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Review

Management of Neuropsychiatric Symptoms of Dementia: A Comprehensive Review of the Current Literature

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Abstract

***Background*:** Dementia is a progressive and debilitating condition that affects millions of patients in the United States with an enormous impact on healthcare costs, caregivers, and society. Patients with dementia often experience dementia-related neuropsychiatric disturbances, commonly known as Behavioral and Psychological Symptoms of Dementia (BPSD) and more recently Neuropsychiatric symptoms (NPS) in dementia. These symptoms include verbal and physical agitation, aggression, disinhibition, affect lability, apathy, psychosis, depression, and anxiety. Symptom management is important to optimize quality of life, minimize further functional decline, and delay institutionalization. We aim to review the existing published literature on pharmacologic and non-pharmacologic management of NPS.

***Methods*:** PubMed, Google Scholar, and Cochrane were searched for available reviews, systematic reviews, meta-analysis, and randomized controlled trials on diagnostic tools and treatment strategies for NPS. Some of the searched terms used included, "neuropsychiatric symptoms of dementia treatment," "NPS treatment," "pharmacologic treatment NPS," "non-pharmacologic treatment NPS," "scales NPS." We also searched for the term "BPSD" instead of "NPS" and "neurocognitive disorder" instead of "dementia."

***Recent Findings*:** There are different treatment modalities to address NPS, including pharmacologic and non-pharmacologic approaches, but the evidence throughout the years has been controversial and mostly studied in Alzheimer's disease population making less generalizable to other dementia populations.

***Summary*:** NPS continues to be a prevalent and debilitating condition in the elderly population with dementia. Non-pharmacologic strategies continue to be the first-line treatment for NPS despite lack of strong evidence because of their potential benefit and absence of side effects. Conversely, pharmacologic strategies have a potential risk for side effects in addition to the lack of strong evidence about their benefits in NPS; therefore, deprescribing is an important consideration in the management of these patients.

Keywords

Behavioral and psychological symptoms of dementia (BPSD); neuropsychiatric symptoms (NPS); dementia; pharmacologic treatment; non-pharmacologic approach; agitation; aggression; psychosis

1. Introduction

Dementia is a disorder characterized by a decline in cognition involving learning and memory, language, executive function, complex attention, perceptual-motor, and social cognition. The decline is severe enough to impact daily function and independence [1]. The most common type of dementia is Alzheimer's disease (AD) which affects around 5.4 million of Americans and its prevalence will continue to grow [2]. Patients with dementia often present with neuropsychiatric disturbances which have been referred to as Behavioral and Psychological Symptoms of Dementia (BPSD) and more recently described as Neuropsychiatric Symptoms (NPS) of dementia [3].

The reported prevalence of NPS varies but has been documented to be as high as 96%. This includes verbal and physical agitation, aggression, disinhibition, irritability, affect lability, apathy, psychosis, depression, and anxiety [4, 5]. Patients can present with one or more symptoms and although there have been efforts to classify these symptoms there is not a unique classification system, which could help clinicians determine treatment for target symptoms. In an effort to better understand NPS, Lyketsos et al [6] looked at the range of NPS in patients with AD and identified three categories of symptoms. Class A included patients with one or less symptoms; class B included patients who experienced 3-6 symptoms in the affective domain such as depression, anxiety, irritability, apathy, and aberrant motor behavior; and class C included patients who experienced 3-7 symptoms consistent with a psychotic syndrome, with both hallucinations and delusions, being the smallest group. Lastly, they found that non-specific agitation was present in all three classes and accounted for 20% of symptoms.

The cause of the behavioral disturbances is often multifactorial and can occur in all types of dementias. Common etiologies include metabolic disturbances such as electrolyte and glucose abnormalities, acute kidney injury, hepatic encephalopathy, hypoxia, and thyroid dysfunction. Other medical contributing causes include pain, infection, medications' side effects, cerebrovascular accidents, traumatic brain injury, seizures, constipation, or sleep-related

conditions. Psychological causes include depression, grief/loss, posttraumatic stress disorder, underlying primary psychotic and/or mood disorder, and anxiety. Lastly, environmental factors can also trigger symptoms and these include changes in home environment and caregivers, hospitalizations, and lack of trained caregivers [4, 5]. One important consideration when recognizing NPS is differentiating it from delirium because their treatment approaches vary and delirium can present with negative outcomes with high mortality if left untreated [7, 8]. NPS has also been associated with negative outcomes such as faster progression of dementia and increased mortality. Additionally, poor quality of life, functional decline, higher healthcare costs, reduced time to institutionalization, and caregiver distress are other common negative outcomes [5, 9-15].

Therefore, recognition and management of NPS is important, however identification of symptoms, as well as treatment have demonstrated to be challenging. There is still no consensus about the use of a specific screening measure nor an ideal treatment approach for these patients despite extensive literature exploring pharmacologic and non-pharmacologic treatment strategies for NPS. It is possible that the lack of robust evidence is due to the complexity and variety of symptoms within NPS. But there are additional reasons that may be contributing to the gaps in the literature such as various study designs with different types of dementias resulting in less generalizable findings, studies targeting different symptoms within NPS, the use of different validated scales to identify and track severity of NPS, as well as implementation of different treatment designs even within the same category. This has led to clinicians treating these symptoms in a more empirical manner and researchers to continue to explore options following similar study trends. The present review aims to provide guidance for clinicians and researchers regarding treatment for NPS by summarizing up-to-date literature on the pharmacologic and non-pharmacologic management of NPS in patients with dementia, including a variety of study designs and findings, in addition to information about most utilized assessment tools and the role of deprescribing in this population.

