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Citalopram, QTc Prolongation and Torsades de Pointes

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Abstract

Objectives: The aim of this systematic review is to identify case reports of citalopram use resulting in QTc prolongation and/or Torsades de Pointes (TdP) in the medical literature. **Methods:** A literature search was conducted of PubMed, MEDLINE, EMBASE, Scopus and PsycINFO databases for case reports published in any language that reported the relationship between citalopram use and the development of QTc prolongation and/or TdP. Also, bibliographic databases of published articles were search for additional cases. **Results:** A total of eighteen case reports of citalopram use resulting in QTc prolongation were identified. Of these, ten cases were also associated with the development of TdP. A total of fourteen cases occurred in women and four in men. There were seven cases involving an overdose with citalopram. Of the eighteen cases, twelve occurred in individuals who were < 60 years and six were in individuals who were > 60 years in age. In eight of the eighteen cases, the individuals were taking citalopram between 20 and 60 mg a day. Hypertension was the most common comorbid medical condition as seen in five of the cases. **Conclusions:** QTc prolongation and/or Torsades de Pointes (TdP) are infrequent adverse effects associated with citalopram use.

Introduction

Citalopram is a Selective Serotonin Reuptake Inhibitor (SSRI) that is used to treat various psychiatric disorders in both younger and older adults [1, 2]. However, a drug safety communication by the United States Food and Drug Administration (FDA) and a drug safety update by the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) indicates that citalopram causes dose-dependent QTc interval prolongation and this can result in Torsades de Pointes (TdP), ventricular tachycardia and sudden death [3,4]. For citalopram, the recommendations include a maximum daily dose of 40 mg a day for adults and 20 mg a day for individuals > 60 years in age, those with hepatic impairment, CYP 2C19 poor metabolizers and those individuals who are taking concomitant CYP2C19 inhibitors. Furthermore, citalopram is not recommended for use in individuals with congenital long QT syndrome, bradycardia, hypokalemia or hypomagnesemia, recent acute myocardial infarction and uncompensated heart failure. The FDA recommends citalopram to be discontinued in individuals who are found to have persistent QTc interval greater than 500 ms.

Major treatment studies have used citalopram at higher doses than what has been recommended by the FDA and the MHRA without any serious cardiovascular adverse effects [5, 6]. However, the recommendations by the FDA and the MHRA have created significant concerns among clinicians prescribing citalopram [7, 8]. These concerns include the clinical destabilization of individuals who had been doing well on higher doses of citalopram when the dose is lowered, the concern to use higher doses of citalopram in individuals who may benefit from these doses of the drug and the fear of using this medication at any dose in individuals who might benefit from it.

Three excellent reviews have evaluated the case reports in the literature on citalopram use resulting in QTc prolongation and/or TdP [5, 9, 10]. In the review Viweg et al, the investigators searched PubMed on October 13, 2011 with the terms "citalopram and QTc" and "citalopram and torsade". They found a total of nine cases of citalopram use resulting in QTc prolongation and/or TdP [5]. In the review by Beach et al, the authors found a total of twelve case reports of citalopram use resulting in QTc prolongation and/or TdP [9]. The authors of the report indicate that this was a non-systematic review where articles were identified initially through PubMed using the search terms "QT prolongation," "Torsades de pointes," and "antipsychotics." This search strategy was supplemented via a search of reference lists from articles identified in the initial search. In a more recent review, Kogut et al found eight case reports of citalopram use resulting in QTc prolongation and TdP [10]. The authors of this review had a well-defined search strategy that included all six SSRIs and TdP as MESH terms, but they only searched three databases: Medline, EMBASE and Cochrane.

Although the three previous reviews have identified a number of case reports, they are limited by their search strategy. The current review aims at adding to the information available from the previous reviews. The plan is to conduct a systematic search of multiple databases using specific

search terms over a definite time period. The goal is to be inclusive with the search strategy in order to obtain as many published cases as possible of citalopram use resulting in QTc prolongation and/or TdP.

