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REVIEW

Tailoring the therapeutic interventions for behavioral and psychological symptoms of dementia

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ABSTRACT

Introduction: Behavioral and psychological symptoms of dementia (BPSD) are symptoms of non-cognitive nature, which frequently develop during the course and different stages of dementia. The diagnosis of BPSD is complex due to symptom variety, and relies on detailed clinical evaluation and medical history. Accurate assessment of BPSD is crucial in order to tailor therapeutic intervention (non-pharmacological and pharmacological) for each individual and monitor patient response to therapy.

Areas covered: This review encompasses the epidemiology, classification, assessment and etiology of BPSD, as well as their impact on caregiver distress, and gives an overview of current and emerging non-pharmacological and pharmacological therapeutic options, as well as potential BPSD biomarkers, in order to provide a framework for improving BPSD diagnosis and developing novel, targeted and specific therapeutic strategies for BPSD.

Expert opinion: Due to the large heterogeneity of BPSD and of the fact that drugs available only alleviate symptoms, finding an adequate treatment is very challenging and often involves a polytherapeutic approach. Non-pharmacologic interventions have shown promising results in improving BPSD, however further research is needed to confirm their beneficial effects. Thus, the modification of pre-existancing as well as the development of novel pharmacologic and non-pharmacologic solutions should be considered for BPSD therapy.

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Assessment; behavioral and psychological symptoms; classification; dementia; etiology; impact; prevalence; therapy

1. Introduction

The behavioral and psychological symptoms of dementia (BPSD), also known as the neuropsychiatric symptoms (NPS), frequently develop at multiple stages of dementias, such as Alzheimer's disease (AD). These symptoms are non-cognitive and affect 90–97% of people with dementia [1], and include a wide range of emotional, perceptual, and behavioral disturbances [2–6]. BPSD occur also in subjects with mild cognitive impairment (MCI), with a higher prevalence (about 60%) than in the general population, but lower than in dementia [5]. Patients with MCI that also present with BPSD show increased symptom severity associated with global, cognitive and functional disturbances, and they are at an increased risk of developing dementia [5].

The term BPSD includes aggression, agitation, anxiety, apathy, depression, disinhibited behaviors, nocturnal disruption, psychotic symptoms, vocally disruptive behaviors and wandering [7,8]. It can sometimes be useful to group BPSD into psychopathologically recognized symptom clusters (such as, depressive syndrome or psychotic syndrome); or organize them by function (such as disorders of sleep) or altered behavior (such as hitting or wandering). Finkel et al. (1996) suggested a simple method of BPSD grouping according to symptoms, which is mainly assessed on the basis of interviews with the patients and their relatives (to identify anxiety, depressive mood, hallucinations and delusions), while other symptoms are usually identified on the basis of observation of the behavior of the patient (aggression, screaming, restlessness, agitation, wandering, culturally inappropriate behaviors, sexual disinhibition, hoarding, cursing and shadowing) [7]. Other authors suggested that it might be clinically useful to classify BPSD into five domains: cognitive/perceptual, motor, verbal, emotional, and vegetative [9].

BPSD are heterogeneous and usually very unpredictable with different clinical presentations occurring in different types of dementia, suggesting various neurobiological backgrounds [10,11]. They also often co-occur, which further increases their burden in individuals diagnosed with the dementia. In clinical practice, it is very important to recognize these symptoms early. BPSD worsen the course of dementia, leading to faster progression, influencing the quality of life of the patients, and have a strong negative impact on the caregivers and family members [4,12,13]. They also increase the risk of physical abuse and the burden on caregivers, the misuse of psychotropic medication, elevate the healthcare costs, lead to increased need for hospitalization and earlier placing in nursing homes, and predict poorer clinical outcomes [4,12,13]. More severe BPSD might result in higher stress levels, reduced physical activity, social isolation, negative

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Article highlights

- BPSD occur frequently and represent a significant problem in clinical practice, due to high prevalence, severity and burden, as well as therapy often being non-effective
- The etiology of BPSD is still unclear; however, it involves complex interactions of various biopsychosocial factors
- In addition to the patient, BPSD can also negatively affect the caregiver's general health and quality of life
- Both pharmacologic and non-pharmacologic solutions should be considered for BPSD therapy
- Due to symptom variety, choosing adequate BPSD treatment is challenging and often includes a personalized and polytherapeutic approach
- Person-centered therapeutic approach to BPSD needs to be tailored based on dementia stage, behavioral and cognitive symptoms, comorbidities, physical fitness and individual preferences

health outcomes and a lower quality of life [14], and can therefore affect the management of dementia patients, as well as choice of medication used for treatment [15]. Since individuals with BPSD show faster cognitive decline, are often associated with a poorer clinical outcome, have higher mortality rates and earlier institutionalization for the patients [16–18], it has been recommended that care for severely demented patients with BPSD should consist of person-centered interventions in order to respect their dignity and to improve their quality of life [19].

2. BPSD prevalence

The prevalence of non-cognitive symptoms reported in dementia varies considerably from one study to another [2,6,20–24]. This observed variability of BPSD prevalence rates could be due to the study settings, the population's origin and demographics, the duration of disease, the age of patients or their level of education, the evaluation methods or the severity of the cognitive impairment [2,25]. It was previously shown that the severity of some BPSD is associated with the stage of dementia, becoming exacerbated over the course of the disease. For example, delusions, agitation/aggression, apathy/indifference, aberrant motor behavior, nighttime behavior disturbances, as well as appetite and eating abnormalities, appear more severe at the moderate or severe stage of dementia [26]. In contrast, affective symptoms are not related to the stage of dementia [6].

BPSD often precede the onset of dementia, as has been shown for MCI [27], but also for mild behavioral impairment (MBI), a stage in which prolonged and significant neuropsychiatric symptoms occur before the development of the cognitive symptoms or prior or combined with MCI [28]. In addition, in cognitively healthy older adults there is a high prevalence of MBI, suggesting that MBI may be useful in predicting the future development of dementia during the pre-dementia clinical stage [28].

