Selective serotonin reuptake inhibitors and *torsade de pointes*: new concepts and new directions derived from a systematic review of case reports

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Abstract

Objective: In the light of the recent United States Food and Drug Administration (FDA) warning to clinicians on using previously approved doses of citalopram because of the purported higher risk of *torsade de pointes* (TdP), we pursued the broader question: are selective serotonin reuptake inhibitor (SSRI) antidepressant agents as a group unsafe because they might induce QTc interval prolongation and TdP?

Method: We reviewed the literature and found only 15 case reports (6 of fluoxetine, 1 of sertraline and 8 of citalopram) of SSRI-associated QTc interval prolongation linking to TdP.

Results: A total of 13 cases contained sufficient information for analysis. In the setting of TdP, QTc interval prolongation does not clearly relate to SSRI dose.

Conclusion: Applying conventional statistics as the FDA does may not be the best tool to study this phenomenon because SSRI-associated TdP is a very rare event and hence best understood as an 'extreme outlier'. Despite the limitations inherent in case report material, case reports on drug-associated QTc interval prolongation and TdP provide valuable information that should be considered along with other sources of information for clinical guidance.

Keywords: antidepressant drugs, QTc interval prolongation, SSRIs, *torsade de pointes*

Introduction and literature review

Recently, a variety of reports and findings have raised concerns about the potential for selective serotonin reuptake inhibitors (SSRIs) to prolong left ventricular repolarization leading to QTc interval prolongation and with it provocation of *torsade de pointes* (TdP), a potentially life-threatening polymorphic ventricular tachyarrhythmia (PVT). Review of the public version of the United States Food and Drug Administration (FDA) Adverse Event Reporting System (AERS) led to a publication by Poluzzi and colleagues [Poluzzi *et al.*, 2009] listing drugs associated with cases of TdP ranked by the number of reports. SSRIs included citalopram (12 cases), fluoxetine (12

cases) and paroxetine (11 cases). This publication formed the bases for a paper by Doyle & Rosenthal [Doyle *et al.* 2013] linking these SSRIs to QTc interval prolongation, TdP and sudden cardiac death.

SSRIs and a cross-sectional study of electronic health records

Castro and colleagues [Castro *et al.* 2013] sought to quantify the impact of citalopram and other SSRIs on QTc interval judged by them to be a marker for TdP risk. They studied 38,397 adult patients with an electrocardiogram (EKG) recorded after antidepressant or methadone prescription between February 1990 and August

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2011. The authors found that drug dose related to QTc interval prolongation for citalopram [adjusted beta 0.10, standard error (SE) 0.04; $p < 0.01$], escitalopram [adjusted beta 0.58 (SE 0.15), $p < 0.001$], and amitriptyline [adjusted beta 0.11 (SE 0.03), $p < 0.001$] but not for other antidepressants examined including fluoxetine, paroxetine, sertraline, bupropion, duloxetine, mirtazapine, nortriptyline and venlafaxine:

‘Within-subject paired observations supported the QTc prolonging effect of citalopram (10 mg to 20 mg, mean QTc increase 7.8 (SE 3.6) msec, adjusted $p < 0.05$; and 20 mg to 40 mg, mean QTc increase 10.3 (4.0) msec, adjusted $p < 0.01$).’ [Castro *et al.* 2013].

Castro and colleagues [Castro *et al.* 2013] concluded that citalopram administration was associated with a modest QTc interval prolongation. Their study also identified other antidepressants with similar observed risk. However, the authors did not mention that drug-induced QTc interval prolongation less than 25 ms is of questionable clinical significance [Camm *et al.* 2004].

Emerging strategies to manage citalopram overdose

Isbister and colleagues [Isbister *et al.* 2007] sought to determine whether single-dose activated charcoal (SDAC) administration after overdose with citalopram might reduce citalopram-induced QTc interval prolongation. The authors retrospectively analyzed data from eight emergency departments and found a beneficial effect of SDAC. The median number needed to treat was 13.3 and the authors estimated the absolute risk difference to be 7.5%.

Waring and colleagues [Waring *et al.* 2010] evaluated a QT nomogram for TdP risk assessment after citalopram (and other antidepressants) overdose. The authors conducted a retrospective case-control study of patients presenting to the emergency department after overdosing on citalopram, mirtazapine or venlafaxine. The authors found 858 EKGs from 541 patients. The QT interval was above the nomogram in 2.4% of subjects. A QTc interval ≥ 440 ms was found in 23.1% and ≥ 500 ms in 1.1% of subjects. Of the three antidepressants studied, citalopram was most likely to be associated with QTc interval ≥ 440 ms. Waring *et al.* [Waring *et al.*, 2010] concluded that the nomogram was superior to conventional QTc interval criteria and warranted further

investigation in a clinical setting. Interestingly, none of the patients developed TdP.

