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Role of citalopram in the treatment of agitation in Alzheimer's disease

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SUMMARY

Neuropsychiatric symptoms (NPS) are common among individuals with Alzheimer's disease (AD), associated with excess morbidity and mortality, greater healthcare use, earlier institutionalization, and caregiver burden. Agitation presents as emotional distress, excessive psychomotor activity, aggressive behaviors, disruptive irritability and dishibition. There is an unmet need to find pharmacologic treatment for agitation in patients with AD that can be safely and effectively used as a concurrent treatment alongside psychosocial interventions. A recent, multicenter, randomized, placebo-controlled trial explored the efficacy of a 30-mg daily dose of citalopram for agitation in patients with AD and showed a significant decrease in agitation for citalopram compared with placebo. Both QTc prolongation and cognitive worsening, as measured by the Mini Mental State Examination, were observed in the citalopram group and present a concern to clinicians. Citalopram at a 20-mg daily dose should be considered as a possible first-line treatment in addition to psychosocial intervention.

Keywords

agitation; Alzheimer's disease; antidepressants; citalopram; neuropsychiatric symptoms; selective serotonin reuptake inhibitors; treatment

Background

Individuals with Alzheimer's disease (AD) often experience neuropsychiatric symptoms (NPS) in addition to cognitive and functional impairment. These symptoms are also referred

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to as behavioral and psychological symptoms of dementia (BPSD) and include depression, anxiety, apathy, delusions, hallucinations, agitation and aggression [1]. NPS are highly prevalent, often persistent and are associated with excess morbidity, mortality, increased healthcare use, earlier nursing home placement, greater caregiver distress, depression and difficulty with employment [2]. Specifically, studies have shown that potentially reversible psychiatric symptoms, such as depression and agitation, are significant predictors of institutionalization, suggesting that treatment interventions could delay or prevent nursing home placement [3]. Agitation is one of the most common and costly neuropsychiatric symptoms and negatively affects patients with AD during all stages of their disease, creating excess disability. Agitation lacks commonly accepted consensus definition but presents as emotional distress, excessive psychomotor activity, aggressive behaviors, disruptive irritability and disinhibition [4]. Despite modest benefits and associated side effect burden, antipsychotics have historically been the treatment of choice for agitation in Alzheimer's disease. Risks associated with antipsychotic use range from weight gain and drowsiness to increased cerebrovascular events and mortality rate in the elderly [5], which has led to black box warnings and focused efforts to limit their use in older adults. The US FDA has not yet approved any medication for treating NPS, causing nonpharmacologic methods to become the new first-line treatment [6]. They can be targeted towards the patient, caregiver or both. These treatments include psychosocial interventions, often grounded in the presupposition of a "heightened vulnerability to the environment as cognitive ability declines" [2]. Psychosocial interventions focus on the latent cause of behavior and educating the caregiver on the understanding and prevention of agitated or aggressive behavior [2]. Due to practical obstacles such as lack of training and time constraints, clinicians are often unable to effectively use non-pharmacologic treatments [2]. Additionally, individuals diagnosed with Alzheimer's dementia often show limited or partial improvement with these interventions alone [7,8], leaving clinicians with little choice but to treat unremitting agitation with off-label psychotropic medications (i.e., atypical antipsychotics) despite their FDA black box warning [9]. There is an unmet need to find a safe and effective pharmacologic treatment for agitation in patients with AD that can be successfully used as a concurrent treatment alongside psychosocial interventions.

The neuropsychiatric symptoms of Alzheimer's disease are associated with a combination of serotonergic, noradrenergic, cholinergic and dopaminergic neurotransmitter system dysfunction. It is hypothesized that agitation in AD is caused by disruption in the afferent brain monoamine system, specifically the gradual erosion and eventual destruction of ascending serotonergic pathways by disease-associated neurodegeneration, leading to an imbalance in the serotonergic–dopaminergic axis. Consequently, research has focused on manipulating both the dopaminergic and serotonergic system in order to successfully treat agitation. In contrast to both atypical antipsychotics that target mainly dopaminergic pathways and tricyclic antidepressants with anticholinergic properties that have significant side effects, selective serotonin reuptake inhibitors (SSRIs) target serotonergic neurotransmission and appear better tolerated [1]. Studies involving individuals diagnosed with various dementia types have shown good tolerability with SSRIs, illustrated by comparable withdrawal rates due to adverse events between active drug and placebo groups [8]. A study comparing risperidone to the SSRI citalopram in patients with dementia-related

agitation illustrates this well and found that while both groups had a similar reduction in agitation, risperidone was associated with a significant amount of side effect burden [10]. More recently, a small, randomized study comparing risperidone to escitalopram found that while both inter ventions reduced agitation, escitalopram was better tolerated [11]. SSRIs such as citalopram offer an alternative treatment to atypical antipsychotics where the side effect profiles offset the potential benefits.

