REVIEW ARTICLE

Drugs Aging 2009; 26 (12): 997-1012
1170-229X/09/0012-0997/$49.95/0

Proarrhythmic Risk with Antipsychotic and Antidepressant Drugs

Implications in the Elderly

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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.[1-16] 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.[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 formulae may be used to correct (normalize) the QT interval (QTc interval) for heart rate.[19] The Bazett formula[20] (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]

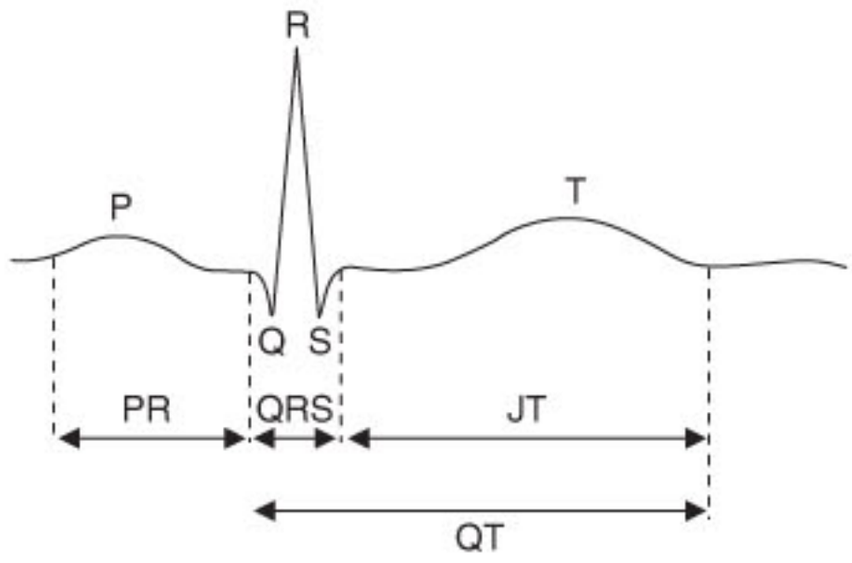

Fig. 1. Typical lead II electrocardiographic tracing showing standard intervals. The P wave is atrial electrical depolarization and immediately precedes mechanical right and left atrial contraction. The QRS interval is electrical ventricular depolarization and immediately precedes mechanical left and right ventricular contraction. The ST segment is the isoelectric portion of ventricular repolarization and the T wave is the directional component of ventricular repolarization. The QRS interval, ST segment and T wave on the surface ECG make up the QT interval, and this interval consists of the QRS interval and JT interval (ST segment and T wave). Most of the QT interval represents ventricular repolarization.

Figure 3 shows the action potential of a single ventricular muscle cell. Shown are sodium (Na^+), calcium (Ca^{2+}) 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 (I_{Kr}) 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

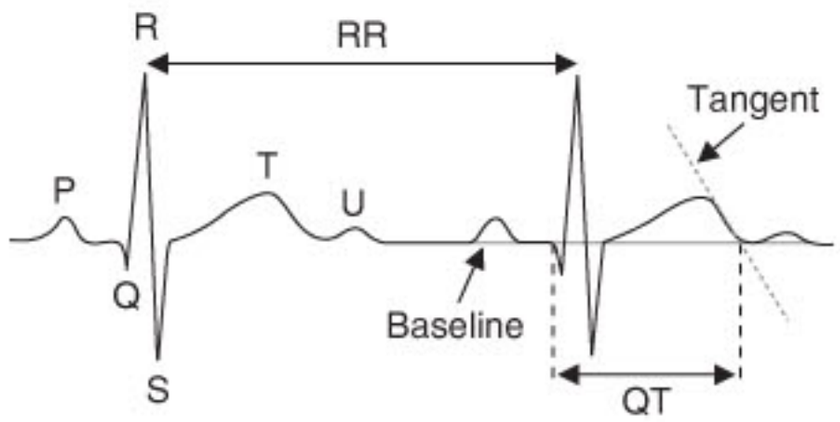

Fig. 2. Shown is the tangent method of measuring the QT interval (see figure 1) using lead II of the surface ECG. In this method, a tangent is drawn to the steepest slope of the last limb of the T wave. The intersection of the tangent with the baseline defines the end of the QT interval (reproduced from Postema et al.,[18] with permission from the Heart Rhythm Society).

