

Patient Safety

Sudden cardiac death & The Reverse Dodo Verdict

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Abstract. Adverse effects of treatment on cardiac QT intervals were first reported 50 years ago. A clear link to sudden death was established, but the problem remained relatively unknown. The issue of treatment related effects on the heart, and the contribution this might make to sudden cardiac deaths in general, came more clearly into focus 20 years ago, linked to regulatory actions. In an era of polypharmacy, and mixing of prescribed and non-prescribed pharmacologically active agents it is now becoming increasingly clear that unanticipated cardiac effects may be common and a significant cause of mortality. There is likely underreporting and also underdiagnosis, as recognition requires a timely ECG. This paper proposes two methods to handle the problem.

Keywords: QT intervals, antipsychotics, antidepressants, polypharmacy, reverse dodo verdict, adverse event databases, cardiac apps

1. The problem

In 2000, a 15 year old girl, prescribed cisapride for a mild eating disorder, collapsed without warning and died in front of her family [1]. A bill introduced to the Canadian Parliament by the father of the girl, Terence Young, looks set to lead to mandatory adverse event reporting in Canada.

Cisapride lengthens QT intervals, as do conditions such as eating disorders that produce metabolic disturbances. Prolonged QT intervals are a risk factor for arrhythmias of which the best known ‘Torsades de Pointes’ causes sudden and unexpected cardiac death.

Groups who are higher risk of prolonged QT interval are women, and those with electrolyte disturbances often produced by medications. Other chronic conditions such as thyroid problems, diabetes, renal and liver problems increase risk. Older patients are at greater risk than younger ones. In addition, older patients take an average of 7 drugs, and the existence of multimorbidity is common [2].

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However it is not just older people who are at risk. Drugs that prolong QT intervals are now so frequently prescribed to younger populations that co-prescription is inevitable. Antidepressants are now prescribed to 10% of the adult population in most developed countries and QT prolonging antibiotics such as macrolides, and fluoroquinolones, along with antimalarials are increasingly common.

Clinicians however seem disengaged from the problem. One hospital study found that only a third of patients on two or more QT prolonging drugs had an ECG despite a computer generated alert system. For those patients who had ECG recordings before and after the alert was overridden, 51% had QT prolongation and 31% were considered at increased risk for Torsades de Pointes [3].

There has been an “epidemic” of sudden deaths in selected populations, such as troops in the US military, with no clear idea what is happening [4]. Many are on psychotropic drugs. Looking at the top ten drugs from the FDA’s Adverse Events Database, seven are psychotropics - clozapine, quetiapine, citalopram, risperidone, olanzapine, ziprasidone and methadone – making it quite possible these deaths stem from treatment effects on the heart.

There has been longstanding concern about an increased risk of cardiac events in patients taking second generation antipsychotics but the focus has been on the metabolic effects of these drugs, about which relatively little can be done, rather than on their QT interval lengthening properties, where there are potential mitigating strategies especially when polypharmacy is involved.

2. The Mellaril story

The history of this issue starts with the launch of the antipsychotic drug thioridazine (Mellaril) in North America in 1959.

In 1963, Kelly et al. reporting on 28 electrocardiograms (ECGs) suggested that Mellaril had a quinidine-like effect on ventricular repolarization (prolongation of the QT interval) in doses as low as 200 mg a day. T-waves were flattened and sometimes inverted, occasionally S-T segments became convex and new waves appeared. There were two fatal cases of arrhythmia [5].

Sandoz, the makers of Mellaril, approached Tom Ban to compare the cardiac effects of thioridazine, chlorpromazine and trifluoperazine. In 1964 Ban et al. reported that thioridazine “modifies the terminal portion (S-T segment, T and U waves) of the human ECG.” They found that, whereas similar changes took place in only 1 of 6 taking trifluoperazine, and in 3 of 6 taking chlorpromazine, such changes were noted in all 6 of the 6 patients on 200 to 400 mg of thioridazine [6].

Before the study published, the authors were alerted to a case in which a patient on 1500 mg thioridazine per day suddenly became unconscious and passed into a state of shock. A physician and cardiologist present did an ECG that demonstrated ventricular tachycardia. A prior ECG of the patient, six weeks after the initiation of thioridazine therapy, had shown bradycardia and prolongation of the QT interval [7].

