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Management of Neuropsychiatric Symptoms in Dementia

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Abstract

Purpose of review—The purpose is to review the results and clinical implications of recent studies of neuropathology in relation to neuropsychiatric symptoms (NPS) in Alzheimer's disease and related dementias, and discuss new therapeutic approaches based on evidence from clinical trials.

Recent findings—In a large autopsy series from a national consortium, multiple neuropathologies of dementia subtypes were common and increased severity of specific NPS during life was associated with greater severity of neuropathology across diagnoses. Based on three clinical trials, brexpiprazole, which is an antipsychotic with dopamine and serotonin receptor partial agonism properties, was recently approved for the treatment of agitation in Alzheimer's dementia by the FDA. Its therapeutic profile indicates modest efficacy with high safety. Brexpiprazole has not been compared to other antipsychotics that are commonly prescribed to treat agitation in dementia, though none of them have been approved for this indication. Other drugs that showed positive results in Phase 2 trials are being tested in Phase 3 trials. These include cannabinoids and drug combinations that inhibit dextromethorphan metabolism peripherally, thereby increasing its bioavailability in the brain. Apathy is common in several types of dementia, and there is initial evidence that treatment with methylphenidate, a psychostimulant, may be efficacious with good tolerability.

Summary—Greater understanding of the associations between NPS and dementia subtypes can improve clinical management of these disorders. In addition to the approval of brexpiprazole to treat agitation in Alzheimer's dementia, there is optimism about other medications based on ongoing clinical trials. Along with short-term improvement, altering the adverse impact on NPS on long-term prognosis remains an important challenge for the field.

Keywords

Neuropathology; neuropsychiatric symptoms; apathy; agitation; psychosis; antipsychotics; combination drug treatment

INTRODUCTION

The diagnostic criteria for dementia, including Alzheimer's disease which is the most common form of dementia, require cognitive and functional decline [1,2]. Most patients

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will also manifest psychiatric symptoms at some point during the disease course. These neuropsychiatric symptoms (NPS) include apathy, anxiety, depression, agitation, aggression, irritability, delusions, hallucinations, sleep disturbances, and euphoria [3,4,5]. NPS, particularly agitation or aggression and psychosis (delusions or hallucinations), are associated with poor outcomes: more rapid cognitive decline, worse quality of life, greater caregiver burden, escalating healthcare costs, and increased mortality [6,7].

Among NPS, agitation has gained the most attention because of its adverse clinical and prognostic impact and the lack of effective treatments for this condition. The International Psychogeriatric Association developed provisional criteria for agitation in 2014 with an update in 2023 [8,9]. These criteria require the presence of cognitive impairment or dementia, emotional distress accompanying behavioral changes, excessive motor activity or verbal or physical aggression, and symptoms causing excess disability that are not solely attributable to other psychiatric, medical, or substance-related disorders. These criteria are now used to define agitation clinically and for patient eligibility in relevant clinical trials. The neurodegenerative process is the most common explanation for the manifestation of NPS, particularly agitation and psychosis, in dementia. Since many other etiologies are reversible, the initial presentation of NPS requires investigation for underlying infectious (urinary tract infection, pneumonia), metabolic (electrolyte, hepatic, renal abnormalities), inflammatory, nutritional, and endocrine causes, and medication toxicity [10]. Several of these factors also predispose to delirium. The clinician needs to rule out these underlying causes before proceeding to specific behavioral or pharmacologic treatment.

Neurobiology

Investigations into the underlying neurobiology of depression, psychosis and agitation in AD have led to a range of findings for multiple neurotransmitters that include serotonergic, dopaminergic, noradrenergic and cholinergic abnormalities, but many uncertainties remain [10,11]. One theory is that impulsive, agitated and psychotic behaviors may be driven by subcortical activity that lacks sufficient cortical inhibition due to neuronal degeneration [11]. The growing availability of large, often multicenter, collections of autopsied brains in patients with dementia has led to greater emphasis on neuropathological findings.

