Neuropsychiatric Symptoms in Dementia

Advances have been made in the management of psychosis, agitation, apathy, and sleep in patients with Alzheimer disease and related disorders.

By Jeffrey L. Cummings, MD, ScD

Alzheimer disease (AD) is characterized by progressive cognitive decline, loss of function, decreased ability to perform activities of daily living, and an increasing emergence of neuropsychiatric symptoms (NPS) as the disease progresses. These clinical changes reflect the accumulation of pathologic changes in the brain characterized by amyloid plaques, neurofibrillary tangles, inflammation, and neurodegeneration.[1] Multiple neurotransmitter deficits accompany the histologic changes, including alterations in norepinephrine and serotonin physiology.

Progress is being made in the development of new treatments for AD. Aducanumab has been approved for treatment of patients with mild cognitive impairment (MCI) and mild dementia due to AD.[2] Conventional treatments, including cholinesterase inhibitors and memantine, are available. There are no drugs specifically approved for the treatment of NPS in AD. Pimavanserin is approved for the treatment of psychosis in Parkinson disease (PD)[3] and is the only agent specifically approved for any NPS in any neurodegenerative disease.

Recent successes in clinical trials for treatment of NPS in AD and related disorders (ADRD) have occurred and advanced our understanding of how to manage several NPS occurring in ADRD including psychosis, agitation, apathy, and sleep (Table). There have been no recent trials for treatment of depression in ADRD, and management of mood disorders is not addressed in this review.

Systematic Approach to Managing NPS in ADRD

Nonpharmacologic interventions have few adverse events, are usually more acceptable to care partners than use of drugs, and, when efficacious, are preferable to pharmacologic interventions. Nonpharmacologic interventions are applicable across a wide array of NPS in ADRD, including agitation, psychosis, apathy, and sleep disorders. Agitation and psychosis-related behavioral disturbances can be reduced by avoiding confrontation, not insisting on the correction of false beliefs, and redirecting to activities the patient typically finds pleasant. Apathy may respond to nonpharmacologic motivational strategies (eg, increased emphasis on collaborative activities and involvement through social connectedness). Nonpharmacologic adjustments appropriate for sleep disorders include avoiding caffeinated substances and stimu-

Table. Pharmacologic Agents And Highest Doses Used To Treat Neuropsychiatric Symptoms In Alzheimer Disease

Symptom	Agent	Dose[a]
Psychosis	Pimavanserin	34 mg/day
	Risperidone	0.5-2 mg/day
	Quetiapine	25-200 mg/day
Agitation	Risperidone	0.5-2 mg/day
	Quetiapine	25-200 mg/day
	Citalopram	30 mg/day
	Escitalopram	15 mg/day
	Dextromethorphan (DM)/quinidine	30 mg/10 mg twice daily
	DM/bupropion[b]	45 mg/105 mg twice daily
	Prazosin	4 mg in the morning and 6 mg in evening
	Cannabidiol (CBD)	Depends on type and ratio of CBD to THC
Apathy	Methylphenidate	20 mg/day
Sleep	Zolpidem	5 mg at hour of sleep
	Zopiclone	2 mg at hour of sleep
	Trazodone	25-50 mg at hour of sleep
	Suvorexant	20 mg at hour of sleep
	Lemborexant	15 mg at hour of sleep

Abbreviation: THC, tetrahydrocannabinol.
[a]Doses given are the highest used in clinical trials or in practice and are usually reached by titration. [b]Investigational agent.

lants close to the time of retiring to bed, avoiding excess fluids in the evening that might result in awakening to urinate, employing nonsteroidal anti-inflammatory agents to reduce minor pain that might awaken the patient during the night, establishing a comfortable and low-light sleep environment, and avoiding stimulating activities (eg, television and computer or cell phone use) while in bed.

Application of a structured behavioral assessment strategy may help identify appropriate treatments for NPS—both pharmacologic and nonpharmacologic. The Describe, Investigate, Create, and Evaluate (DICE) approach is one such strategy (Figure).[4] Behaviors are described by the care partner (usually not observed by the clinician) and investigated for predisposing conditions and circumstances. The clinician then creates a care plan that responds to the observations collected during the investigation of the behavior, and the intervention is evaluated to determine its success to make appropriate adjustments. An emphasis on shared decision-making involving the patient, care partner, and clinician is key to successfully applying the DICE approach.

