An in-depth look at QT prolongation and the U.S. Food and Drug Administration’s safety alert on citalopram.

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Learning Objectives:

I. Describe the mechanism and risk factors of drug-induced QT interval prolongation and torsade de pointes (TdP).
II. Describe the evidence regarding citalopram-induced QT prolongation and TdP.
III. Understand the regulatory decision-making process regarding the QT prolonging potential of medications.
IV. Assess the appropriateness of the citalopram safety alert and its potential impact on clinical practice.
The QT interval

A. Measures the time between the onset and end of ventricular electrical activity\(^1,2\) and is measured from the beginning of the QRS complex to the end of the T wave.\(^1,3\)

B. Repolarization is faster, and thus the measured QT interval changes when the heart beats more rapidly; therefore the QT interval should be corrected for heart rate.\(^2-5\)
   a. Rate-correction formulas (QTc) include Bazett’s and Fridericia’s\(^3,4\), with Bazett’s applied the most exclusively.
   b. Using Bazett’s correction, the widely accepted upper limits for normal QTc interval is 450 msec in males, 470 msec in females and 460 msec in children (regardless of gender).\(^2,4\)

C. Ventricular depolarization and repolarization is mediated by channels that regulate influx or efflux of ions in cardiomyocytes.

   a. Depolarization is mediated by inward currents primarily through Na\(^+\) and Ca\(^{2+}\) channels.
   b. Repolarization is mediated by outward currents primarily through K\(^+\) channels.

D. Impairments in ion channels can occur and may be either congenitally acquired, which is a rare occurrence, or drug-induced.
   a. Congenital impairments occur as a result of mutations in ion channel subunits\(^1\) and mutations in genes that code for regulatory proteins involved in ion channel functions, trafficking and kinetics.\(^1,6\)
      i. The autosomal dominant type or Romano-Ward syndrome (eleven known subtypes) is more common than the recessive type or Jervell and Lange-Nielsen syndrome (two subtypes).
      ii. The most prevalent dominant subtypes are LQT1 and LQT2, due to mutations in the K\(^+\) channel and LQT3, due to mutations in the Na\(^+\) channel.
         1. LQT1 events are usually triggered by exercise or stress, LQT2 events by emotional stress, and LQT3 events most often occur during sleep or at rest and have the highest fatality rates.
   b. Drug-induced impairments occur by one or more mechanisms.
      i. Primary mechanism: blockade of I\(_{kr}\), the rapid component of the delayed rectifier K\(^+\) channel responsible for the efflux of K\(^+\) ions in repolarization.\(^1,6\)
         1. Encoded by the human ether-a-go-go-related gene (HERG) and can be inhibited by many structurally diverse compounds.\(^6\)
      ii. Other mechanisms:
         1. Blockade of I\(_{ks}\), the slow component of the delayed rectifier K\(^+\) channel\(^1,6\)
         2. Blockade of I\(_{na}\), responsible for the depolarizing Na\(^+\) current.\(^1,6\)
      iii. Excessive intracellular positive ions results in delayed ventricular repolarization and prolongation of the QTc interval.
      iv. QTc prolongation may result in early afterdepolarizations (EAD), which may induce reentry and provoke torsade de pointes (TdP) and fatal ventricular arrhythmias [sudden cardiac death (SCD)].\(^1\)
E. Risk factors for QTc prolongation
   a. Congenital long QT syndrome (LQTS) – clinical and subclinical forms
   b. Age >65 years
   c. Female sex
      i. Longer QTc than men and twice the risk of drug-induced TdP
      ii. 67-70% of drug-associated TdP occurs in women
   d. Heart disease
      i. Myocardial hypertrophy
      ii. Congestive heart failure
      iii. Atrial fibrillation
      iv. Bradycardia
   e. Electrolyte disturbances (hypomagnesemia, hypokalemia)
   f. Drugs

F. Drug-induced QTc prolongation
   a. Both cardiac and non-cardiac drugs have been implicated.
      i. Class I and III antiarrhythmics (e.g. quinidine, sotalol, amiodarone)
      ii. Psychotropics
         1. Antipsychotics [e.g. thioridazine, pimozide, haloperidol (IV), ziprasidone, quetiapine]
         2. Antidepressants (TCAs, SSRIs)
      iii. Opiate agonists (methadone)
      iv. Anti-infectives (e.g. moxifloxacin, clarithromycin)
      v. Antihistamines (e.g. astemizole, terfenadine)
   b. Simultaneous use of multiple QTc prolonging drugs (pharmacodynamic interactions), inhibition of drug metabolism or clearance (pharmacokinetic interactions), high concentrations of the drugs due to overdose, or rapid infusion further increases the risk.
      i. Pharmacodynamic (PD) interaction example
         1. Patient is stabilized on sotalol, a Class III antiarrhythmic with $I_{kr}$-blocking activity, is then prescribed moxifloxacin, a fluoroquinolone with mild QTc-prolonging effects, for acute infection.
      ii. Pharmacokinetic (PK) interaction examples
         1. Patient is taking terfenadine, an antihistamine with potent $I_{kr}$-blocking activity, and is then prescribed ketoconazole, a potent CYP3A4 inhibitor, which significantly increases terfenadine levels.
         2. Concomitant use of a diuretic, which can cause hypokalemia and hypomagnesemia, and thioridazine.

