Trial Design Innovations: Clinical Trials for Treatment of Neuropsychiatric Symptoms in Alzheimer’s Disease

J Cummings1 and K Zhong1

Neuropsychiatric symptoms are common in Alzheimer’s disease (AD) and other neurodegenerative disorders. Recent progress has been made with clinical trials, advancing new therapies for psychosis in Parkinson’s disease (PD), agitation in AD, and apathy in AD. Definitions have emerged for agitation and apathy in patients with cognitive impairment, facilitating recruitment of clinical trial populations. Progress in clinical trial design and the agents being assessed promise to advance therapies for disabling symptoms and improve quality of life for patients and caregivers.

BACKGROUND

AD is characterized by cognitive decline, progressive functional impairment, and the emergence of multiple neuropsychiatric symptoms. Both neurotransmitter-based and disease-modifying therapies are being developed to treat AD. Cognitive and functional impairments are currently treated with cholinesterase inhibitors and memantine. Major constellations of neuropsychiatric symptoms occurring in AD include mood symptoms (depression, anxiety, irritability), psychosis (delusions, hallucinations), agitation, apathy, and sleep disturbances. More than 90% of AD patients exhibit neuropsychiatric symptoms in the course of their disease. Similarly, other neurodegenerative diseases (NDD) including Parkinson’s disease (PD) patients exhibit depression, anxiety, psychosis, and apathy.

No treatments have been approved specifically for the treatment of behavioral changes in AD or PD. All current prescribing is off-label based on responses in phenomenologically similar conditions. Antipsychotic agents—commonly used to treat agitation and psychosis in AD—have a black box warning in the prescribing instructions noting the increased risk of mortality associated with these agents when used to treat behavioral changes in the elderly with dementia. Preliminary evidence of efficacy of antipsychotic agents for psychosis and agitation of AD has been generated but no regulatory approval has been awarded. Other neuropsychiatric symptoms in NDD also lack approved therapies.

Progress is being made in advancing new treatments of neuropsychiatric symptoms of AD and other NDD. A definition of agitation critical to identifying patients appropriate for clinical trials has been advanced,1 a trial of pimavanserin (Nuplazid) demonstrated reduction of symptoms of psychosis in PD,2 a trial of citalopram showed improved agitation in AD,3 a trial of dextromethorphan/quinidine (DMQ) (Nuedexta) reduced agitation symptoms in AD,4 and a methylphenidate trial demonstrated efficacy for apathy in AD.5

DEFINITION OF BEHAVIORAL SYNDROMES FOR CLINICAL TRIALS

Syndromic definitions are critical to drug development. Specific populations of patients appropriate for trials must be defined before rating scales can be used to quantify the symptom severity at baseline and to assess the change in symptoms in the course of the trial. Definitions of psychosis of AD and PD and depression of AD and PD have been developed and used to inform previous trials.

Agitation is among the most common and challenging symptoms of AD and other NDD, but no consensus definition exists. A provisional consensus definition of agitation in cognitive impairment was developed through a transparent, inclusive, iterative process of the International Psychogeriatric Association (IPA).1 The criteria of the definition are shown in Table 1. Patients meeting the criteria are cognitively impaired; have exhibited the behavior for at least 2 weeks; experience subjective distress; exhibit motor hyperactivity, physical aggression, or verbal aggression; have sufficient symptoms to cause disability in excess of that attributable to cognitive impairment; and have agitation not entirely attributable to another disorder or to environmental circumstances. This definition will assist research on agitation of all types—epidemiology, biology, brain imaging—and will advance clinical trials of antiagitation agents. Populations defined...
**Table 1 Consensus provisional definition of agitation in cognitive disorders**

| A. | The patient meets criteria for a cognitive impairment or dementia syndrome (e.g., Alzheimer’s disease, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, other dementia, a pre-dementia cognitive impairment syndrome such as mild cognitive impairment or other cognitive disorder) |
| B. | The patient exhibits at least one of the following behaviors that are associated with observed or inferred evidence of emotional distress (e.g., rapid changes in mood, irritability, outbursts). The behavior has been sustained or persistent for a minimum of two weeks duration and represents a change from the patient’s usual behavior |
|   | a. Excessive motor activity (examples include: pacing, rocking, gesturing, pointing fingers, restlessness, performing repetitive mannerisms) |
|   | b. Verbal aggression (e.g., yelling, speaking in an excessively loud voice, using profanity, screaming, shouting) |
|   | c. Physical aggression (e.g., grabbing, shoving, pushing, resisting, hitting others, kicking objects or people, scratching, biting, throwing objects, hitting self, slamming doors, tearing things and destroying property) |
|   | D. While co-morbid conditions may be present, the agitation is not attributable solely to another psychiatric disorder, suboptimal care conditions, medical condition, or the physiological effects of a substance |

**CITALOPRAM FOR AGITATION IN ALZHEIMER’S DISEASE**

Citalopram is a selective serotonin reuptake inhibitor (SSRI) widely used for the treatment of depression and anxiety. A recent trial assessed its ability to reduce agitation in patients with AD. In all, 186 patients were randomized to active treatment or placebo and 169 completed the trial. The primary outcome measures were the Neurobehavioral Rating Scale Agitation subscale (NBRS-A) and the modified Alzheimer Disease Cooperative Study–Clinical Global Impression of Change (mADCS-CGIC). Secondary outcomes included scores on the Cohen-Mansfield Agitation Inventory (CMAI) and the Neuropsychiatric Inventory (NPI). Forty percent of patients treated with citalopram had moderate or marked improvement in agitation compared to 26% of patients treated with placebo (estimated treatment effect: −0.93 (CI: −1.80 to −0.06); P = 0.04). Statistically significant effects in favor of citalopram also were evident on the Neurobehavioral Rating Scale–Agitation subscale. There was a significant reduction in CMAI scores (treatment effect: −2.38 (CI: −4.13 to −0.63); P = 0.008). Total NPI scores improved with active therapy but NPI agitation scores showed no significant difference between drug and placebo. The citalopram dose of 30 mg was associated with cognitive decline (~1 point on the Mini-Mental Status Examination) and significant QT interval prolongation indicating the need for caution in using this dose in agitated AD patients.