2. Materials

The authors searched PubMed, Google Scholar, and Cochrane for available reviews, systematic reviews, meta-analysis, and randomized controlled trials over the last 15 years regarding treatment strategies and validated scales for NPS. Search terms were: “neuropsychiatric symptoms of dementia treatment,” “NPS treatment,” “pharmacologic treatment NPS,” and “non-pharmacologic treatment NPS.” Additionally, the terms “BPSD” and “neurocognitive disorder” in lieu of “NPS” and “dementia” were also searched. For validated scales, the terms “scales” and “diagnostic tools” were used in addition to searching for each of the individual validated scales.

3. Tools to Measure NPS

Due to the challenges in recognizing NPS, the use of scales can be tremendously helpful for clinicians and caregivers [3]. There are multiple validated scales available to help identify neuropsychiatric symptoms. Our literature review demonstrated that the most commonly utilized scales are Behavioral Pathology in Alzheimer’s disease Rating Scale (BEHAVE-AD), Cohen–Mansfield Agitation Inventory (CMAI), Neuropsychiatric Inventory Questionnaire (NPI), the Brief

Psychiatric Rating Scale (BPRS), and Clinical Global Impression (CGI). Other used measures include the Pittsburgh Agitation Scale (PAS) and the Neurobehavioral Rating Scale (NBRS).

Assessment tools can address symptoms differently and agitation and aggression are good examples of that. These are common NPS that can contribute to hospitalizations, difficulty with placement, and caregiver burden. Volicer at al proposed that agitation and aggression are different constructs. Agitation being increased in verbal and motor activity, while aggression being a behavior with the intent to cause harm. This appears to be a relevant difference because each of these symptoms can correlate with the severity of the dementia, in addition to help identify the support a patient may need. Scales that assess aggression and agitation as one entity include the Positive and Negative Syndrome Scales (PANSS), Neuropsychiatric Inventory Questionnaire (NPI), and Cohen–Mansfield Agitation Inventory (CMAI). On the other hand, some other scales treat these syndromes as separate features such as the Brief Psychiatric Rating Scale (BPRS), Neurobehavioral Rating Scale (NRS), and BEHAVE-AD [16].

The Behavioral Pathology in Alzheimer's disease Rating Scale (BEHAVE-AD) is one of the first scales developed to screen for NPS [17]. This scale evaluates 25 characteristics on a 4-point severity scale in AD patients. It includes symptoms of paranoia/delusional ideation, hallucinations, activity disturbances, aggressiveness, diurnal rhythm disturbances, affective disturbances, and anxiety/phobias. The BEHAVE-AD-FW was later developed to add frequency-weighted dimensions in order to improve sensitivity, and the Empirical BEHAVE-AD (E-BEHAVE-AD) was developed to include assessment of direct observation of symptoms. Therefore, these three versions of the BEHAVE-AD help to assess for affective, motor, and psychotic NPS specific to AD and not symptoms associated with cognitive and/or functional domains of AD [18].

The Cohen–Mansfield Agitation Inventory (CMAI) was created in 1986 with the purpose of evaluating the frequency of agitation in the elderly living at nursing homes. There are currently other versions developed including a long form with expanded definitions helpful for caregivers, a short form, a community form, and one developed to evaluate for disruptiveness of behaviors. It can be delivered by a caregiver or a trained staff and evaluates 29 behaviors, each rated in a 7-point scale, being limited to the assessment of verbal and motor agitation/aggressive behaviors [19].

The Neuropsychiatric Inventory Questionnaire (NPI) screens for delusions, hallucinations, dysphoria, anxiety, euphoria, agitation/aggression, aberrant motor activity, disinhibition, and irritability/lability. One important difference with the BEHAVE-AD is the fact that it screens for irritability, apathy, and disinhibition which can be present not only in AD, but also in other types of dementias [20].

Other scales that have been used in dementia treatment studies include the Brief Psychiatric Rating Scale (BPRS) which was originally developed in 1962 to mainly screen for symptoms of depression, anxiety, and psychosis, as well as the Clinical Global Impression (CGI) developed as a clinicians' assessment of a patient's global functioning before and after a study medication, in addition to evaluation of illness severity [21-23].

Although these scales can be helpful to identify NPS, detailed clinical assessment and collateral information gathering are recommended in order to assess for baseline symptoms, disease progression, severity, and environmental factors contributing to symptoms [24]. Ismail et al [25] compared E-BEHAVE AD, NBRS, and NPI to determine detection of behavioral disturbance and psychosis, as well as response to treatment. They found that the E-BEHAVE-AD was able to detect

agitation in more cases compared to the other measures, while NPI detected greater improvement of agitation compared to others. Becoming familiar with these scales can be helpful because there is not a single instrument that works for all patients and studies have implemented different scales based on the target symptoms they are studying [16, 24].

4. Management Strategies

NPS management can be divided into pharmacologic and non-pharmacologic treatment options. There are no FDA approved medications for the treatment of NPS and evidence is conflicting. The non-pharmacologic interventions continue to be recommended as first-line treatment [26, 27]**.**

5. Non-Pharmacologic Treatments

Multiple non-pharmacologic interventions have been studied, but no defined group of strategies has been clearly recommended for the management of NPS. The lack of robust evidence may be the result of studies including different dementia types, the fact that NPS has a wide range of symptoms, as well as the wide variety and designs of non-pharmacologic strategies studied. Despite of this, some non-pharmacologic strategies have shown to improve symptoms, particularly when used within an integrated and multidisciplinary approach. Additionally, they can help increase involvement and support from caregivers, and more importantly, there are no documented side effects which is significant, especially when compared to pharmacologic treatments. Therefore, these interventions continue to be the first-line treatment to manage NPS [24, 27].