However, it seems that the relationship between the stage of dementia and BPSD expression depends on the type of dementia. Considering that different types of dementia vary in their etiology, different profiles of neuropsychiatric symptoms are expected in each dementia subtype. Namely, BPSD and the stage of dementia stage found to be positively correlated in the AD subjects, but not in subjects suffering from dementia with Lewy bodies (DLB) [29]. Among the various types of dementia, BPSD have been studied best in AD. A meta-analysis [2], which included 48 articles dealing with the neuropsychiatric symptoms of AD, reported apathy as the most frequent with an overall prevalence of 49%, followed by depression (42%), aggression (40%), anxiety (39%), sleep disorder (39%), irritability (36%), appetite disorder (34%), aberrant motor behavior (32%), delusions (31%), disinhibition (17%), and hallucinations (16%), with euphoria (7%) as the least prevalent. When compared to AD, vascular dementia (VaD) is characterized by a higher prevalence and severity of depression and anxiety, similar rates of psychotic symptoms, and less severe aberrant motor behavior [30]. In subjects with DLB, delusions (misidentification, theft) and hallucinations (usually visual) occur more frequently than in AD patients [31]. Frontotemporal lobar degeneration (FTLD), characterized by stereotypic behavior, appetite changes and loss of social awareness, is associated with complex ritualized behaviors more frequently than AD [32]. Frequency of BPSD among various types of dementia are shown in Table 1.

On the other hand, in individuals with MCI, the most prevalent neuropsychiatric manifestations are depression (29.8%), sleep disturbances (18.3%), and apathy (15.2%), whereas hallucinations (0.75%), euphoria (1.25%), and aberrant motor behavior (1.5%) are the least prevalent [38]. Depression was observed as the most prevalent neuropsychiatric manifestation of MCI [38] and some studies report an increased risk of AD in MCI patients with depression [39–41]. However, other studies have shown that symptoms of anxiety can predict which MCI patients will develop dementia [42] and that patients who present with both amnestic-MCI and apathy have an almost seven-fold risk of the progression to AD [43]. Nevertheless, our understanding of the differences in the prevalence of BPSD across different subtypes of MCI remains incomplete.

The persistence of BPSD also differs according to specific symptoms [16]: high persistence was determined for the symptoms of hyperactivity, apathy, irritability, agitation and wandering, while low or moderate persistence and moderate incidence were found for the symptoms of depression, anxiety, elation and sleep problems. For the psychotic symptoms, a low persistence and a moderate or low incidence was detected [16]. In addition, there are also sex-related differences in BPSD [44]. Specifically, in patients with AD who had mild dementia, the females had higher depression/dysphoria symptoms than the males [44]. Moreover, sex differences were detected in large groups of individuals with severe dementia, controlled for the effect of comorbidities, cognition, age, race and function [22]. This study revealed that female subjects had more symptoms of anxiety and sadness than males, while male subjects reported more apathy and aggressive behavior [22]. In Taiwanese patients with AD, the female subjects showed higher presence of delusions and disinhibition than the males, and this difference was independently affected by the stage of AD [45]. However, a recent comprehensive review and meta-analysis revealed that the prevalence of affective

Table 1. The most frequent BPSDs occurring in the different subtypes of dementia.

Study	AD	FTD	VaD	DLB	MXD
[33] Sample: 296 patients (69.2% AD, 9.8% FTD, 7.8% DLB, 13.2% MXD) Behavioral assessment instruments: MFS, BEHAVE-AD, CMAI, CSDD	Activity disturbances Aggressiveness	Disinhibition Emotional disturbances Aspontaneity Speech disturbances Aggressiveness Activity disturbances Restlessness	NA	Delusions Hallucinations	Activity disturbances Aggressiveness
[34] Sample: 137 patients (54.8% AD, 8.4% FTD, 20.6% VaD, 4.5% DLB, 11.6% other dementias) Behavioral assessment instruments: BEHAVE-AD	Anxiety Phobias	Activity disturbances	Paranoid and delusional ideation Affective disturbance	Hallucinations Aggressiveness	NA
[35] Sample: 214 patients (51.4% AD, 38.3% FTD, 10.3% DLB) Behavioral assessment instruments: NPI	Apathy Depression Irritability	Agitation Disinhibition Irritability	NA	Hallucinations Delusions Anxiety	NA
[36] Sample: 107 patients (61.7% AD, 17.8% FTD, 10.3% VaD, 3.7% DLB, 6.5% MXD) Behavioral assessment instruments: NPI	Apathy Agitation Irritability Depression Sleep disorders Anxiety	Aberrant motor behavior Agitation Apathy Appetite and eating disorders Sleep disorders Irritability	Depression Anxiety Apathy Irritability	Hallucinations Agitation Apathy Sleep disorders Delusions Depression Anxiety Irritability Appetite and eating disorders	Agitation Irritability Apathy Depression Sleep disorders
[37] Sample: 131 patients (42.0% AD, 25.2% VaD, 32.8% MXD) Behavioral assessment instruments: NPI	Delusions Hallucinations	NA	Uninhibitedness Aberrant motor behavior	NA	Delusions Aberrant motor behavior

AD – Alzheimer's disease; FTD – Fronto-temporal dementia; VaD – Vascular dementia; DLB – dementia with Lewy bodies; MXD – mixed dementia; NA – data not available for a certain type of dementia; MFS – Middelheim Frontality Score; Behave-AD – Behavioral Pathology in Alzheimer's Disease Rating Scale; CMAI – Cohen-Mansfield Agitation Inventory; CSDD – Cornell Scale for Depression in Dementia; NPI – Neuropsychiatric Inventory.

symptoms (apathy, depression and anxiety) did not differ according to the stage of AD (mild, moderate or severe) [6].

3. Classification and assessment of BPSD

BPSD can be divided into two main subgroups of the symptoms: behavioral symptoms and psychological symptoms, which are similar to those seen in the different psychiatric disorders. The behavioral symptoms most often include physical aggression, restlessness, agitation, socially and culturally unacceptable and inappropriate behavior, sexual disinhibition, swearing and gathering unnecessary things. Psychological symptoms include anxiety, depressed mood, hallucinations and delusions.