Meanwhile in 1964, Wendkos published a paper on “pharmacologic studies in a hitherto unreported benign repolarization disturbance among schizophrenics” [8]. In a symposium convened to look at the issue Wendkos re-stated his position that recorded ECG changes “represent a benign repolarization disturbance rather than an adverse cardiac effect” [9]. His expenses to attend this meeting were funded by Sandoz.

Ban conducted a survey to determine the incidence of cardiac conductance changes with thioridazine. Of the 92 patients receiving drugs other than thioridazine, 13% displayed an abnormal ECG. Seventeen (77.3%) patients receiving thioridazine had abnormal ECG’s [10, 11]. In 1965, Ban and colleagues reported that “the lowest dose (of thioridazine) which brought about changes was 150 mg per day” [12].

In 1964 Graupner and Murphree also described ECG changes on thioridazine [13]. From the 55 patients they studied, 44% developed abnormal ECGs. Most of the changes concerned the T-wave. They appeared at all dose levels from 150 to 900 mg per day [13].

In 1974 Gallant et al. reported a double-blind ECG comparison of thioridazine and thiothixene [14]. “Only one of the 13 thiothixene patients had prolongation of the QT but 13 out of 13 patients on 800 mgs a day of thioridazine, and 7 of 13 on 400 mgs a day had prolongation of the QT interval. We published that. In fact, my cardiology fellow that read the ECGs could identify thioridazine, blind After we published, somebody from Sandoz called and started yelling on the phone at me, criticizing me, saying I was unethical for publishing the data. This was 1972 and I was shocked that someone from a pharmaceutical firm would start telling me I’m unethical for publishing these findings” [15].

Despite these early warnings Mellaril was pitched as especially suitable for geriatric use, a population at risk of cardiac complications. In 1978 Simpson and co-workers found that it was precisely in the elderly that thioridazine prolonged QT intervals [16]. “I stopped using thioridazine at that time,” Simpson later said [17].

An analysis of Mellaril advertisements in *Diseases of the Nervous System* showed that Sandoz launched four major ad campaigns featuring elderly “patients”. For example in three ads between May and July 1983, an elderly woman was shown with text stating that Mellaril “helps keep the disturbed geriatric at home” [18]. An ad featuring an older male golfer (“effective control of psychotic symptoms”) ran 14 times [19]. In 1980 Ban noted that “thioridazine has become one of the most extensively employed psychotropic drugs in the aged” [20].

Twenty years later, in July 2000, Novartis Pharmaceuticals (Sandoz) sent letters to physicians warning that the use of Mellaril should be significantly curtailed. The preparation should henceforth be restricted only to those schizophrenic patients “who fail to show an acceptable response . . . to other antipsychotic drugs.” The reason? “Mellaril has been shown to prolong the QT interval in a dose related manner, and drugs with this potential, including Mellaril, have been associated with torsades de pointes-type arrhythmias and sudden death” [21].

Simultaneously, Psychiatric News cautioned that thioridazine “will include a new boxed warning regarding potentially fatal cardiovascular effects and will be restricted to second-line use.” The reason: “TdP (torsades de pointes) develops spontaneously, usually without warning, and requires immediate emergency intervention.” The note said that the risk of sudden death was “high” [22].

3. From sertindole to seroquel

In 1985, an intravenous formulation of a Janssen dopamine antagonist, domperidone, was withdrawn for causing QT problems. The oral formulation of domperidone is still on the market.

In 1995, pimozide, another Janssen dopamine antagonist, was flagged up as causing QT problems. Meanwhile the antispasmodic agent terodiline had been withdrawn in 1991.

Later in 1995 QT intervals became headline news. There was intense competition to bring the first atypical antipsychotic to a market opened up by clozapine [23]. Lilly’s Zyprexa was jockeying for position with Astra Zeneca’s Seroquel and Pfizer’s Geodon. They were scooped by sertindole (Serdolect) made by Lundbeck which launched first in Europe, where it sold well.

Serdolect was being brought to the US market by Abbott. It came to an FDA psychopharmacologic drugs advisory committee (PDAC) in 1995 before Zyprexa or Seroquel. The hearing was dominated by

cardiac experts debating the effect sertindole had on QT intervals. Was the number of sudden cardiac deaths seen in Lundbeck trials excessive? No one appeared to know.