The DICE approach has demonstrated to be a helpful tool for clinicians and can be easily implemented when assessing NPS in patients with dementia. This approach includes description of the behaviors, investigation of possible underlying reversible causes, creation of a collaborative team to develop a treatment plan, and evaluation of the effectiveness of implemented strategies. The DICE approach can be implemented in all settings in combination with other strategies used for the management of NPS [26, 28].

Caspar et al [29] divided non-pharmacologic treatment alternatives in indirect interventions when being targeted to the caregivers and multidisciplinary treatment teams, and direct interventions when strategies are directed to the patient. During the last few years, there have been several studies looking at different non-pharmacologic strategies in both direct and indirect domains. Within the indirect group, one relevant study was completed by Gitlin et al [30] who developed a program to help reduce environmental stressors and improve caregiver skills. This program showed some improvement of patients' behaviors in addition to decrease caregiver burden with activities being better handled and less time consuming.

Within the direct domain, music therapy has been widely studied [31, 32]. Vink et al [33] completed a randomized controlled trial with 94 patients and compared music therapy (listening to music, sung or played by the therapist, as well as participation in music activities via singing, dancing or playing a music instrument) with recreational activities. They found a short-term decrease in agitation measured by the CMAI for both groups and although music therapy resulted in greater decrease of scores, the difference was not statistically significant. Ray et al [34] used music therapy (therapeutic singing, music and movement, and a tonal protocol) in 132 nursing

home patients with moderate-severe dementia and found that it reduced agitation measured by the CMAI, as well as depression, when compared to usual care, but there was no improvement in wandering behaviors. Music therapy was later included in the papers by Livingston et al with similar findings. Another frequently used strategy within the direct domain is aromatherapy. Press-Sandler et al [35] completed a review of the literature about the effectiveness of aromatherapy in managing NPS. They found significant heterogeneity between studies regarding target population, type of oil, method of administration, and duration. There were positive and negative results with proximity to the nose in inhalation therapy being a common finding for the positive studies.

Livingston et al [36] completed a systematic review to compare non-pharmacologic interventions for the management of agitation in patients with dementia. They found supporting evidence for music therapy and sensory interventions in care homes. These strategies have shown to reduce emergent agitation. Conversely, these activities have no long-term effect or impact on severe agitation. Training caregivers for person-centered skills and communication has shown to be effective for severe agitation and there is some preliminary data on the prevention of emergent agitation. Individual observation and assessment have shown some benefit in care homes only. On the contrary, light therapy, home-like care, and aromatherapy have not shown to improve agitation. There is insufficient evidence regarding exercise, family training in behavioral management, cognitive behavioral therapy, unsupervised staff training, and environmental interventions for management of agitation.

Abraha et al [37] completed another systematic review and found great variation between studies. They categorized the wide variety of interventions in different groups: a) sensory stimulation interventions such as shiatsu/acupressure, aromatherapy, massage therapy, light therapy, sensory garden/horticultural activities, music/dance therapy, Snoezelen multisensory stimulation therapy, and transcutaneous electrical nerve stimulation; b) cognitive/emotion-oriented interventions like cognitive stimulation, reminiscence therapy, validation therapy, and simulated presence therapy; and c) behavior, multicomponent, and other interventions including exercise therapy, animal-assisted therapy, and dining room environment-based interventions. Out of 38 systematic reviews/meta-analyses and 129 primary studies, they found music therapy to be effective in reducing agitation. Additionally, they found home-based behavioral techniques, communication skills training for caregivers and staff, as well as patient-centered care and dementia care mapping to be effective in the management of NPS, in particular for cases of severe agitation.

In summary, there have been many studies about non-pharmacologic strategies for NPS with positive and negative findings, but overall these strategies continue to be recommended as first-line treatment due to common findings regarding their easy implementation and the possibility of positively impacting patients' outcomes. 1) Non-pharmacologic strategies are safe and have minimal side effects; 2) most strategies can be implemented in different settings from hospitals to nursing homes; 3) non-pharmacologic approaches can be provided by people on different roles from caregivers to medical providers; 4) communication skills training and patient-centered care have consistently shown to improve NPS [38].

6. Pharmacologic Interventions

There is extensive literature about pharmacologic interventions to manage NPS, but the evidence continues to be controversial in particular for agitation for which there is still no FDA-approved medication. Most of the studies have been completed on AD population, making the findings not generalizable to all dementia subtypes. Additionally, there are not randomized placebo-controlled trials on most pharmacologic agents and outcome measured differ between studies making the identification of target symptoms for the various pharmacologic agents challenging [39].

Recognizing the neurobiology behind NPS can help understand why certain pharmacologic agents have been studied to target some areas of the central nervous system with the goal to treat NPS. Studies looking at AD have found that NPS can be the result of central nervous system dysfunction in multiple areas of the brain, including circuit disconnection at the frontal-subcortical and cortico-cortical networks. Also, can be a dysfunction in monoaminergic systems that involve serotonin, norepinephrine, and dopamine neurons located in the brain stem and projecting to various regions of the brain. Additionally, there are studies suggesting the potential role of glutamate-mediated excitatory neurotoxicity [13, 40]. Multiple pharmacologic groups have been studied for the treatment of NPS and these include antipsychotics, antidepressants, anticonvulsants and mood stabilizers, acetylcholinesterase inhibitors, cannabinoids, prazosin, among others.