Search Strategy

We performed a literature search of PubMed (Jan 1996 – March 2014), MEDLINE (Jan 1996 – March 2014), EMBASE (Jan 1996 – March 2014), Scopus (Jan 1996 – March 2014) and PsycINFO (Jan 1996 – March 2014) databases using the following keywords: QT, Torsades de Pointes, arrhythmia, or Long QT Syndrome [MeSH] combined with citalopram. The search was not restricted by language. However, only articles in English or with an English translation were included in the final review. Furthermore, we reviewed the bibliographic databases of published articles for additional case reports. Information obtained from published database reviews, systematic reviews, meta-analyses and randomized controlled trials (RCTs) obtained during the search was used in the discussion section.

The Naranjo-Adverse Drug Reaction (ADR) Probability Scale was used to assess the likelihood that a change in electrocardiographic studies was related to therapy with citalopram [9]. The Naranjo criteria classify the probability that an adverse event is related to drug therapy based on a list of weighted questions. The ADR Probability Scale consists of 10 questions that are answered as either Yes, No, or "Do not know". Different point values (-1, 0, +1 or +2) are assigned to each answer. The ten questions are as follows: 1. Are there previous conclusive reports of this reaction? 2. Did the adverse event appear after the drug was given? 3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given? 4. Did the adverse reaction reappear upon re-administering the drug? 5. Were there other possible causes for the reaction? 6. Did the adverse reaction reappear upon administration of placebo? 7. Was the drug detected in the blood or other fluids in toxic concentrations? 8. Was the reaction worsened upon increasing the dose? Or, was the reaction lessened upon decreasing the dose? 9. Did the patient have a similar reaction to the drug or a related agent in the past? 10. Was the adverse event confirmed by any other objective evidence? The total scores range from -4 to +13. The reaction is considered definite if the score is 9 or higher, probable if 5 to 8, possible if 1 to 4, and doubtful if 0 or less. The Naranjo criteria do not take into account drug-drug interactions. Drugs are evaluated individually for causality and points deducted if another factor may have resulted in the adverse event, thereby weakening the causal association.

For the ease of understanding, the case reports are arranged in ascending order of the year of publication, with the earliest case being noted first and the latest case being noted last (Tables I, II & III).

Results

Insert PRISMA flow diagram here

Of the eighteen case reports, twelve reports were in individuals who were < 60 years and six were in individuals who were > 60 years in age. Only four of the reports were in men whereas fourteen reports were in women. There were a total of seven cases of overdose with citalopram resulting in QTc prolongation and/or TdP. Five of these overdoses cases were in women. In one case, it is unclear if there was an overdose. In fourteen of the eighteen cases, citalopram had been prescribed for the management of depression. In two cases, the primary reason for the citalopram prescription was unclear.

Insert Table I here

Of the eighteen cases of citalopram use resulting in QTc prolongation, ten cases were also associated with TdP [14, 17-19, 21, 23-25]. Only one of these cases was a citalopram overdose [19]. Eight of the ten cases of TdP occurred in women. In two cases, QTc prolongation occurred without any other cardiac rhythm abnormality [13, 29]. In two cases, QTc prolongation was associated with bradycardia [12, 22]. In one case each, QTc prolongation was associated with supraventricular tachycardia [16] and ventricular fibrillation respectively [26].

Insert Table II here

In eight of the eighteen cases, the individuals were talking citalopram between 20 and 60 mg a day. Among these eight individuals, four were taking citalopram 20 mg a day [17, 18, 22, 24], two were taking 40 mg a day [12, 25] and two individuals were taking 60 mg a day [23, 28]. Among the eight cases, there was no correlation between higher doses and greater QTc interval. One individual was taking citalopram 80 mg a day [27]. The individual taking citalopram 80 mg a day had a mean QTc which was similar to one individual taking 60 mg a day [28] and lower than the QTc interval for the other individual taking the 60 mg a day dosing [23]. There was no correlation between the dose of citalopram ingested, QTc prolongation and/or the development of TdP. In three cases, the individuals were also taking an antipsychotic medication along with citalopram: risperidone 2 mg a day [18], olanzapine 1.25 mg a day [22] and quetiapine 50 mg three times a day [23].

The mean Naranjo Scale score for these cases was 5.9 ± 2.0, indicating that the ADR of citalopram use resulting in QTc prolongation and/or TdP is probable. Please see Table III for the details of the Naranjo-Adverse Drug Reaction (ADR) Probability Scale score for each case.