FDA rejected the application – the first time an application had been rejected for this reason. The chief beneficiary was Lilly whose Zyprexa as a consequence was first to the US market and became the best-selling psychotropic drug in the world, worth over \$4 Billion per annum.

Ironically the next company to suffer QT blight was Lilly. Lilly had lined up the serotonin reuptake inhibiting r isomer of fluoxetine, dexfluoxetine (Zalutria), as the successor to its SSRI antidepressant Prozac. The clinical trials of dexfluoxetine were done and the marketing application lodged with FDA, when the company withdrew the application on the grounds that dexfluoxetine had significant effects on QT intervals [24].

If dexfluoxetine has significant QT interval effects it follows logically that Prozac must have too and if QT interval changes can lead to sudden death there must have been deaths on Prozac from this source.

Meanwhile in 1996 in Europe Lundbeck launched an SSRI antidepressant, citalopram. Forest brought this to the market in the United States in 1998 as Celexa. After approval of a drug, FDA is obliged to make their medical and statistical reviews of the drug publicly available. These occasionally have the names of investigators or other material redacted. But the FDA reviews of Celexa (citalopram) have large amounts of the cardiac sections of these reviews redacted.

The marketing of Celexa, and its follow-up s-isomer, escitalopram, Lexapro, was extraordinarily successful, especially in the United States where each of these drugs in turn were among the best-selling antidepressants in the field. It is now clear that both these drugs in dose dependent fashion cause QT prolongation and that this can lead to death.

In 2000 warnings were finally put on Mellaril. Soon after that, Lundbeck's depot antipsychotic Clopixol was withdrawn ostensibly because of QT interval lengthening, as was Janssen's droperidol. In these latter two cases the withdrawal of older antipsychotics even though they had lower reported rates of QT interval lengthening than any newer agents, could be interpreted as aimed at helping the marketing of newer drugs.

While Pfizer's atypical antipsychotic ziprasidone was held up for 5 years for QT interval problems and has never been licensed in the UK for this reason, there has been little heard of the QT lengthening properties of antipsychotics, such as quetiapine or olanzapine.

4. Risk benefit

In 1998 and 1999, the antihistamines terfenadine and astemizole were withdrawn for QT interval changes. In 2000 cisapride (Prepulsid), was also withdrawn.

These cases raised the profile of QT interval effects because of the discrepancies between the risks run and the benefits likely to be obtained. Death is not a reasonable outcome for someone taking a drug for a mild eating disorder.

Greater understanding of channelopathies and in particular of the role of the potassium channel in Q-T interval effects makes it much clearer now how women with eating disorders ran a particular risk taking a drug like cisapride.

Other work has led to the identification of 13 or more genetic variations leading to lengthening of Q-T intervals [25].

There is as a result much greater regulatory emphasis on Q-T interval changes now than before, but there are two problems that regulation may not be able to solve. First many psychotropic drugs causing Q-T interval problems will continue to be given for conditions like eating disorders and to the elderly

even if companies do not seek to market their drugs for these indications. Second, what happens in an era of polypharmacy when several different drugs all causing some Q-T interval lengthening are combined?

5. Reverse Dodo Verdict

The sequence of events above brought QT intervals into view but not to wider consciousness. For instance a recent series of articles has shown that patients with schizophrenia have raised mortality rates. Cardiovascular deaths have been among the most prominent causes of death. These articles have suggested that the effects of antipsychotic drugs on cholesterol and blood sugar levels might explain the excess mortality [26–28]. The possible effects of treatment on QT intervals have gone almost unremarked.

Similarly, clozapine is well known to cause cholesterol elevations and other metabolic problems, along with myocarditis and cardiomyopathy, but few if any doctors know that it is the drug most commonly reported to FDA as causing QT interval lengthening.

What happens when someone is put on several drugs all of which can lengthen QT intervals? For instance patients on several QT prolonging drugs could be offered a short course of a QT prolonging antibiotic in an out of hours clinic for whooping cough, for suspected mycoplasma pneumonia, for chlamydia at a sexual health clinic, or in a travel clinic when antimalarials are prescribed. The QT lengthening with clarithromycin and cisapride for example is 6 ms for each individual drug, but combined is 25 ms with each increase of 10 ms corresponding roughly to a 5–7% increase in the risk of torsades [29].

