Alzheimer’s disease: effect of citalopram on agitation

A US and Canadian randomised, placebo-controlled trial found that citalopram 30 mg daily reduced agitation in people with Alzheimer’s disease who were receiving a psychosocial intervention. However, citalopram 30 mg daily worsened cognition and was associated with adverse cardiac effects (an increase in QT-interval). This study provides no reason to depart from the recommendations for managing behavioural and psychological symptoms of dementia in the NICE/SCIE guideline and the Alzheimer’s Society’s best practice guide, which recommend non-pharmacological treatment initially for most people.

Overview and current advice

Managing behavioural and psychological symptoms in people with dementia is challenging. However, several resources discuss management in this area and, in particular, the use of non-pharmacological rather than pharmacological interventions.

The NICE/SCIE guideline Dementia: supporting people with dementia and their carers in health and social care advises that people with dementia who develop non-cognitive symptoms that cause them significant distress or who develop behaviour that challenges should be offered an early assessment to establish the likely factors that may generate, aggravate or improve such behaviour. Non-pharmacological interventions tailored to the individual person's preferences, skills and abilities are recommended initially for most people; with pharmacological interventions only recommended if people have severe non-cognitive symptoms (psychosis and/or agitated behaviour causing significant distress). The NICE/SCIE guideline advises that people may be offered treatment with an antipsychotic drug after various conditions have been met. People may also be offered an acetylcholinesterase inhibitor or memantine under certain conditions.

Non-cognitive symptoms and behaviour that challenges are included in the NICE quality standard on dementia. A NICE Pathway brings together all related NICE guidance and associated products on dementia in a set of interactive topic-based diagrams.
In September 2010, the Department of Health published an implementation plan for Living well with dementia: a national dementia strategy. In July 2011, a best practice guide, Optimising treatment and care for people with behavioural and psychological symptoms of dementia, was produced by the Alzheimer's Society and endorsed by the Department of Health. These resources build on the NICE/SCIE guideline on dementia and include strategies to reduce inappropriate prescribing of antipsychotics.

The harms and limited benefits of using antipsychotic drugs for treating dementia in people who exhibit challenging behaviours are well recognised. They have been the subject of several previous reviews and Medicines and Healthcare Products Regulatory Agency (MHRA) warnings and advice, collated in the May 2012 edition of Drug Safety Update. The use of antipsychotic drugs in people with Alzheimer's disease was also discussed in a previous Medicines Evidence Commentary from December 2013.

In the study reviewed here, researchers investigated the use of citalopram (a selective serotonin reuptake inhibitor [SSRI]) for the treatment of agitation in people with Alzheimer's disease. Citalopram is known to cause adverse cardiac effects, and was the subject of MHRA warnings in 2011 because of a dose dependent effect on QT interval prolongation. Older people have a higher exposure to citalopram due to an age-related decline in metabolism and elimination. Therefore, the maximum dose of citalopram has been restricted to 20 mg daily in people older than 65 years.

New evidence

A US and Canadian randomised controlled trial (RCT; CitAD) has evaluated the efficacy and safety of citalopram for the treatment of agitation in people with Alzheimer’s disease².

This multicentre, double-blind, placebo-controlled RCT included 186 people with probable Alzheimer’s disease and clinically significant agitation for which a clinician had determined that medication was appropriate. People with major depression or psychosis requiring antipsychotic treatment were excluded from the study. The mean age of participants was 78 years, 46% were women and the mean Mini-Mental State Examination (MMSE) score was 15.7 (standard deviation [SD] 6.7). Withdrawal of psychotropic medication, other than rescue medication with lorazepam or trazodone, was required. However, stable doses of acetylcholinesterase inhibitors (69% of participants) and memantine (42% of participants) were allowed.

Participants were randomised (allocation concealed) to receive a psychosocial intervention plus either citalopram (n=94) or placebo (n=92) for 9 weeks. The target dose of citalopram was 30 mg each morning from a starting dose of 10 mg titrated over 3 weeks based on response and tolerability. The psychosocial intervention included educational materials, 24-hour availability for crisis management and a 20 to 30 minute counselling session at each study visit, which included care planning. Baseline characteristics were similar except participants in the placebo group had lower MMSE scores, indicating poorer functioning (17.0 in the citalopram group, 14.4 in the placebo group).

Primary efficacy outcomes were based on scores from the agitation subscale of the Neurobehavioral Rating Scale (NBRSA) and the modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC). At week 9, these agitation outcome measures improved in both the citalopram and placebo group, but there was a statistically significant difference in favour of citalopram. The NBRSA estimated mean treatment difference with citalopram compared with placebo was −0.93 (p=0.04) and results from ADCS-CGIC showed 40% of people taking citalopram had moderate or marked improvement from baseline compared with 26% in the placebo group (see table).
Citalopram (n=94) | Placebo (n=92) | Analysis
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**Primary agitation outcome: change in the agitation subscale of the Neurobehavioral Rating Scale (NBRS-A)**<sup>a</sup> | Estimated mean score at week 9 (n=86): 4.33 (SE 0.31) from baseline of 7.4 (SD 3.3) | Estimated mean score at week 9 (n=81): 5.26 (SE 0.31) from baseline of 7.8 (SD 3.0) | Estimated mean treatment effect −0.93 (95% CI −1.80 to −0.06; p=0.04) favouring citalopram

**Primary agitation outcome: change in the modified Alzheimer Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC)**<sup>b</sup> | At week 9 (n=86), 40% had moderate or marked improvement from baseline severity | At week 9 (n=81), 26% had moderate or marked improvement from baseline severity | Estimated treatment effect<sup>c</sup> OR 2.13 (95% CI 1.23 to 3.69; p=0.007) favouring citalopram

