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A review of citalopram dose restrictions in the treatment of neuropsychiatric disorders in older adults

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Abstract

Introduction: Neuropsychiatric disorders affect millions of older adults. Despite this, there are relatively few older adults included in clinical trials evaluating treatments for psychiatric disorders. Citalopram has been evaluated in older adults with neuropsychiatric disorders and has largely been found beneficial, making the 2011 US Food and Drug Administration (FDA) safety advisory on citalopram extremely impactful.

Methods: A literature search was completed using the PubMed database. Results were limited to clinical trials conducted in older adults that were published in English.

Results: Review of the literature confirms the efficacy of citalopram in depression, anxiety, depression associated with Parkinson disease, and behavioral and psychological symptoms of dementia. Additionally, no adverse cardiac outcomes have been described related to citalopram.

Discussion: The FDA's evidence for applying this safety advisory to citalopram is minimal and largely based on surrogate markers, such as the QTc interval rather than clinical and safety outcomes. Citalopram is known to increase the QTc, but this increase has not been linked to adverse cardiac outcomes. The evidence for efficacy and against adverse outcomes suggests that a reevaluation of the dosing restrictions in older adults with neuropsychiatric disorders is needed.

Keywords: citalopram, neuropsychiatric disorders, safety, depression, anxiety, behavioral and psychological symptoms of dementia (BPSD), Food and Drug Administration (FDA)

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Introduction

Neuropsychiatric disorders such as depression, anxiety, and behavioral and psychological symptoms of dementia (BPSD) affect millions of older adults,[1] and most current

treatments have limited evidence supporting their use in this population. Citalopram represents a reasonably well-tolerated therapeutic option for many neuropsychiatric disorders. Originally indicated for depression, citalopram has a relatively good evidence base for a wide array of disease states.

In 2011, the US Food and Drug Administration (FDA)[2] issued a drug safety warning for citalopram that included a recommendation for a maximum daily dose of 20 mg in patients over the age of 60 years. This was in response to new information regarding a dose-dependent increase in the QTc interval. Citalopram use in older adults declined precipitously after the FDA warning,[3,4] which likely means many older adults are receiving medications with suboptimal evidence for the treatment of their neuropsychiatric disorders. This narrative review will evaluate the risk-benefit balance of using citalopram in geriatric patients with depression, anxiety, BPSD and depression in Parkinson disease (PD).

Methods

A literature search was conducted in the PubMed MEDLINE database. PubMed results were limited to human studies published in the English language. All relevant literature, regardless of publication date, was selected for review. Medical subject heading (MeSH) terms used in the search were *citalopram*, *aged*, *aged 80 and over*, *anxiety*, *depression*, *Parkinson Disease*, and *dementia*. Keywords and MeSH terms related to QTc prolongation and medication safety were also used.

Results

Depression

Citalopram, when used as monotherapy[5-7] or in combination with methylphenidate,[8,9] has demonstrated an improvement in multiple measures in depressed older adults. Raffaele and colleagues demonstrated a 60% reduction (baseline 32.5, final 13.0, $P < .001$) in Hamilton Depression Rating Scale (HAM-D) after 28 days of citalopram therapy at 40 mg/d with no major adverse reactions noted (age range 60 to 79, mean 63.8 years).[5] In an evaluation comparing sertraline 50 mg/d and citalopram 20 mg/d for their effects on several markers of depressive symptoms, the 2 medications performed equally well.[6] The citalopram 12-month data showed a 55% reduction ($P < .001$) in the HAM-D and a 42% reduction in the Geriatric Depression Scale compared to baseline (similar results to sertraline). In addition, 53% of subjects in the citalopram group reached remission by the end of the study period (vs 42% for sertraline use). Citalopram's impact on cognition was also evaluated. The Trail Making Test (more commonly known as TMT), Mini-Mental State Examination (MMSE), Weschler Memory Scale (WMS), and verbal fluency tests all showed improvement in the group treated with citalopram compared to baseline (all P values $<.05$, all similar to sertraline). A more recent subanalysis of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial confirmed citalopram's efficacy in patients aged 65 and over.[7] This analysis further demonstrated improvements in the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), the Work and Social Adjustment Scale (WSAS), and the mental component scale of the Medical Outcomes Study Short Form (SF-12 MCS), highlighting citalopram's ability to positively impact multiple aspects of depression management in older adults. Of note, none of the studies above excluded subjects specifically for existing cardiac abnormalities.