Insert Table III here

Discussion

The data from this systematic review indicates that there are eighteen case reports of citalopram use resulting in QTc prolongation and/or TdP. The mean Naranjo scale for these reports of 5.9 ± 2.0 indicates that this ADR with citalopram is probable. There were a significantly greater

number of cases involving women (3.5:1). In the overdose cases, five of the seven cases involved women. Twelve of the eighteen cases (67%) occurred in individuals who were < 60 years in age. Hypertension was the most common comorbid condition that was identified in five cases followed by Long QT syndrome and diabetes mellitus noted in two cases each. Long QT Syndrome (LQTS), a common genetic arrhythmia syndrome causing TdP and seen in 5% to 10% individuals who develop drug induced TdP [30]. In this review, the longest QTc interval was noted in a 58 year old woman who took 60 mg a day dose of citalopram (QTc =720 ms) [23].

How does the data from this systematic review compare to the data from the three previous reviews that included case reports [7, 9, 10]? The current review identified nine additional case reports of citalopram use resulting in QTc prolongation and/or TdP when compared to the review by Viweg et al and six more case reports than indicated in the review by Beach et al [7, 9] Additionally, this review identified ten case reports of QTc prolongation and TdP related to citalopram use when compared to seven case reports noted in the review by Kogut et al [10]. As noted in the prior reviews, this review found that a majority of the published cases occurred in women. Furthermore, the dose of citalopram ingested did not correlate with QTc interval prolongation or the development of TdP.

How does citalopram cause QTc prolongation? Although the exact mechanisms are still unclear, proposed mechanisms include the direct blockade of the rapid potassium delayed rectifier current (Ikr) which is encoded by the human ether related gene (HERG) and the species specific metabolite didesmethyl-citalopram (DDCT) [7, 31, 32]. Citalopram is metabolized to desmethyl-citalopram (DCT) in the liver via CYP 2C19 and CYP 3A4 and to DDCT by CYP 2D6 [7]. High concentrations of DDCT which occur when higher doses of citalopram (>4 times normal adult dose) are consumed. High concentrations of DDCT have been associated with QTc prolongation and death in Beagle dogs [33]. In normal adults, DDCT is a minor metabolite of citalopram in adults but it may assume significance in individuals (2% of US) who are CYP 2D6 ultra-rapid metabolizers [7].

How does the data from this review compare to the data from other studies that have evaluated the issue of citalopram use resulting in QTc prolongation and/or TdP? Although it is difficult to draw definitive conclusions from these additional studies, available evidence indicates that citalopram may prolong the QTc interval more often than other SSRIs. However, the risk of developing TdP still remains unclear. Additionally, it remains uncertain if heart disease, age > 65 years and female sex are unique risk factors for citalopram use resulting in TdP or any medication use leading to TdP. Table IV details the information from other pertinent studies on this topic. Information in Table IV is arranged in a chronological order with data from the earliest study being noted first to information from the latest study being provided last.

Insert Table IV here

This current study has its limitations. Despite being a systematic review, we limited our search to case reports of citalopram use resulting in the development of QTc prolongation and/or TdP. We only included case reports in English language or the ones that had a translation in English in our final review. Due to this restriction, we did not use data from one additional case report which was in Finnish language [41]. Without a comparison group, a cause-and-effect relationship between citalopram use and the development of QTc prolongation and/or TdP cannot be established. Additionally, these case reports are subject different biases including sampling, recall and publications bias.

Despite these limitations, this current report can be beneficial to both clinicians and researchers. This review is a compendium of all the cases of citalopram use resulting in QTc prolongation and/or TdP to have been published in the medical literature and collected in a systematic manner. Kogut et al state that due to the rarity of drug-induced TdP, systematic large group studies to identify risk factors that lead from a prolonged QTc interval to TdP are not possible [10]. They indicate that in such a scenario, case reports provide a good alternative to study those risk factors. Furthermore, they opine that 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. Similarly, we believe that a compilation of case reports as accomplished in this review can educate medical providers regarding the risk factors for the development QTc prolongation and/or TdP with the use of citalopram.