The problem is that while more than 60 drugs in common use have been linked to QT interval lengthening, none carry clear warnings as the lengthening is not so marked as to warrant a warning for an individual drug. The Hitchhiker's Guide to the Galaxy refers to a Somebody Else's Problem (SEP) Field. This might be a useful term to describe what happens.

Or borrowing from Alice in Wonderland what's involved might be termed a Reverse Dodo Verdict. The Dodo verdict is that "All have won and all must get prizes". The Reverse Dodo Verdict would be "All are culpable but no-one gets penalized".

Even in 2014, QT interval changes are a code for conductance effects on the heart of which QT lengthening is but one manifestation. Many of the drugs producing QT lengthening can also shorten QT intervals in some patients. Some drugs that lengthen QT are more prone to cause Torsades de Pointes than others. The antiarrhythmic drugs are more likely to cause lethal arrhythmias, as are haloperidol and methadone. In contrast amiodarone markedly prolongs the QT interval but poses a low risk for Torsades, and verapamil has never been associated with Torsades. These drugs appear to have other effects on repolarization channels, but it still remains difficult to predict risks.

6. The drugs that stop hearts

The QT interval problem differs from other adverse effects. In this case, no company is likely to warn about a hazard from their drug which when used in low doses in monotherapy is relatively minimal.

The problem develops when patients are on more than one drug, in doses that are higher than average and when background factors increase their risk. Data from the 4.6 million reports to FDA's Adverse Event Reporting System (AERS) presented in Tables 1 and 2 help to flesh out a range of scenarios. These data do not include all cardiac rhythm abnormalities and are simply aimed at giving a sense of different drug groupings rank (See Legend).

Table 1
Drug groups linked to QT interval lengthening (2004–2012)

Drug group	Number of reports
Antipsychotics	2224
Antidepressants	1807
Anti-Infectives	1600
Antihypertensives	1273
Small Molecule Kinase Inhibitors (Nibs)	749
Heart Failure Treatments	730
Anti-arrhythmic Agents	726
Gut preparations	648
Benzodiazepines	533
Opiates	497
Anticonvulsants	444
Disease Modifying Anti-Rheumatic Drugs	404
PPIs & H2 Blockers	236
Stimulants	145
MABs (Monoclonal Antibodies)	141
Statins	120
Osteoporosis Drugs	117

These data come from FDA's Adverse Event Database hosted on RxISK.org. They are based on RxISK defined drug groups – the drugs in each group are available on request. The data are simply those for QT-interval prolongation (Medra Code 10014387). They do not include QT interval abnormalities, Torsades de Pointes or Cardiac Arrest. The data was compiled in April 2013.

The AERS data in these Tables stems from reports submitted from 2004 onwards, so groups like antihistamines are likely under-represented as are data on the monoclonal antibodies (MABs) and tyrosine kinase inhibitors which have more recently entered clinical practice, or drugs like fluoxetine (Prozac) whose sales dropped from 2001 when it went off patent. The data is also close to exclusively drawn from the United States so some drugs not available in the US are not represented here.

Only 1–5% of adverse drug reactions are reported [30]. Given that patients are unlikely to be aware of QT interval changes, this adverse reaction would seem less likely than most to be reported unless the patient is forewarned about palpitations or syncopal episodes or the risk of interactions with other conditions or non-prescribed drugs such as energy drinks. The true numbers for Table 1 above therefore might be a hundred fold greater than listed.

Breaking these figures out by specific drug adds further detail (Table 2). A patient with a history of drug abuse on methadone given citalopram for depressive symptoms is now on two of the top ten drugs from FDA's AERs database. If prescribed an atypical antipsychotic, such as quetiapine, this previously fit patient will be on three high risk drugs. The risk of QT prolongation appears cumulative [31], putting this patient at higher risk of arrhythmias or sudden cardiac death. Because he has had no previous health problems, he will likely never have had an ECG done.