Early evidence linking the SSRI fluoxetine to drug-induced QTc interval prolongation

Within 5 years of its introduction into the United States in 1987, fluoxetine-induced syncope surfaced as a clinical concern [McAnally *et al.* 1992]. By 1997, concerns of fluoxetine-induced profound weakness, orthostatic hypotension and tachycardia were reported [Azaz-Livshits and Danenburg, 1997]. In 2001, Varriale [Varriale, 2001] reported a case of fluoxetine-induced QTc interval prolongation (560 ms) and claimed that earlier studies of the drug found no such effect on the EKG [Fisch, 1985; Upward *et al.* 1988; Gintant *et al.* 2001]. However, also in 2001, Darpö [Darpö, 2001] listed fluoxetine among the 20 drugs most commonly associated with TdP between 1983 and 1999 (20 cases of TdP and one fatal case). This emphasizes the importance of assessing case reports.

R-fluoxetine

R- and S-fluoxetine are components of racemic fluoxetine and are metabolized to R- and S-norfluoxetine, respectively. In a study designed to compare brain levels of R-fluoxetine and racemic fluoxetine in healthy subjects using fluorine-19 (^{19}F), the 120 mg/day R-fluoxetine group developed a mean increase in QTc intervals of 44 ms (one subject reaching 89 ms) [Henry *et al.* 2005]. The authors concluded that higher doses of R-fluoxetine may not be tolerated. In November 2000, Eli Lilly and Company halted all clinical trials of R-fluoxetine [Psychiatric News, 2000].

hERG models to predict hERG liability and QT interval prolongation

Pharmacological inhibition of cardiac potassium (K^+) channel proteins encoded by the ‘human ether-a-go-go related gene’ (hERG) is strongly associated with drug-induced QT interval prolongation and risk of TdP. Electrophysiological assays of hERG channel inhibition constitute an important component of preclinical safety testing of new drugs [Gintant, 2008; Hancox *et al.* 2008]. hERG is responsible for channels mediating the cardiac rapid delayed rectifier current, I_{Kr} , which is critical for normal ventricular repolarization [Sanguinetti and Tristani-Firouzi, 2006; Hancox *et al.* 2008]. Readers seeking a more in-depth understanding are referred to recent reviews [Sanguinetti and Tristani-Firouzi, 2006; Gintant, 2008; Hancox

et al. 2008; Witchel, 2011]. We focus here on SSRIs and their hERG-related drug toxicity.

Fluoxetine

In 2002, two reports of inhibition of hERG K⁺ channel ionic current (I_{hERG}) by fluoxetine appeared [Thomas *et al.* 2002; Witchel *et al.* 2002]. Therapeutic plasma levels of fluoxetine in human reached approximately 0.14–1.4 μM (serum levels 47–469 $\mu\text{g/l}$) [Orsulak *et al.* 1988], thought to be sufficient to induce inhibition of open hERG channels (with the caveat that free plasma concentration is likely below serum concentration because of protein binding) [Witchel *et al.* 2002]. Thomas and colleagues [Thomas *et al.* 2002] suggested that fluoxetine inhibits open hERG channels, with a reduced block on strong depolarization suggestive of a preferential action on channels in open over inactivated states.

Direct hERG channel inhibition may contribute to both acute and chronic cardiac actions of fluoxetine, but a focus on direct channel block alone overlooks an important second action of the drug, i.e. that of inhibiting trafficking of hERG channels to the cell membrane [Hancox and Mitcheson, 2006]. Indeed, there is evidence that when applied acutely to cardiac cells or tissues, fluoxetine can inhibit L-type calcium current [Pacher *et al.* 2000; Fossa *et al.* 2007], which may be able partially to offset hERG block by fluoxetine or norfluoxetine [Fossa *et al.* 2007]. However, through inhibition of hERG channel trafficking, fluoxetine may additionally reduce the number of functional hERG channels available to generate repolarizing K⁺ current. The hERG channel trafficking and acute channel block data of Rajamani and colleagues were presented along with a case of an adult patient with marked QT interval prolongation (QTc of 625 ms) following intentional fluoxetine overdose [Rajamani *et al.* 2006].