Torsade de pointes (TdP)

A. Risk of TdP is correlated with the extent of QTc prolongation with antiarrhythmic drugs, but this may not necessarily true for non-cardiac drugs.
   a. With non-cardiac drugs, TdP is not highly predictable despite known risk factors.
   b. Is a rare occurrence with an estimated incidence in the range of 1 in 100,000 patients (cisapride) to substantially lower for other drugs

B. Despite the small risk, the potential outcome of SCD is serious and the small risk must be weighed against the potential drug benefits.

C. FDA actions have been prompted by this need to balance risks and benefits.
FDA alert: citalopram-induced QTc prolongation

A. Prompted by post-marketing reports of QTc prolongation and TdP associated with citalopram.
B. Also prompted by the results of "Thorough QT/QTc" studies of citalopram and escitalopram. a. Both were randomized, multi-center, double-blind, placebo-controlled, positive-controlled (moxifloxacin), crossover studies.

Table 1. Citalopram and Escitalopram: Dose-dependent Change in Corrected QT Interval (QTc)

<table>
<thead>
<tr>
<th>Citalopram (n=119)</th>
<th>Escitalopram (n=113)</th>
</tr>
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<tbody>
<tr>
<td><strong>Dose</strong></td>
<td><strong>Change in QTc</strong></td>
</tr>
<tr>
<td></td>
<td>(90% Confidence Interval) (msec)</td>
</tr>
<tr>
<td>20 mg</td>
<td>8.5 (6.2, 10.8)</td>
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<tr>
<td>40 mg*</td>
<td>12.6 (10.9, 14.3)</td>
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<tr>
<td>60 mg</td>
<td>18.5 (16.0, 21.0)</td>
</tr>
<tr>
<td>Moxifloxacin 400 mg</td>
<td>13.4 (10.9, 15.9)</td>
</tr>
</tbody>
</table>

* Estimate based on the relationship between citalopram (and escitalopram) blood concentrations and QT interval

C. Changes to citalopram labeling
a. Standard risk management warnings (e.g. caution in electrolyte disturbances or use with other QTc-prolonging drugs)
b. New maximum dose of 40mg/day due to the following:
   i. The QTc prolongation seen with the 60 mg/day dose is “clinically significant”. 8
   ii. A meta-analysis of nine studies did not show any added effectiveness of citalopram at 60 mg/day versus 40 mg/day. 8
   c. Maximum dose of 20mg/day in the following:
      i. Hepatic impairment
      ii. Age > 60 years
      iii. CYP 2C19 poor metabolizers or concomitant use of CYP2C19 inhibitor

Evidence regarding citalopram-induced QTc prolongation and TdP

A. Mechanism
a. Parent drug
   i. Blocks cardiac HERG-encoded K+ channel at level of potency similar to imipramine and amitriptyline but less than fluoxetine.9
   ii. Also blocks cardiac L-type calcium channel, I_{Ca,L} (inward-directed current) which is theorized to help offset QT-prolongation associated with HERG-blockade.
      1. I_{Kr} inhibition >> I_{Ca,L} inhibition9
b. Metabolite: Didesmethylcitalopram - DDCT
   i. Minor metabolite produced through CYP2D6 metabolism of major metabolite; <10% of steady-state citalopram metabolites in humans.10
   ii. Considered cardiotoxic10 and is theorized to be of concern in humans as its total amount increases (i.e. in overdose).
      1. A minimum cardiotoxic level has not been found.
   iii. Assays of DDCT plasma concentrations in 2020 humans showed that DDCT levels rarely exceeded 70nM; the highest measured level of DDCT in human overdose was 138nM.10
   iv. Percentage of metabolite is much higher in other animal species (e.g. beagle dogs-major metabolite)
1. In one study of PO citalopram, five out of nine dogs administered 8mg/kg (reportedly equivalent to a human dose of approximately 240mg/day) died suddenly between weeks 17 and 31 of treatment.10