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: Sertindole 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 nonsedating antihistamines terfenadine and astemizole, both of which were ultimately withdrawn from the market.

Sertindole 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. Sertindole 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 I. Recommended Bazett-corrected QTc interval measurements for diagnosing QT interval prolongation[19]

Rating	Adult men (msec)	Adult women (msec)
Normal	<430	<450
Borderline	430–450	450–470
Prolonged	>450	>470

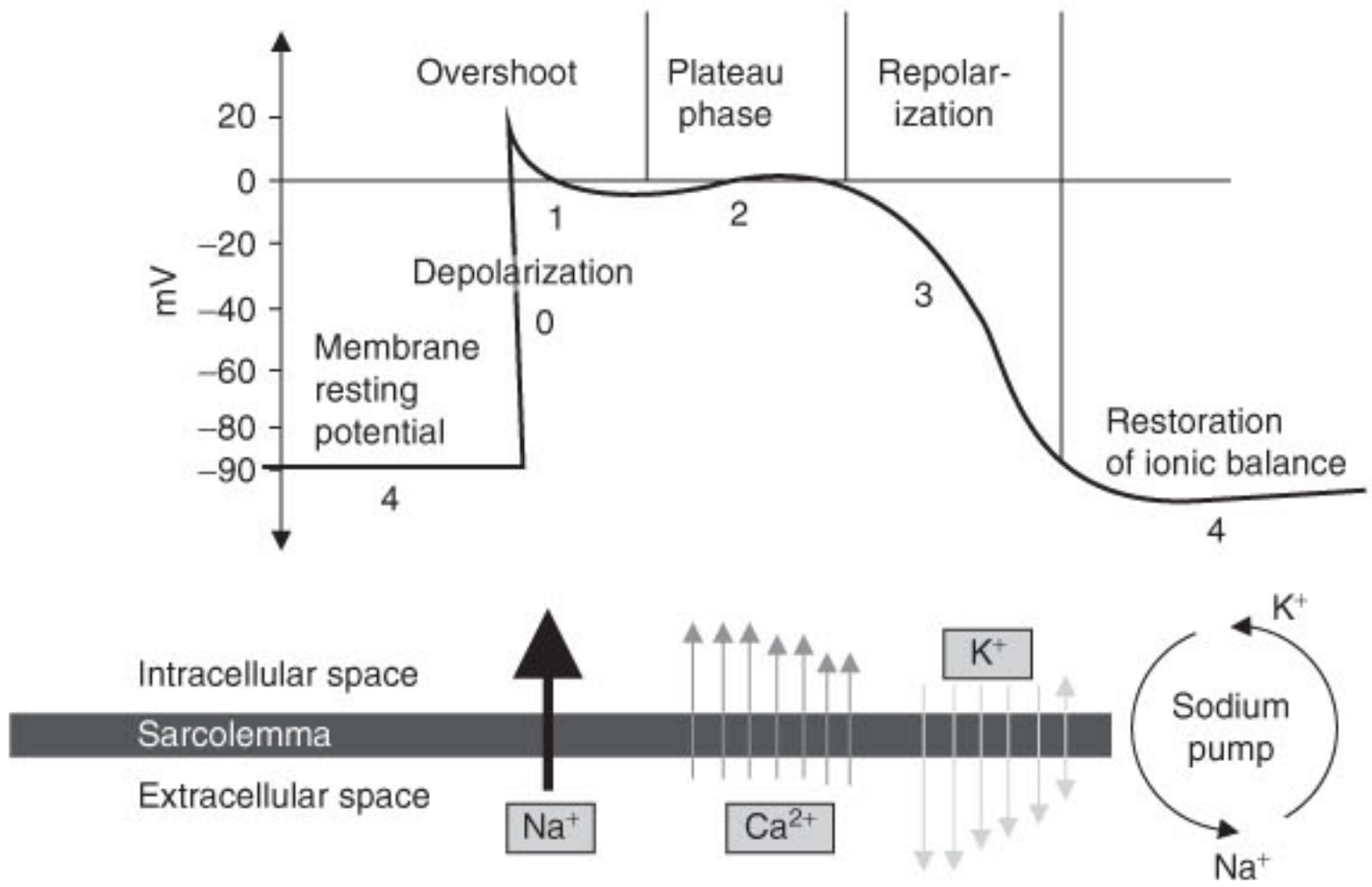

Fig. 3. Myocardial action potential. Shown is the action potential of a ventricular muscle cell. The numbers 0, 1, 2, 3 and 4 represent the phases of the action potential. The membrane resting potential is largely determined by the ratio of extracellular to intracellular potassium (phase 4). This phase is associated with ventricular diastole. The sudden surge of sodium (sodium 'fast' channel) into the ventricular muscle cell (phase 0) represents the onset of cellular depolarization and is the rapid depolarization phase. The slope of phase 0 represents the maximum rate of depolarization of the cell and is known as V_{max}. Phase 0 is due to the opening of the fast sodium channels, which causes a rapid increase in the membrane conductance to sodium and a rapid influx of sodium ions into the cell, creating sodium current. The QRS interval (ventricular depolarization) on the surface ECG (figure 1) represents the initial electrical energy of the action potential of all the myocardial muscle cells. Phase 1 of the action starts with inactivation of the fast sodium channel. Following this phase, the 'plateau' phase (phase 2) appears and is sustained by the inward movement of calcium (calcium 'slow' channels) and outward movement of potassium through the slow delayed rectifier potassium channels. During phase 3 (repolarization), outward flow of potassium via the rapid delayed rectifier potassium channel is the main ion channel causing the cell to repolarize and return to the membrane resting potential (phase 4) [adapted from Vieweg and McDaniel,[8] with permission]. **Ca^{2+}** = calcium; **K^+** = potassium; **Na^+** = sodium.

3. Risk Factors for QT Interval Prolongation in the Elderly

3.1 Age

Su et al.[32] 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).[32] 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