Citalopram has been studied in combination with methylphenidate in older adults.[8,9] A small 10-week pilot study (mean age 78.1 years) showed a significant reduction in HAM-D scores compared to baseline ($P < .0001$), but the lack of a placebo comparator or citalopram monotherapy group limits the applicability regarding citalopram efficacy.[8] However, the participants received a mean citalopram dose of 27.5 mg/d with no cardiac adverse effects noted. A larger, more recent study evaluated citalopram (mean dose 32 mg/d), methylphenidate, or the combination for improvement in various scales related to depression management (mean age 69.7 years).[9] The combination of citalopram and methylphenidate was superior to either drug alone for reducing the HAM-D score, and the combination also improved remission rates significantly ($P = .003$). Additionally, citalopram monotherapy and combination therapy resulted in improved language, while only citalopram monotherapy showed improved attention when compared with baseline. The majority of the 2508 patients receiving citalopram for depression in these studies were given doses greater than 20 mg/d, with none of the studies reporting any cardiac-related adverse effects from the intervention. The latter study excluded subjects who had an existing atrial or ventricular arrhythmias, while the former had no cardiac-related exclusion criteria.

Depression in PD

Research has suggested that the pathophysiology of depression in PD is different[10-13] and thus, specific guidelines exist (recently retired) to treat this patient population.[14] Citalopram has been evaluated in several studies[15-18] of patients with PD and depression (Table 1). The study[15] with the longest duration (4 months) demonstrated improvements in HAM-D and Beck Depression Inventory (BDI) scores at 1 month and 4 months of treatment ($P < .05$). These findings were subsequently

TABLE 1: Citalopram use for depression in Parkinson Disease

Study	No. Subjects	Citalopram Trial Dosing, mg/d	Comparator	Study Length	Outcomes
Rampello et al[15] (2002)	46	10, titrated to 20	Placebo	4 mo	Subjects with baseline depression showed improved HAM-D and BDI scores at 1 and 4 mo with CIT
Menza et al[16] (2004)	10	10, titrated up as needed (mean 10.9, range 10 to 40)	None	8 wk	Reduction in HAM-D scores from 24.2 to 14.9 at wk 8 and 50% of subjects experienced a 50% reduction or more in HAM-D
Devos et al[17] (2008)	48	20	Placebo DES 75 mg by mouth daily	30 d	Both CIT and DES improved Montgomery Asberg Depression Rating Scale scores after 30 d of therapy
Wermuth et al[18] (1998)	37	Age <65 = mean 23.2 Age ≥65 = mean 14.8	Placebo	6 wk	CIT improved HAM-D scores compared to baseline, but not compared to placebo

BDI = Beck Depression Inventory; CIT = citalopram; DES = desipramine; HAM-D = Hamilton Depression Rating Scale.

corroborated by 2 additional studies.[16,17] The dose of citalopram varied among studies, with the majority of subjects taking 20 mg/d. A study[18] using a lower dose showed a modest impact on depression for subjects aged 65 and over.

Historically, a major concern regarding the use of SSRI therapy in PD is the potential for motor symptom worsening. Thwaites and colleagues[19] reported a single case of neurotoxicity and severe extrapyramidal symptoms likely due to citalopram initiation. However, earlier data from a small Italian patient population with PD[20] did not indicate an increased risk with several SSRIs, including citalopram, and Rampello and colleagues[15] demonstrated an improvement in bradykinesia in patients with PD taking citalopram to treat depression.

Anxiety

Prevalence of generalized anxiety disorder in community-dwelling elders is estimated to be as high as 7.3%.[21,22] A small, blinded, 8-week pilot study in older adults (mean age 70.7 years) demonstrated a 65% response rate to citalopram use (dose range 20 to 30 mg/d) as indicated by a 50% reduction in the baseline Hamilton Rating Scale for Anxiety score.[23] Side effects were similar between citalopram and placebo with no cardiac-related adverse events reported. These data were validated by another small study of older adults (mean age 69 years) with anxiety disorders, where a similar number of participants demonstrated a beneficial response to the medication (mean dose 21.8 mg/d, range 10 to 40 mg/d).[24] The subjects who responded to citalopram also demonstrated significant improvements in an instrument subscale measuring social functioning, vitality, and general mental health, as well as in the Pittsburgh Sleep Quality Index (all P values $<.05$). Again, no cardiac-related adverse events were reported, and neither study excluded patients based on existing cardiac abnormalities.

