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

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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, reiterative process of the International Psychogeriatic 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

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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 repetitious 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)
C. Behaviors are severe enough to produce excess disability which in the clinician's opinion is beyond that due to the cognitive impairment and including at least one of the following:
a. Significant impairment in interpersonal relationships
b. Significant impairment in other aspects of social functioning
c. Significant impairment in ability to perform or participate in daily living activities
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

with the criteria can be compared and refinements such as exploring the relationship of agitation and aggression can be advanced. Prospective validation of the criteria and of elements of the definition (e.g., motor hyperactivity, physical aggression, verbal aggression) are required.

Apathy is commonly observed in AD and other NDD but few trials have attempted to relieve this symptom. Recent trials define apathy and advance trial methods.[5] Apathy, like agitation, can be a disabling symptom in NDD and criteria allowing populations to be constructed for trials is an essential step in advancing interventional research.

PIMAVANSERIN FOR PSYCHOSIS OF PARKINSON'S DISEASE

Pimavanserin is a 5-HT_{2A} inverse agonist developed for the treatment of psychosis of PD. In a pivotal phase III clinical trial, 199 patients were randomized to drug or placebo.[2] On the primary outcome of the trial (Scale for Assessment of Positive Symptoms–Parkinson's disease (SAPS-PD)), pimavanserin was associated with a 5.79 point decrease in SAPS-PD scores compared with a 2.73 point reduction for placebo (difference −3.06, 95% CI −4.91 to −1.20; $P = 0.001$). Compared with placebo, patients in the pimavanserin group had greater improvements in investigator-assessed measures of antipsychotic benefit, including Clinical Global Impression–Severity (CGI-S) and Clinical Global Impression–Improvement (CGI-I). In exploratory analyses, caregivers of patients in the pimavanserin group reported a reduction in burden compared with caregivers of patients who received placebo. Participants reported improvements in nighttime sleep for pimavanserin compared with placebo. The primary outcome of the trial was performed by centralized raters remote from the trial sites; the CGI-S and CGI-I were performed by site raters; and the family observation data were elicited by interview of the primary caregiver. The three perspectives concurred in establishing the benefit of treatment; the convergence of data increase the confidence in the test agent. Side effects occurring more commonly with pimavanserin included peripheral edema, confusion, and falls. Pimavanserin is currently under review by the US Food and Drug Administration (FDA).

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.[3] 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.[4] 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.

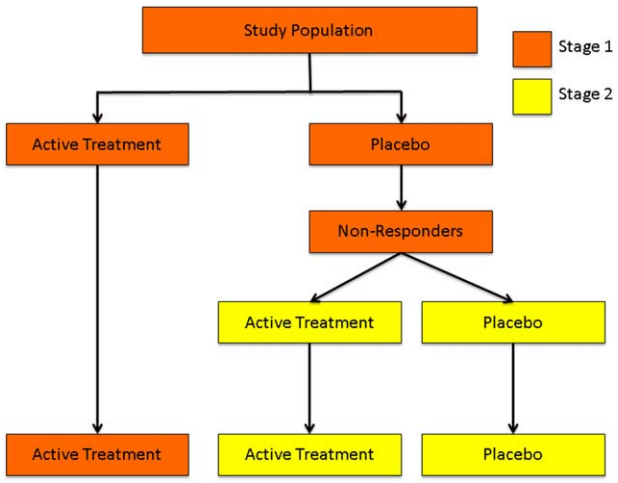

Figure 1 Structure of the sequential parallel comparison design (SPCD).

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.*[5] 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

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