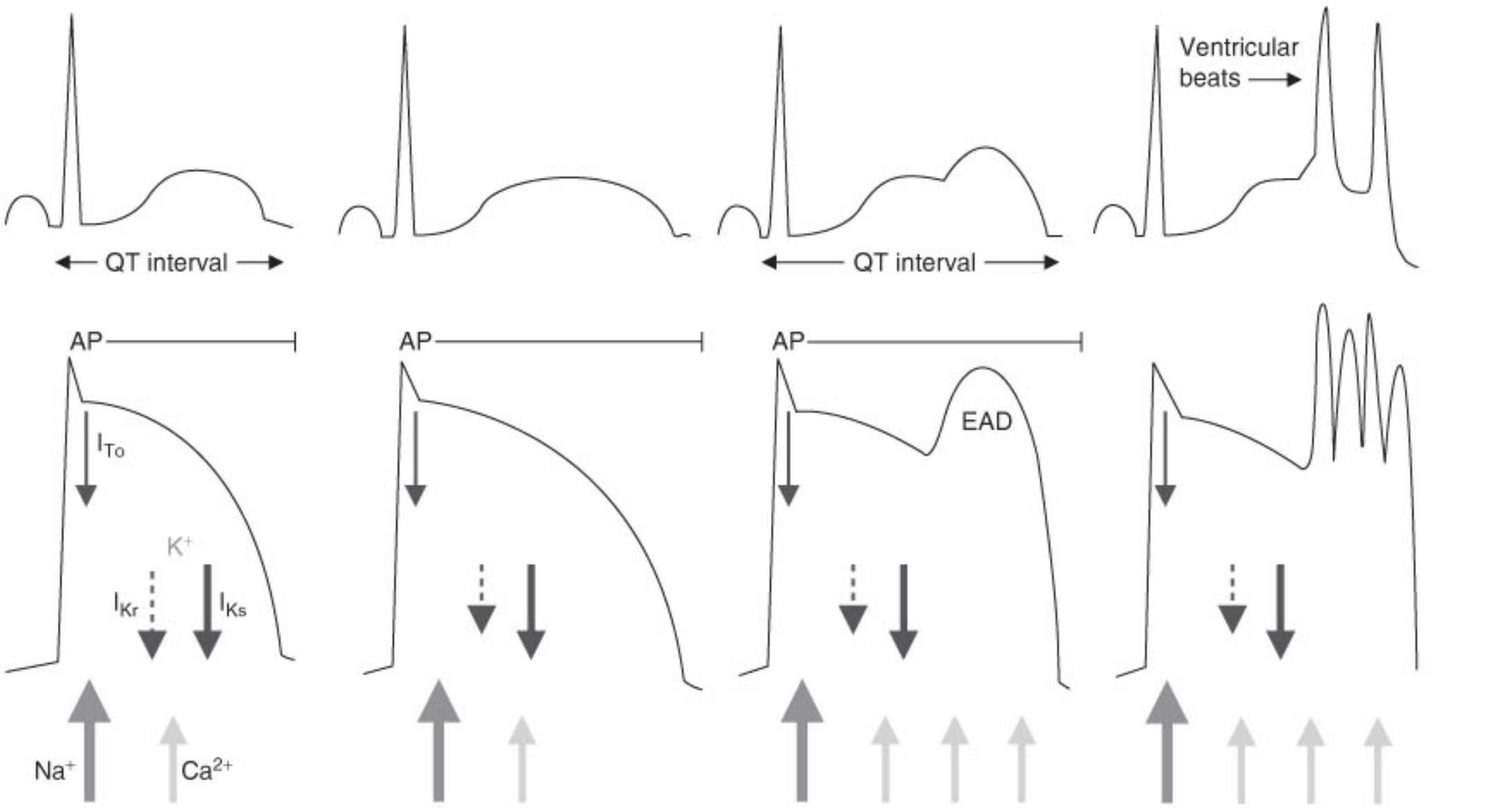

Fig. 4. ECG, myocardial cell action potential and *torsade de pointes* (*TdP*) [data from Viskin et al.,[22] with permission]. **AP** = action potential; **Ca^{2+}** = calcium; **EAD** = early after depolarization of the AP; **I_{Kr}** = rapid delayed rectifier potassium current; **I_{Ks}** = slow delayed rectifier potassium current; **I_{To}** = transient outward potassium current; **K^+** = potassium; **LQTS** = long QT syndrome; **Na^+** = sodium; **PVC** = premature ventricular contraction.

medication for marketing,[33] individual patient/drug changes of less than 20 msec may not be clinically significant due, in part, to differences in measurements by separate clinicians.[34] Thus, the documented changes in the QTc interval over 4 years by Su et al.[32] may have limited clinical utility.

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.[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.[36]

3.3 Sex

The QTc interval does not vary by sex at birth.[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.[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.[4] Age-matched subjects with cardiovascular disease tend to have longer QTc intervals than subjects without cardiovascular disease.[4]