Behavioral and Psychological Symptoms of Dementia

Treatment options for behavioral and psychological symptoms of dementia (BPSD; eg antipsychotics) have modest evidence for efficacy and have significant limitations, including the propensity to increase metabolic disorders, falls, drug interactions, and mortality.[25-28] Citalopram has been studied in several capacities[29-35] regarding its potential to manage multiple manifestations of BPSD (Table 2). The exact mechanism of how citalopram is efficacious for BPSD is largely unknown; however, it is likely not owed completely to sedation.[29]

In placebo-controlled studies,[30-32,34,36] citalopram demonstrated reductions in various BPSD-related outcomes despite relatively short study duration and smaller numbers of included subjects. The most prominent of these trials was the Citalopram for Agitation in Alzheimer Disease (CitAD) trial,[31] which demonstrated significant improvement in several key measures of agitation with a target citalopram dose of 30 mg/d. Post-hoc analyses of these patients showed significant reductions in delusion, anxiety, and irritability/lability subscores of the Neuropsychiatric Inventory (NPI).[32,36] Nyth and colleagues[34] previously reported improvements in mood, irritability, anxiety, and restlessness with citalopram treatment in patients with Alzheimer dementia. Siddique and colleagues[30] reported an approximate 50% reduction in the irritability and apathy subscores of the NPI with citalopram treatment. The vast majority of individuals in each of these trials received the maximum older adult dose of 20 mg/d, but it should be noted some patients were receiving up to 80 mg/d.

TABLE 2: Citalopram use in behavioral and psychological symptoms of dementia (BPSD)

Study	No. Subjects	Citalopram Trial Dosing, mg/d	Comparator	Study Length	Outcomes
Siddique et al[30] (2009)	34	Median dose = 30 (Range 10 to 80)	Placebo	Range 14-306 d	41% to 60% reduction in NPI irritability and apathy subscores
Porsteinsson et al[31] (2014) CitAD Trial	186	10, titrated to 30	Placebo	9 wk	Improved agitation scores with CIT vs placebo (several agitation scales, all $P < .05$)
Leonpacher et al[32] (2016) CitAD Trial subanalysis	186	10, titrated to 30	Placebo	9 wk	Improved delusion, anxiety, and irritability/lability subscores of NPI (all $P < .05$)
Pollock et al[33] (2002)	85	10, titrated to 20	Placebo, PER	17 d	Improved NBRS scores vs baseline Superior NBRS scores vs placebo ($P < .002$), but not vs PER ($P = .14$)
Nyth et al[34] (1990)	91	10, titrated to 20 to 30	Placebo	16 wk	Improved GBS for mood, confusion, anxiety, fear-panic, restlessness, and irritability
Pollock et al[35] (2007)	103	10, titrated to 20 or 40 Mean dose = 29.4	RISP 1-2 mg by mouth daily Mean dose = 1.25 mg/d	12 wk	Improved agitation scores with CIT vs placebo ($P = .05$) but not with RISP vs placebo ($P = .3$) Psychosis scores improved with both CIT and RISP vs baseline More adverse drug events with RISP

CIT = citalopram; GBS = Gottfries-Brane-Steen geriatric rating scale; NBRS = neurobehavioral rating scale; NPI = Neuropsychiatric inventory; PER = perphenazine; RISP = risperidone.

Citalopram has also been evaluated in active comparator studies.[33,35] When citalopram was compared to both risperidone and placebo in a randomized, controlled study, both active comparator groups achieved significant reductions in the psychosis subscale of the Neurobehavioral Rating Scale (NBRS). However, only citalopram significantly impacted the agitation subscale of this instrument. More adverse events were reported in the risperidone group than either the citalopram or placebo groups.[35]

Many patients in these clinical trials[30-36] received a dose of citalopram higher than the 20 mg/d recommended by the FDA. Given this, one might expect cardiac adverse events to be seen at a higher frequency than those receiving placebo. This was not the case. One patient did experience ECG changes that were determined to be from digoxin toxicity and resolved following digoxin dose adjustments.[34] Other reported adverse effects were minimal, and the vast majority of those reported were non-cardiac adverse effects already known to occur with the use of SSRIs, such as nausea, headache, and insomnia.[30-32,34-36]

QTc Prolongation and Citalopram Safety

Citalopram is known to increase the QTc interval.[37] A meta-analysis of SSRI use and QTc prolongation confirmed that citalopram is more likely to increase the QTc interval than other SSRIs.[38] This meta-analysis did not evaluate the impact of citalopram on any negative clinical outcomes associated with the increase. The FDA warning recommending the maximum dose of 20 mg in older adults was based solely on the dose-dependent QTc increase seen with the agent. QTc data in the FDA's original drug safety warning showed an approximate 4 ms difference between 20 mg/d (8.5 ms; 95% confidence interval [CI], 6.2 to 10.8) and 40 mg/d (12.6 ms; 95% CI, 10.9 to 14.3). However, this data does not provide any information regarding the clinical impact of this QTc interval increase. A subanalysis of the CitAD trial confirmed citalopram's propensity to increase the QTc interval, but only 1 patient in the citalopram group experienced a rhythm abnormality, and there was no cardiac-related mortality in either the citalopram or placebo groups.[39]