2. In a second study of IV citalopram in beagle dogs, DDCT caused QT prolongation at doses producing peak DDCT levels of 810 to 3250nM (39-155 times the mean steady state DDCT levels measured at the maximum recommended human daily dose of 60mg).10

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B. Case reports involving citalopram and a finding of prolonged QTc12–23 – summary (see Appendix A)

a. Most cases of QTc-prolongation involved overdose ingestions of at least 400mg citalopram.

b. Cases involving QTc-prolongation despite only therapeutic doses occurred in the setting of electrolyte abnormalities, patient of advanced age with ESRD or suspected congenital LQTS.

c. QTc-prolongation can be delayed, with longest measured duration many times occurring 13-18 hours post-ingestion of high doses.

d. Most fatal cases reported (6/7) involved co-intoxication with other drugs.


a. Data-mining review of cases of drug-induced TdP present in the public version of the FDA Adverse Event Reporting System (AERS)

b. Methods: all reports of TdP from January 2004-December 2007 were retrieved from the AERS database and then associated with a primary suspect drug, secondary suspect drug or drug-interaction.

c. Results

   i. 1,301,839 records downloaded from AERS; 1665 reports of TdP retrieved with 376 active substances identified as suspected or interacting drugs.

   ii. Highest number of TdP reports: amiodarone (113), followed by methadone (83), levofloxacin (61), fluconazole (48), sotalol (46) and moxifloxacin (41).

   iii. Citalopram was the suspect or interacting drug in 12 cases. Other implicated antidepressants: fluoxetine (12), paroxetine (11) and mirtazapine (10).
d. Study strengths
   i. Database has raw data accessible to the public and independent researchers alike.
   ii. Database covers very large population: reports came not just from the USA (~33%) but also Europe (~50%) and Japan (13%).
   iii. Large databases are helpful when investigating a rare event like TdP.

e. Study limitations
   i. Citalopram was one of the most prescribed antidepressants during the evaluation time period.
   ii. Database drawbacks
      1. Lack of details useful to assess causal association
      2. Generalized underreporting bias
      3. Over-reporting for drugs involved in safety alerts or regulatory measures (notoriety bias)
      4. Dependence of reporting rate on the time on the market of each drug (the Weber effect)
      5. Quality of data (i.e. missing data, ‘extreme duplication’ and multiple records)
   iii. No literature support of TdP or unexpectedly high reports of TdP for certain drugs implicated in the review – digoxin, beta-blockers, donepezil, famotidine.


   a. Data mining review of cases of TdP reported to the Swedish pharmacovigilance database, SWEDIS (Swedish drug information system.)
      i. Other study aims: investigate if this ADR was included in the product labeling for the implicated drugs and investigate the prevalence of possible predisposing factors
   b. Methods
      i. SWEDIS was searched for all case reports of the ADR TdP from January 1, 1991 - February 1, 2006.
      ii. Information taken from each case: gender, age, year of incident, suspected drug(s), administration route, dose, treatment time, concomitant drugs, hypokalemia, heart disease and outcome for the patient
      iii. Risk factors studied: female gender, heart disease, hypokalemia, age > 65 years and concomitant drugs.
   c. Results
      i. 61,788 ADRs reported to SWEDIS, with 101 cases of suspected drug-induced TdP identified.
         1. 88 cases were included for review
         2. 13 cases were excluded due to involving a withdrawn drug (10) or involving drug intoxication (3).
      ii. Citalopram implicated in 9 cases; 5 cases involved citalopram as sole agent
      iii. Other implicated antidepressants: fluoxetine (2), amitriptyline, nortriptyline and paroxetine (1 each).
      iv. In addition to drug treatment, ≥2 risk factors were present in 85% (75/88) cases.
      v. Heart disease (79/88) was the most common risk factor, followed by age >65 years (63/88) and female gender (62/88).
   d. Study strengths
      i. Database has raw data accessible to the public and independent researchers alike.
      ii. Database was established in 1965.
      iii. Large databases are helpful when investigating a rare event like TdP.
   e. Study limitations
      i. Did not include hypomagnesemia as risk factor for evaluation
      ii. General database drawbacks (as above in Section c.v.2)
   a. Data mining review of citalopram intoxication cases in the database of the toxicologic laboratory (a 7-day, 24-hour toxicologic service) of the Central Hospital Pharmacy in The Hague, Netherlands.
   b. Methods
      i. All intentional citalopram intoxication cases with a known medical outcome from January 1997-December 2006 were included.
      ii. Information taken from each case: demographics, details of citalopram intoxication and clinical parameters for each patient
   c. Results
      i. QTc prolongation (>450 msec) occurred in 8/26 cases reviewed. No severe arrhythmias, including TdP, occurred.
         1. Reported ingested citalopram doses in these 8 cases ranged from 200-2700mg.
         2. Co-intoxicants were found in all cases, however none of the co-ingested drugs were agents known to prolong QTc.
         3. One fatality occurred: both citalopram and verapamil at toxic concentrations
      ii. Other cardiac effects noted in a few cases were tachycardia, bradycardia and AV block.
   d. Study strengths
      i. Toxicologic database that receives data about all toxicologic events from six area hospitals
      ii. Data gathered was extensive and provided for a more complete medical picture for each patient reviewed
   e. Study limitations
      i. Small sample size
      ii. All patients received activated charcoal after first blood sample taken, which may decrease drug absorption and possibly toxic effects.
      iii. Only cases with toxic citalopram level (200ng/mL) were included. Significant symptomatic intoxications with lower citalopram concentrations may have been missed.
      iv. General database drawbacks (as above in Section c.v.2)

