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Update on Pharmacological Treatment of Neuropsychiatric Symptoms of Dementia

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Abstract

Purpose of Review Neuropsychiatric symptoms (NPS) commonly occur in dementia and are a major source of burden and distress for both patients and their caregivers. Nonpharmacological treatments are often of limited benefit, particularly when NPS are severe, and at present no medication is approved by the Food and Drug Administration to treat any NPS. This paper reviews the most recent evidence available for nine proposed treatments (eight medications or classes, plus electroconvulsive therapy (ECT)). Guidance will also be provided regarding a suggested algorithm for pharmacological treatment selection.

Recent Findings The strongest evidence is for atypical antipsychotics, but they have a high burden of adverse effect in dementia, including increased mortality risk. Selective serotonin reuptake inhibitors (SSRIs) are likely safer, but evidence for efficacy is currently less strong. The strongest evidence exists for citalopram, but increased risk for QTc prolongation may limit use. Research suggests that mood stabilizers use may be ineffective and unsafe, although select patients may benefit. Benzodiazepines have had limited study, and due to high adverse effect burden, should be reserved for patients who have not responded to or cannot tolerate other classes of medication, and used only after careful weighing of risks and benefits. Cannabinoids, prazosin, dextromethorphan/quinidine, and pimavanserin all have some limited but promising data supporting their use. Electroconvulsive therapy may be helpful for severe NPS, but its impracticality likely limits use.

Summary NPS in dementia cause marked burden and suffering. In severe cases for which pharmacological treatment is indicated, the strongest evidence exists for atypical antipsychotics, but given their high adverse effect burden, SSRIs should be considered, if deemed appropriate, as first line treatment. Third or lower tier treatments can include anticonvulsants, cannabinoids, prazosin, dextromethorphan/quinidine, and pimavanserin. Benzodiazepines should be reserved for select situations with careful weighing of risks and benefits. ECT may be effective for severe NPS, but is likely of limited practical use.

Keywords Dementia · Alzheimer's disease · Neuropsychiatric · Behavioral · Antipsychotic · Selective serotonin reuptake inhibitor

Introduction

Neuropsychiatric symptoms (NPS) (e.g., agitation, aggression, irritability) are nearly universal in dementia [1] and when severe are a major source of distress for both patients and their caregivers. NPS are associated with greater impairment in activities of daily living, decreased quality of life, increased mortality, earlier institutionalization, increased depression in caregivers, and up to $10,000 annually of additional care costs [2, 3, 4]. While nonpharmacological (e.g., behavioral) interventions are recommended by most experts as first line treatment, they are often of only modest benefit, and even less so when NPS are severe. [5, 6]. In such cases, medication treatment is usually indicated, but at present, none is FDA-approved to treat any NPS in dementia, nor does any consensus algorithm exist to guide medication use. Current research suggests that medications within some psychotropic classes (e.g., antipsychotics, antidepressants) are of mild to modest benefit, while others (e.g., benzodiazepines, anticonvulsants), have limited evidence to support their use. Additional studies support consideration of less conventional treatments, such as cannabinoids, prazosin, dextromethorphan/quinidine,

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pimavanserin and electroconvulsive treatment (ECT). This paper will discuss the current evidence for use of nine proposed treatments for NPS in dementia and provide guidance in choosing an order for treatment selection. Although both dementia and NPS are heterogenous in nature, most of these studies focused on participants with Alzheimer's disease (AD) who were exhibiting agitation and/or aggression.