Conclusions

Available evidence indicates that QTc prolongation and TdP are uncommon adverse effects associated with citalopram use as there are only eighteen such cases published in the medical literature. Seven of these cases involved an overdose with citalopram. A significantly greater number of cases involved women. Additionally, a greater number of cases were noted in individuals < 60 years of age and the dose of citalopram ingested did not correlate with the development of QTc prolongation and TdP. Furthermore, it can be inferred that the issue of citalopram use resulting in QTc prolongation and/or TdP is complex and further evaluation is needed prior to reaching any definitive conclusions.

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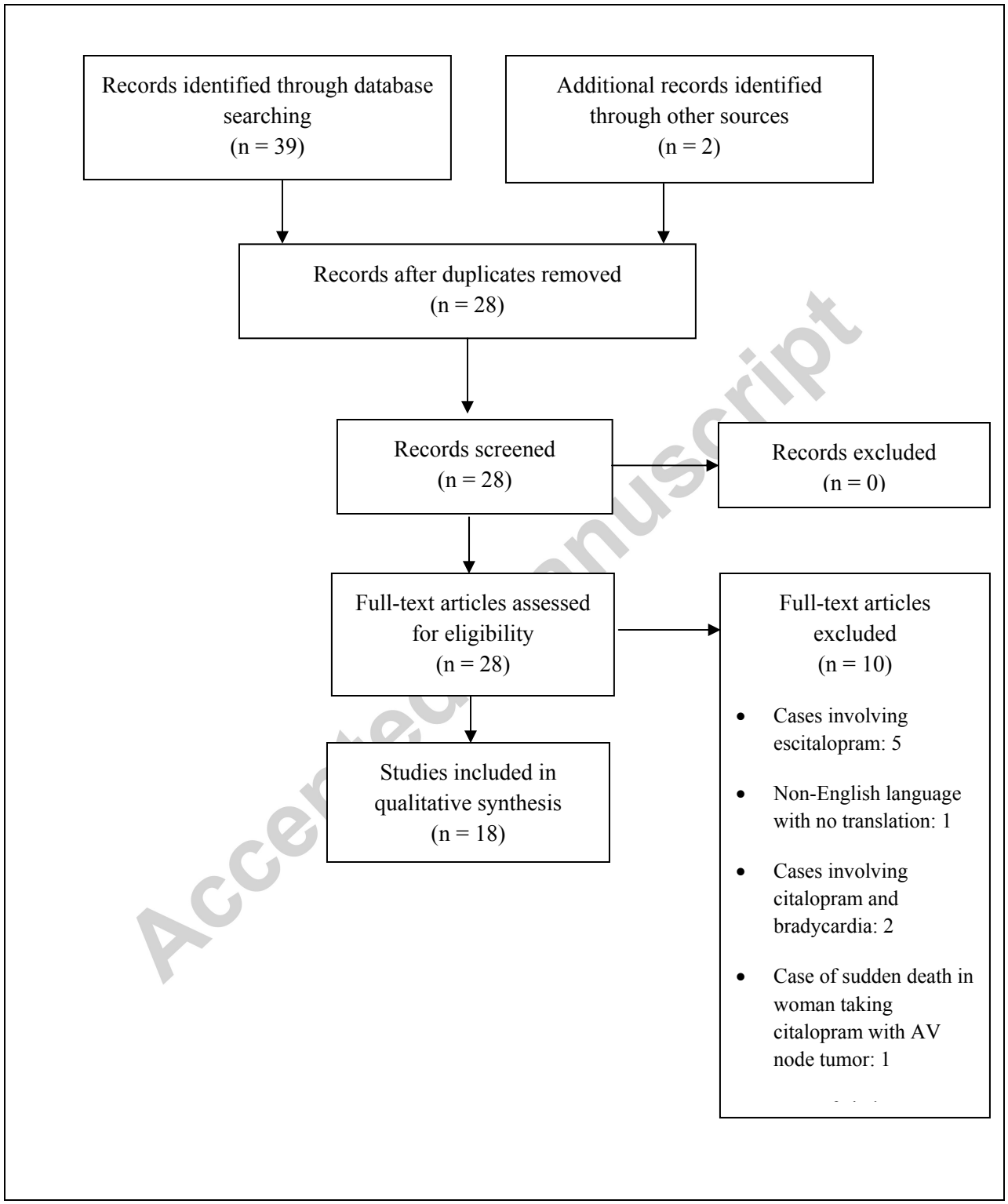
Table I. Summary of case reports