   a. One prospective study in healthy volunteers – R/DB/PC study to assess intra-individual variability of the QTc interval, differences in QTc intervals at steady state on citalopram 60 mg/day versus placebo, and the relationship between QTc and levels of citalopram and its metabolites.
      i. Mean QTc intervals remained within the normal range for both citalopram- and placebo-treated patients throughout the study. (Figure 2)
      ii. No statistically significant difference in mean QTc intervals between the two groups at steady state (days 29, 30, 31) (p=0.46)
      iii. No relationship found between QTc intervals and plasma concentrations of DDCT.
b. Pool of three prospective studies in ill patients — 1) a 6-week PC comparison of citalopram doses of 10, 20, 40, and 60 mg/day in outpatients (aged 18-65 years, N=650) with moderate to severe depression; 2) an 8-week comparison of citalopram 40 mg/day and fluoxetine 20 mg/day in inpatients and outpatients (aged 18-65 years, N=316) with major depression, and 3) a 12-week PC comparison of fixed doses of citalopram (dose range, 5-40 mg/day) in elderly patients (aged 65-92 years, N = 494) with Alzheimer’s disease.
   i. 2,831 EKGs from 1,035 patients was collected at baseline and at each study end’s: 2,036 EKGs from 754 patients aged <60 years and 795 EKGs from 281 patients aged ≥60 years
   ii. QTc intervals >435 msec were relatively common at baseline and during treatment.
   iii. There were no differences between citalopram and placebo groups in the proportion of patients with QTc intervals >435 msec during treatment, regardless of age or baseline QTc
   iv. No relationship found between QTc and the citalopram doses used.

C. Retrospective analyses - All clinical trials conducted from 1978-1996 were assessed to identify any effects of citalopram on EKG parameters. Trials varied in design (both open and double-blind) with citalopram doses typically in the range of 20-60mg daily. Analyses focused on data from patients with baseline and at least one on-treatment EKG.
   i. 4,471 EKGs from 1,116 patients treated with citalopram for 1 week up to ≥1 year, and 381 EKGs from 118 patients treated with placebo for up to 8 weeks.
   ii. Mean QTc intervals in citalopram patients ranged between 400-425 msec at all time points. (Figure 3)
   iii. No differences between the groups at any time point up to 8 weeks of treatment. (Figure 3)
   iv. No differences in mean QTc intervals in citalopram-treated patients aged <60 years compared with patients aged ≥60 years. (Figure 3)
   v. There was a statistically significant ($p < 0.05$) decrease in heart rate (4-8 bpm) in citalopram-treated patients compared with placebo, regardless of age.

d. Conclusions
   i. No significant effects on PQ, QRS, or QTc intervals in any of the studies
   ii. Citalopram has no effect on cardiac conduction and repolarization during short- or long-term treatment with therapeutic doses.
   iii. The only effect on EKG parameters was a small reduction in heart rate.

e. Study strengths
   i. Data was pooled from multiple studies
   ii. Large sample size

f. Study limitations
   i. Potential bias - manufacturer sponsored all included studies
   ii. Details about design and methods for certain studies were not included
   iii. Multiple EKGs not collected and potential EKG confounders not addressed
Figure 3. Mean QTc intervals over time in patients treated with citalopram or placebo.

