is important that the clinician inspects the ECG him- or herself using the Phoon rule of thumb described above. The clinician should also ask a cardiology colleague interested in QTc interval issues and TdP to review the tracing. Ultimately, however, nothing in these recommendations replaces meticulous attention to the FDA guidelines set out in the package insert of each drug.

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