6.1 Antipsychotics (Table 1)

Antipsychotics have been the most studied group of medications for the management of NPS. There have been research studies looking at antipsychotics for management of NPS, which have demonstrated improvement of some types of behavioral disturbances in dementia; however this group of medications continues to not be recommended as first-line treatment despite these findings mainly due to concerns for side effects, poorly conducted studies, and lack of generalizability of results among all dementia subtypes [41, 42]. The American Psychiatric Association (APA) developed guidelines about the use of antipsychotics to treat agitation and/or psychosis in patients with dementia and here are some important aspects of these guidelines [27]. APA recommends against using this group of medications as first line unless the agitation and/or psychosis are severe enough to pose a safety risk on the patient or others. APA also recommends that if antipsychotics are not effective after a 4-week trial with an adequate dose, they should be discontinued. First generation antipsychotics (FGA) such as haloperidol have shown to have increased mortality risk in patients with dementia when compared to second generation antipsychotics (SGA)[43, 44]. Due to the great number of studies on haloperidol, there is a specific recommendation not to use this medication as first line for non-emergent situations; however the use of haloperidol in emergent cases such as delirium is appropriate as long as it is not for long-term use [45, 46].

Table 1 Antipsychotics for the treatment of NPS.

Study	Design	Sample Size	Dementia Type	NPS Measure
1999 De Deyn et al. [47]	13-week double-blind study comparing placebo with risperidone or haloperidol.	344	AD Vascular Dementia Mixed	BEHAVE-AD CMAI CGI
2006 Schneider et al. (CATIE-AD) [48]	Double-blind, placebo-controlled trial to assess treatment differences between olanzapine, risperidone, quetiapine, and placebo for the management of psychosis, aggression or agitation.	421	AD	CGI
2007 Rainer et al. [49]	8-week, rater-blinded, randomized trial to compare quetiapine and risperidone.	72	AD Vascular Dementia Mixed Frontotemporal	NPI CGI CMAI
2009 Rappaport et al. [50]	Double-blind, placebo-controlled trial to evaluate tolerability of intramuscular (IM) aripiprazole in patients with agitation.	129	AD Vascular Dementia Mixed	PANSS-PEC ACES CGI
2011 Barak et al. [51]	6-week randomized, double-blind, controlled trial comparing risperidone and escitalopram.	40	AD	NPI
2013 Teranishi et al. [52]	8-week, rater-blinded, randomized trial comparing risperidone, Yokukansan and fluvoxamine.	82	AD LBD Vascular Dementia	NPI (nursing home version)
2014 Freund-Levi et al. [53]	12-week randomized open-blind, controlled trial comparing galantamine and risperidone.	100	AD	NPI
Non-Randomized Controlled Trials				
2017 Yoshida et al. [54]	Post-hoc analysis of CATIE-AD trial	421	AD	BPRS

AD: Alzheimer's disease; Mixed: Alzheimer's and vascular dementia; LBD: Lewy Body Dementia; NPI: Neuropsychiatric Inventory Questionnaire; CMAI: Cohen–Mansfield Agitation Inventory; CGI: Clinical Global Impression; BEHAVE-AD: Behavioral Pathology in Alzheimer's Disease Rating Scale; BPRS: Brief Psychiatric Rating Scale; PANSS-PEC: Positive and Negative Syndrome Scale Excited Component; ACES: Agitation-Calmness Evaluation Scale.

6.1.1 SGA

Second generation antipsychotics have been widely studied for the management of NPS with agitation and aggression being the symptoms better targeted by SGAs. Out of all SGAs, risperidone,

quetiapine, aripiprazole, and olanzapine have been the most studied agents within that class. One important consideration about the literature on SGAs for the management of NPS, is the fact that the findings have evolved and changed over time, especially with regards to side effects and efficacy of SGAs when compared to other pharmacologic classes. Therefore, highlighting some of these studies, their designs, and the conflicting findings can help illustrate the challenges of NPS treatment and the value of being cautious when utilizing SGAs in this group of patients [55].

The Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD0) study [48] was a randomized controlled trial conducted to assess treatment differences between olanzapine, risperidone, quetiapine, and placebo for the management of psychosis, aggression or agitation in 412 patients with AD. It showed no significant differences between antipsychotics regarding improvement of symptoms measured by Clinical Global Impression of Change (CGIC). Subsequently, a post hoc analysis of the CATIE-AD demonstrated that improvement of symptoms with the use of olanzapine, risperidone, or quetiapine at 2 weeks was associated with response to such medications at 8 weeks. Additionally, they found reduction in symptoms in 2 weeks that was associated with response at week 8 [54].

Out of all SGAs, risperidone has been most commonly studied and found to improve symptoms of agitation and aggression. In 1999, De Deyn et al [47] compared risperidone and haloperidol with placebo in 344 patients with AD finding that patients on risperidone had higher improvement of BEHAVE-AD scores with aggression being the symptom primarily reduced. No significant extrapyramidal symptoms (EPS) were noticed with risperidone. Rainer et al [49] did an 8-week rater-blinded randomized trial in 72 patients looking at the differences between risperidone and quetiapine in management of NPS measured by NPI, CMAI, and CGI. Both medications resulted in improvement of all three measures, without significant differences between them. Additionally, both SGAs were well tolerated without significant differences regarding adverse events including EPS. Freund-Levi et al [53] completed a 12-week randomized, controlled open-label study to compare use of galantamine versus risperidone in 100 patients with AD and found that both medications improved symptoms measured by NPI, but risperidone was significantly superior treating irritability, as well as agitation.