These divergent symptoms are clustered together into different domains [11]: the affective domain (anxiety and depression), the disinhibition/hyperactivity domain (aggression, impulsivity, and motor hyperactivity), the apathy domain, the psychosis domain (hallucinations, delusions, and paranoia); and the euphoria domain [46]; however, there is not a consensus on these domain groupings (Figure 1). Namely, some symptoms overlap, while other symptoms (apathy, sleep and eating disturbances) do not cluster satisfactorily [11]. As previously mentioned, BPSD can be also divided into five symptom clusters or domains in order to facilitate the clinical evaluation: the cognitive/perceptual domain (delusions and hallucinations), the motor domain (pacing, wandering, repetitive movements, physical aggression), the verbal domain (yelling, calling out, repetitive speech, verbal aggression), the emotional domain (euphoria, depression, apathy, anxiety, irritability), and the vegetative domain (disturbances in sleep and appetite) [9].

The diagnosis of BPSD is complex due to the variety of symptoms, and it requires detailed clinical evaluation, taking into account the etiology of dementia, the exclusion of all other potential causes of comorbid conditions, and the gathering of relevant information from the patients and their caregivers [30,47]. The previous criteria for the diagnosis of dementia, the Diagnostic and Statistical Manual of Mental Disorders (DSM)–IV and the International Classification of Diseases (ICD)–10, did not provide definitions of behavioral disturbance or any guidelines for the diagnosis of BPSD; however, the current criteria defined in the DSM 5 require clinicians to state whether BPSD are present and to specify their degree of severity. Today, there are more than 100 geriatric rating scales that allow some level of assessment of the behavioral and psychological symptoms in patients with dementia. The most commonly used scales are the Alzheimer's Disease Rating Scale (BEHAVE-AD), the Cohen-Mansfield Agitation Inventory (CMAI), and the Neuropsychiatric Inventory (NPI),

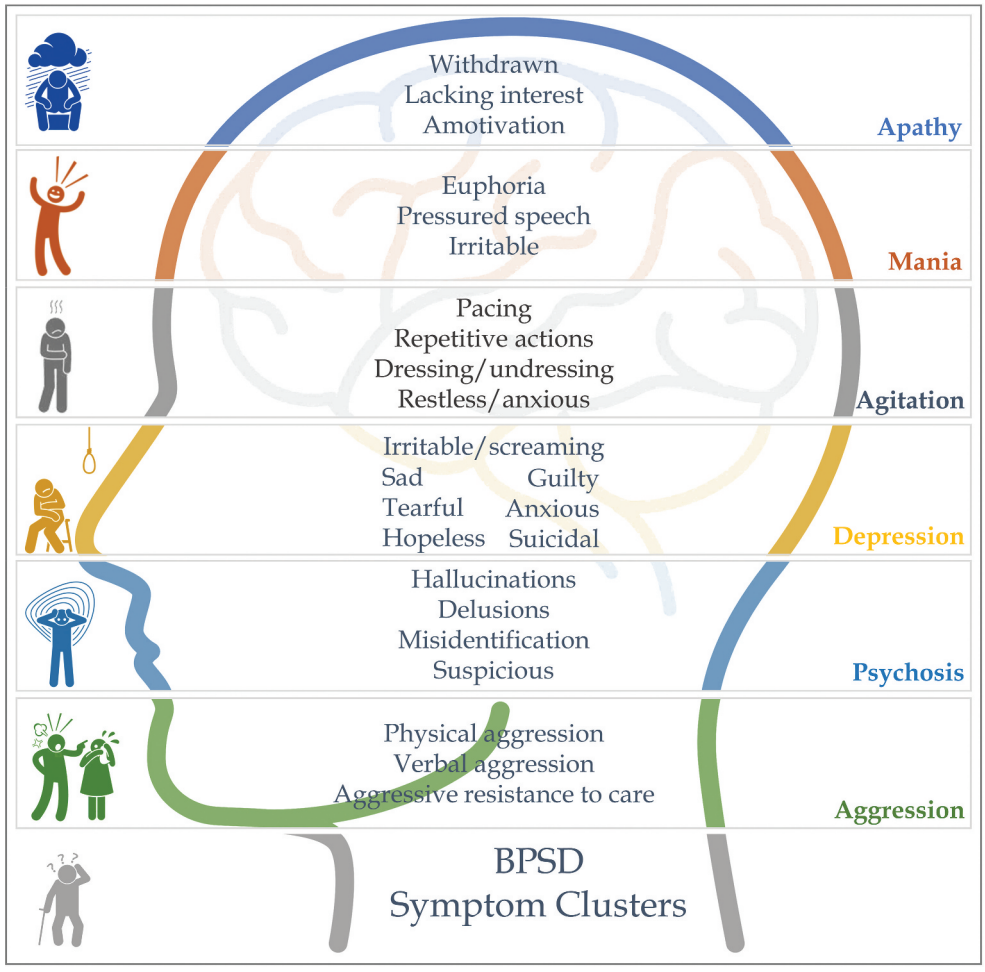

Figure 1. The BPSD symptom clusters: The various symptoms are clustered together into different domains: affective (anxiety and depression), disinhibition and hyperactivity (aggression, impulsivity, and motor hyperactivity), apathy, psychosis (hallucinations, delusions, and paranoia); and euphoria (mania) domain; however a consensus on these domains does not currently exist.

because of their specificity and reliability in the diagnosis of BPSD [48].

The BEHAVE-AD is an original behavioral scale specifically designed for patients suffering from AD [49–51]. The scale consists of two parts: the first part concentrates on the symptomatology, and the second part includes the scoring according to the severity of individual symptoms. The scale evaluates 25 behavioral symptoms divided into 7 symptomatic categories: paranoia and delusions, hallucinations, changes in activities, aggression, sleep disorders, mood, and anxiety. The BEHAVE-AD scale is designed to be useful for prospective behavioral symptom studies and for documenting and quantifying symptoms in pharmacological trials.