When there is imminent threat of harm to the patient or others, a pharmacologic intervention may be chosen simultaneously with the nonpharmacologic intervention. Pharmacologic intervention may also be chosen when nonpharmacologic interventions fail. Both during and after any discontinuation of pharmacologic treatment, nonpharmacologic strategies should be continued to decrease the likelihood of recurrence. The integration of pharmacologic and nonpharmacologic strategies is an important strategy for managing NPS in patients with ADRD.

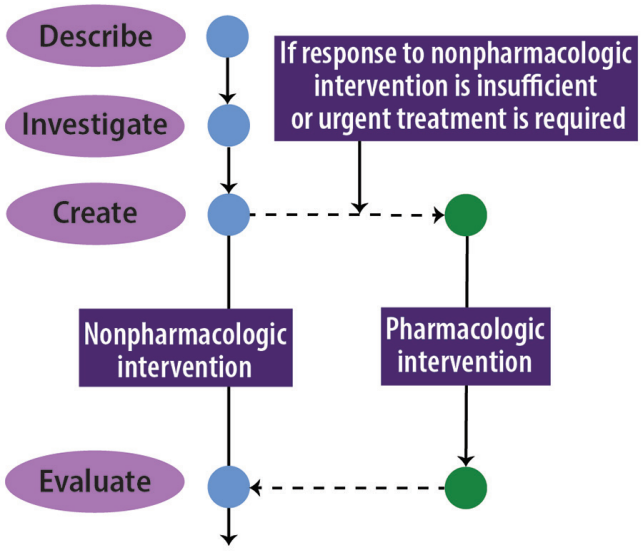

Figure. The Describe, Investigate, Create (a treatment plan), and Evaluate (DICE) framework integrates nonpharmacologic (blue) and pharmacologic (green) management of neuropsychiatric symptoms. If response to nonpharmacologic intervention is insufficient or urgent treatment is required, pharmacologic therapy is added. Nonpharmacologic therapies continue after drug treatment is discontinued to ameliorate or prevent future behavioral disturbances.

Psychosis in ADRD

In a double-blind, placebo-controlled trial, participants with PD who had pimavanserin treatment had a statistically significant reduction in delusions and hallucinations and a notable sleep benefit.[3] A trial of pimavanserin in people with AD residing in nursing homes demonstrated a benefit at 6 weeks of treatment, although the continued improvement in the placebo group led to a nonsignificant drug-placebo difference after 12 weeks of therapy.[5] Patients with more severe psychosis had a more robust response to pimavanserin than those with less severe psychosis.[6] Agitation improved in those in whom the psychosis was reduced and not in those who had no treatment effect on their hallucinations and delusions.[7]

The successful use of pimavanserin in PD psychosis and AD psychosis led to a trial designed to assess the durability of the response to pimavanserin. The trial incorporated a randomized discontinuation strategy in which all patients were treated with pimavanserin initially. Among those who had a therapeutic benefit at 8 weeks that was sustained at 12 weeks, random assignment to continue pimavanserin or receive placebo instead was used to determine if there was a higher relapse rate with placebo vs active treatment.[8] Participants in this trial had any of 5 types of dementia including AD, PD, dementia with Lewy bodies, frontotemporal dementia, and vascular dementia. A significantly greater rate of psychosis relapse occurred in those who were switched to placebo, meeting the primary outcome of the trial. Participants with PD psychosis had a robust response to pimavanserin that accounted for a substantial portion of the drug-placebo difference. Further studies and analyses exploring the therapeutic response in the other diagnostic groups are ongoing.

Pimavanserin is a selective inverse agonist of the serotonin 5-HT_{2A} receptor,[9] suggesting this receptor may modulate circuit activity mediating delusions and hallucinations in ADRD.

Another mechanism being explored for the treatment of psychosis in AD involves muscarinic receptor agonists. Preliminary observations suggests that these agents may be effective in reducing psychosis and agitation in ADRD.[10]

Atypical antipsychotics have been shown effective in reducing psychosis in AD and mixed dementia;[11] agents with fewer side effects are needed.

Agitation in ADRD

Agitation is among the most common NPS in ADRD, occurring at some point in approximately 70% of people with AD. Neuropsychologic studies, imaging investigations, and autopsy observations suggest agitation is a neurobiologic phenomenon mediated by increased involvement of the frontal

lobes, particularly by a greater abundance of neurofibrillary tangles in those with vs without agitation.[12]

The International Psychogeriatric Association (IPA) defines agitation as a disorder consisting of hyperactivity, physical aggression, or verbal aggression for at least 2 weeks that causes a patient distress.[13] The agitation must be sufficiently severe to cause disability and cannot be attributable to another NPS (eg, depression) or due to a substance or physiologic condition. This definition has been used extensively in clinical trials to define a population with agitation sufficiently severe to warrant therapy with psychotropic agents.