Differing from these previous studies, risperidone has demonstrated to have increased side effect burden when compared to other medications and some common side effects include sedation, falls, constipation, and EPS. One example is the comparison of risperidone with selective serotonin reuptake inhibitor (SSRIs) antidepressants, resulting in no significant differences regarding improvement of NPS, however risperidone consistently showing increased EPS side effects [51, 52].

Aripiprazole has been studied primarily to target psychotic symptoms in patients with NPS with favorable results in three placebo-controlled trials. Additionally, Rappaport et al [50] completed a placebo-controlled trial to evaluate the tolerability of intramuscular aripiprazole in agitated patients and found improvement in the Positive and Negative Syndrome Scale (PANSS) Excited Component (PEC) score, the Agitation Calmness Evaluation Scale (ACES), CGI-S and CGI-I rating scales. From a safety perspective, aripiprazole has shown to increase sedation but no EPS, weight gain, or cardiovascular side effects [56]. More recently, Brexpiprazole has been studied in this population, however no definite results found and more research needed to determine efficacy and safety in patients with dementia [57].

Second Generation Antipsychotics and Side Effects. In addition to side effects described above, SGAs have shown to increase the risk of cerebrovascular events (CVE) in elderly patients with dementia. The mechanisms that could explain this elevated risk of CVE are their cardiovascular (CV) side effects, including blood pressure elevation, orthostatic hypotension, arrhythmias, as well as dehydration, thromboembolic effects, venous stasis, and hemoconcentration possibly due to sedation and sedentary lifestyle. Additionally, hyperprolactinemia has been associated with increased endothelial dysfunction and platelet aggregation, in addition to decreased insulin sensitivity. Indirectly, SGAs have metabolic side effects such as weight gain, diabetes, and hyperlipidemia resulting in increased CV risk [58, 59].

QT prolongation is another negative CV side effect of antipsychotics and there have been multiple studies looking at the QT interval effect of these medications. Gareri et al [59] completed the largest cardiac safety study regarding the impact of antipsychotics on QT interval and which is referenced by the Food and Drug Administration (FDA). Thioridazine had the greatest risk of prolonging QT interval followed in descending order by ziprasidone, quetiapine, chlorpromazine, risperidone, olanzapine, aripiprazole, and haloperidol. Beach et al [60, 61] completed a review of QT prolongation and risk of Torsade de Pointes in association with psychotropic medications. They highlighted important risk factors for QT prolongation which are particularly relevant in geriatric populations including history of long QT syndrome, being female, advanced age, electrolyte abnormalities, diuretic use, bradycardia, heart failure, myocardial infarction, renal and/or hepatic dysfunction, hypertension, hypoglycemia/diabetes, hypothyroidism, CNS injury, malnutrition, and polypharmacy. They reported that thioridazine continues to have the greatest risk among typical antipsychotics and ziprasidone among atypical antipsychotics compared to olanzapine, risperidone, and quetiapine, which have not been clearly associated with Torsades de Pointes. Besides antipsychotic medications, they reported that selective serotonin reuptake inhibitors (SSRIs), especially citalopram and tricyclics can lead to QT prolongation.

6.2 Antidepressants (Table 2)

Prevalence of depression in patients with dementia is as high as 40% [14] and antidepressants have been studied not only to target depressive symptoms, but also to treat behavioral disturbances. A Cochrane review by Seitz et al [62] looked at studies comparing SSRIs to placebo, typical, and atypical antipsychotics. They found poor evidence given heterogeneity in the way agitation was measured, as well as small sample size studies. There were some findings suggesting that citalopram and sertraline were more effective than placebo, but no significant differences were found when compared to antipsychotics. Barak et al [51] completed a 6-week randomized double-blind controlled trial and did not find significant differences between escitalopram and risperidone, however risperidone's tolerability was lower and side effects included EPS. Teranishi et al [52] did an 8-week rater-blinded, randomized trial and compared risperidone, fluvoxamine, and yokukansan and found no significant differences between groups. Fluvoxamine was found not to impact cognition although described side effects included hallucinations, delusions, refusal to eat, and falls; for risperidone EPS was described. The Citalopram for Agitation in Alzheimer Disease (CitAD) study [63] showed that the addition of citalopram to a psychosocial intervention improved agitation when compared to placebo. Patients on the citalopram group had increased anorexia, diarrhea, fever, worsening cognitive abilities, and QT interval impact. Viscogliosi et al [64]

completed a 6-month longitudinal study and found that citalopram had similar effects compared to olanzapine and quetiapine with fewer side effects, including falls, all-cause hospitalizations, and orthostatic hypotension. No differences were observed for cognitive, functional decline, and QTc prolongation.

Table 2 Antidepressants for the treatment of NPS and depressive symptoms comorbid with dementia.

Study	Design	Sample Size	Dementia Type	NPS Measure
2010 **Rosenberg et al. [65]** **Weintraub et al. [66]**	Randomized double-blinded treatment comparing sertraline to placebo.	131	AD	mADCS-CGIC CSDD
2011 **Barak et al. [51]**	6-week randomized, double-blind controlled trial comparing risperidone and escitalopram.	40	AD	NPI
2013 **Teranishi et al. [52]**	8-week, rater-blinded, randomized controlled trial comparing risperidone, yokukansan and fluvoxamine for the treatment of NPS.	82	AD LBD Vascular Dementia	NPI (nursing home version)
2014 **Porsteinsson et al.** **(CitAD) [63]**	Randomized placebo-controlled, double-blind trial looking at citalopram.	186	AD	NBRS-A mADCS-CGIC CMAI NPI
2017 **Viscogliosi et al. [64]**	Longitudinal 6-month study randomized to citalopram, quetiapine, or olanzapine.	75	AD	NPI mADCS-CGIC
Non-Randomized Controlled Trials				
2011 **Seitz et al. [62]**	Cochrane Review about safety and efficacy of antidepressants for management of NPS.	692	AD Vascular Dementia Mixed	CGI NPI GBS CMAI BEHAVE-AD NBRS BRSD
2012 **Sepehry et al. [67]**	Meta-analysis of the efficacy of SSRI and SNRI medications for depression comorbid with dementia.	598 studies	AD	N/A
2002 **Bains et al. [68]** **2018 (update)** **Dudas et al. [69]**	Cochrane review about effectiveness of antidepressants to manage depression in patients with dementia.	1592	Any type (DSM criteria)	N/A