The NPI was developed to enable the assessment of neuropsychiatric symptoms and a wider range of psychopathology in patients with AD and other neurodegenerative diseases [52,53]. NPI monitors 12 neuropsychiatric domains that often occur in dementia: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behavior, nighttime behavior disturbances, and eating behavior abnormalities. Based on the clinician's interview with the caregiver, scoring is performed for each domain regarding the frequency and the severity of the symptoms, but also with regard to how disturbing these symptoms are for the caregiver. The total number of points on each domain depends on the frequency and severity of the symptoms (frequency x severity). Very often, in routine clinical practice, a brief questionnaire form of the NPI is used, the NPI-Q [54]. There are also other versions of NPI available, like the NPI-Nursing Home (NPI-NH) for patients living in nursing homes [55], and NPI-Clinician, in which the symptoms are assessed by the caregiver, the clinician and the patient [56].

The CMAI was developed for behavior assessment in elderly adults living in nursing homes [57]. This 29-item scale assess agitation through an interview with the caregiver. It assesses physically aggressive behavior (such as hitting, pushing, biting others), physically non-aggressive behavior (pacing, intentionally falling, hiding things), verbally aggressive (screaming, cursing) and verbally non-aggressive behaviors (repeating sentences or questions, complaining, making strange noises). Each item is rated given the frequency and the severity of behaviors associated with the agitation. Kupeli

and colleagues [58] developed a shorter version of CMAI for use in the acute general hospital setting.

The accurate assessment of BPSD is crucial for treating these neuropsychiatric symptoms and monitoring the patient's response to therapy. This assessment must include a detailed review of the medical history, physical and neurological examination, cognitive assessment and evaluation of the individual neuropsychiatric symptoms in order to determine their frequency, severity and diurnal variation. The effective assessment of BPSD is key to tailoring the intervention (non-pharmacological and pharmacological) for each individual with dementia.

4. Etiology of BPSD

The etiology of BPSD is still not clear, but it is assumed to be multifactorial in origin, and that a combination of biopsychosocial factors is responsible for their development [9]. The etiological underpinning includes numerous interactions between biological and non-biological factors. These factors are neuroanatomical and neurotransmitter (cholinergic, noradrenergic, dopaminergic, serotonergic, and glutamatergic) alterations, disturbances associated with premorbid personality traits and psychiatric disorders, prior experiences, and environmental influences [9]. Since BPSD also develop in various dementia subtypes, such as AD, vascular dementia and mixed dementia subtypes [7], the differing presentations across these subtypes might be reflective of the varying etiopathogenetic background of the subtypes of dementia [59]. BPSD cannot be explained only by cognitive decline, so various contributing factors have been investigated in order to elucidate the appearance of this group of symptoms in dementia. Factors affecting the BPSD include the factors related to the person with dementia, the caregiver factors, and the environmental influences. In addition, there are caregiver and environmental effects that can stimulate these behaviors independently, or in a combination, with the circuit disruptions seen during brain degeneration [2].

Factors related to the person with dementia, such as undiagnosed medical issues, can contribute to the development of behavioral disturbances [1]. Moreover, various medical issues, especially infections such as urinary tract infection, meningitis or encephalitis, may trigger BPSD in the patients with dementia, while in healthier patients these symptoms are absent. Other medical conditions associated with BPSD include electrolyte abnormalities in sodium, calcium or magnesium, hypo- or hyperglycemia, cerebrovascular accident, traumatic brain injury, constipation, urinary retention, dehydration, malnutrition, and pain, among others. When investigating the medical causes of BPSD, it is important to consider delirium, particularly in a sudden acute onset of new BPSD, due to the complex, and possibly overlapping relationship, between dementia, delirium and BPSD. Specifically, dementia is a risk factor for delirium, although most patients with BPSD will not experience delirium and most patients who have dementia with delirium will not develop BPSD [60]. Furthermore, there are the psychological factors such as premorbid personality structure, history of trauma, and preexisting psychiatric disorders that play a significant role in the development of dementia [61]. Premorbid neuroticism correlates with aggression and mood disturbance, while premorbid psychiatric disorders are associated with an increased risk for developing dementia and BPSD – specifically depression, bipolar disorder, schizophrenia, anxiety disorders and alcohol use disorder [62].

The manifestations of BPSD may be influenced by different factors, but they primarily reflect the pathophysiological changes happening in the brain. Dementia could disrupt the brain circuitry involved in the emotions and behavior, and thus lead to the development of BPSD. Different neuroanatomic circuits are implicated in the onset of BPSD in AD: these include gray matter loss in the temporal, entorhinal parietal lobes and hippocampus, loss of white matter in the temporal lobe, and atrophy in the anterior cingulate region [62]. Furthermore, dementia-related brain lesions and changes in the neurotransmission are linked to specific BPSD [15]. Neuronal loss in several brain regions, including the hippocampus, parahippocampal gyrus and various brain stem nuclei, are associated with psychotic symptoms in AD, whereas vascular factors may be triggers of hallucinations, illusions, anxiety, dysphoria, aggression and delirium in combined (vascular and AD) dementia [63]. Changes in cholinergic activity in the frontal and temporal cortices of the AD brain may be linked to aberrant motor activity and aggressive behavior [64]. In addition, reduced dopamine concentration in the temporal cortex [65], and decreased norepinephrine in the locus coeruleus neurons, are associated with aggression in AD patients [66]. Moreover, some findings suggest genetic risk factors exist for BPSD. Patients who have AD and carry the ApoEε4 allele have more delusions and agitation/aggressive behaviors than AD patients who are not carriers of this allele [67].

The role of the family caregivers is very important in the complexity of dementia. The self-efficacy, subjective well-being, and physical health are significantly lower in people who care for the person with dementia than in other caregivers, while their levels of psychological stress and distress are higher [68]. Rates of depression range from 23% to 85% in the people caring for patients with dementia [69]. Negative forms of communication, such as anger, screaming, or negative affect, coping abilities and strategies, and the mismatch between the expectations of the caregiver and the stage of illness are also factors related to caregivers that can stimulate or exacerbate behaviors [70]. Therefore, explaining to the caregivers that the patient´s behaviors are not volitional and that the patient is not "doing this on purpose" is beneficial [1].