3.5 Electrolyte Abnormalities

Electrolyte abnormalities, particularly hypokalaemia and hypomagnesaemia, may contribute to or even cause QTc interval prolongation.[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.[23] This may induce EADs and *TdP*. Five to ten percent of European Americans are 'poor metabolizers' (pharmacokinetic factor) of certain drugs.[12] 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.[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.

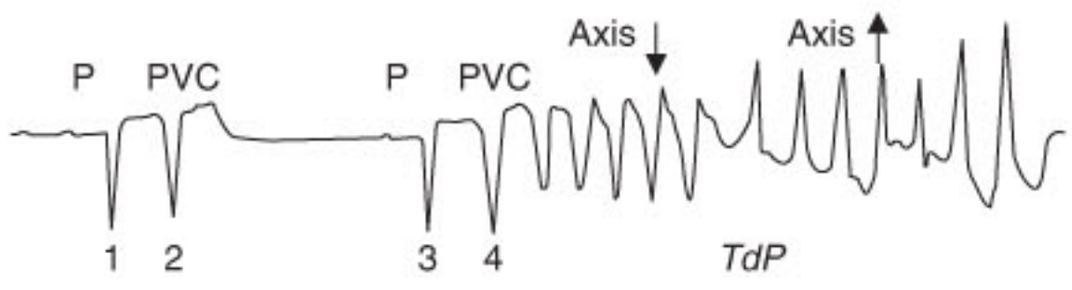

Fig. 5. *Torsade de pointes* (*TdP*). Shown is the typical pattern found in the *TdP* type of polymorphic ventricular tachycardia (PVT). A sinus beat with a normal QRS interval (**1**) is followed by premature ventricular contraction [PVC] (**2**) with a short coupling interval. After a compensatory pause, another sinus beat (**3**) with a normal QRS interval is followed by another PVC (**4**) with a short coupling interval. The second PVC (**4**) is the first beat in a PVT of the *TdP* type. The sequence of beats 1–4 comprises the typical electrocardiographic features of short-long-short RR intervals followed by *TdP* (adapted from Vieweg and McDaniel,[8] with permission). ↑ and ↓ signify direction of QRS axis.