Antipsychotics

Antipsychotic medications are the most comprehensively studied class of psychotropics for the treatment of NPS in dementia, and the weight of evidence suggests that they are of modest benefit [7, 8]. In a pivotal study by Schneider et al., [9], risperidone, olanzapine, quetiapine, and placebo were compared to each other, and no significant difference was noted among agents in the "time to discontinuation for any reason", although risperidone and olanzapine (though not quetiapine) were superior to placebo when time to discontinuation for "lack of efficacy" was assessed. When analyzing specific symptoms, some benefit was noted for risperidone and olanzapine in the treatment of anger, aggression, and paranoid ideation [6, 9]. Studies of newer atypical antipsychotics, such as aripiprazole, are generally not more encouraging [10, 11], although recent research suggests that brexpiprazole may have efficacy along with a more favorable safety profile than other atypical antipsychotics [12, 13*]. Unfortunately, use of atypical antipsychotics is limited by adverse effects including, but not limited to, sedation, gait abnormality, orthostasis, extrapyramidal symptoms, metabolic syndrome, cerebrovascular events, and worsening of cognition. Atypical antipsychotics have also consistently been shown to be associated with an increased risk of mortality when used in dementia [14]. In 2005, based on a review of 17 studies suggesting a 1.6 to 1.7 times increased mortality risk for atypical antipsychotics when used to treat the elderly with dementia, the FDA issued a black box warning regarding use for this indication [15]. Conventional antipsychotics have been demonstrated to be no more effective and may be even more dangerous [16], and in 2008, the FDA black box warning was extended to this medication class as well [17] This does not mean that antipsychotics should never be used in the elderly with dementia, but rather that the risk and benefits for an individual patient should first be carefully weighed. The consensus among most experts is that antipsychotic treatment is appropriate in dementia if an individual has dangerous agitation, and this is discussed in more detail in the American Psychiatric Association practice guidelines on the use of antipsychotics to treat agitation or psychosis in patients with dementia [18].

Selective Serotonin Reuptake Inhibitors (SSRI)

Due to the safety concerns regarding the use of atypical antipsychotics to treat NPS of dementia, SSRIs may be a more advantageous initial option. Among SSRIs, the strongest evidence exists for citalopram. In the pivotal CitAD (Citalopram for Agitation in AD) trial [19], 186 participants with AD and agitation were randomized to receive either citalopram (up to 30 mg daily) or placebo over 9 weeks. Forty percent of those receiving the citalopram had improvement of agitation, as opposed to 26% of those in the placebo group. However, worsening of cognition and increase in the QTc interval [20] were noted in the citalopram group, and the authors concluded that these adverse effects may limit the "practical application" of citalopram, at least at the 30 mg dose. (The current maximum daily dose recommended by the FDA for citalopram in the elderly is only 20 mg). Sertraline, which is less frequently associated with QTc prolongation may be a safer option; however, evidence supporting efficacy is less robust. A Cochrane Review by Seitz et al. [21] found citalopram and sertraline to be of "modest" benefit in treating agitation in dementia in two placebo-controlled studies . Escitalopram, the S-enantiomer of citalopram, has been suggested as an alternative option. In the CitAD study [19], the S-enantiomer of citalopram was noted to be more associated with response than the R-enantiomer, which is more associated with adverse effects [22]. A randomized pilot study of 40 participants with AD and NPS receiving either escitalopram or risperidone found both to be similar benefit [23]. Currently, the S-CitAD study, a randomized, controlled, multicenter clinical trial of escitalopram for agitation in AD is underway. Paroxetine should be prescribed with extra caution due to its anticholinergic effects, and fluoxetine should be avoided due to its long half life. All SSRIs can increase the risk of the risk of hyponatremia, and patients should be monitored for this.

Mood Stabilizers

Anticonvulsants can aid in decreasing impulsivity in patients with mood disorders, and it is reasonable to hypothesize that they may be of benefit in treating NPS in dementia. Research results however have overall been unimpressive. A Cochrane review of valproic acid use for agitation in dementia [24] found valproic acid to be both ineffective and associated with an "unacceptable" rate of adverse effects (e.g., falls, infection). Xiao et al., [25] performed a meta-analysis of five randomized clinical trials of mood stabilizers for agitation in dementia and concluded that they were "ineffective and even

harmful." Gallagher and Herrmann [26] note that the strongest, albeit still limited, evidence supporting use is for carbamazepine. A case series by Devanand et al., [27] found that 6 patients with agitation or psychosis of AD or Frontotemporal dementia responded to low dose lithium. Currently, the Lithium Treatment for Agitation in Alzheimer's disease (Lit-AD) study, the first placebo-controlled trial of lithium for this indication, is underway. While select patients may have significant improvement with mood stabilizers, adverse effects, including sedation and ataxia, limit clinical use. Mood stabilizer medications may be helpful in situations in which agents with stronger supporting evidence (e.g., atypical antipsychotic, SSRI) have been ineffective, are contraindicated, or have been poorly tolerated by the patient.