Other drugs

There is some evidence for QTc interval prolongation by fluvoxamine in animal and human studies [De La Torre *et al.* 2001; Ohtani *et al.* 2001, Brzozowska and Werner, 2009], and for ventricular arrhythmia during fluvoxamine poisoning [Manet *et al.* 1993]. Fluvoxamine has been reported to inhibit I_{hERG} with an IC_{50} of 3.8 μM [Milnes *et al.* 2003], exhibiting a rapidly developing mixed channel state dependent blockade, the basis for which is distinct

from that produced by canonical hERG blocking agents [Milnes *et al.* 2003]. Following evidence of QTc interval prolongation with citalopram overdose [Grundemar *et al.* 1997; Personne *et al.* 1997a, 1997b], Witchel and colleagues observed that citalopram blocked hERG expressed in mammalian cells with an IC_{50} of 3.97 μM [Witchel *et al.* 2002]. The I_{hERG} blocking potency of citalopram was slightly lower than that of fluoxetine (IC_{50} of 1.50 μM) in direct comparison. A subsequent study, also using mammalian cell hERG expression, reported a lower IC_{50} for hERG block of 0.95 μM [Fossa *et al.* 2007]. Like fluoxetine, citalopram can also inhibit L-type calcium current, though this effect is much weaker than the hERG blocking action [Witchel *et al.* 2002; Fossa *et al.* 2007; Zahradnik *et al.* 2008] with reported IC_{50} values ranging from 38 to 64.5 μM . The serotonin–norepinephrine reuptake inhibitor venlafaxine has been associated with QTc interval prolongation (QTc of 582 ms) in the absence of obvious QRS interval prolongation [Letsas *et al.* 2006]. It has been reported to inhibit hERG with an IC_{50} of 28 μM and L-type calcium current with an IC_{50} of 360 μM [Fossa *et al.* 2007]. These *in vitro* effects are weaker than its reported potency against cardiac Na current (estimated IC_{50} of 8 μM [Khalifa *et al.* 1999]).

Beyond hERG in understanding SSRI-associated TdP

A detailed review of the electrophysiology of TdP is beyond the scope of this paper. Nevertheless, an important concept when considering drug-induced TdP is that both hERG channel inhibition and delayed repolarization are surrogate markers for TdP, rather than automatic correlates [Gintant, 2008; Hancox *et al.* 2008]. Sequelae of excessive hERG/ I_{Kr} block include cellular arrhythmogenic early-after depolarizations (EADs) and increased transmural heterogeneity (dispersion) of ventricular repolarization. These phenomena are likely to form substrates favorable to initiation and maintenance of TdP [Yap and Camm, 2003; Gintant, 2008; Hancox *et al.* 2008]. For further information, interested readers are referred [Yap and Camm, 2003; Gintant, 2008; Hancox *et al.* 2008; Vieweg *et al.* 2009]. It is also important to note that psychotropic drug-induced PVT and attendant complications were reported before Dessertenne introduced the concept of TdP [Dessertenne, 1966].

Moving from Gaussian distributions to extreme outliers in understanding SSRI-associated QTc interval prolongation and TdP

In the 1980s, preclinical toxicology studies in beagle dogs showed that citalopram administration linked to QTc interval prolongation and fatal cardiac arrhythmias of the TdP type [Rasmussen *et al.* 1999]. Five of 10 beagle dogs administered oral doses of 8 mg/kg/day (four times the maximum recommended daily human dose of 60 mg on a mg/m² basis) died suddenly between weeks 17 and 31 following the start of treatment. Further investigation showed that the didemethyl metabolite of citalopram [didesmethylcitalopram (DDCT)], under conditions of long-term dosing, reached high plasma levels (>300 ng/ml) in beagles but not in mice, rats or humans. [In beagle dogs, citalopram (CYP2C19, CYP3A4) → desmethylcitalopram (CYP2D6) → DDCT.] Investigators concluded that DDCT was the culprit for TdP but we now know that citalopram itself might also have contributed to TdP formation. In a random study of 23 human volunteers conducted in 1997 in steady state, there were no differences in QTc interval measurements between 12 taking citalopram 60 mg/day and 11 taking placebo (data on file, Forest Laboratories, Inc., 1997). Subsequently, however, reports of QT interval prolongation and TdP with citalopram have appeared (e.g. see Table 1, [Jimmink *et al.* 2008; Hayes *et al.* 2010]). Recently, the FDA and European Medicines Agency (EMA) released safety updates for citalopram and escitalopram based on double-blind crossover 'thorough QT' data from healthy volunteers [FDA, 2011; Bazian, 2012]. The citalopram manufacturer studied the effects of 20 mg and 60 mg doses on the QTc interval in 2011 (Fridericia correction [Franz, 2008]). It was found that the mean change from baseline was 7.5 ms for the 20 mg dose and 16.7 ms for the 60 mg dose, suggesting that the 1997 study was underpowered [Forest Laboratories, 2011]. For escitalopram, 10 mg of the drug was associated with a 4.5 ms QTc interval prolongation whilst 30 mg was associated with 10.7 ms QTc interval prolongation [FDA, 2012]. Neither the citalopram manufacturer nor the FDA reported citalopram-induced QTc interval prolongation >500 ms for TdP in this 2011 study, although the EMA Pharmacovigilance Working Party commented on spontaneous reports of TdP, mostly for female patients with other risk factors [EMA, 2011]. A recent review mentioned spontaneous reporting to the FDA AERS between 2004