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).[42] Schwartz and colleagues[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.[45-47] Ray et al.[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 (JT interval) prolongation is most suspect.[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 ≥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.[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.[13] In a general review of sex and *TdP*, Woosley and Sketch[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.[75] reported on 18 men (36.7%) and 31 women (63.3%).

Twenty-seven (73.0%) 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.[4]

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.[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

Table II. Patients aged ≥60 years who experienced corrected QT (QTc) interval prolongation, ventricular arrhythmias including polymorphic ventricular tachycardia (PVT) and *torsade de pointes* (*TdP*) and/or sudden cardiac death thought to be due to antipsychotic or antidepressant drug administration

Patient number	Study and year	Age (y), sex	Drugs	Risk factors	Complications
1	Fowler et al.,[48] 1976	64, female	Thioridazine, mesoridazine	Female sex	Syncope, sinus arrest, ventricular bigeminy, ventricular fibrillation, multifocal ventricular tachycardia
2	Fowler et al.,[48] 1976	73, female	Chlorpromazine, nortriptyline and then amitriptyline	Female sex, hypertensive cardiovascular disease, congestive heart failure, diuretic use	Ventricular fibrillation, multifocal ventricular tachycardia, LBBB
3	Fowler et al.,[48] 1976	71, female	Thioridazine, mesoridazine	Female sex	Syncope, cardiac arrest, multifocal ventricular beats and bigeminy
4	Ko et al.,[49] 1982	71, male	Doxepin (40 mg daily), trifluoperazine (4 mg daily), thioridazine (100 mg daily)	Seizures, hypertension	QTc prolongation to 620 msec, syncope, *TdP*, cardioversion on one occasion for *TdP*, temporary transvenous catheter placement to treat recurrent *TdP*
5	Flugelman et al.,[50] 1982	71, female	Clomipramine (200 mg daily)	Female sex, three generations of a family with congenital long QT syndrome	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
6	Herrmann et al.,[51] 1983	81, female	Maprotiline	Female sex, hypothyroidism, diabetes mellitus	QTc interval prolongation to 710 msec, syncope, *TdP*
7	Davison,[52] 1985	71, female	Amitriptyline	Female sex, QRS duration 120 msec	QTc interval prolongation to 570 msec, *TdP*
8	Jerjes Sanchez Diaz et al.,[53] 1985	65, female	Amitriptyline	Female sex, serum potassium 3.2 mmol/L	QTc interval prolongation to 520 msec, syncope, *TdP*
9	Zee-Cheng et al.,[54] 1985	63, female	Haloperidol overdose (420 mg)	Female sex, hypocalcaemia	QTc interval prolongation to 680 msec, recurrent *TdP* requiring ventricular overdrive pacing
10	Zee-Cheng et al.,[54] 1985	60, female	Haloperidol overdose (1000 mg)	Female sex, hypocalcaemia	QTc interval prolongation to 480 msec, recurrent *TdP* requiring ventricular overdrive pacing
11	Casazza et al.,[55] 1986	60, female	Desipramine, dothiepin (dosulepin)	Female sex	QTc interval prolongation to 540 msec, syncope, *TdP*
12	Fayer,[56] 1986	Elderly female	Haloperidol (up to 15 mg daily)	Female sex, hypertension, sick sinus syndrome with bradycardia of 30 beats/min	QTc interval prolongation to 600 msec, *TdP*, recurrent bradycardia requiring permanent ventricular pacemaker placement
13	Wilt et al.,[57] 1993	63, female	Haloperidol (IV 489 mg over 36 hours)	Female sex	QTc interval prolongation to 670 msec, *TdP*