In addition to the factors related to the person with dementia and to the caregiver, there are also the environmental influences. Processing and responding to environmental stimuli are difficult for patients with dementia. Due to a decreased ability to process stimuli, the stress threshold of people with dementia becomes lower, and the potential for higher levels of frustration increases concordantly. Changes in the patient's routine or environment, understimulation or overstimulation from their environment, and requirements that exceed their functional capabilities may increase the level of stress in patients with dementia [71].

Crowded housing conditions, sensory overstimulation, attitudes of the care staff toward challenging behaviors and/or the size of the units in which the patients reside throughout the day, are all the characteristics of the psychosocial or physical environment that can affect the presence of BPSD [72]. Additionally, if patients are restrained or subjected to multiple moves and procedures could contribute to a range of BPSD symptoms, particularly wandering and aggression [73]. However, lower levels of BPSD are in associated with well-being of nursing home residents due to the essential environmental factors such as unobtrusive safety features, the variety of spaces in environments with single and calm rooms available, small facility size, and optimization of the levels of stimulation, carefully considering the capacities of each patient [15].

5. BPSD impact on caregiver distress

Although cognitive decline is the hallmark of dementia, and memory-related symptoms represent a great burden to a caregiver, they were not reported as the major cause of distress among caregivers [1,21]. Instead, BPSD causes distress to both the patient and the caregiver, and in addition to affecting the patient's well-being, they can negatively influence the caregiver's general health, increasing their depression and anxiety behavior, interfering with their social and professional life, and decreasing their overall quality of life [74].

The caregiver's management of BPSD may vary from increasing the serious adverse effects and having negative impact on patient's health and well-being, to decreasing the mortality, and exerting the beneficial effects in some individuals [75]. The caregiver burden is a result of a complex network that includes both the patient's neuropsychological symptoms, their frequency, and the severity and the duration of the illness as the obvious predictors. Characteristics of the caregiver that can also have an effect include their sex, age, general health, personality traits (level of the confidence or neuroticism), the quality of their relationship with the patient, and their knowledge about the disease, as well as the socioeconomic status and level support [76,77].

The most common psychiatric changes due to the act of caregiving are depressive and anxiety symptoms, which are prevalent in 34% and 44% of caregivers respectively, as well as the frequent presence of minor or major depression [78]. Being female, of non-black ethnicity and of younger age are also significant predictors of depression in the caregiver, along with a lower financial income, bad relationship with the patient, family history of psychiatric disorders and the number of hours of caregiving in a day [79,80]. On the other hand, the patient's anxiety and depression, as well as the severity of the illness, result in more hours of care and limited amount of time for leisure activities, and both correlate significantly with anxiety in the caregiver [81,82]. It was noticeable that the caregiver who are also the patient's spouse showed greater depressive and anxiety-related symptoms [70,83]. The physical changes seen in the caregivers, especially ones who reported high levels of patient BPSD, include significantly higher levels of morning salivary cortisol than in non-caregiver subjects, as well as blunted cortisol response, which could indicate chronic stress overload and a decreased ability to cope with it [70]. Additionally, low-grade increases of the C reactive protein and tumor necrosis factor-α levels was also associated with being a caregiver and length of caregiving [84].

Although there is no evidence of a significant modulatory role of vascular risk factors on BPSD in AD patients [85], there are reported increases in levels of stress hormones and inflammatory factors in both the patients and the caregivers, as well as sleeping and eating disturbances, sedentary behavior and higher incidence of alcohol and cigarette consumption represent an increased risk of hypertension, coronary heart disease, autoimmune diseases and chronic conditions, as well as lower immunity and increased mortality risk [80]. The other factors influencing the caregiver's well-being are social isolation and work-related challenges such as higher unemployment rate, decreased working hours, early retirement and lower income [82].

The negative impact of neuropsychological symptoms on the caregiver's well-being has been thoroughly investigated, but it is still not clear which symptoms or symptom clusters, and in what manner, show the highest association with distress in the caregiver. Additionally, not only the type of symptoms, but also their frequency and the severity, significantly contribute to the caregiver's distress [13]. A recent meta-analysis [13] showed that the most distressing symptom for caregivers was depression, followed by aggressive behavior and apathy, while euphoria was the least distressing. This suggests that mood-related behavior strongly affects the caregiver's burden, while memory-related symptoms, despite being universally present in patients with dementia and the most frequent type of symptoms, were not reported as highly distressing [86], nor was the caregiver distress affected by the degree of severity of the dementia [87]. Numerous studies have shown that depression-related symptoms were highly distressing for caregivers [88], and that the prevalence of depression in patients was commonly accompanied with depression in the caregiver [89].

Violent behavior, including physical and verbal aggression, and irritability, was reported as the second most distressing symptom [13], although there was a distinction between verbal and physical aggression due, to a lower prevalence of physical aggression compared to verbal aggression. Aggressive behavior can represent a great stress and even threat to the caregiver, in addition to being interpreted as purposefully confrontational behavior, since it is not a commonly attributed symptom of dementia, and can result in a lack of understanding and poor management of symptoms by the caregiver [82]. Paranoid or delusional neuropsychological symptoms and hallucinations could deeply disturb and frighten the caregiver and lead to a greater burden when compared with patients without psychotic symptoms [90,91], while sleep disturbances and eating disorders could result in the caregiver's own sleep loss and inferior self-care [92]. Inappropriate social and sexual behavior are one of the most common types of disinhibition symptoms and, although they can be stressful to handle, these symptoms were not reported

to be as burdensome as the other ones, possibly due to their relatively low prevalence in patients with dementia generally, as this behavior is more characteristic for frontotemporal dementia [93].

However, neuropsychological symptoms and the caregiver's response to them form a bidirectional relationship. BPSD negatively affect not only the caregiver's burden, but also how the caregiver manages these symptoms, and their own characteristics can modulate the course of BPSD [82]. Dealing continuously with stressful neuropsychological symptoms, combined with a lack of the emotional support for the caregiver, may lead to the caregiver experiencing emotional detachment, irritability, impatience and loss of empathy for the patient, and this altered relationship can worsen symptoms and agitation of the patient [94]. The caregiver's own emotional state, stress, time and financial resources, as well as their ability to communicate, knowledge about the illness and cultural context also represent significant factors associated with the development and the course of the BPSD and consequently their own distress [13].