In the case of methadone, as of April 2005, the World Health Organisation's adverse reactions data base included 255 reports of heart rate and rhythm disorders. These included 24 reports of Torsades, 26 reports of QT prolongation and 117 reports of cardiac arrest [32]. This led US guidance for methadone prescription to mandate ECG monitoring of QT intervals prior to and after initiation and annually. Such advice is rare however.

Table 2
Reports for individual drugs prolonging QT intervals (2004–2012)

Cardiac drugs	Antidepressants	Anti-infectives	Antipsychotics	Miscellaneous
Amiodarone 343	(s)/ Citalopram 471	Moxifloxacin 216	Clozapine 460	Cisapride 648
Furosemide 165	Paroxetine 180	Ciprofloxacin 147	Quetiapine 371	Nilotinib 455
Dofetilide 159	(Des) Venlafaxine 173	Levofloxacin 133	Risperidone 300	Methadone 274
Sotalol 138	Fluoxetine 150	Fluconazole 118	Olanzapine 297	Donepezil 129
Hydrochlorothiazide 85	Mirtazapine 142	Clarithromycin 102	Ziprasidone 288	Atomoxetine 127
Amlodipine 84	Sertraline 109	Azithromycin 93	Haloperidol 167	Lithium 86
Digoxin 81	Duloxetine 102	Ritonavir 60	Aripiprazole 83	Methylphenidate 75

The same applies to a patient on a combination of lithium and an antidepressant who is put on a fluoroquinolone antibiotic.

QT intervals lengthen with age [33]. A fit 70 year old woman prescribed donepezil (24th in FDA's adverse event database) for memory problems will be at greater risk than a younger woman. If prescribed citalopram her risk will rise further. A more typical 70 year old, prescribed these two drugs, if also on amiodarone and furosemide, may end up on 4 of the 30 most dangerous drugs to add to the risk linked to aging.

One of the striking features of the drugs that feature in Table 2 is how many of them are linked to dependence and withdrawal problems, raising the possibility that some of the dependence problems witnessed with antipsychotics and antidepressants may stem from this kind of effect rather than a direct receptor effect. Drugs more often used as anti-arrhythmics may be worth exploring as an aid to withdrawal.

7. Stopping hearts stopping

The problem outlined here needs a systems based approach. It's not realistic to do an ECG on everyone before and after starting a new drug or changing a dose. Few doctors will be aware of data like the data in Tables 1 and 2 and therefore they are not well placed to select patients at risk who should be monitored by ECG. Even pharmacists with more resources to check these issues are not well-placed to spot a problem.

Empowering consumers, who have both a vested interest in the safety of their medications, and direct experience of the effects of treatment, may be the best solution.

An Adverse Event Database that offers patients, doctors and pharmacists an option to enter a combination of drugs on the spot and see the rate of reporting of QT interval changes linked to each drug offers possibilities for someone to spot a hazard. This allied with information about metabolic conditions or other risk factors, such as the congenital QT lengthening that affects 1 in 2500, might enable appropriate planning of treatment elements in a treatment cocktail and appropriate use of ECG monitoring.

A mobile phone based App that monitored QT intervals and their changes would allow people on treatment to determine for themselves if they were actually approaching a hazardous situation rather than being notionally at risk. However this technology is some time away and the knowledge on the precise level at which QT interval length intersects with the risk of arrhythmia is still a matter of debate.

The intersection of factors – disease-drug, drug-drug, drug-physiology, drug-constitution, – creates a window for tragedy.

The problem seems best addressed by a solution that enables people contemplating treatment to see that window and be involved assessing the background risk, environmental factors, treatment options and disease consequences. QT monitoring when reliable technology is widely available will be an ideal situation for near patient testing in offices, pharmacies or directly by the public. Until then access to QT reports offers a first step.

These tools will strengthen the conversations between doctors and patients. Where monitoring for risk factors in general leads to increased rates of prescribing, QT interval lengthening is a hazard which if detected would lead to more discriminate prescribing.

In 2013, a bill introduced by Terence Young, a Member of the Canadian Parliament, passed through the Canadian Parliament, proposing mandatory reporting of adverse events in hospitals. If enacted, this may impact on the field of adverse events in general.

Legislating a shift in gaze from efficacy alone to take safety into account is an important move in improving the quality and cost effectiveness of healthcare.

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