Figure 4. Simulated plasma concentrations (-----) and QT intervals (---) vs. time for a patient with typical PK and PD parameters after an overdose of 1200mg citalopram, without taking charcoal.


a. Development of a pharmacokinetic-pharmacodynamic (PKPD) modeling to describe the time-course of QT interval prolongation after citalopram overdose.

b. Overall conclusions – based on the modeling results
   i. QTc duration is linearly dependent on the predicted citalopram concentration (Figure 4)
   ii. Citalopram can cause delayed prolongation of QTc (Figure 4)
   iii. QTc duration is predicted to be higher in women than men and to increase with age
Regulatory actions regarding the potential QTc prolonging effects of drugs

A. Potential manufacturer actions
   a. Cessation of new molecular entity (NME) development
   b. Voluntary removal of approved drugs

B. Potential FDA actions
   a. Non-approval for NMEs
   b. Withdrawal of approved drugs
   c. Updated labeling for approved drugs

C. Historically (pre-2005), FDA and manufacturer actions were guided by post-marketing data of an association between an already-approved drug and its potential adverse cardiac effects.

D. Today, those actions are primarily guided by the results of thorough QT/QTc studies (TQTs) and often occur during NME development.
   a. History
         1. Implemented in the US, EU, but not yet in Japan.
         2. Must be performed for all NMEs
      ii. The US FDA’s Internal Review Team (IRT) (established 2007) is responsible for overseeing the clinical assessment of QT prolongation for all drugs reviewed.
         1. As of April 2009, IRT has reviewed 112 studies submitted to the agency.
         2. The FDA EKG Warehouse (established 2007) accepts all EKGs from TQTs.
      iii. Timing and methods of TQTs should be individualized and is left up to the drug sponsor.
   b. Aims
      i. Designed to identify drugs that may prolong QTc to determine if QTc should be assessed more carefully in clinical trials or in routine use of the drug
      ii. Does not establish the extent to which a drug is proarrhythmic or can cause TdP
   c. Timing of TQTs
      i. During pre-clinical safety assessments
         1. In vitro HERG K+ channel assays to determine inhibition
         2. In vivo evaluation of QTc in animals (dogs, non-human primates, etc)
      ii. During the latter part of Phase II, for drugs with negative results in pre-clinical assessments
      iii. Early on in clinical development for drugs in pharmacological class known to prolong QTc (e.g. fluoroquinolones)
      iv. During clinical development, but after clinical benefit has been established, if drug being developed for potentially-life threatening conditions
      v. During post-marketing upon FDA request
   d. Method of TQTs
      i. Cross-over vs. parallel design
      ii. Single dose vs. multiple doses
      iii. Positive control (generally moxifloxacin 400mg)
      iv. Placebo
      v. Subjects
         1. Balanced gender representation recommended
         2. Healthy volunteers (unless safety concern exists e.g. cytotoxic drugs)
vi. QTc measurements
   1. Fully or partially automated
   2. Fully manual or manually adjudicated
vii. Analysis of QTc measurements
   1. Analyses of central tendency (e.g. means, medians)
   2. Categorical analyses (e.g. absolute QT/QTc intervals or changes from baseline)
e. Thresholds
   i. A mean change of QTc of >5 msec is considered the official “threshold of regulatory concern.”
      1. < 5 msec: no concern
      2. 5-20 msec: inconclusive concern
      3. > 20 msec: significant concern
   ii. For manufacturers, QTc >500 msec or prolongation >60 msec over baseline are commonly used unofficial “thresholds of concern.”
E. The magnitude of QTc prolongation, with or without documented arrhythmias, first determines whether or not the FDA will take any action.
F. The extent of any actions/recommendations made will then depend on:
   a. Morbidity/mortality associated with the untreated condition and the clinical significance of any beneficial effects of the drug
   b. Demonstration of therapeutic benefits in patients who are refractory to, intolerant of, or not candidates for available treatments (use may be limited to such patients)
   c. Availability of therapeutic alternatives that are otherwise similar in efficacy but lack or have less QTc prolonging effects (terfenadine and astemizole examples)
      i. The risk–benefit assessment will involve comparing the new drug to other class members (grepafloxacin example)
   d. Existence of dose- or concentration-effect issues that could make dosing errors potentially dangerous
   e. Primary metabolic pathways of the drug: there is a risk of significantly elevated levels in poor metabolizers or when used with interacting drugs (terfenadine and citalopram examples).
      i. Genetic polymorphisms (e.g. CYP2D6, CYP2C19)
      ii. Inhibition by many drugs (e.g. CYP3A4)
   f. Susceptibility to drug–drug interactions at the level of transporter proteins
   g. Applicability and feasibility of any risk management options recommended

FDA actions throughout the years - summary (see Appendix B)

A. Drug withdrawal
   a. Seven drugs have been withdrawn from the US market due to poor risk/benefit ratio.
B. Patient and healthcare professional alerts with updated drug labeling to reflect new information
   a. Black box warnings (e.g. droperidol, thioridazine)
   b. Suggested risk management strategies, which vary widely between drugs
      i. Maximum recommended doses (e.g. citalopram, ondansetron)
      ii. Specified age restrictions (e.g. citalopram) vs. general “elderly” warnings (e.g. azithromycin, ondansetron)
      iii. PK/PD interactions, drug-drug contraindications
      iv. Frequency of EKG monitoring
Alert appropriate?