Neuropathology

There is consistent evidence that older adults with dementia typically manifest multiple neuropathologies [12,13]. In a recently published series of 1,808 brain autopsies from the National Alzheimer’s Coordinating Center (NACC) database in the U.S., we found that apathy was the most prevalent NPS, reaching 80% in patients with hippocampal sclerosis. Frontotemporal lobar degeneration was associated with increased apathy, increased disinhibition, and decreased psychosis and agitation compared to AD [13]. More severe pathology was consistently associated with increased NPS, e.g., Lewy Body Disease (LBD) was associated with an increase in hallucinations from brain stem to limbic to neocortical pathology. Hallucinations were more common in participants with AD and LBD (31.5%) compared with those with AD without LBD (21.6%) and those with LBD without AD (19.6%). Across diagnoses, severity of neuropathology was associated with NPS severity,

indicating that NPS may reflect underlying Alzheimer's Disease and Related Disorders (ADRD) pathology [13].

Treatment

For NPS, nonpharmacological interventions are the recommended first line treatments [14]. The evidence from clinical trials is limited and shows on average a small to medium effect size [15]. In these studies, the primary focus has been caregiver education to implement behavior modification. Methodologically, in addition to the intrinsic problem of the patient/caregiver not being blind to the intervention, all these studies have lacked a control group in which the patient received as much clinician time as the intervention group [15]. Clinically, behavioral strategies may be beneficial for some patients with mild agitation, but pharmacological treatments are often needed for moderate to severe symptoms of psychosis and agitation.

Commonly prescribed pharmacological treatments for agitation in dementia include antipsychotics, sedative/hypnotics, anxiolytics, mood-stabilizing anticonvulsants, acetylcholinesterase inhibitors, NMDA receptor antagonists like memantine, and antidepressants. Other than the antipsychotic brexpiprazole, however, pharmacological treatments currently are not approved for agitation in patients with Alzheimer's dementia in the United States. A few countries have approved the use of other atypical antipsychotics in limited circumstances in patients with dementia and NPS. Many patients are treated off-label with antipsychotics; randomized, placebo-controlled clinical trials of these medications have shown some efficacy with small effect sizes. Both psychosis and agitation, which often co-exist, have shown modest improvement in these trials. Risperidone has been studied the most, and in the dose range of 0.5 to 2 mg daily has shown moderate efficacy with a small to medium effect size for both psychosis and agitation in AD and mixed dementia [16]. Discontinuation of risperidone has been shown to increase the risk of relapse in a placebo-controlled discontinuation trial [17]. Olanzapine at 5 mg daily may have some efficacy with reduced side effects compared to higher, equally effective, doses [18]. Prescribing these medications for agitation or psychosis, however, remains off-label in the U.S.

Antipsychotic use in patients with dementia is associated with increased risk of mortality with an odds ratio of 1.6 that led the FDA to issue a boxed warning in 2005 [19]. Antipsychotic use in older patients with dementia and psychosis can also be associated with other adverse reactions including extrapyramidal signs (EPS), autonomic side effects, and cognitive impairment. Studies of electronic health records show that the risk of adverse effects and mortality increases markedly for higher compared to lower doses for all commonly used antipsychotics [20]. In the large NIMH-sponsored Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease (CATIE-AD) trial, which compared olanzapine, quetiapine, and risperidone to placebo to treat psychosis, aggression, and agitation in AD, the benefits of antipsychotic treatment on psychotic and other behavioral symptoms appeared to be offset by side effects [21]. Pharmacokinetic and pharmacodynamic changes that occur with aging lead to an increased sensitivity to the adverse effects of several medications, especially antipsychotics. These include EPS, tardive dyskinesia (uncommon with second generation antipsychotics), orthostatic hypotension,

cognitive impairment, falls, and anticholinergic effects that impair cognitive functioning. Lower antipsychotic doses, typically a quarter to a third of the dose prescribed in young adults, are recommended to reduce adverse effects and mortality risk. Awareness of these risks, as well as regulatory efforts by the Center for Medicare and Medicaid Services (CMS) to restrict antipsychotic use in nursing homes, has led to a decrease in antipsychotic prescribing that sems to have been replaced by a concomitant increase in anticonvulsant prescribing even though evidence for anticonvulsant efficacy is lacking [22].