Study	Age	Sex	Overdose	Dose	Max QTc	Naranjo Score	Reference
Favre et al. 1999	47	Female	No	40mg	463ms	5	12
Catalano et al. 2001	21	Female	Yes	400mg	457ms	8	13
Meuleman et al. 2001	51	Female	No	Not reported	572ms	9	14
Engebretsen et al, 2003	31	Male	Yes	400mg	506ms	8	15
Cuenca et al. 2004	23	Male	Yes	920mg	446ms	7	16
Kourgiannidis et al. 2005	81	Female	No	20mg	600ms	3	17
Blaschke et al. 2007	77	Female	No	20mg	490ms	4	18
Tarabar et al. 2008	36	Female	Yes	1000mg	600ms	8	19
Venkatraman et at. 2008	23	Female	Yes	220mg	Not reported	4	20
Kanjanauthai et al. 2008	81	Male	No	Not reported	695ms	7	21
Bruggisser et al. 2009	76	Female	No	20mg	526ms	7	22
Digby et al. 2010	58	Female	No	60mg	720ms	4	23

Fayssoil et al. 2010	83	Female	No	20mg	526ms	4	24
de Gregorio et al. 2011	48	Female	No	40mg	670ms	4	25
Liotier et al. 2011	54	Female	Yes	Not reported	670ms	8	26
Deshmukh et al. 2012	40	Female	No	80mg	535ms	4	27
Ibrahim et al. 2012	65	Male	No	60mg	600ms	4	28
Unterecker et al. 2012	46	Female	es	1400mg	542ms	8	29



PRISMA flow diagram for systematic review of case reports

Table II. Additional information on the cases

Study	Reason for drug use	Concomitant medications	Medical history	Reference
Favre et al. 1999	Depression	Atenolol 50mg/daily	Anxiety	12
Catalano et al. 2001	Depression	Alprazolam 0.25mg, Oral Contraceptives	Migraines	13
Meuleman et al. 2001	Depression	Not reported	No active medical illness	14
Engebretsen et al, 2003	Not stated	None reported	None reported	15
Cuenca et al. 2004	Depression	Ativan 1 mg IV (1 dose), Adenosine 6mg IV (1 dose)	No active medical illness	16
Kourgiannidis et al. 2005	Depression	Bisoprolol 2.5mg/daily, HCTZ 6.25mg/daily, Perindopril 4mg/daily, Benserazide 150mg/daily, Levodopa 600mg/daily, clomethiazole 192mg/daily, trazodone 100mg/daily	Hypertension, long QT syndrome, Parkinsonism	17
Blaschke et al. 2007	Depression	Ramipril, Nifedipine, Risperidone 2mg/daily	Hypothyroidsm, diabetes mellitus II and hypertension	18

Tarabar et al. 2008	Bullimia/Anorexia Nervosa	None	Alcohol abuse	19
Venkatraman et at. 2008	Not stated	Lamotrigine 9200 mg, chlorphenaramine 56 mg	None reported	20
Kanjanauthai et al. 2008	Depression	Not Reported	Hypertension, diabetes and end stage renal disease	21
Bruggisser et al. 2009	Depression and Schizophrenia	20 mg	Cognitive impairment, rheumatoid arthritis, dyslipidemia	22
Digby et al. 2010	Chronic Alcohol Abuse	Quetiapine 50mg/TID, and 200mg QHS, HCTZ 25mg/Daily, Clonazepam 1mg/TID, Acamprosate 333mg/TID, Atenolol 25mg/BID, Ranitidine 150mg/Daily, Mirtazipine 30mg/QHS, Rosuvastatin 10mg/Daily	Congestive heart failure, chronic obstructive pulmonary disease, obstructive sleep apnea, hypertension	23
Fayssoil et al. 2010	Depression	Amiodarone 200mg, Fluindion, Losartan 50mg, Lercanidipine 10mg	Hypertension, and atrial fibrillation	24
de Gregorio et al. 2011	Depression	Furosemide 25mg/daily	Systolic hypertension	25