Benzodiazepines

Limited data is available on the use of benzodiazepines in the treatment of NPS in dementia. Tampi and Tampi [28] performed a systematic search and found five randomized clinical trials in which benzodiazepines were used for this indication. The studies were noted to be heterogenous in nature (e.g., one compared alprazolam to oxcarbazepine, and another compared lorazepam to olanzapine and placebo). The authors noted that in 4 of the 5 studies, there was no significant efficacy difference "between the active drugs". Tampi and Tampi [28] concluded that benzodiazepines may still be appropriate in certain situations, such as when other classes of psychotropic medication are deemed to be less safe for the patient and/or when tolerability of alternative agents is of concern. While a benzodiazepine may calm an agitated or excessively anxious patient with dementia and NPS, this often comes at the cost of causing sedation, gait impairment, falls, and worsening cognitive decline. Therefore, before initiating a benzodiazepine, thoughtful consideration should be given first to weighing the risks and benefits posed to the individual.. For most patients, lorazepam would be an appropriate first choice benzodiazepine, as it has no active metabolites and a medium half-life duration. Starting doses should be very small, such 0.25 mg once or twice daily.

Cannabinoids

Some recent interest has focused on the use of cannabinoids in the treatment of NPS in dementia. Tetrohydrocannabinol (THC) is a cannabinoid 1 and cannabinoid 2 agonist that is the active ingredient of marijuana. However, studies of its use have been mixed [29, 30, 31, 32]. van den Elsen et al. [1, 30] randomized 50 participants with NPS and either AD, vascular dementia, or mixed dementia to receive either 4.5 mg of THC or placebo, and they found "no benefit" in the treatment group for NPS, quality of life, or activities or daily living. THC was described as well-tolerated, and no participants felt, or was noted by others to be behaving, "high." A crossover randomized controlled trial of THC by van den Elsen et al., [2, 31] similarly found that THC "did not reduce NPS in dementia but was well-tolerated." The low doses used (1.5–4.5 mg) may have played a role in lack of benefit noted (van den Elsen et al., [1, 30]; van den Elsen et al. [2] [32].

Dronabinol, a synthetic isomer of THC was studied by Woodward et al. [33] by a retrospective chart review of 40 hospitalized participants with dementia and NPS or appetite disturbance, and the authors found dronabinol use to be associated with a decrease in all domains of the Pittsburgh Agitation Scale [34]. The most common adverse effects noted were sedation (23%) and delirium (10%). Currently, a 3-site placebo-controlled 3-week clinical trial of dronabinol in inpatients with AD and NPS is underway. Using a target dose of 10 mg daily. This study will also include no lower limits in cognitive functioning in order to allow inclusion of even the most severely cognitively impaired participants.

Nabilone, a synthetic partial agonist at cannabinoid receptors 1 and 2, has also been hypothesized to have potential benefit for the treatment of NPS in dementia [35*]. In a 14-week randomized placebo-controlled crossover study by Herrmann et al. [35*] of 39 participants with AD and agitation who were either residing in long term care facilities or seen in geriatric psychiatry clinics, the participants treated with nabilone were found to have a significant decrease in agitation over the six weeks of the study compared to placebo. The authors report that the benefit of nabilone in the treatment of agitation in dementia was greater than what has been noted in prior studies of cannabinoids, and that less cognitive worsening was also seen. Sedation, however, was noted to be the most common adverse event of nabilone treatment, and more so than with other cannabinoids. A larger multicenter study to validate this early finding is indicated.

Prazosin

Prazosin is an alpha-1 noradrenergic antagonist which is FDA approved for the treatment of hypertension and benign prostatic hypertrophy. Evidence also supports its use in the treatment of sleep disruption and nightmares in post-traumatic stress disorder [36]. Noting research suggesting that the alpha-1 adrenoreceptor may play a role in agitation and aggression in dementia, Wang et al. [37] studied 22 participants, both outpatient and residing in a long term care, in an 8 week randomized placebo-controlled trial of prazosin at a mean dose of 5.7 mg and found significant improvement on both the Neuropsychiatric Inventory (NPI) [38] and Brief Psychiatric Rating Scale (BPRS) [39]. Onset of improvement was reported as being "rapid" and adverse effects did not

differ between treatment groups, including for hypotension. Two randomized and placebo-controlled pilot studies [40] of 22 and17 participants respectively with AD and behavioral symptoms similarly showed both improvement in the NPI and no increase in hypotension was seen with prazosin compared to placebo. A multicenter, double-blind, placebo-controlled clinical trial, The Prazosin for Disruptive Agitation in Alzheimer's disease (PEACE-AD) study is currently underway.