6. Therapeutic options for BPSD

Since BPSD are characterized by a large variety in the symptom clusters and multifaceted etiopathogenesis with various mediators [15], determination of an adequate treatment assessment is challenging, and often involves a polytherapeutic approach [60,95]. BPSD management should consider both the patients and their caregivers [15]. Therapeutic approaches for BPSD also include pain management, and the treatment of certain comorbid somatic disorders that appear in BPSD patients [15,60]. Due to a risk of potential side effects from pharmacotherapy, which is usually prescribed, a non-pharmacological approach is suggested as a first choice in BPSD management [15].

6.1. Non-pharmacological options for BPSD therapy

Non-pharmacological (or ecobiopsychosocial) approaches are very heterogeneous; however, there is still a lack of clear evidence about the effect of such therapeutic options [1,15]. This approach includes interventions for the caregivers and the patients, such as physical activity, aromatherapy, bright light and music therapy, psychoeducational and psychotherapeutic interventions, reminiscence, validation therapy, cognitive stimulation, and nursing care [15,60,96].

Physical activity has many benefits to human behavior and cognition. It has been assumed that physical activity in the form of walking might reduce BPSD symptoms [15]. In addition, some studies demonstrated that physical activity did not reduce BPSD, but showed positive results among the caregivers [96,97]. Aromatherapy is an intervention that is used for alleviating some of the behavioral symptoms in dementia [98]. Aromatherapies include the usage of different essential oils, such as lavender and melissa oil, diffused into the environment. It is known that lavender has many beneficial properties, including reducing agitation in patients with BPSD, alone or in a combination with acupressure [96,99]. A pilot study showed that aromatherapy in combination with the pharmacotherapy showed better results in comparison to the pharmacotherapeutic approach alone [100]. However, mixed results about aromatherapy as an intervention in BPSD patients have also been noted, whereas treatment duration and the type of essential oil did not make any difference to symptoms [99,101].

Bright light therapy (BLT) is used to normalize the circadian rhythm, which might be disturbed in BPSD, through the stimulation of suprachiasmatic nuclei. BLT has shown benefits in reducing agitation and depression in BPSD patients. Positive outcomes are also noticed in cognitive and sleep improvement [96,99]. Music therapy is an approach used to reduce various BPSD, including stress, agitation, apathy, irritability, anxiety, sleep disturbances, and delusions [99,102]. However, the effect of music therapy observed on depression was small. Although positive feelings after music therapy might activate the amygdala, the underlying mechanisms are still unknown [103].

Psychoeducational and psychotherapeutic interventions might reduce BPSD through single or group therapy. These include counseling, supporting the patients and providing assistance for the caregiver, which are all mostly beneficial in alleviating the burden of the caregivers. A combination of these two approaches showed great effect in decreasing aggression, depression, anxiety and, agitation [15]. Reminiscence therapy is an approach used to improve mood through memory stimulation [15]. It involves the patients, the caregivers and family members. By using objects such as photographs, books and familiar items, the aim of this therapy is to share experiences [98]. On the other hand, validation therapy is focused only on BPSD patients, in order to encourage positive feelings, through a reduction of negative feelings [15,99]. Finally, cognitive stimulation includes gardening, puzzles, word games, cooking and other activities, usually performed in small groups [98]. Some studies showed that cognitive stimulation had beneficial effects in BPSD reduction [98].

Although the non-pharmacological interventions were found to be useful, versatile, and potentially cost-effective in improving outcomes and a quality of life in the individuals with dementia, and in general have fewer adverse effects than pharmacotherapy [104,105], their widespread use faces many difficulties, such as a shortage of trained personnel, the limited knowledge about their efficacy, the preferences and opinions of the staff, as well as the time needed for symptom relief [4]. Moreover, a non-pharmacological approach sometimes does not show the expected efficacy in the BPSD patients, due to the wide range of symptoms expressed. In that case, an approach based on pharmacotherapy should be applied in order to alleviate the various symptoms [95].

6.2. Pharmacological options for BPSD therapy

Oral pharmacotherapy is quicker and easier than non-pharmacological interventions, it does not require involvement of professional staff, and allows the adjustment of treatment by titrating the drug dose. Nevertheless, pharmacological strategies, especially those that include an antipsychotic treatment, are not

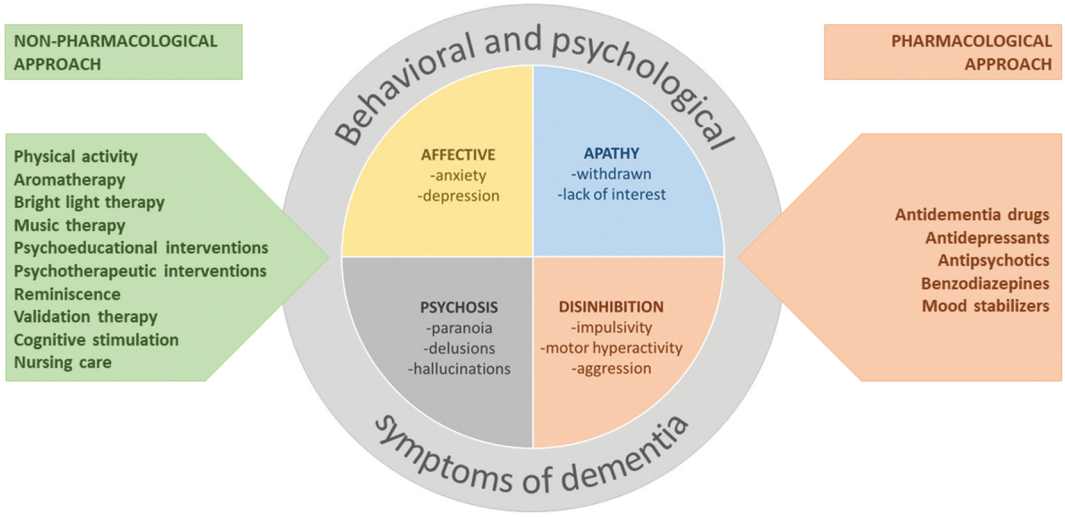

Figure 2. BPSD therapy: The combination of different non-pharmacological approaches is highly recommended for BPSD treatment. However, if necessary, a pharmacological approach should also be applied.

recommended, due to potential drug interactions and serious adverse effects, as well as increased mortality in patients with dementia [4]. Therefore, the pharmacological approach is used only when there is no adequate response to non-pharmacological treatment, and when the symptoms are not associated with any effect of the previous medication, as well as in the case of great distress of the patients, or if they represent danger to themselves or others [60,95].