Since the release of the safety announcement in August 2011, several analyses have evaluated citalopram's clinical outcomes related to QTc prolongation. One population-based retrospective cohort study[40] determined that citalopram increased the risk of hospitalization, compared with sertraline or paroxetine, because of ventricular arrhythmias in the first 90 days after medication initiation (relative risk 1.53; 95% CI, 1.03 to 2.29). However, the clinical significance of this finding is questionable given that the absolute increase observed was 0.06% versus 0.04%. This would represent 2 additional hospitalizations because of ventricular arrhythmias for every 10 000

patients initiated on citalopram. A retrospective cohort study[41] failed to show an increased risk of out-of-hospital sudden cardiac death with citalopram when compared with fluoxetine (hazard ratio [HR] 1.24; 95% CI, 0.75 to 2.05), paroxetine (HR 0.75; 95% CI, 0.45 to 1.24), escitalopram (HR 0.84; 95% CI, 0.40 to 1.75), and sertraline (HR 1.53; 95% CI, 0.91 to 2.55) of equivalent doses, including high-risk patient groups such as those over 60 years or with high cardiovascular risk. Additionally, a large Veterans Health Administration (VHA) cohort study[42] demonstrated that citalopram doses of >40 mg/d resulted in *fewer* ventricular arrhythmias (Adj HR 0.68; 95% CI, 0.61 to 0.76), *reduced* all-cause mortality (Adj HR 0.94; 95% CI, 0.90 to 0.99), and *reduced* noncardiac mortality (Adj HR 0.80; 95% CI, 0.74 to 0.86) than other dosing ranges for the drug, with 1 to 21 mg/d having the highest risk. Further data in VHA patients demonstrated a significant increase in all-cause hospitalization or death (Adj HR 4.5; 95% CI, 4.1 to 5.0) after dose reductions due to the medication safety advisory.[4] These same patients also experienced an increase in hospitalizations for depression or all-cause death (Adj HR 2.2; 95% CI, 1.0 to 1.7).

A review of case reports related to citalopram-induced QTc prolongation or torsades de pointes found 18 total cases with two-thirds occurring in patients <60 years of age. Eight of the cases involved daily doses higher than 20 mg/d. An additional 7 cases involved an overdose.[43] These data demonstrate that arrhythmias related to citalopram use occur infrequently and the criteria set forth for using caution (age >60, dose >20 mg/d) do not appear to match with observed outcomes.

Discussion

Citalopram continues to have a role in the treatment of neuropsychiatric disorders in older adults. Established and emerging data confirm its efficacy related to depression, anxiety, BPSD, and depression in PD. It is a well-tolerated SSRI with few drug interactions, and prior to the 2011 FDA warnings, was a mainstay of therapy in these disorders. The major limiting factor for its use has been that FDA-issued medication safety warning related to citalopram's propensity to prolong the QTc. This warning was met with much controversy given the lack of clinical outcomes at the time of the advisory statement. The available data since the 2011 warning point to a lack of negative clinical outcomes related to citalopram use, including doses higher than currently recommended by the FDA. In some cases, dose reductions resulted in *increased* negative effects.[42]

A QTc interval of >500 ms is considered to be a risk factor for arrhythmia.[44] The FDA's warning also recommends discontinuing citalopram when the QTc reaches 500 ms. Given that citalopram has been demonstrated to increase the QTc 12.6 ms at 40 mg/d and most healthy adults have a QTc <440 ms, the chances of the average older adult reaching this highest risk group through citalopram alone are small, even at doses higher than recommended. Truly, this supports a more patient-specific approach to evaluating the risks and benefits of citalopram therapy and may increase the number of patients who can be safely treated with the medication. Support exists for monitoring the electrocardiogram in patients with pre-existing cardiac risk factors prior to initiating other medications known to prolong the QTc interval,[44] which could also be a reasonable approach for citalopram.

Citalopram use has declined since the medication safety advisory announcement.[3,4] Citalopram has documented efficacy in several difficult-to-treat geriatric neuropsychiatric disorders. Additionally, treatments for these disease states are limited, as other options are associated with their own FDA boxed warnings and potential for significant adverse effects. The QTc prolongation by citalopram has not been associated with increased adverse cardiac outcomes. The FDA's safety concern from a surrogate marker (QTc interval) has resulted in an effective treatment option for elderly patients being restricted. The current evidence demands another evaluation of this valuable medication by the FDA and prescribers caring for these patients in light of the clinical outcomes reported since the FDA warning.

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