A. Remaining unknowns about the background of the safety alert
   a. Total number of post-marketing reports of QTc prolongation and TdP received by the FDA
   b. The TQTs remain unpublished
   c. Number of patients in study that reached “clinically significant” prolongation of >500msec
   d. Why age >60 years was chosen as the age cut-off for lower doses
      i. Literature has shown age >65 as a risk factor for QTc prolongation
      ii. FDA/ICH guidance document mentions age >65 as a “sub-group of particular interest”

B. What should be clinically significant?
   a. >20 msec change in mean QTc?
   b. >60 msec change in QTc from a patient’s baseline?
   c. >500 msec absolute QTc interval duration?

C. Sparse evidence supporting QTc prolongation at therapeutic doses
   a. Greater evidence showing QTc prolongation in cases of substantially supratherapeutic doses

D. Sparse evidence that doses >40mg have no added benefit in depression treatment
   a. Off label uses which have shown a dose-response relationship and can sometimes require higher doses
      (e.g. OCD) were not addressed.
   b. Off label use and risk management strategies during such use were addressed in the updated haloperidol labeling (IV administration), for example.

E. Based on current regulatory atmosphere, public alert may be appropriate.

F. Based on current evidence, changes in maximum recommended doses not appropriate.

Conclusions

A. The rare incidence of TdP has forced regulators to search for a marker that can be identified earlier in drug development before use in the general public. QTc prolongation has come to serve as that single regulatory biomarker of proarrhythmic risk.

B. Despite well-meaning efforts to identify potentially proarrhythmic drugs and warn the public and healthcare providers, regulatory actions on widely-used non-cardiac drugs like citalopram generally have the unintended consequences of decreasing drug use.

C. Citalopram is widely-regarded as a first line agent for the treatment of a variety of psychiatric disorders, due to minimal drug-drug interactions, long-half life which allows once-daily dosing and contributes to minimal discontinuation symptoms, demonstrated safety in elderly and medically fragile patients, low cost and relative effectiveness.

D. Changes in maximum recommended doses will limit the future utility of the medication.

E. Official labeling of citalopram as a QTc-prolonging drug may eventually contribute to increased reports of QTc-prolongation, TdP and SCD to the FDA and possibly contribute to future withdrawal of the drug, given the availability of therapeutic alternatives.
References

38. Haloperidol lactate package insert (June 2009). Available at
## Appendix A – Case reports of citalopram and QTc prolongation/TdP