Liotier et al. 2011	Depression	Zopiclone 7.5mg (1 tablet)	No active medical illness	26
Deshmukh et al. 2012	Depression	None	Long QT syndrome	27
Ibrahim et al. 2012	Depression	Ciprofloxacin 500mg/BID, Albuterol 90mcg Inh	Emphysema and recent urinary tract infection	28
Unterecker et al. 2012	Depression	Opipramol 50mg (10 tablets)	No active medical illness	29

Table III. Naranjo adverse drug reaction (ADR) probability scale score for each case

Case/Question	1	2	3	4	5	6	7	8	9	10	Total Score	Reference
Favre et al. 1999	1	2	1	0	-1	0	0	1	0	1	5	12
Catalano et al. 2001	1	2	1	0	2	0	1	0	0	1	8	13
Meuleman et al. 2001	1	2	1	2	2	0	0	0	0	1	9	14
Engebretsen et al, 2003	1	2	1	0	2	0	1	0	0	1	8	15
Cuenca et al. 2004	1	2	1	0	2	0	0	0	0	1	7	16
Kourgiannidis et al. 2005	1	2	0	0	-1	0	0	0	0	1	3	17
Blaschke et al. 2007	1	2	1	0	-1	0	0	0	0	1	4	18
Tarabar et al. 2008	1	2	1	0	2	0	1	0	0	1	8	19
Venkatraman et at. 2008	1	2	1	0	-1	0	0	0	0	1	4	20
Kanjanauthai et al. 2008	1	2	1	0	2	0	0	0	0	1	7	21
Bruggisser et al. 2009	1	2	1	0	2	0	0	0	0	0	7	22
Digby et al. 2010	1	2	1	0	-1	0	0	0	0	1	4	23
Fayssoil et al.	1	2	1	0	-1	0	0	0	0	1	4	24

2010												
de Gregorio et al. 20011	1	2	1	0	-1	0	0	0	0	1	4	25
Liotier et al. 2011	1	2	1	0	2	0	1	0	0	1	8	26
Deshmukh et al. 2012	1	2	1	0	-1	0	0	0	0	1	4	27
Ibrahim et al. 2012	1	2	1	0	-1	0	0	0	0	1	4	28
Unterecker et al. 2012	1	2	1	0	2	0	1	0	0	1	8	29

Table IV. Data from other pertinent studies

Name of the Study	Type of Study	Pertinent Information	Reference
Personne et al, 1997	Database review	EKG changes usually occur only when the dose of citalopram consumed is > 600 mgs.	34
Rasmussen et al, 1999	Review	Citalopram causes a small reduction in heart rate (≥8 beats per minute) and no other EKG changes.	33
Kelly et al, 2004	Retrospective review	Citalopram was associated with a significantly longer QT interval on EKG recording ($p < 0.0001$) but the mean QTc durations were not significantly different from venlafaxine, mirtazapine and nefazadone after overdose. There were no arrhythmias.	35
Aström-Lilja et al, 2008	Pharmacovigilance database review	Nine cases of citalopram causing TdP were noted. In five cases citalopram was the concomitant drug. For all drugs grouped together, heart disease, age > 65 years and female sex were risk factors for the development of TdP.	36
Castro et al, 2013	Database review	Dose-response association with QTc prolongation for citalopram: 10 mg to 20 mg, mean QTc increase 7.8 ms, adjusted $P<0.05$ and 20 mg to 40 mg, mean QTc increase 10.3, adjusted $P<0.01$.	37
Zivin et al, 2013	Cohort study	Citalopram dosages >40 mg a day was not associated with greater risks of ventricular arrhythmia, all-	38

		cause, cardiac or non-cardiac mortality compared to 1 to 20 mg a day.	
Funk and Bostwick, 2013	Systematic review	Eleven cases of SSRI associated QTc prolongation: escitalopram (1 case), fluoxetine (6 cases), fluvoxamine (1 case) and sertraline (3 cases). Citalopram not included in this review.	6
Beach et al, 2014	Meta-analysis	QTc prolongation for citalopram, 10.58 ms, 95% CI, 3.93 to 17.23, P=0.0018 when compared to placebo.	39
Porsteinsson et al, 2014	RCT	Citalopram associated with greater increase in the QTc interval than placebo: 18.1 ms, 95% CI, 6.1 to 30.1, P=0.004. Citalopram versus placebo, QTc > 30 ms from enrollment to week 3, 7 vs 1, P=0.05.	40