Agitation is commonly treated with antipsychotic agents (eg, quetiapine and risperidone). Several trials show risperidone effectively reduces agitation in AD.[14] Evidence for efficacy of quetiapine is less certain, and several trials have shown no drug-placebo difference in antipsychotic effects at the doses tested. Neither risperidone nor quetiapine is approved by the Food and Drug Administration (FDA) for the treatment of agitation or psychosis in ADRD. Antipsychotics have a variety of adverse side effects including extrapyramidal syndromes, metabolic syndrome, and an increased mortality rate.

The antipsychotic brexpiprazole was assessed in clinical trials and the higher dose assessed (2 mg/day) produced a statistically significant reduction in agitated behavior.[15] Brexpiprazole may have similar side effects to those observed with conventional and other atypical antipsychotic agents. An FDA approval and permitted on-label prescription would reduce the jeopardy associated with off-label prescribing of treatments with substantial adverse effects.

Several other pharmacologic agents have been evaluated for treatment of agitation in clinical trials. Citalopram decreased agitation in patients with AD.[16] Prolongation of the QTC interval on electrocardiogram (ECG) and a decrease in cognition as measured by the Mini-Mental State Exam prompted investigators to design trials of other agents in this class of antidepressants that may reduce agitation with fewer side effects. A trial of escitalopram is ongoing.

An investigational combination of dextromethorphan and quinidine similarly reduced agitation in AD in a blinded controlled trial,[17] and follow up trials are ongoing. A combination of dextromethorphan and bupropion is also being investigated. Like quinidine, bupropion is a CYP2D6 inhibitor that increases central nervous system (CNS) levels of dextromethorphan when administered in combination.

Prazosin is an $\alpha 1$ adrenergic antagonist used to treat hypertension that has also been shown to reduce symptoms of post-traumatic stress disorder. A preliminary trial of prazosin in patients with agitation due to AD showed a reduction in agitated behaviors,[18] and a clinical trial is ongoing.

Cannabinoid agonists are increasingly viewed as potential therapies for agitation in AD.[19] A preliminary trial suggested modest efficacy in reducing agitation. Trials of additional agents including nabilone, dronabinol, and tetrahydrocannabinol-free cannabidiol are proceeding.

Dexmedetomidine is used as a sedating agent for agitated patients in intensive care units. A dexmedetomidine oral film is being evaluated for outpatient treatment of agitation in AD.

Apathy in ADRD

Apathy is the most common NPS in AD and is often severe in other CNS disorders, including frontotemporal dementia, progressive supranuclear palsy, and vascular dementia.[20] Apathy is a cause of frustration and burden for care partners. Apathetic patients are less autonomous and require greater care and greater supervision in accomplishing activities of daily living.

Recently the International Society for CNS Clinical Trials and Methodology (ISCTM) Apathy Work Group developed a consensus definition of apathy emphasizing the multiple dimensions of apathy including diminished initiative, decreased interest, and reduced emotional expression/responsiveness.[21] Each of these dimensions and their overlapping occurrence leads to substantial reductions in activity and engagement. This definition will be helpful in identifying populations appropriate for clinical trials of investigational agents intended to reduce apathy.

Recent trials suggest methylphenidate reduces apathy in AD. A previous trial supported the use of methylphenidate for apathy but the prespecified primary outcome of the trial was not met.[22] A more recent trial of methylphenidate for apathy, however, met the primary outcome of reducing apathy scores on the Neuropsychiatric Inventory (NPI) apathy subscale.[23] There was greater weight loss but no increase in agitation or psychosis in those treated with methylphenidate vs placebo. Previous trials with modafinil and atomoxetine showed no reduction in apathy and no improvement in cognition.[24,25] The specific mechanisms of methylphenidate may contribute to the reduction in apathy observed with this agent and not demonstrated with other stimulants.

Sleep Disturbances in ADRD

Excessive daytime sleepiness is common in PD. Rapid eye movement (REM) sleep behavior disorder commonly occurs with dementia with Lewy Bodies and other synucleinopathies (eg, PD and multiple system atrophy).[26] People with AD often have diurnal rhythm disorders characterized by agitation in the late afternoon and early evening hours ("sundowning"), insomnia with nighttime wakefulness, and nighttime agitation.[27] Nighttime behavioral disorders are among the most distressing events for caregivers because wakefulness in the patient often requires wakefulness in the care partner, leaving both sleep deprived.