**DEXTROMETHORPHAN/QUINIDINE FOR AGITATION IN ALZHEIMER’S DISEASE**

DM/Q is a combination that uses quinidine as a cytochrome P450 enzyme inhibitor to raise levels of dextromethorphan and increase bioavailability. The therapy is approved for treatment of pseudobulbar affect and was recently tested in a trial targeting agitation in AD. The trial employed the sequential parallel comparative design (SPCD) utilized to provide insight into treatment effects in trial populations prone to high rates of placebo response (Figure 1). SPCD has previously been used in pain and depression studies; this was its first application in agitation or in an NDD. SPCD has 2 stages; the first is a conventional randomization to drug or placebo (more patients are assigned to placebo than to active agent in this stage); the second stage involves rerandomization of the stage 1 placebo-nonresponders. This second stage allows assessment of treatment effects in patients selected for lack of placebo responses.
DM/Q was associated with significant reductions in agitation within 1 week of treatment initiation. The NPI Agitation/Aggression scale showed a 3.6 point decline in the treatment group by week 10 compared to a 1.9 point reduction in the placebo group when both stages were analyzed together according to the prespecified analytic plan. DM/Q reduced the NPI Agitation/Aggression scale score by 47% in Stage 1 and 26% in Stage 2 (vs. 22% and 6.7% for placebo). Side effects included more falls, diarrhea, and urinary tract infections in those receiving DM/Q. This agent will be advanced to phase III trials further assessing its utility in treating agitation in AD.

METHYLPHENIDATE FOR APATHY OF ALZHEIMER’S DISEASE

Apathy is a prominent and common symptom in AD occurring in mildly affected patients, persisting throughout the illness, and contributing to excess disability. Apathy in patients is a source of distress and burden for caregivers. There has been limited attention to potential therapies for this important symptom. Rosenberg et al. performed a randomized, parallel group study of a single dose of methylphenidate. Sixty patients were randomized to active treatment (10 mg twice daily) or placebo and followed for 6 weeks. There was a significant reduction on the CGIC and the NPI Apathy Domain (−1.8 change in apathy score (CI: −3.4 to −0.3); \( P = 0.02 \)) but not on the Apathy Evaluation Scale. Twenty-one percent of patients were moderately or markedly improved on methylphenidate compared to 3% on placebo as measured by the CGIC (overall \( P = 0.02 \)). Side effects of methylphenidate included anxiety and weight loss. The study established a model trial design for assessment of treatments of apathy in NDD.

COMMENT

Recent trials show progress in defining neuropsychiatric symptoms in AD and other NDD and successfully assessed new agents with the potential to reduce neuropsychiatric symptom burden. The repertoire of classes of agents being tested is broadening and new mechanisms of action are being explored. Advances in drug development for neuropsychiatric symptoms will improve quality of life for patients and caregivers.

AUTHOR CONTRIBUTIONS

J. C. and K. Z. participated in planning, writing, editing, and approving the article.

CONFLICT OF INTEREST/DISCLOSURES

Dr. Cummings has received in-kind research support from Avid Radiopharmaceuticals and Teva Pharmaceuticals; Dr. Cummings has provided consultation to Abbvie, Acadia, ADAMAS, Alzheon, Anavex, Avanir, Biogen-Idec, Biote, Boehringer-Ingelheim, Chase, Eisai, Forum, Genentech, Grifols, Intracellular Therapies, Lilly, Lundbeck, Merck, Neurotrope, Novartis, Nutricia, Otsuka, QR Pharma, Resverlogix, Roche, Suven, Takeda, and Toyoma companies; Dr. Cummings had provided consultation to GE Healthcare and MedAvante; Dr. Cummings owns stock in ADAMAS, Prana, Sonexa, MedAvante, Neurotrax, and Neurokos; Dr. Cummings owns the copyright of the Neuropsychiatric Inventory; Dr. Cummings has provided expert witness consultation regarding olanzapine and ropinerol. Dr. Zhong has no disclosures.

© 2015 The Authors. Clinical Pharmacology & Therapeutics published by Wiley Periodicals, Inc. on behalf of American Society for Clinical Pharmacology and Therapeutics. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

1. Cummings, J. et al. Agitation in cognitive disorders: International Psychogeriatric Association provisional consensus clinical and research definition. Int. Psychogeriatr. 27, 7–17 (2015).
2. Cummings, J. et al. Pimavanserin for patients with Parkinson’s disease psychosis: a randomised, placebo-controlled phase 3 trial. Lancet 383, 533–540 (2014).
3. Porsteinsson, A.P. et al. Effect of citalopram on agitation in Alzheimer disease: the CitAD randomized clinical trial. JAMA 311, 682–691 (2014).
4. Cummings, J. et al. Dextromethorphan/quinidine (AVP-923) efficacy and safety for treatment of agitation in persons with Alzheimer’s disease: results from a phase 2 study (NCT01584440) [abstract]. American Academy of Neurology 67th Annual Meeting (2015).
5. Rosenberg, P.B. et al. Safety and efficacy of methylphenidate for apathy in Alzheimer’s disease: a randomized, placebo-controlled trial. J. Clin. Psychiatry 74, 810–816 (2013).