In caring for patients with Alzheimer’s disease, the challenges facing neurologists are multi-faceted. Effective treatment of the disease itself may be the primary goal of therapy, but effective management of behavioral symptoms is a significant unmet need for both patients and caregivers. Patients with Alzheimer’s disease often exhibit agitation and aggression toward caregivers, and currently there are no pharmacological therapies indicated for the management of these behaviors.

Findings from a recent Phase 2 study evaluating the efficacy of a combination agent suggest that effective management of agitation in Alzheimer’s disease may be on the horizon. Ahead, Jeffrey Cummings, MD, Director of the Cleveland Clinic Lou Ruvo Center for Brain Health and lead author of the study, reflects on the significance of the findings as well as the impact this agent could have on Alzheimer’s disease treatment.

What are the challenges of managing agitation both pharmacologically and non-pharmacologically?

“Agitation is a very disabling phenomenon that occurs commonly in the course of Alzheimer’s disease, particularly later in the illness,” says Dr. Cummings. “It involves shouting, cursing, kicking, hitting, shoving, and actively resisting care of providers and caregivers.” Roughly 70 percent of patients experience these symptoms, and they present major challenges for caregivers, who themselves may be at an advanced age, according to Dr. Cummings.

Several agents are often used in patients displaying symptoms of agitation or aggression, but Dr. Cummings points out that none are approved for this use. “Many physicians use anti-psychotic drugs like quetiapine and risperidone, but despite some evidence of their efficacy, these drugs can have substantial side effects,” he observes. Since anti-psychotics are already approved and available for other indications, there is little incentive for manufacturers to fund continued studies in this area.

Given the challenges of pharmacologic interventions for agitation and aggression, non-pharmacologic interventions are generally recommended. “The goal of non-pharmacologic intervention is to teach caregivers the ABCs of caring for Alzheimer’s patients: Antecedent, Behavior, and Consequences,” according to Dr. Cummings. For antecedents, caregivers should consider what happened before the behavior in hopes of better understanding it. “Is there some kind of precipitant that’s causing agitation?” Then, it’s important to identify the exact characteristics of the behavior, whether that’s kicking, shoving, etc. Finally, with consequences, caregivers should consider whether their responses to agitated behaviors might inadvertently encourage the behavior itself. Regardless of the agitation level, “It is important for caregivers to give the patient more attention,” says Dr. Cummings. Most strategies for curbing the behaviors may only be minimally effective, but Dr. Cummings observes that sometimes distraction can be effective.

Can you discuss the combination agent you studied and the significance of your findings?

“AVP-923 is a combination of dextromethorphan hydrobromide/quinidine sulfate and is currently approved for control of pseudobulbar affect—abnormal laughing and crying—which occurs in some neurological diseases,” says Dr. Cummings. “In the course of those studies, there were clinical observations that patients who were agitated appeared less agitated while on the drug.” Dr. Cummings explains. These observations spurred further inquiry into the potential of this combination as an anti-agitation agent.

In the study led by Dr. Cummings, 220 patients were recruited and randomized to receive either the AVP-923 (Avanir...
Breaking Down the Phase 2 Study

The 10-week randomized, double-blind, placebo-controlled, multicenter phase 2 study evaluated efficacy, safety, and tolerability of AVP-923 for the treatment of agitation in Alzheimer’s patients. The design consisted of two consecutive double-blind treatment stages, each of five-week duration, and researchers enrolled 220 Alzheimer’s patients between the ages of 50 and 90 years at 42 sites. In stage 1, eligible patients were randomized in a 3:4 ratio to receive either AVP-923 (dose escalated from dextromethorphan 20mg/quinidine 10mg once per day to dextromethorphan 30mg/quinidine 10mg twice per day) or placebo. At the end of week five, patients who initially received placebo were stratified according to their response to treatment and subsequently re-randomized in a 1:1 ratio to receive either AVP-923 or placebo for the remainder of the study (an additional 5 weeks of treatment). Patients who initially received AVP-923 continued to receive the drug at a dose of dextromethorphan 30mg/quinidine 10 mg twice per day for the remainder of the study.

The primary efficacy endpoint was change from baseline in the agitation/aggression domain of the Neuropsychiatry Inventory (NPI), a well-accepted scale developed to assess neuropsychiatric symptoms and psychopathology of patients with Alzheimer’s disease and other neurodegenerative disorders. In stage 1, mean NPI agitation/aggression scores were reduced by 3.3 points with AVP-923 and by 1.7 points with placebo. In stage 2, in which only placebo non-responders were included in the primary analysis, mean NPI agitation/aggression scores were reduced by 2.0 points with AVP-923 and by 0.9 points with placebo.

Results showed that AVP-923 significantly improved agitation/aggression, which, according to Dr. Cummings, bodes well for continued studies. “This trial was a proof-of-concept study, and it showed that this drug deserves to be studied in a well for continued studies. “This trial was a proof-of-concept study, and it showed that this drug deserves to be studied in a

Pharmaceuticals) combination or placebo to determine its effect on agitation. All patients had Alzheimer’s disease and had at least moderate levels of agitation. Dr. Cummings also notes that the study allowed for a wide range of medications. “Most of the patients were on an acetylcholinesterase (AChE) inhibitor with or without memantine, whereas other patients were on psychotropic medications, antipsychotics, and anti-depressants, just like any population with agitation a clinician might see.”

How would you characterize the potential for this agent to shape Alzheimer’s care moving forward?

“It’s really exciting,” Dr. Cummings notes. “There has been a dearth of compounds approved for any neuropsychiatric condition, so this would be a breakthrough in terms of the larger issue of addressing behavioral abnormalities in brain disorders,” he continues. Moreover, should AVP-923 achieve an expanded indication, it will likely be just the beginning of further exploration of pharmacologic interventions for agitation in Alzheimer’s disease and other neurological conditions, as well as sleep abnormalities in dementia syndromes. “The approval of one drug will be very encouraging, as it would suggest that the FDA is receptive to drugs being developed in various capacities,” says Dr. Cummings.

What would you like to see emphasized in future efforts in Alzheimer’s research and care?

Dr. Cummings believes that the ideal Alzheimer’s regimen consists of three components, all to be used together. “We need drugs that are disease modifying and actually slow progression of disease or delay its onset.” Then, he says, “We also want to improve patients cognitively, so we will need newer and more powerful cognitive enhancing agents.” Finally, “Some patients are going to have behavioral disturbances, so we want low side-effect medications that can target those disturbances.”

Regarding how the development of AVP-923 reflects new directions in Alzheimer’s care, Dr. Cummings believes that both caregivers and physicians have reason to be optimistic. “There are many agents being studied for Alzheimer’s, psychosis, and Parkinson’s disease, so we should be optimistic that there may soon be new medications available.” But when it comes to agitation and aggression, Dr. Cummings feels that is important to emphasize that these behaviors are often the result of many factors related to how the disease affects an individual’s life. Non-pharmacologic interventions will be essential in helping patients and caregivers manage these behaviors. “Non-pharmacologic interventions are important to keep in mind whether or not drug interventions are being pursued,” he says.

Jeffrey Cummings, MD, ScD, is Director of the Cleveland Clinic Lou Ruvo Center for Brain Health. Dr. Cummings has served as a consultant to Avanir Pharmaceuticals.