AD: Alzheimer's Disease; Mixed: Alzheimer's and vascular dementia; LBD: Lewy Body Dementia; NPI: Neuropsychiatric Inventory Questionnaire; CMAI: Cohen–Mansfield Agitation Inventory; CGI: Clinical Global Impression; mADCS-CGIC: Modified Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change; BEHAVE-AD: Behavioral Pathology in Alzheimer's disease Rating Scale; CSDD: Cornell Scale for Depression in Dementia; GBS: Global Behavior Scale; NBRS: Neurobehavioral Rating Scale; BRSD: Behavioral Rating Scale for Dementia.

Depression can also contribute to NPS in patients with dementia. In review of the literature for depression management, Bains et al [68] completed a Cochrane review about antidepressant use in dementia and found that sertraline was superior compared to other antidepressants. On the other hand, a more updated Cochrane review by Dudas et al [69] showed that antidepressant treatment had no effect on depression rating scales however found some positive evidence regarding depression remission when compared to placebo. No differences were found within antidepressant groups. The DIADS-2 study [65, 66] did not find any effect of sertraline versus placebo at 12 and 24 weeks of treatment. Additionally, Sepehry et al [67] conducted a meta-analysis and found that there is no evidence to support efficacy of SSRIs for the treatment of depression comorbid with Alzheimer's dementia. HTA-SADD trial [70] also found no significant differences between sertraline, mirtazapine and placebo. Additionally, the sertraline group had gastrointestinal side effects compared to placebo.

In summary, antidepressants have not shown robust evidence in the management of agitation and/or depression in patients with dementia, however when compared to atypical antipsychotics, they have better side effect profile.

6.3 Anticonvulsants and Mood Stabilizers (Table 3)

6.3.1 Valproic Acid (VA)

VA has been studied for the management of behavioral disturbances in dementia and the available data does not suggest that VA is an effective treatment for NPS, in particular for agitation [71]. Meinhold et al [72] conducted a retrospective analysis to asses for the impact of VA on NPS. They found that VA as monotherapy and in combination with benzodiazepines and/or antipsychotics provided some benefit in managing NPS symptoms. VA as monotherapy showed improvement of cognitive skills, including daily decision making and short-term memory. Tariot et al [73] conducted a 6-week double-blind, placebo-controlled clinical trial in 153 nursing home residents with AD and agitation. They looked at improvement of NPS through BPRS comparing VA with placebo and found no significant difference between groups. Forester et al [12] completed a 6-week open label naturalistic pilot study to assess efficacy of VA as monotherapy or in combination with SGA as measured by the CMAI and NPI (nursing home version). They found that use of VA both as monotherapy and in combination with SGA to help physical aggression and irritability, with lower doses of VA needed when used combined. VA was least effective on physical non-aggression and verbal agitation. A recent Cochrane Review [74] on VA for agitation in patients with dementia showed that VA is probably ineffective in treating agitation and the risk for adverse effects is increased. There was variability in the way studies accounted for symptoms and use of agitation scales. There have been randomized controlled trials on VA however none have shown positive results for the use of it in patients with NPS.

Table 3 Anticonvulsants for the treatment of NPS.

Study	Design	Sample Size	Dementia Type	NPS Measure
1998 Tariot et al. [75]	6-week randomized, multisite, parallel-group study to evaluate efficacy, safety and tolerability of carbamazepine.	51	AD	BPRS CGI
2001 Olin et al. [76]	6-week randomized, double-blind, placebo-controlled trial with carbamazepine.	21	AD	CGI BPRS
2005 Tariot et al. [73]	6-week double-blind, placebo-controlled clinical trial using valproic acid.	153	AD	BPRS CGI-C CMAI
2007 Forester et al. [12]	6-week open label naturalistic pilot study to assess efficacy of VA as monotherapy or in combination with second generation antipsychotics.	15	Dementia (DSM-IV)	CMAI NPI (nursing home version) CGI
2009 Sommer et al. [77]	8-week multicenter, randomized, double-blind placebo-controlled study using oxcarbazepine.	103	AD Vascular Dementia Mixed	NPI BARS
2010 Mowla et al. [78]	8-week double-blind randomized trial comparing topiramate and risperidone.	89	AD	CMAI NPI CGI
2015 Suzuki et al. [79]	16-week open-label trial to look for efficacy of lamotrigine.	40	AD	NPI
Non-Randomized Controlled Trials				
2005 Meinhold et al. [72]	Retrospective analysis to assess impact of valproic acid in nursing home residents.	3302	Not specified	Minimum Data Set (MDS)
2012 Yeh et al. [71]	Review study to look at efficacy of mood stabilizers for NPS.			
2013 Cooney et al. [80]	Retrospective design of consecutive cases of patients managed with gabapentin for NPS over 6-month period.	7	AD Vascular Dementia Mixed	Clinical evidence of behavioral disturbance.
2018 Baillon et al. [74]	Cochrane review of randomized and placebo-controlled trials to assess efficacy and adverse effects of VA when used to treat agitation in patients with dementia	430	Any type (DSM criteria)	BPRS CMAI CGI SDAS OAS
2019 Supasitthumrong et al. [81]	Systematic review looking at gabapentin and pregabalin for NPS management.	24 studies	Any type (DSM criteria)	Variety of measures