and 2007 of 12 cases of TdP with citalopram, 12 with fluoxetine and 11 with paroxetine [Wenzel-Seifert *et al.* 2011], whilst a review of spontaneous reports of TdP to a Swedish pharmacovigilance database noted 9 TdP cases in which citalopram was suspected [Astrom-Lilja *et al.* 2008]. Such information highlights the desirability of having detailed case reports available for scrutiny and analysis.

As pointed out above and as argued by Zeltser and colleagues [Zeltser *et al.* 2003] in a review of risk factors for TdP among subjects taking noncardiac drugs, female sex, heart disease, electrolyte imbalances, excessive dosing, drugs interactions and a family history of long QT syndrome are easily identifiable from the medical history and/or clinical evaluation. Zeltser and colleagues identified 249 subjects with TdP associated with noncardiac drugs [Zeltser *et al.* 2003]. Female sex was the most common risk factor (71%); almost all their subjects had at least one risk factor and 71% had two or more risk factors. They concluded that clinicians planning to prescribe noncardiac drugs associated with TdP could easily identify risk factors for this potentially fatal cardiac arrhythmia before prescribing the culprit drug.

Extreme outliers ('Black Swans')

Taleb [Taleb, 2010] defined events as 'Black Swans' if they had the following properties: (1) extreme outliers; (2) deliver extreme impact; and (3) stimulate a search for understanding after the fact to make the event explainable and predictable. Drug-induced/associated TdP seems to meet these criteria, emphasizing its unpredictability. QTc interval prolongation *per se* (>450 ms for men and >470 ms for women [Goldenberg *et al.* 2006]) may not be an extreme outlier. QTc interval prolongation (particularly as it exceeds 500 ms [Bednar *et al.* 2002]) is the major risk factor for TdP [Yap and Camm, 2003], but it is 'silent' (unrecognized) and appears highly unpredictable. We suspect that in the setting of TdP, QTc interval prolongation is no longer normally distributed and is no longer subject to parametric statistical analysis [Bednar *et al.* 2001].

Scalable randomness and TdP

Raschi and colleagues [Raschi *et al.* 2009] reviewed models for predicting hERG liability (I_{Kr} blockade) and QTc interval prolongation. The authors reported that 40–70% of new model entries considered as potential therapeutic drugs are abandoned early in drug development because

Table 1. Case reports of patients developing TdP while taking selective serotonin reuptake inhibitors (SSRIs).