Brexpiprazole

Brexpiprazole, an antipsychotic with dopamine and serotonin receptor partial agonism properties that are similar to aripiprazole, has been approved by the FDA for the treatment of agitation in AD. This approval was based on two 12-week randomized, double-blind, placebo-controlled parallel-arm studies [23] and a subsequent trial presented at a conference [24]. The initial two studies were a fixed dose study and a flexible dose study. In the fixed dose study, 433 patients with AD and agitation were randomized to brexpiprazole 2 mg daily, 1 mg daily, 0.5 mg daily (stopped after 20 patients because of evidence indicating lack of efficacy) or placebo. On the Cohen-Mansfield Agitation Inventory (CMAI), which was the primary outcome measure, brexpiprazole 2 mg daily but not 1 mg daily showed greater efficacy than placebo. In the flexible dose study, 270 patients with AD and agitation were randomized to brexpiprazole 0.5–2.0 mg daily or placebo. In the primary analysis, flexible dose brexpiprazole was not superior to placebo on the CMAI but posthoc analyses showed that the subgroup of patients who received 2 mg daily improved more than the placebo group at week 4. Also, there was greater improvement in Clinical Global Impression-Severity ratings on brexpiprazole 2 mg daily compared to placebo. In both studies, the efficacy advantage for brexpiprazole 2 mg daily over placebo was small. In the more recent clinical trial, 345 patients with AD and agitation who were selected for having more frequent agitated behaviors were randomized, double-blind, to brexpiprazole 2 mg daily, 3 mg daily, or placebo in a 12-week trial. Both active drug doses showed a similar efficacy advantage over placebo. Across the three studies, side effects were not significantly greater on brexpiprazole compared to placebo, with marginally greater rates of headache, insomnia and somnolence on brexpiprazole compared to placebo. The rate of EPS and other neurological side effects did not differ between brexpiprazole and placebo, indicating good tolerability. Overall, the evidence suggests that brexpiprazole 2 or 3 mg/day is a useful treatment option for agitation in AD, although its efficacy compared to other antipsychotics to treat agitation in AD is not established.

Antidepressants for Agitation in Dementia

In the CItAD trial, the SSRI citalopram 30 mg/day was more efficacious than placebo for agitation in AD, but there were increased cardiac and cognitive adverse effects on citalopram that may have been related to the use of a relatively high dose [25]. The ongoing s-CItAD trial examines an initial open non-pharmacologic behavioral treatment followed by a randomized, double-blind, trial of escitalopram versus placebo. The study design and choice of drug is based on the CitAD finding that adverse effects were less with the es-citalopram component of citalopram compared to the l-citalopram component of

citalopram [26]. In a large clinical trial for agitation in patients with dementia in the U.K., the antidepressant mirtazapine was not superior to placebo [27].

Cannabinoids

Endogenous cannabinoid receptors are of two types: CB1 and CB2. CB1 receptors are expressed predominantly in the brain while CB2 receptors are expressed primarily in peripheral tissues [28,29]. Cannabinoids may reduce agitation by mechanisms that include increasing serotonergic signaling and inhibiting glutamate release. Cannabinoids have other properties with potential clinical relevance: reduction in oxidative stress and neuroinflammation, and reduction in excitotoxicity of neurons. Completed clinical trials with different cannabinoids have involved small samples with both positive and negative results [30,31,32,33]. Cannabinoids are sedating and it remains unclear if the purported efficacy of this class of agents is due to sedation or more specific anti-agitation properties. Another issue is the formulation and dosage of the cannabinoid which vary widely across published studies. Dronabinol and Nabilone, both of which are synthetic cannabinoids, have shown evidence of efficacy for agitation in preliminary trials [33,34] and are now being tested in larger clinical trials.

Formulations that combine two drugs to treat agitation

Dextromethorphan is a widely used ingredient in cough syrup brands. Dextromethorphan has effects on several neurotransmitters. Its high affinity action as a σ−1 receptor agonist inhibits presynaptic glutamate release and its low affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist properties modulate post-synaptic glutamate. Dextromethorphan also acts as a serotonin and norepinephrine reuptake inhibitor and it is a nicotinic α3β4 receptor antagonist. Dextromethorphan's penetration across the blood-brain barrier is minimal. The pharmacological strategy that is being pursued is to combine dextromethorphan with another drug that prevents its CYP-450 metabolism, markedly increasing its plasma bioavailability and thereby its brain concentration [35,36].