VA: Valproic Acid; AD: Alzheimer's disease; Mixed: Alzheimer's and vascular dementia; NPI: Neuropsychiatric Inventory Questionnaire; CMAI: Cohen–Mansfield Agitation Inventory; CGI: Clinical Global Impression; BARS --

Brief Agitation Rating Scale; BPRS: Brief Psychiatric Rating Scale; SDAS -- Social Dysfunction and Aggression Scale; OAS – Overt Aggression Scale.

6.3.2 Topiramate

Topiramate has also been studied for the treatment of behavioral symptoms in patients with dementia. Mowla et al [78] did an 8-week double-blind randomized controlled trial using CMAI and NPI as outcome measures to compare topiramate with risperidone. They found improvement of symptoms in both groups without significant differences and not significant changes in cognitive status noticed. One important consideration is that topiramate was used in low doses to prevent decline in cognitive function. Despite this one study, there have been no randomized placebo-controlled trials to determine efficacy of topiramate in NPS and the literature suggests cognitive side effects which need to be taken with caution in patients with underlying neurocognitive disorder.

6.3.3 Carbamazepine

Yeh et al [71] reviewed all antiepileptic medications for the treatment of behavioral symptoms of dementia. They found a meta-analysis and three randomized controlled trials regarding carbamazepine which showed to be effective in treating aggression, hostility and possibly agitation. Despite having the most supportive evidence for management of NPS within this group of medications, carbamazepine has serious adverse effects including Stevens-Johnson syndrome and drug-drug interaction which are significant side effects that require extreme caution [75, 76].

6.3.4 Gabapentin, Lamotrigine, and Oxcarbazepine

In a retrospective design of cases Cooney et al [80] found that low-dose gabapentin could be effective in treatment of aggression in patients with vascular dementia. A recent systematic review by Supasitthumrong et al [81] about evidence of gabapentin and pregabalin in the management of NPS found low-evidence for the use of these medications for that matter. There are case series showing positive results with gabapentin, however there are no randomized controlled trials [71]. Suzuki et al [79] completed a preliminary open-label trial to determine efficacy of lamotrigine in treatment of NPS in patients with AD and found that administration of lamotrigine decreased NPI scores, including subscales for anxiety and irritability. No randomized controlled trials have been completed for lamotrigine. There is one randomized controlled trial on oxcarbazepine and lacks positive results for the treatment of NPS [71, 77].

6.4 Acetylcholinesterase Inhibitors (AChEIs) (Table 4)

AChEIs have been widely studied for their positive effects on cognition. They have limited evidence for the treatment of NPS, specifically agitation and aggression, but have good evidence for their effect on depression, dysphoria, apathy, and anxiety [82, 83]. Holmes et al [84] completed an open-label randomized trial and found that donepezil compared to placebo had positive effects for the treatment of NPS. To the contrary, Howard et al [85] completed a 12-week randomized trial and did not find that donepezil was more effective than placebo. Freund-Levi et al [53] studied galantamine versus risperidone for the treatment of NPS in a randomized,

controlled, open-blind trial and significant reduction in symptoms was found in both groups with risperidone being more effective targeting irritation and agitation. Galantamine also showed improvement of cognitive symptoms. When looking specifically at side effect profile of AChEIs, Pariente et al [86] found an increased risk for myocardial infarction among older patients treated with AChEIs in combination with antipsychotics. Arrhythmias and hypotension are also known cardiac side effects of these medications.

Table 4 AChEIs for the treatment of NPS.

Study	Design	Sample Size	Dementia Type	NPS Measure
2004 Holmes et al. [84]	Open label randomized trial looking at effectiveness of donepezil compared to placebo.	96	AD	NPI
2004 Howard et al. [85]	12-week randomized controlled trial comparing donepezil to placebo for the management of NPS	272	AD	CMAI NPI
2014 Freund-Levi et al. [53]	12-week randomized open-blind, controlled trial comparing galantamine and risperidone.	100	AD	NPI

AD: Alzheimer's disease; Mixed: Alzheimer's and vascular dementia; NPI: Neuropsychiatric Inventory Questionnaire; CMAI: Cohen–Mansfield Agitation Inventory.

6.5 Newer Studied Agents (Table 5)

Although there are a great number of recent studies targeting NPS with newer pharmacologic agents, more research and high-quality study designs are needed in order to determine efficacy and safety of these medications.

Table 5 Novel agents for the treatment of NPS.

Study	Design	Sample Size	Dementia Type	NPS Measure
2015 Cummings et al. [87]	12-week multicenter, double-blind, placebo-controlled trial to compare efficacy, safety and tolerability of dextromethorphan hydrobromide–quinidine sulfate.	220	AD	NPI
2015 Van den Elsen et al. [88]	Randomized double-blinded, placebo-controlled trial looking at efficacy of tetrahydrocannabinol.	22	Not specified	NPI
Non-Randomized Controlled Trials				
2014 Woodward et al. [89]	Retrospective systematic review.	40	Any type (DSM criteria)	PAS CGI GAF

AD: Alzheimer's disease; Mixed: Alzheimer's and vascular dementia; NPI: Neuropsychiatric Inventory Questionnaire; CMAI: Cohen–Mansfield Agitation Inventory; CGI: Clinical Global Impression; PAS: Pittsburgh Agitation Scale; GAF: Global Assessment of Functioning.