The current pharmacological treatment of BPSD encompasses different groups of medication, such as antidementia drugs, antidepressants, antipsychotics, benzodiazepines and mood stabilizers [15,60,95].

For the treatment of BPSD, antidepressants are the most commonly used drugs, because they are usually associated with only mild side-effects [60]. Antidepressant therapy has shown positive outcomes in terms of cognitive improvement and the alleviation of affective symptoms [15]. The efficacy of antidepressants at alleviating agitation has been reported, while smaller positive effects have been observed in treating depression, psychosis, apathy and aggression [60]. While tricyclic antidepressants and paroxetine are not recommended due to certain anticholinergic side effects, selective serotonin reuptake inhibitors (SSRIs) showed good response and tolerability [15,95]. Sertraline and citalopram demonstrated good response in reducing agitation, when compared with placebo administration [95]. Patients who have been taking citalopram also showed cognitive improvement, as well as a reduction in tension, aggression and psychosis. Likewise, SSRI treatment with trazodone demonstrated a good outcome in BPSD treatment, including an alleviation of sleep disturbances [60,95].

Antidementia drugs, such as memantine and cholinesterase inhibitors might also represent a good treatment choice for BPSD [15]. For example, donepezil has been reported to be effective at alleviating of depression, irritability and apathy. Similar results were observed with rivastigmine and galantamine. While cholinesterase inhibitors are useful for reducing negative symptoms, memantine has been proven more efficient at reducing positive symptoms, such as aggression, hallucinations and delusions [15]. However, memantine in combination with citalopram or donepezil, as well as donepezil in combination with choline alphoscerate, demonstrated better effects on cognition and alleviating symptoms than each of these medications did alone [106–108]. Furthermore, treatment with Ginkgo biloba extract EGb 761® showed improvement in most of the BPSD symptoms [15,109].

On the other hand, the administration of antipsychotics is not recommended for dementia treatment, with the exception of risperidone, olanzapine and aripiprazole [15,60]. Atypical antipsychotics are effective in the treatment of certain symptoms, like aggression, agitation, excitation, abnormal behavior and psychotic symptoms [15,110], while haloperidol is only recommended for alleviating delirium [60]. Due to the adverse effects of antipsychotics, they are not proposed as a first-choice therapy for BPSD. Their side effects include seizures, metabolic syndrome, anticholinergic effects, extrapyramidal symptoms, sedation, delirium and weight gain [15,95].

Mood stabilizers also induce large adverse effects, therefore they are usually not recommended for BPSD treatment, with the exception of valproic acid [15]. Due to adverse effects, such as cognitive impairment, dizziness, depression, falls and sedation, treatment with benzodiazepines should be limited and used only in the cases of great distress, or when other pharmacological approaches have failed [15].

Due to a great variety of symptoms, a combination of different non-pharmacological approaches is highly recommended for BPSD treatment (Figure 2) [15], and a pharmacological approach should be applied only if it is necessary. According to published data, the most beneficial response in the BPSD patients has been observed following a polytherapeutic approach.

7. Biomolecules as potential biomarkers of BPSD

The neuroanatomical and neurochemical correlates of BPSD have been extensively investigated in order to elucidate the underlying neurobiology and involved biomolecules, and to

offer new biomarkers for better BPSD diagnosis and prognosis, as well as to help in the development of new, more effective treatments. White matter changes, atrophy patterns and vascular damage are the functional and structural parameters, which together with alternations in neurotransmission and neuromodulation, contribute to the development of BPSD [15]. AD-related damage in the brain areas containing serotonergic, noradrenergic and dopaminergic neurons is one possible reason for the monoamine deficiency observed in BPSD [111]. This decrease in monoamines in the AD brain is similar to the deficits observed in depression and anxiety disorders. Since these neurotransmitters are closely related to mood, energy, and reward, it is clear that depletion of their levels could lead to depression, apathy and other BPSD.

In addition, in AD cases who present with depression, apathy and aggressive behaviors also showed changes in GABA plasma levels [112], and dysfunction of N-methyl-D-aspartate (NMDA) receptor-related neurotransmission [113]. For instance, both GABA levels and the glutamate/GABA ratio showed significant negative correlations with depression in AD [114]. Therefore, AD patients with BPSD could benefit from treatments that target GABA and NMDA function. Sodium benzoate, an NMDA enhancer, which inhibits the D-amino acids oxidase (DAAO), has been shown potentially improve cognitive function in a subgroup of BPSD patients of both sexes [115], as well as in female BPSD patients with a later-phase dementia [116].

The primary finding of neuroimaging and biomarker investigations has been decreased function of monoaminergic neurotransmitters, such as those for serotonin, norepinephrine and dopamine, as well as lower frontoparietal metabolism in depressed AD patients [117]. Some postmortem studies observed a higher burden of neuropathology in AD subjects with depression [118,119]. It has been demonstrated that the neurotoxic effects of elevated cortisol levels in the hippocampus, present in chronic depression, can accelerate the neurodegenerative changes of AD [120]. Moreover, several areas of the AD brain revealed decreased concentrations of serotonin, with reduction of the 5-HT1 and 5HT-2 receptors seen especially in the cerebral cortex, suggesting a disturbed serotoninergic system [121]. In addition, subjects with dementia and depressive symptoms demonstrated a loss of noradrenergic cells, due to degeneration of the locus coeruleus [121].