Citalopram for Agitation in Alzheimer's Disease Study

In a recent multicenter, randomized, placebo-controlled, double-blind, parallel group clinical trial, the efficacy of a 30-mg daily dose of citalopram for agitation in patients with Alzheimer's disease without major depression was compared with placebo. The Citalopram for Agitation in Alzheimer's Disease Study (CitAD) study also measured safety and tolerability of the active treatment, as well as its effect on caregiver distress. The primary results, details of methodology and statistical analysis have been presented elsewhere [4]. The study enrolled 186 participants diagnosed with probable Alzheimer's disease by National Institute of Neurological and Communication Disorders and Stroke-Alzheimer's Disease and Related Disorders Association criteria [12] (Mini Mental State Examination [MMSE] score between 5 and 28 points) that experienced clinically significant agitation. Medications for the treatment of AD (cholinesterase inhibitors and memantine) at stable doses within the month preceding randomization were allowed. Withdrawal of psychotropic medications other than predefined rescue medications was required. Subjects were allocated in a 1:1 ratio to receive a 30-mg daily dose of citalopram (titrated up from 10 mg over 3 weeks, as indicated and tolerated) or placebo in addition to psychosocial treatment over a 9-week time period. The psychosocial treatment included a 20–30-min counseling session at each study visit, provision of education materials and 24-h crisis availability.

Outcomes

The CitAD study had multifaceted results. On one hand, there was a statistically significant and clinically apparent reduction in agitation in the citalopram group over the placebo group on both primary outcome measures, the Neurobehavioral Rating Scale agitation subscale (NBRS-A; the raw NBRS-A scores [unadjusted mean] for the citalopram group were 4.1 [SD: 3.0] and for the placebo group were 5.4 [SD: 3.2; crude difference: 1.3; 95% CI: 2.6–3.5; $p = 0.01$]) and modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (mADCS-CGIC), which showed that 40% of participants receiving the medication were rated as much or very much improved compared with 26% in the placebo group, with an estimated treatment effect from the proportional odds model including participants with week-9 data (odds ratio [OR] of being at or better than a given CGIC category) of 2.13 (95% CI: 1.23–3.69; $p = 0.007$). The Cohen–Mansfield Agitation Inventory (CMAI) and Neuropsychiatric Inventory (NPI) total score supported this finding and also revealed an improvement in caregiver distress; all statistically significant in favor of citalopram [4]. Citalopram was associated with known SSRI-mediated side effects that were predominantly mild to moderate in severity, illustrated by high completion rates (90%) where approximately 80% remained on treatment; percentages that were similar in the active and placebo group. On the other hand, MMSE results unexpectedly revealed a modest but

statistically significant cognitive decline in the citalopram group compared with placebo (−1.05 points; 95% CI: −1.97 to −0.13; p = 0.03), although this was not considered to reach clinical significance (MMSE Minimal Clinically Important Difference [MCID] is a 1.4-point change by estimates of one group of experts [13]). The citalopram group showed an anticipated change from a baseline mean score of 17.00 to 16.83 at week 9. Conversely, the placebo group showed an unexpected and notable increase from 14.4 to 15.33. These results may potentially be explained by a baseline difference between the two groups and a subsequent drift towards the mean for both groups as there is currently neither scientific nor clinical evidence supporting the association between citalopram and cognitive worsening. This decline in MMSE scores should, however, remain a consideration for clinicians prescribing citalopram in patients with dementia until more research is conducted.

Prolongation of the QTc interval at the 30-mg dose was demonstrated on ECG (mean elongation: 18.1 ms; 95% CI: 6.1–30.1; p = 0.004), and was consistent with the recent FDA-required change to the label for citalopram, warning against its use at doses above 20 mg daily in patients older than 60 years of age. This prolongation of the QTc interval observed in the 30-mg citalopram group is concerning and should be carefully considered by clinicians when prescribing higher doses of citalopram in older adults. A recent retrospective study researching the association between cardiac outcomes and citalopram use was unable to establish a relationship; instead higher doses were associated with fewer cardiac events [14], bringing the validity of this concern into question. The prospective findings in the CitAD study do validate the FDA warning and higher doses of citalopram should be used with caution.

Treatment for AD patients with agitation

The optimal approach to treating agitation in Alzheimer’s disease requires assessing the individual patient’s circumstances, including symptom severity, value of improvement, cognitive function and change, cardiac conduction, vulnerability to adverse effects, and effectiveness of behavioral interventions. Psychosocial interventions may have a positive impact on both the patient and the caregiver, and are considered first-line therapy. There is a wide variety of proposed nonpharmacologic treatments including music therapy, dog therapy and bright light therapy, but the more conservative ideas such as concentrating on distraction, exercise, individualized outlets for pent up energy and avoidance of behavioral triggers, along with the provision of support and education to the caregiver, are most promising. While understanding that response to interventions is unpredictable, a meta-analysis of various psychological approaches found that behavior management therapies and specific types of caregiver and residential care staff education had the most lasting benefits for the management of NPS in dementia patients in comparison to music therapy and sensory stimulation, which have positive but short-lived effects [15]. For the patients that do not adequately respond to nonpharmacologic interventions, a judicious pharmacologic intervention is indicated.