Dextromethorphan/quinidine 20 mg/10 mg twice daily is approved for the treatment of pseudobulbar affect and this dose is not associated with a marked increase in QTc interval that can occur with higher doses of quinidine when it is used as an antiarrhythmic drug [37]. After an initial positive trial to treat agitation in AD [38], subsequent studies have been equivocal though the drug combination continues to be investigated for potential efficacy. Dextromethorphan/bupropion is a drug combination that is FDA-approved to treat major depression in adults [39]. To treat major depression, the initial dose of dextromethorphan 45 mg with buproprion 105 gm daily needs to be doubled after 3 days if well tolerated. The dextromethorphan/buproprion combination showed promising results when compared to buproprion alone or placebo in a Phase 2 trial of agitation in dementia and is now being investigated in a Phase 3 trial.

Dexmedetomidine

Dexmedetomidine is a selective α2-adrenergic receptor agonist that is used intravenously for sedation in surgery and other procedures [40,41]. Safety monitoring for bradycardia, orthostatic hypotension and sedation is indicated. Based on initial results that build on

efficacy for agitation in bipolar disorder and schizophrenia [40,41], a sublingual formulation is now being tested in a placebo-controlled trial as a treatment for agitation in AD.

Pimavanserin for dementia-related psychosis

Pimavanserin has been approved for the treatment of psychosis in Parkinson's disease in the U.S.A. In a relapse prevention trial in patients with dementia-related psychosis, defined as psychosis occurring in patients with dementia across dementia subtypes, responders to 12 weeks of open treatment were randomized, double-blind, to continue pimavanserin treatment or switch to placebo. Pimavanserin continuation was associated with significantly lower relapse compared to patients who were switched to placebo [42]. In that study, patients with Parkinson's dementia and psychosis showed a significant advantage for continuation pimavanserin versus switch to placebo, while in patients with other subtypes of dementia the advantage for pimavanserin over placebo did not reach statistical significance. The FDA-approved indication for pimavanserin currently is restricted to psychosis in Parkinson's disease.

Depression and apathy

Clinically, apathy is more common than depression in AD though the difficulty in distinguishing these two conditions may partly explain the lack of a clear advantage for antidepressants over placebo to treat depression in AD [43,44]. Treatment of apathy has not been studied as often as treatment of depression in AD. A recent trial of methylphenidate 20 mg daily versus placebo in 200 patients with apathy in AD showed moderate efficacy with good tolerability [45].

Conclusion

Neuropsychiatric symptoms, particularly agitation and psychosis, are common in AD and other dementias. These symptoms are difficult to treat effectively and are associated with a poor prognosis. For psychosis, neuropathological overlap between AD and LBD is more common than previously appreciated. There have been advances in treatment for agitation with brexpiprazole that is now approved by the FDA, and the likelihood of approval for other medications based on ongoing clinical trials is on the horizon. Depression is difficult to identify with high accuracy and advantages for antidepressant treatment over placebo remain to be established in AD. Apathy is increasingly recognized as a cardinal feature of several types of dementia, and there is initial evidence that treatment with methylphenidate, a psychostimulant, may be effective with good tolerability. Clinically, identifying specific NPS is important because there is growing evidence that the use of specific medications for agitation, psychosis and apathy may have clinical utility. Along with short-term improvement, altering the adverse impact on NPS on long-term prognosis remains an important challenge for the field.

Conflicts of interest:

Research support: National Institute on Aging, Alzheimer's Association, Karuna Therapeutics.

Scientific Advisory Board: Acadia, Corium, TauRx.

Data Safety and Monitoring Board: BioXcel.

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Key Points

1. Neuropsychiatric symptoms, particularly agitation and psychosis, are common in most dementias, difficult to treat effectively, and associated with a poor prognosis.
2. Multiple neuropathologies in individual brains are common, and severity of NPS, particularly psychosis, is associated with increased pathology.
3. Brexpiprazole was recently approved by the FDA for the treatment of agitation in Alzheimer's dementia.
4. Apathy is common in several types of dementia and there is initial evidence that treatment with methylphenidate, a psychostimulant, may be effective for apathy with good tolerability.
5. While new therapeutic approaches may have short-term efficacy, the adverse effects of NPS on long-term prognosis is an important challenge that needs to be addressed.