Benzodiazepines have traditionally been used as hypnotics for the treatment of insomnia but tend to increase cognitive

impairment and may disturb balance, resulting in more falls and increased risk of fracture. Nonbenzodiazepine hypnotics (eg, zolpidem and zopiclone) represent alternatives to benzodiazepine hypnotics but have not been extensively studied for their efficacy or safety in people with ADRD.[28] The benzodiazepine clonazepam is reported to suppress symptoms of REM sleep behavior disorder[29]

Melatonin has been assessed for its hypnotic properties in AD and did not produce a detectable effect.[30] Trazodone, a selective serotonin reuptake inhibitor, was shown to be useful in reducing sleep disturbances in AD.[31]

Recently, dual orexin antagonists have been assessed for efficacy in treating sleep disorders in AD. In a double-blind, placebo-controlled phase 3 trial in participants with AD,[32] treatment with suvorexant increased total sleep time and decreased wakefulness after sleep onset. No major adverse events were observed. The specific indication for suvorexant was not changed because it was already approved for insomnia and shown to be effective for insomnia in those with AD. The clinical trial information derived from the trial in AD is included in the clinical pharmacology section of the prescribing information and the adverse events were noted in the safety section. Lemborexant, also a dual orexin antagonist, was tested in a trial for treatment of irregular sleep-wake rhythm disorder (ISWRD) in AD and at higher doses consistently improved measures of nighttime sleep and daytime wakefulness, consistent with a restoration of the normal diurnal/circadian rhythm.[33] Amyloid-β protein is removed from the brain during sleep and improved sleep may result in a reduced rate of amyloid plaque formation and disease modification.[34]

NPS in ADRD: Treatment & Trial Issues to Resolve

There are several important clinical trial-related issues to be resolved to facilitate the development of new and better treatments for NPS with ADRD. Clinical trials in people with ADRD typically do not require biologic confirmation of the diagnosis, and observations from trials of disease-modifying agents demonstrate that up to 40% of people with mild cognitive symptoms attributed to AD and 20% of those with moderate cognitive decline attributed to AD do not have the characteristic pathologic changes of AD on amyloid positron emission tomography.[35] Trials for the treatment of NPS in ARD will include a proportion of participants who have cognitive impairment of unknown etiology. This may affect the response to the test agent, the symptom trajectory in the placebo group, or the profile of behavioral symptoms observed in the individual. The evolution of plasma biomarkers that are predictive of the presence of brain amyloid consistent with the biologic diagnosis of AD may be integrated into trials of NPS to construct more diagnostically homogeneous treatment populations.[36]

Few trials of NPS in nonAD dementias have been conducted. Trials of antipsychotics and antidepressants have been pursued in PD, but few other neurodegenerative diseases with NPS have been involved in clinical trials, including dementia with Lewy bodies, frontotemporal dementia, progressive supranuclear palsy, corticobasal degeneration, multisystem atrophy, or Huntington disease. The cross-disease applicability of trials results is yet to be determined.

The effect of disease-modifying therapies on NPS in ADRD will also need to be assessed. In a clinical trial of aducanumab there was a substantial drug-placebo difference in favor of aducanumab on the NPI, a tertiary outcome assessment of the trial. It is anticipated that disease-modifying therapies will slow the course of ADRD, resulting in a reduced emergence of new behavioral changes during the therapeutic period.

A robust placebo response is often observed in trials of the treatment of NPS in ADRD.[37] Such trial-induced and placebo-related responses make it more difficult to assess the success of the pharmacologic intervention. More information is required regarding trial design and likely placebo responders to assist in constructing clinical trials that will ameliorate the placebo response.

Summary

NPS are among the most disabling aspects of ADRD. They are distressing for patients, increase burden for care partners, and decrease quality of life for both patients and families. Understanding the neurobiology of NPS may assist in developing more biologically targeted interventions for NPS in ADRD. Better selection of candidate compounds for NPS through more informative animal models might improve the success of developing pharmacologic interventions for NPS. Improved trial conduct strategies including patient selection and outcome measures will accelerate drug development for treatment of NPS in ADRD. Progress in these areas promises to produce improved pharmacologic therapies for NPS including treatments for psychosis, agitation, apathy, and sleep disorders. These agents will make important contributions to improving the quality of life for patients with ADRD. ■

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Jeffrey L. Cummings, MD, ScD
Joy Chambers-Grundy Professor of Brain Science
Director, Chambers-Grundy Center for Transformative Neuroscience
Department of Brain Health
School of Integrated Health Sciences
University of Nevada Las Vegas (UNLV)
Las Vegas, NV

Disclosures

JLC has disclosures at practicalneurology.com