6.5.1 DM-Quinidine

There is growing interest in medications that affect the glutamate system as potential treatment for NPS. Dextromethorphan hydrobromide (DM) modulates glutamate, and also acts as a serotonin and norepinephrine reuptake inhibitor in addition to being neuronal nicotinic receptor antagonist. DM-quinidine (DM/Q) is an FDA-approved treatment for pseudobulbar affect and its symptoms has some overlap with agitation in AD [87]. The first randomized placebo-controlled trial found that DM/Q significantly reduced agitation compared to placebo. Regarding side effects, there were no deaths; however, falls occurred in a great percentage of DM/Q patients, followed by diarrhea, urinary tract infections, and dizziness. There were no significant changes in vital signs and/or electrocardiogram and no evidence of cognitive decline or somnolence [57, 87].

6.5.2 Cannabinoids

Cannabinoids have been found to be neuroprotective in dementia and have an impact on reducing pain sensation, which could potentially improve NPS symptoms; however the exact mechanism is unknown [13]. Cannabinoid receptor agonist, dronabinol, has shown to improve anorexia, agitation, and nocturnal disturbances in patients with dementia; however, these studies have been low-quality with small sample sizes, therefore more research is needed. Woodward et al [89] completed a retrospective chart review studying 40 patients who were treated with dronabinol for behavioral problems or appetite symptoms and found significant decrease on agitation scale (PAS), CGI scores, as well as sleep duration and meals intake. A randomized double-blind controlled trial by van den Elsen et al [88] using tetrahydrocannabinol to manage NPS found no significant differences in the NPI scores compared to placebo.

6.5.3 Other

Some studies have suggested that norepinephrine at the α1-adrenoceptor may contribute to the pathophysiology of dementia-related agitation and aggression and the theory is that Prazosin may reduce adrenalin in the brain leading to less behavioral problems. Scyllo-inositol has also been studied and thought to improve synaptic activity in networks underlying NPS by regulating brain myoinositol metabolism and phosphoinositol signaling, in addition to providing protection from oligomer-induced toxicity due to beta-amyloid anti-aggregation effects; however, no positive studies found. Other medications that have been studied and do not have enough supporting evidence include Primavanserin a 5-HT2A inverse agonist approved for treatment of Parkinson's disease psychosis; Lumateperone a serotonin re-uptake inhibitor on 5-HT2A receptor at low doses and modulating D2 and D1 receptors; ORM-12741 selective alpha 2c adrenergic receptor antagonist being developed for AD [57].

7. Deprescribing

After review of the current literature for the treatment of NPS in patients with dementia, it is evident that multiple medication groups have been studied however placebo-randomized controlled trials are lacking, most studies are low-quality, and have demonstrated conflicting results for using pharmacologic agents to treat NPS, with findings about increased risk for side

effects. On the other hand, non-pharmacologic treatment strategies have shown to improve NPS without the complicated side effect profile of medications. It is important to recognize that lack of training of caregivers, poor person-centered care, understaffing of healthcare centers, and lack of understanding of the natural progression of dementia can lead to inadequate assessment of NPS, poor implementation of non-pharmacologic strategies, as well as the overuse of pharmacologic agents (especially antipsychotics) [90]. In addition to increased availability and easy implementation of non-pharmacologic measures, consideration of deprescribing can result in improvement of NPS in elderly patients with dementia. Deprescribing can help decrease medication side effect burden (e.g., anticholinergic symptoms), sedation, gastrointestinal discomfort, sleep disturbances, among others. Another important role of deprescribing is discontinuing medications that are contraindicated in certain populations but are prescribed for short-term management of NPS or even without clear indication. One common example is patients with Lewy Body Dementia who are prescribed antipsychotics which can often worsen some symptoms [91]. One important step providers should take in the process of deprescribing is become more familiar with the literature available on pharmacologic agents and the natural course and end-of-life care of dementia, in addition to understand the barriers for discontinuing medications in the older adult population [92-96].

8. Conclusion

NPS in dementia is common, distressing for both patients and caregivers, and known to result in negative outcomes. Being able to recognize the wide range of symptoms within NPS is crucial and can be done by utilizing the various validated scales that are available in combination with in-person interview for patients and their caregivers. While there is extensive literature offering guidance on pharmacologic and non-pharmacologic interventions, there is no strong evidence to support either group of strategies. Consequently, there is no consensus about ideal strategies to implement in the management of NPS. Regardless, non-pharmacologic options continue to be recommended as first line treatment because they can be implemented in various settings and have minimal side effects. Strategies including music therapy, communication skills training, and patient-centered care have shown to be most helpful. On the contrary, there are many studies about pharmacologic strategies, but such studies continue to show conflicting results in addition to significant concern about potential serious side effects, therefore consider the value of deprescribing in the management of NPS in dementia. Lastly, treatment of NPS requires involvement of the patient, family, surrogate decision makers, and the multidisciplinary team of providers [97].

Abbreviations and Acronyms

AChEIs, Acetylcholinesterase inhibitors; AD, Alzheimer's disease; APA, American Psychiatric Association; BPSD, Behavioral and Psychological Symptoms of Dementia; CV, cardiovascular; DICE, Describe, Investigate, Create, and Evaluate; ECT, Electroconvulsive Therapy; FGA, First generation antipsychotics; NPS, Neuropsychiatric symptoms; RCT, Randomized Controlled Trial; SGA, Second generation antipsychotics; SSRIs, Selective Serotonin Reuptake Inhibitors.

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