<table>
<thead>
<tr>
<th>Authors</th>
<th>Case type</th>
<th>Reported, relevant facts</th>
<th>Reported citalopram dose/levels</th>
<th>Concomitant medications reported (Tox/RX)</th>
<th>QTc (msec)</th>
<th>Outcome</th>
<th>Author conclusions</th>
</tr>
</thead>
</table>
| 1. Ostrom et al (1996) | Overdose (suicide attempt) – 6 cases | • 2 males  
• 4 females  
• Ages: 23-56 YO  
• Hx of chronic pulmonary insufficiency in 1 case; hx of DM in 1 case; unknown in other cases | • Unknown in 2 cases  
• 840mg(?)-3920mg(?) in other 4 cases | Tox: Intoxicants in 5/6 cases (EtOH, diazepam, zopiclone, APAP)  
RX: not reported | Not reported | All fatal | • one possible cause of death is cardiac arrhythmias  
• seizures as cause of death cannot be ruled out  
• mentioned one report of QTc 504msec in 44 YOF after ingesting CIT 840mg  
• recommend the same precautions as TCAs when prescribing CIT |
| 2. Grundemar et al (1997) | Overdose (suicide attempt) – 5 cases | • 3 males  
• 2 females  
• Ages: 26-41 YO | 400(?)-5200mg | Tox: not reported  
RX: not reported | QTc prolonged in all patients | All non-fatal | • seizures and EKG changes characteristic of CIT overdose  
• generalized seizures, metabolic acidosis, hypokalemia, and EKG changes after severe CIT overdose might result in fatal cardiac arrhythmia |
| 3. Personne et al. (1997) | Overdose (poisonings) – 108 cases | 14-84 YO | 140-5200mg | Tox: not reported  
RX: not reported | EKG changes noted: widening of QRS complex, extraventricular beats, and changes in the ST-T region | All non-fatal | • Doses <600mg causes “mild” symptoms (N/V, drowsiness, tremor)  
• Doses >600mg resulted in EKG changes and seizures  
• Doses > 1900mg caused above symptoms in all patients  
• Clinically significant arrhythmias rare  
• SSRIs less toxic than TCAs |
| 4. Catalano et al (2001)<sup>15</sup> | Overdose (suicide attempt) | 21 YOF | Negative cardiac history | CMP WNL | 400mg | Tox: BDZ | RX: alprazolam 0.25mg (upon admission, pt had taken only one) | BAC: 121 mg/dL | 380 (1 hour post-ingestion) 438 (2 hrs) 450 (7 hrs) 457 (13 hrs) 393 (20 hrs) 353 (21 hrs) | Non-fatal | patient ingested <7x max daily dose (60mg) and developed QTc changes  
- do not recommend in patients with cardiac disease  
- delayed changes in QTc due to time required for metabolite to appear  
- margin of safety of CIT smaller than other SSRIs |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 5. Engebretsen et al (2002)<sup>16</sup> | Overdose (suicide attempt) | 31 YOM | Negative cardiac history | K+: 4.7 mmol/L | 400mg | Tox: negative | RX: not reported | BAC: Not done but pt consumed unknown amount of EtOH | 506 (13 hours post-ingestion) 495 (13.5 hours post-ingestion and NaHCO3 dose) | Non-fatal | <1 month supply of CIT can have potentially lethal effects  
- Should be used with caution in underlying cardiac disease or with other QT-prolonging meds |
| 6. Kanjanauthai et al (2007)<sup>17</sup> | Concomitant illness/elderly | 81 YOM | Hx of HTN, DM, ESRD(on dialysis) | CMP and Mg2+ WNL | Unknown, but started 4 months prior | Tox: not reported | RX: not reported | 695 (on admission), normalized by Day 3 | Non-fatal | 2 episodes of TdP  
- recommend EKG prior to starting CIT with periodic monitoring  
- caution in patients with renal impairment or taking other QT-prolonging meds |
| 7. Tarabar et al (2008)<sup>18</sup> | Overdose (suicide attempt) | 36 YOF | Hx of BN/AN and EtOH abuse | Mg2+: 2.5mg/dL  
K+: 3.1 mmol/L | 1000mg | Tox: negative | RX: unknown | 572-600 (2 days post-ingestion) 529 (24 hrs) 442 (48 hrs) | Non-fatal | 1 episode of TdP 2 days post-ingestion  
- cardiotoxic manifestation may be delayed  
- recommend prolonged observation with CIT-induced QT prolongation |
| 8. De Gregorio et al (2009)<sup>19</sup> | Concomitant illness/medications | 48 YOF | Hx of 5-day diarrhea  
K+: 2.1mEq/L  
Mg2+: 1.6mg/dL | 40mg daily | Tox: not reported | RX: furosemide 25mg daily | 670 (on admission), normalized by Day 5 | Non-fatal | 3 episodes of TdP within 24 hours of admission  
- recommend careful co-administration of diuretics and SSRIs  
- caution in diarrhea, dehydration, other brief illnesses |
<table>
<thead>
<tr>
<th>Case Study</th>
<th>Type</th>
<th>Age</th>
<th>Gender</th>
<th>EKG Findings</th>
<th>Blood Levels</th>
<th>Treatment</th>
<th>Outcome</th>
<th>Key Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liotier et al (2011)</td>
<td>Overdose (suicide attempt)</td>
<td>54 YOF</td>
<td>Unknown</td>
<td>Tox: negative</td>
<td>RX: zopiclone 7.5mg/day</td>
<td>BAC: 20mg/dL</td>
<td>Non-fatal</td>
<td>Clinicians prescribing SSRIs should screen patients with an EKG. Cardiotoxic manifestation may be delayed and longer monitoring may be warranted.</td>
</tr>
<tr>
<td>Unterecker et al (2012)</td>
<td>Overdose (suicide attempt)</td>
<td>46 YOF</td>
<td>Unknown</td>
<td>Tox: opipramol 500mg</td>
<td>RX: opipramol</td>
<td>BAC: 218 mg/dL</td>
<td>Non-fatal</td>
<td>Strong correlation between CIT level and QTc interval duration. Parallel overdose of TCA (opipramol) to lesser degree than CIT (2.5-fold vs. 35-fold max dose) but small contribution to EKG changes cannot be ruled out.</td>
</tr>
<tr>
<td>Lung et al (2012)</td>
<td>Overdose (suicide attempt)</td>
<td>24 YOF</td>
<td>Unknown</td>
<td>Tox: BUP unknown (estimated up to 13,500mg)</td>
<td>BUP level: 440ng/mL (admission blood)</td>
<td>Baseline EKG and routine monitoring.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Key:**
- CIT – citalopram
- BUP – bupropion
- BDZ – benzodiazepines
- BAC – blood alcohol content
- BN/AN – bulimia nervosa/anorexia nervosa