Case	Age and sex	Drug/daily dose	QTc (ms)	Risk factors
#1 [Appleby <i>et al.</i> 1995]	74-year-old woman	Fluoxetine 20 mg	600	Female sex, age and fluoxetine
#2 [Michalets <i>et al.</i> 1998]	59-year-old woman	Fluoxetine 30 mg	500	Female sex, fluoxetine, droperidol, hypokalemia and polypharmacy
#3 [Deamer <i>et al.</i> 2001]	41-year-old woman	Fluoxetine 20 mg	710	Female sex, high-dose levomethadyl acetate, fluoxetine, cannabinoids, hypomagnesemia and, possibly, cocaine
#4 [Wilting <i>et al.</i> 2006]	83-year-old woman	Fluoxetine 20 mg	478	Female sex, age and fluoxetine
#5 [Buchanan Keller and Lemberg, 2008]	50-year-old woman	Fluoxetine (dose not given)	620	Female sex, fluoxetine, clarithromycin and hypokalemia
#6 [Patanè <i>et al.</i> 2009]	72-year-old woman	Sertraline (dose not given)	548	Female sex, age, sertraline, sotalol and heart disease
#7 [Blaschke <i>et al.</i> 2007]	77-year-old woman	Citalopram 20 mg	490	Female sex, age, bradycardia, citalopram, risperidone, cotrimoxazole, chronic medical disease and heart disease
#8 [Kanjanauthai <i>et al.</i> 2008]	81-year-old man	Citalopram (assumed to be 20 mg)	695	Age, citalopram and chronic medical illness including endstage kidney disease
#9 [Tarabar <i>et al.</i> 2008]	36-year-old woman	Citalopram (overdose 50 × 20 mg tablets = 1000 mg)	600	Female sex, citalopram overdose and hypokalemia
#10 [Digby <i>et al.</i> 2010]	58-year-old woman	Citalopram 60 mg	720	Female sex, quetiapine, citalopram, hypokalemia and heart disease
#11 [Fayssoil <i>et al.</i> 2011]	83-year-old woman	Citalopram 20 mg	526	Female sex, age, heart disease, amiodarone, citalopram and hypokalemia
#12 [De Gregorio <i>et al.</i> 2011]	48-year-old woman	Citalopram 40 mg	670	Female sex, citalopram and hypokalemia
#13 [Deshmukh <i>et al.</i> 2012]	40-year-old woman	Citalopram 40 mg BID	535	Female sex, possible concealed long QT syndrome and high-dose citalopram

BID, twice-daily; SSRI, selective serotonin reuptake inhibitor; TdP, *torsade de pointes*.

of testing positive for hERG blocking liability. However, lack of hERG blocking liability does not preclude a drug from linking to QTc interval prolongation and TdP. However, it is also known that whilst arrhythmias are more common with QTc interval prolongation of >500 ms, there is no straightforward relationship between the extent of drug-induced QTc interval prolongation and occurrence of TdP [Yap and Camm, 2003].

Taleb [Taleb, 2010] discussed the concept of scalable randomness. In this approach, added and unanticipated complexity explains the occurrence of a rare phenomenon rather than a statistically predictable association. It follows that added and unanticipated risk factors appear in patients

destined to develop TdP independent of the original drug prescription. The QTc interval-prolonging drug is a prerequisite but, by itself, may not be sufficient to cause TdP. Therefore, multiple risk factors including the drug itself add complexity and uncertainty sufficient to negate parametric statistical analysis alone to explain drug-associated TdP. A case report format that provides detailed clinical histories including comorbidities is likely to identify additional risk factors contributing to TdP formation.

Methods

A systematic review searching for cases of SSRI and TdP (until and including 3 March 2013) was

conducted entering the following Medical Subject Headings (MeSH) terms: 'fluoxetine', 'sertraline', 'paroxetine', 'fluvoxamine', 'citalopram', and 'escitalopram' serially and 'torsade de pointes' into three databases: Medline (38), EMBASE (170) and Cochrane (0) only for case reports. There were no language limits and only human studies were included. We also reviewed reports from our files and reference lists. Titles and abstracts were independently reviewed by two investigators (W.V.R.V. and A.B.). Disagreement was resolved by consensus.

Results

We identified 15 cases of TdP associated with fluoxetine (6), sertraline (1) and citalopram (8). Thirteen cases (12 women and 1 man) provided sufficient information for detailed evaluation (Table 1). Five patients received fluoxetine, one sertraline, and seven received citalopram. Multiple risk factors were present in each case, with female sex the most common one.

For the six subjects receiving nonoverdose citalopram, the Pearson r was -0.059 ($p = 0.912$) for citalopram dose and QTc interval at the time of TdP. That is, there was no correlation between drug dose and QTc interval duration in the setting of TdP.

All but one of our study subjects were women and almost all were middle-aged or elderly, consistent with our earlier findings involving case reports of the proarrhythmic risks of antipsychotic and antidepressant drugs in the elderly [Vieweg *et al.* 2009]. All 13 study subjects had multiple risk factors for drug-associated TdP and female sex was the most common risk factor ($n = 12$). Additional risk factors included elderly age ($n = 6$), co-administration of drugs associated with QTc interval prolongation ($n = 9$), hypokalemia ($n = 6$), chronic medical illness ($n = 2$) and heart disease ($n = 3$).