Continued next page

Table II. Contd

Patient number	Study and year	Age (y), sex	Drugs	Risk factors	Complications
14	Metzger and Friedman,[58] 1993	61, male	Haloperidol (IV 96 mg over the preceding 24 hours)	Respiratory failure secondary to chronic obstructive pulmonary disease requiring intubation, bacterial pneumonia, dilated and hypokinetic right ventricle and decreased systolic contraction, hypocalcaemia, hypotension	QTc interval prolongation to 500 msec, sudden cardiac death
15	Hunt and Stern,[59] 1995	76, female	Haloperidol (IV 44.5 mg over 10 hours)	Female sex, coronary artery disease, congestive heart failure, hypomagnesaemia, hypocalcaemia, severe anaemia, hypoxaemia	QTc interval prolongation to 670 msec, *TdP*
16	Hunt and Stern,[59] 1995	65, female	Haloperidol (IV 65 mg on post-operative day 1, 300 mg on post-operative day 2, 600 mg on post-operative day 3)	Female sex, coronary artery disease, rheumatic heart disease, congestive heart failure, hypomagnesaemia, atrial flutter and fibrillation	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
17	Di Salvo and O'Gara,[60] 1995	65, male	Haloperidol (IV more than 300 mg over 3 days preceding *TdP*)	Baseline QTc interval prolongation to 490 msec, RBBB, ventricular trigeminy	QTc interval prolongation to 594 msec, *TdP* followed by ventricular fibrillation requiring defibrillation
18	Di Salvo and O'Gara,[60] 1995	65, female	Haloperidol (IV more than 400 mg over 4 days preceding *TdP*)	Female sex, rheumatic heart disease treated surgically, atrial flutter	QTc interval prolongation to 628 msec, *TdP* requiring cardioversion followed by several more episodes of *TdP*
19	Di Salvo and O'Gara,[60] 1995	76, female	Haloperidol (IV more than 40 mg over 2 days preceding *TdP*)	Female sex, coronary artery disease, left ventricular hypertrophy, pulmonary oedema, marked hypertension, baseline QTc interval of 450 msec, hypocalcaemia	QTc interval prolongation to 670 msec, *TdP*
20	Mazur et al.,[61] 1995	74, female	Trazodone (150 mg daily)	Female sex, co-administration of amiodarone, hypertension, coronary artery disease, diastolic heart failure, ventricular demand (VVI) pacemaker	Dizziness following addition of trazodone, paced ventricular rhythm of 70 beats/min with markedly prolonged QTc interval to 777 msec, *TdP*
21	Appleby et al.,[62] 1995	74, female	Fluoxetine (20 mg daily) for 3 weeks after long-term treatment with amitriptyline	Female sex, mild hypertension	QTc interval prolongation to 600 msec, syncope, *TdP*
22	Rialan et al.,[63] 1996	67, female	Maprotiline	Female sex, QRS duration of 120 msec	QTc interval prolongation to 582 msec, syncope, *TdP*