**Secondary safety outcome: change in the Mini-Mental State Examination (MMSE) score**<sup>d</sup> | Estimated mean score at week 9 (n=85): 16.83 (SE 0.32) from baseline of 17.0 (SD 6.2) | Estimated mean score at week 9 (n=79): 15.33 (SE 0.33) from baseline of 14.4 (SD 6.9) | Estimated mean treatment effect −1.05 (95% CI −1.97 to −0.13; p=0.03) favouring placebo

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**Abbreviations:** CI, confidence interval; n, number of patients; OR, odds ratio; SD, standard deviation; SE, standard error; p, p value

<sup>a</sup> range of 0 to 18 with higher scores indicating more severe symptoms

<sup>b</sup> range of 1 to 7 with 1 indicating marked improvement and 7 indicating marked worsening from baseline

<sup>c</sup> odds ratio of being at or better than a given ADCS-CGIC category for citalopram compared with placebo

<sup>d</sup> range of 0 to 30 with higher scores indicating better functioning

Compared with placebo, citalopram also statistically significantly improved scores on the Cohen-Mansfield Agitation Inventory (CMAI), total Neuropsychiatric Inventory (NPI) and the caregiver distress NPI subscale. However, there was no statistically significant improvement with citalopram compared with placebo on the NPI agitation subscale, the Alzheimer Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) or in the use of rescue lorazepam.

Safety was assessed by adverse events and cognitive ability based on MMSE scores. MMSE scores improved slightly in the placebo group but worsened in those receiving citalopram; the difference between the groups was statistically significant in favour of placebo (estimated mean treatment effect −1.05; p=0.03 [see table 1]). Anorexia, diarrhoea, fever, upper respiratory tract infections and falls were all more common in the citalopram group.

ECG monitoring results were available for 48 trial participants (24 in each treatment group). Citalopram was associated with a greater increase in QT-interval than placebo (18.1 ms; 95% confidence interval [CI] 6.1 to 30.1; p=0.004). Three people taking citalopram and 1 person taking placebo showed QTc prolongation (>450 ms for men and >475 ms for women).
This RCT was conducted in a study population broadly representative of those with Alzheimer’s disease. However, limitations included the short duration of treatment (9 weeks), baseline differences in mean MMSE scores, and absence of dose ranging information for citalopram. At week 9, 78% of participants were taking citalopram 30 mg and 15% were taking 20 mg, which was not enough to assess the efficacy of a 20 mg dose.

The authors of this study concluded that although citalopram 30 mg was associated with a clinically meaningful reduction in agitation in people with Alzheimer’s disease in this RCT, the mild cognitive and concerning cardiac adverse effects mean it cannot be generally recommended as a treatment option at that dose. The maximum licensed dose of citalopram for people over 65 years is 20 mg daily, but this RCT had insufficient data to assess the efficacy and safety of this lower dose for treating agitation. Citalopram is not licensed for the treatment of agitation in people with Alzheimer’s disease; therefore use for this indication would be off-label.

Commentary provided by Professor Sube Banerjee (Professor of Dementia, Brighton and Sussex Medical School)

CitAD is an important, well-conducted study in an important area. Behavioural and psychological symptoms in dementia (such as agitation, aggression, wandering, shouting, repeated questioning and sleep disturbance) are common, occurring in up to 90% of cases. Agitation, which can be defined as inappropriate verbal, vocal or motor activity which is not an outcome of need and encompasses physical and verbal aggression, is particularly problematic affecting nearly 50% of people with Alzheimer’s disease over a month. Of people with clinically significant behavioural and psychological symptoms, about 80% still have them 6 months later. Agitation is associated with deteriorating relationships with family and professional carers, institutionalisation, increased costs of care, distress and decreased quality of life.

Antipsychotics, still the current mainstay of drug treatment for agitation in Alzheimer’s disease, do harm. A ministerial enquiry identified that in 2009 a third of people with dementia were receiving these drugs, causing 1800 deaths per year in the UK. Reduction in antipsychotic use in dementia is therefore a Government priority and research into safe, effective alternatives is a research priority. Research into better treatments for agitated behaviours in dementia was identified as a top 10 research priority by the Alzheimer's Society and the James Lind Alliance.

Use of non-pharmacological interventions as first-line treatment for agitation in dementia is best practice and remains so after this trial. However, there is a need for second-line treatments when these fail; and the main reason for the widespread use of antipsychotics is the limited evidence for alternative drug treatments. Other drug treatments used off-label include anticonvulsants, such as carbamazepine, and antidepressants.

The CitAD trial adds to the evidence base for citalopram and provides good quality evidence that a target dose of citalopram 30 mg per day has a positive effect on agitation in people with Alzheimer’s disease. However, the adverse cardiac effects identified in the trial, and to a lesser extent the cognitive impairment observed, are likely to limit its use in clinical practice. So while this is not a trial that will change clinical practice directly and immediately, it is an important proof of the concept that antidepressants may have a role in the management of agitation in dementia as an alternative to antipsychotics. This trial has direct and immediate research impacts, and further work to clarify the impact of citalopram at lower doses, for longer periods and in different forms of dementia is needed. The CitAD trial also provides a framework for successful evaluation that can be used in designing new RCTs investigating the effectiveness and safety of other antidepressants and other classes of drugs in managing behavioural and psychological symptoms in people with dementia.
Study sponsorship

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References


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