**Reported therapeutic levels:**
- CIT: up to 120ng/mL (Engebretsen 2002)
- CIT: 20-200ng/mL (Lung 2012)
- BUP: 25-100ng/mL (Lung 2012)
- DCT: 14-40ng/mL (Tarabar 2008)
## Appendix B – Examples of FDA actions in response to QTc-prolonging effects of various medications

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>Year</th>
<th>FDA Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terfenadine</td>
<td>Antihistamine</td>
<td>1998</td>
<td>Withdrawn due to substantial QTc prolongation (50-100msec) when used in combination with potent CYP 3A4 inhibitors, availability of alternative antihistamines and the clinical development of its active metabolite, fexofenadine.</td>
</tr>
<tr>
<td>Grepafloxacin</td>
<td>Antibacterial</td>
<td>1999</td>
<td>Withdrawn due to poor risk/benefit ratio and availability of alternative antibiotics</td>
</tr>
<tr>
<td>Astemizole</td>
<td>Antihistamine</td>
<td>1999</td>
<td>Withdrawn due to poor risk/benefit ratio and availability of alternative antihistamines</td>
</tr>
<tr>
<td>Cisapride</td>
<td>Gastroprokinetic</td>
<td>2000</td>
<td>Withdrawn due at least 341 reports of heart rhythm abnormalities, including 80 deaths. Still available for veterinary use.</td>
</tr>
<tr>
<td>Thioridazine</td>
<td>Antipsychotic</td>
<td>2000</td>
<td>Black box warning added due to case reports of QTc prolongation, TdP and SCD and the results of three published studies</td>
</tr>
<tr>
<td>Droperidol</td>
<td>Antiemetic/antipsychotic</td>
<td>2001</td>
<td>Black box warning added due to reports of QTc prolongation, TdP and SCD with doses above, within or even below the previously approved range. FDA listed age &gt;65 years as risk factor for prolongation.</td>
</tr>
<tr>
<td>Levacetylmethadol</td>
<td>Opiate agonist</td>
<td>2003</td>
<td>Withdrawn by manufacturer due to reports of severe cardiac-related adverse events, including QT interval prolongation, TdP and cardiac arrest. Alert regarding adverse effects first issued by FDA in 2001. Was also previously removed in Europe in 2001.</td>
</tr>
<tr>
<td>Mesoridazine</td>
<td>Antipsychotic</td>
<td>2004</td>
<td>Withdrawn in 2004. Black box warning initially added in 2000 due to the results of a published study of nine schizophrenic patients, all of whom experienced moderately prolonged QT at the highest tested dose of 300mg and also three published case reports of ventricular tachycardia in association with overdose.</td>
</tr>
<tr>
<td>Haloperidol (IV)</td>
<td>Antipsychotic</td>
<td>2007</td>
<td>Updated labeling due to 28 case reports of QTc prolongation and TdP following IV administration (off-label use), case-control studies of dose-dependent QTc prolongation and 2 TQTs requested by the Italian Pharmacovigilance department. Warnings reiterated that drug was NOT approved for IV use, however recommended frequent EKG monitoring if this route was used.</td>
</tr>
<tr>
<td>Saquinavir</td>
<td>Antiviral</td>
<td>2010</td>
<td>Updated labeling due to results of a TQTs funded by Roche Laboratories which investigated saquinavir “boosted” with ritonavir and found that the maximal mean increase in QTc was ~19 msec for the approved dose and ~30 msec for a supertherapeutic dose.</td>
</tr>
<tr>
<td>Azithromycin</td>
<td>Antibacterial</td>
<td>March 2012</td>
<td>Updated labeling based on the results of a JAMA study that compared the risks of cardiovascular death in patients treated with azithromycin, amoxicillin, ciprofloxacin, levofloxacin, and no antibacterial drug. Warnings were general and primarily prompted by the pharmacological class to which the drug belongs (macrolides).</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Antiemetic</td>
<td>June 2012</td>
<td>Updated labeling due to post-marketing reports and published medical literature describing QTc prolongation and TdP with the drug and also the results of a TQTs conducted at the request of the FDA.</td>
</tr>
</tbody>
</table>

** Sparfloxacin also withdrawn from the market.