Continued next page

Table II. Contd

Patient number	Study and year	Age (y), sex	Drugs	Risk factors	Complications
23	Sharma et al.,[64] 1998	64, female	Haloperidol (IV 115 mg over 10 hours)	Female sex, critically ill	QTc interval prolongation to 605 msec, *TdP*
24	Sharma et al.,[64] 1998	75, female	Haloperidol (IV 85 mg over 27.3 hours)	Female sex, critically ill	QTc interval prolongation to 567 msec, *TdP*
25	Sharma et al.,[64] 1998	71, male	Haloperidol (IV 70 mg over 2.5 hours)	Critically ill	QTc interval prolongation to 521 msec, *TdP*
26	Iglesias et al.,[65] 2000	76, male	Tiapride (300 mg daily)	Mild congestive heart failure, atrial fibrillation	QTc interval prolongation to 600 msec, *TdP*
27	Douglas and Block,[66] 2000	75, male	Haloperidol (IV at a rate of up to 20 mg in 6 hours)	Advanced coronary artery disease, myocardial infarction, acute coronary artery angioplasty	QTc interval prolongation to 615 msec, ventricular fibrillation, cardioversion to normal sinus rhythm
28	Douglas and Block,[66] 2000	68, male	Haloperidol (IV 2 mg/hour with 1 mg boluses to a maximum of 5 mg/hour)	Unstable angina complicated by pulmonary oedema requiring tracheal intubation and mechanical ventilation	QTc interval prolongation to 648 msec
29	Douglas and Block,[66] 2000	77, male	Haloperidol (IV 2 mg) on day 8, haloperidol (IV 2 mg) on day 9, haloperidol (IV 2 mg on two occasions) on day 13	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	QTc interval prolongation to 554 msec on day 8, 509 msec on day 9 and 508 msec on day 13
30	Lentini et al.,[67] 2001	69, female	Maprotiline	Female sex, advanced heart failure with peripheral oedema, coronary artery disease	QTc interval prolongation to 700 msec, *TdP*
31	Kang et al.,[68] 2004	87, female	Risperidone followed by olanzapine	Female sex, hypertension, hypokalaemia (3.1 mmol/L), thiazide diuretic	QTc interval prolongation to 494 msec taking first risperidone and then olanzapine
32	Wilting et al.,[69] 2006	83, female	Fluoxetine (20 mg daily)	Female sex, LBBB	QTc interval prolongation to 478 msec corrected for LBBB, syncope, *TdP*
33	Letsas et al.,[70] 2006	60, female	Venlafaxine (150 mg daily)	Female sex, hypertension, mild left ventricular hypertrophy	QTc interval prolongation to 582 msec
34	Klein-Schwartz et al.,[71] 2007	75, female	Ziprasidone (480 mg)	Female sex	QTc interval prolongation to 470 msec
35	Katagai et al.,[72] 2007	92, female	Haloperidol (0.5 mg IV)	Female sex	QTc interval prolongation to 468 msec
36	Huang et al.,[73] 2007	69, female	Sulpiride	Female sex, coronary artery disease	QTc interval prolongation to 680 msec, syncope, *TdP*
37	Raviña et al.,[74] 2007	Elderly female	Risperidone	Female sex	QTc interval prolongation to 760 msec, *TdP*, asystole, death

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

Drug	Patient number[a]
Antipsychotic drugs	
Chlorpromazine	**2**
Haloperidol IV	13, 14, 15, 16, 17, 18, 19, 23, 24, 25, 27, 28, 29, 35
Haloperidol oral	9, 10, 12
Mesoridazine	**1**, **3**
Olanzapine	**31**
Risperidone	**31**, 37
Sulpiride	36
Thioridazine	**1**, **3**, **4**
Tiapride	26
Trifluoperazine	**4**
Antidepressant drugs	
Amitriptyline	**2**, 7, 8, **21**
Clomipramine	5
Desipramine	**11**
Dothiepin (dosulepin)	**11**
Doxepin	**4**
Fluoxetine	**21**, 32
Maprotiline	6, 22, 30
Nortriptyline	**2**
Trazodone	20
Venlafaxine	33

a 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. Thioridazine appeared three times. In the autopsy survey of sudden death associated with antipsychotic and antidepressant drugs in Finland,[75] thioridazine 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. Darpö[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.[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.[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.[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-syncope, 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.,[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.[82] that most physicians, including many cardiologists, fail to accurately calculate a QTc interval or correctly identify a prolonged QT interval. Bai and Yan[83] extend this lament in an editorial appearing in the same premier journal dedicated to cardiac electrophysiology.

Hongo and Goldschlager[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.[85,86] Malik[87] described the most popular formula for calculating the QTc interval (Bazett, see section 1) as "clearly one of the worst options." Recently, Malik et al.[88] used the Fridericia 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[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.[88] is

labour intensive and unlikely to be adopted on a large scale in the near future.

Phoon[90] 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 antipsychotic 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-syncope 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[90] '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.

Acknowledgements

No sources of funding were used to assist in the preparation of this review. Dr Mehrul Hasnain has received an honorarium from Pfizer Canada Inc. for consultancy services. Dr Anand Pandurangi is on the speakers' bureau of AstraZeneca, Bristol-Myers Squibb (BMS), Janssen and Pfizer and has received research grants from BMS, Janssen and Eli Lilly. The other authors have no conflicts of interest that are directly relevant to the content of this review.

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