Dextromethorphan/Quinidine

Dextromethorphan has multiple mechanisms of action, including as an antagonist of N-methyl-D-aspartate receptors, and quinidine decreases the metabolism of dextromethorphan. This combination has FDA approval for use in treating pseudobulbar affect. Based on data for dextromethorphan/quinidine's efficacy in the treatment of this symptom in persons without dementia, the results of case reports, and "anecdotal" evidence, Cummings et al. [41] performed a 42-site placebo-controlled trial of dextromethorphan/quinidine in 220 participants with moderate to severe probable AD (MMSE ranges from 8 to 28) along with clinically significant agitated behavior. In this 10-week trial (consisting of two consecutive 5-week periods), dextromethorphan/quinidine was associated with significant improvement in the agitation/aggression scale of the NPI. While adverse effects (e.g. falls, diarrhea, and urinary tract infections) were greater in the treatment group, dextromethorphan/quinidine was described as being well-tolerated overall. Potential for QTc prolongation is a concern in deciding whether to start dextromethorphan/quinidine in a patient. Cummings et al. [41] did not find significant electrocardiogram changes in the treatment group (for whom the mean QTc change was 5.3 ms), but individuals with history of QTc prolongation or torsades de pointes were excluded from the study.

While evidence for the use of dextromethorphan/quinidine remains limited, Fralick et al. [42] found that over one half of prescriptions for dextromethorphan/quinidine from 2010 to 2017 were for patients with a diagnosis of dementia or Parkinson's disease, with less than 20 % of prescriptions being for those with multiple sclerosis or amyotrophic lateral sclerosis. In their review, the authors note that pseudobulbar affect is a clinical diagnosis, and while this symptom does occur in some patients with dementia, they were unable to determine whether those in the study were being treated for that specific indication.

Pimavanserin

Pimavenserin is an inverse agonist and antagonist of 5HT2 receptors and is FDA-approved for the treatment of hallucinations and delusions in Parkinson's disease. Ballard et al., [43], noting that evidence from post-mortem, PET, and genetic studies suggest a similar "treatment target" in people with psychosis from AD, completed a 12-week randomized-placebo controlled study of 181 nursing home dwelling participants with psychosis in AD. At 6 weeks follow up, participants who received pimavanserin had a statistically significant decrease in the NPI-nursing home version (NPI-NH) psychosis score (3.76 vs. 1.93). The results at 12 weeks follow-up however, while similar, were described as being not statistically significant. No benefit was found in the treatment of agitation, which was assessed as a secondary outcome. No increase of cognitive impairment was noted in the pimavanserin group. Adverse effects in the treatment group included falls, urinary tract infection (particularly in participants with agitation), peripheral edema, and weight loss. Further analysis demonstrated efficacy to be larger in participants with more severe baseline psychosis [44]. Similar to dextromethorphan/quinidine, the potential for QTc prolongation is of concern, and such was noted to occur in the treatment group in this study. The authors described the benefit noted for pimavanserin as "modest", but also "favorable to previous studies of atypical antipsychotics".

Electroconvulsive Therapy (ECT)

To date, there have not been any placebo-controlled clinical trials for ECT in the treatment of NPS in dementia. Tampi et al. [45*] recently reviewed 20 published reports, consisting of a total of 172 participants, pertaining to the use of ECT to treat NPS of dementia. The available studies included case reports (40%), retrospective chart reviews (25%), and case series (20%). The most common cause of dementia was AD (40%). Bitemporal, right unilateral, and bilateral were the most common ECT methods. Over 90% of participants were found to benefit from ECT, and adverse effects, most commonly cognitive impairment, were described as "infrequent", "mild", and "transient." van den Berg et al. [46] reviewed 17 studies, consisting of 122 participants, also consisting mostly of chart reviews, case series, or case reports, and similarly found a response rate of 88% for clinically significant improvement of agitation and aggression in dementia with ECT. Despite this encouraging evidence, Tampi et al. [45*] and Burgut et al. [47] note that "public perception" of ECT will likely limit its use to cases in which symptoms are treatment refractory, or when slow response or intolerability limit the use of other treatments.