It is likely that the CitAD study will impact practice in the field. Improvement over the course of the trial as measured by mADCS-CGIC was superior in CitAD [4], and was similar to that of antipsychotic drugs in other trials when measured by total NPI scores [11].

Adverse events were generally modest and consistent with known SSRI-mediated adverse events (increases in gastrointestinal complaints, respiratory tract infections and falls), except there was no weight loss or hyponatremia seen. Therefore, favorable tolerability and efficacy make citalopram a good therapeutic choice for clinicians treating agitation in AD. It will not, however, work for all patients, as agitation is such a heterogeneous symptom. Both benefits and side effects indicate that a starting dose of 10 mg daily with an increase to 20 mg daily after 1 week is a good first option, even as more data are gathered to establish efficacy at lower doses. Based on the QT interval prolongation associated with citalopram, a history of prolonged QT syndrome, recent history of electrolyte imbalance and concurrent medications known to meaningfully prolong the QT interval should be considerations before prescribing the medication. Neither clinical data nor the FDA warning suggest that ECGs or electrolyte panels are necessary before using a maximum dose of 20 mg of citalopram daily in older adults. The 30-mg daily dose cannot be generally recommended in view of the FDA warning and as a result of the clinical concerns raised in the CitAD study associated with the cognitive worsening and the QT interval prolongation. In the CitAD study, where the target dose was 30 mg daily, electrolyte panels including magnesium as well as a baseline ECG and a repeat ECG once the 30-mg dose was reached was standard practice. In resistant cases, where agitation is unresponsive to other treatments, clinicians may suggest using this higher dose. In some circumstances, faced with limited alternatives, families may choose to use the higher dose if it is likely to be beneficial despite the possible QT prolongation, particularly if ECGs and electrolyte panels can be used to monitor the risk.

Future perspective

Considering the FDA warning and the side effects associated with a 30-mg dose of citalopram, it would be beneficial for the field to explore the safety, tolerability and efficacy of a 20-mg daily dose of citalopram. The number of participants in the CitAD trial receiving 20 mg of citalopram was too small (n = 12) to establish that patients would receive the same benefits without the side effect burden. A study with a larger sample of participants receiving 20 mg of citalopram would provide more information about the efficacy of the medication at lower doses and provide an opportunity for the finding of cognitive decline to be replicated.

Furthermore, recent studies have indicated that serotonin signaling, including through administration of citalopram, has a positive effect on beta amyloid burden, one of the key physiologic features of Alzheimer’s disease [16,17]. Promising results were seen in transgenic mice. In older plaque-bearing mice, citalopram arrested the growth of pre-existing plaques and reduced the appearance of new plaques by 77%. Existing plaques did not regress. A 50% decrease in brain plaque load was observed in young, non-plaque-bearing mice receiving chronic treatment with citalopram. Research has transitioned to investigating the effect citalopram has on Abeta in humans. Researchers compared amyloid load of older, cognitively normal participants recruited by PET imaging, who have a history of anti-depressant use, mainly SSRIs (including the use of citalopram) to those who did not, and found that those who have used antidepressant medication had a significantly lower amyloid load as measured by PET with Pittsburgh compound B (a radioligand that binds to amyloid plaques) [16]. Similarly, in a study by the same group conducted in healthy adults

(age 18–50 years), citalopram slowed Abeta production by 37% and decreased Abeta concentration by 38% in cerebrospinal fluid when compared with placebo [17]. Despite certain limitations, these results reveal a potentially broader biological and clinical impact that citalopram might have in patients at risk for or diagnosed with Alzheimer's disease. If the findings are successfully replicated, citalopram can be considered for preventative use in a large number of patients to reduce beta amyloid in addition to its role in treating agitation.

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Practice points

- Individuals diagnosed with Alzheimer's disease often experience neuropsychiatric symptoms in addition to cognitive impairment.
- Agitation is common among individuals with Alzheimer's disease and is associated with earlier institutionalization, excess morbidity and mortality, greater healthcare use and caregiver burden.
- In a multicenter, randomized, placebo-controlled trial, the efficacy of a 30-mg daily dose of citalopram for agitation in patients with Alzheimer's disease was compared with placebo.
- Results showed a significant decrease in agitation in the citalopram group compared with placebo.
- QTc prolongation and cognitive worsening, as measured by the Mini Mental State Examination, was observed in the citalopram group and is a concern to clinicians.
- Citalopram at a 20-mg dose may be a good first-line treatment in addition to psychosocial intervention.