Discussion

Risk factors among our patients were similar to those described by other investigators (see paragraph above) [Zeltser *et al.* 2003; Raschi *et al.* 2009]. We showed that QTc interval prolongation in the setting of TdP is not linked to citalopram dose, is not predictable at present, and is not likely Gaussian in distribution. Our data, limited as they are, do not support the notion that QTc

interval is citalopram dose-dependent in the setting of TdP [Forest Laboratories, 2011]. A particularly interesting observation was that in all three cases of elderly patients developing TdP while taking citalopram, the dose of citalopram was 20 mg consistent with the current recommendations of both the manufacturer and the FDA [Forest Laboratories, 2011; FDA, 2011] for patients over 60 years of age.

In animal studies, citalopram was associated with inhibition of hERG current; however, this effect is counteracted by its inhibition of depolarizing current mediated by L-type calcium channels [Witchel *et al.* 2002; Fossa *et al.* 2007]. Despite the fact that the L-type calcium current inhibition by citalopram is somewhat weaker than that of hERG, at concentrations where both effects occur [Witchel *et al.* 2002; Fossa *et al.* 2007], the L-type current block might either partially offset QTc interval prolongation with citalopram, or act to mitigate EADs and subsequent arrhythmias that might derive from selective hERG blockade [Witchel *et al.* 2002].

Weeke and colleagues [Weeke *et al.* 2012] studied all patients in Denmark with out-of-hospital cardiac arrest (OHCA) during the study period 2001–2007. They examined the association between treatment with specific antidepressants and OHCA using conditional logistic regression in case-time-control models. The authors identified 19,110 subjects with OHCA of whom 2913 (15.2%) received antidepressant drug treatment coincident with OHCA. Citalopram was the most frequently used antidepressant (50.8%); tricyclic antidepressants (TCAs) [odds ratio (OR) = 1.69, confidence interval (CI): 1.14–2.50] and SSRIs (OR = 1.21, CI: 1.00–1.47) linked comparably with increased risk of OHCA. They found no association for serotonin–norepinephrine reuptake inhibitors (SNRIs)/noradrenergic and specific serotonergic antidepressants (NaSSAs); OR = 1.06, CI: 0.81–1.39 with OHCA. Citalopram (OR = 1.29, CI: 1.02–1.63) and nortriptyline (OR = 5.14; CI: 2.17–12.2) primarily drove increased risk. Weeke and colleagues [Weeke *et al.* 2012] found an association between cardiac arrest and antidepressant exposure in both SSRI and TCA classes of drugs. However, they did not have enough case report material to determine if citalopram-linked OHCA related to QTc interval prolongation and TdP or if risk factors were present. The authors could not even determine if their study patients took the medications prescribed.

How should we conceptualize the relationship between SSRIs and drug-associated TdP?

However compelling the argument may be that at QTc interval measurements <500 ms there is a positive dose-dependent relationship between drug and QTc interval duration and this relationship fits a Gaussian distribution, this association by itself is not sufficient to predict TdP. That is, factors other than drug and dose must enter into any calculation seeking to explain drug-associated TdP. Raschi and colleagues [Raschi *et al.* 2009] identified many risk factors underlying drug-induced TdP onset including organ impairment, drug interactions, electrolyte imbalance, and genetic mutations leading to reduced repolarization reserve. Genetic variation that influences drug metabolism or that is associated with subclinical variation in repolarization may also play a role [Kannankeril, 2008]. Although we must be cognizant of potential limitations associated with reliance on small numbers [Lauer, 2012], the fact that TdP is a rare (albeit serious) complication of drug use means that extending our understanding of this phenomenon arguably necessitates some reliance on careful scrutiny of case report material.

Limitations of case report material

Case reports on SSRI (or other drug) induced TdP are valuable. However, they have several limitations and are not a substitute for other types of studies. Their inconsistent reporting would preclude drawing inferences about relative risk of TdP with various SSRIs, even after adjusting for prescription-years exposure. Any conclusions drawn from case reports about dose-response association between an SSRI and TdP can also be misleading. Case reports would capture information on risk factors and circumstances that other types of studies do not capture. However, case reports do not capture information provided by other types of studies including studies of hERG affinity, thorough QT and other cardiac safety studies, and pharmacovigilance studies or toxicology studies.

Conclusion

Given the extremely low incidence of drug-induced TdP, systematic large group studies to identify risk factors that lead from a prolonged QTc interval to TdP are not possible. In this scenario, case reports provide a good alternative to study those risk factors. We believe that both drug manufacturers and regulatory agencies should

enhance data collection through case reports to better understand the contribution of multiple risk factors associated with drug-induced TdP.

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