Conclusion

The severe burden and suffering caused by NPS in dementia to both patients and caregivers demands a demonstrably effective treatment approach, yet no such pharmacological or

Table 1 Suggested approach for treatment selection of NPS in dementia

First line	Atypical antipsychotic Selective serotonin reuptake inhibitor
Second line	Atypical antipsychotic Selective serotonin reuptake inhibitor
Third line (or lower)	Mood stabilizer Benzodiazepine Cannabinoids Prazosin Dextromethorphan/quinidine Pimavanserin
Fourth line	Electroconvulsive therapy

non-pharmacological intervention is yet available. In cases where pharmacological treatment is indicated, the treatment plan should also include non-pharmacological approaches as well. Patients should also be assessed first for possibly modifiable conditions contributing to agitation, such as pain. A suggested approach for treatment selection is displayed in Table 1. Among psychotropic treatments, the strongest body of evidence, although modest, supports the use of atypical antipsychotics in cases when NPS are severe and distressing and non-pharmacological interventions have not been of sufficient benefit. Antipsychotics should be initiated at a low dose and then titrated to the minimum effective dose for the behavior. If there is no effect after 4 weeks, the APA guidelines [18] recommend tapering and discontinuing the antipsychotic. If there is benefit, the APA guidelines recommend considering tapering the medication within 4 months, unless the symptoms recur. Long-acting injectable antipsychotic medications should not be used.

While evidence for the use of SSRIs is weaker, this class of medication is generally safer and better tolerated than atypical antipsychotics, and therefore would be reasonable to consider as first line treatment [11]. Among SSRIs, the strongest evidence is currently for citalopram, but due to its association with QTc prolongation, using an alternative SSRI such as sertraline instead would be a reasonable choice. Caution is advised when using paroxetine due to its anticholinergic effects, and fluoxetine due to its long half-life. Suggested starting and upper level doses of commonly used serotonin specific reuptake blockers and atypical antipsychotics, along with safety concerns to watch for, are displayed in Table 2. Anticonvulsants have been demonstrated to be largely ineffective and carry significant adverse effect burden. However, select patients may respond to and tolerate an anticonvulsive medication, particularly at lower doses, and therefore these may be an appropriate third or lower tier choice. Benzodiazepines have been little studied, and the research that is available does not support their use. Especially given their heavy adverse effect burden, benzodiazepines should be reserved for third line or lower use and used only after careful consideration of risk/benefit ratio for an individual patient. Cannabinoids, prazosin, dextromethorphan/quinidine, and pimavanserin have some limited, albeit promising, evidence to support efficacy and acceptable tolerance, but due to the current lack of more extensive data, they would be best relegated to third or lower line treatment options. A review of published reports by Tampi et al., [45*] suggests benefit from ECT for severe NPS, but the negative public perception and stigma are likely to limit its use to particularly challenging clinical situations [45]. A multi-site randomized placebo-controlled trial of escitalopram is underway, and if the medication is demonstrated to be beneficial and well-tolerated, this would be a significant stride toward a safe and effective

Table 2 Suggested dosing ranges for commonly used atypical antipsychotics and serotonin specific reuptake inhibitors, and safety concerns to watch for

Medication	Starting dose	Upper dose	What to watch for
Serotonin specific reuptake inhibitor (SSRI)			
All SSRIs			Nausea, diarrhea, insomnia, tremor, hyponatremia
sertraline	25 mg daily	100 mg daily	
escitalopram	5 mg daily	10 mg daily	Prolonged QTc
citalopram	10 mg daily	20 mg daily	Prolonged QTc
paroxetine	5 mg daily	20 mg daily	Anticholinergic effects
fluoxetine	10 mg daily	30 mg daily	Long half-life
Atypical antipsychotics			
All atypical antipsychotics			Sedation, parkinsonism, metabolic syndrome, QTc prolongation, akathisia, dystonia, rare neuroleptic malignant syndrome, increased mortality risk
risperidone	0.25 mg daily	1 mg daily	More association with parkinsonism
olanzapine	2.5 mg daily	5 mg daily	More association with metabolic syndrome
quetiapine	12.5 mg daily	100 mg daily	More association with increased QTc
aripiprazole	2 mg daily	10 mg daily	Long half-life

treatment for the NPS of dementia, which continue to cause severe suffering to patients and caregivers alike.

Declarations

Conflict of Interest I have no conflicts of interest to disclose.

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