Various studies observed an association of psychosis with neuropathological hallmarks in the AD brain, such as increased levels of beta-amyloid senile plaques and neurofibrillary tangles, as well as significant neuronal loss [122–125]. AD subjects with psychosis also showed elevations in their glycerophosphoethanolamine concentrations, as well as reduced NMDA levels in the temporal, frontal and parietal cortices [126]. Moreover, a variety of data support the role of acetylcholine, serotonin and dopamine imbalance in the pathogenesis of psychosis in both AD and DLB patients [127–131]. For instance, the ratio of serotonin to acetylcholinesterase levels correlates with the psychotic factor at least in women, whereas the function of the serotonergic system also showed a significant correlation with over-activity and psychosis in AD patients [132]. Various genes have been also associated with the psychosis in dementia, including *APOE4, G72, COMT, HTR2A, SERT, DAT*, and *DRD1-4* [128,133–136].

Furthermore, structural atrophy and functional deficits in the medial and frontal regions were observed in AD patients with apathy [108]. Decreased levels of dopamine, and homovanilic acid, as well as altered dopamine receptor density, in specific brain regions were detected in postmortem and *in vivo* studies of AD subjects suffering from apathy [137]. Multiple studies have together revealed the connection between apathy and atrophy, hypoperfusion and hypometabolism of the frontosubcortical cingulate pathways in AD patients [23], as well as subjects with frontotemporal dementia (FTD) [138,139].

Cortical dysfunction in the anterior cingulate, insula, lateral frontal and lateral temporal regions, as well as deficits in cholinergic transmission and the increased D2/D3 receptor availability in the striatum, were found in AD-related agitation and aggression [117]. Additionally, decreases in cholinergic function correlated with the aggressive behavior factor in patients with AD [132].

Increased levels of the neurofibrillary tangles in the orbitofrontal cortex have been linked to agitation [140], while aggressive behavior has been associated with neuronal loss in the locus coeruleus of AD patients [141]. On the other hand, the deterioration of the brain stem regions and the suprachiasmatic nucleus of the hypothalamus has been reported in AD patients with sleep disorders [142].

The development and use of specific new investigation techniques could be useful to better understand the etiological mechanisms of the BPSD and involved biomolecules, as well as to offer novel, efficient and more symptom-focused interventions that will improve the management of neuropsychiatric symptoms in subjects with dementia [2,30].

8. Conclusion

Although cognitive deterioration has been the major focus of dementia research, more recently the investigation of BPSD have also gained significant attention. This is because these neuropsychiatric symptoms occur frequently throughout the course and different stages of dementia and represent a significant problem in everyday clinical practice due to their high prevalence, severity and burden on the patient and the caregiver, as well as significant financial costs and lack of effective therapies. The correct diagnosis and assessment of this heterogeneous group of non-cognitive symptoms and behaviors, consisting of disturbed emotions, mood, perception, thought, motor activity and personality traits, is a crucial aspect of the clinical management of dementia. The multifactorial etiology of BPSD is still not clear, but probably occurs due to a complex interplay of psychological, social, and biological factors. Given the modest efficacy of current non-pharmacological and pharmacological strategies, the correct identification and evaluation of these symptoms, as well as better understanding of their etiological underpinnings and involved biomolecules, is crucial for tailoring the therapeutic intervention for each individual and monitoring the patient's response to the therapy. However, since BPSD also negatively affects the burden on the caregiver, their management

(consisting of the person-centered interventions) needs to consider both the dementia patients themselves and their caregivers. In this review, we discuss the epidemiology, classification and assessment, etiology and impact of BPSD on caregiver distress, current non-pharmacological and pharmacological therapeutic options, as well as various biomolecules as potential biomarkers of BPSD, with the aim of providing the framework for improving the diagnosis and management of BPSD, as well as to encourage the further research needed to offer novel, targeted, and specific therapeutic strategies for BPSD.

9. Expert opinion

The clinical presentation of dementia goes far beyond cognitive decline, and includes a wide variety of neuropsychiatric symptoms, which develop throughout the course and different stages of dementia. The lack of disease-modifying drugs for dementia means that the drugs used only alleviate cognitive symptoms, in combination with administration of various psychotropic medications to target different BPSD. However, due to the heterogeneity of BPSD, the choice of an adequate treatment is very challenging and frequently requires a polytherapeutic approach. Since dementia patients are physically and cognitively frail, with high levels of medical and psychiatric comorbidity resulting the use of multiple medications, clinicians and the caregivers must pay special attention to possible drug interactions and adverse effects. Therefore, the prescription of new medications, including pharmacotherapies for BPSD, should always be introduced slowly and gradually, carefully assessing the response in the dementia patients. The development of the multi-target drugs could represent an effective approach to generate effective and safer therapeutic options, suitable for the elderly patients with BPSD. For instance, vortioxetine, an antidepressant drug with a multimodal mechanism of action [143], demonstrated promising effects in improving cognition in older adults with depressive symptoms and could be useful in BPSD treatment [144]. Similarly, the rapid-acting antidepressant esketamine, which probably functions through influencing BDNF synthesis and exerts anti-inflammatory actions, could represent the first-in-class drug for the treatment of BPSD, and therefore its efficacy and safety in the patients with dementia should be investigated further [145]. In addition, various natural products and food supplements, with potentially lower toxicity and fewer side effects in comparison to the classical pharmacotherapy, may alleviate some neuropsychiatric symptoms of dementia and could be beneficial as a complementary therapy [146]. However, given the limitations of pharmacotherapy available for treating dementia patients, non-pharmacological treatment strategies are recommended as a first choice in the management of BPSD. Non-pharmacologic approaches, such as physical exercise, aromatherapy, bright light and music therapy, psychoeducational and psychotherapeutic interventions, activity therapies and other similar programs, have shown promising results in ameliorating BPSD, but further research is needed to validate their beneficial effects. On the other hand, the goal of the non-pharmacological treatment is not limited to the alleviation of the neuropsychiatric symptoms, since it may also lower the consumption of psychotropic drugs and significantly improve quality of life in dementia patients. Nevertheless, implementing non-pharmacologic treatment strategies can be challenging due to a lack of adequate staff training and the time required for the implementation of such interventions. Finally, it should be kept in mind, that BPSD negatively affects not only the patient, but also the burden on the caregiver, and that the caregiver's management of these symptoms can significantly affect the course of BPSD. Therefore, interventions directed toward alleviating the caregiver's distress and building the problem-solving abilities of the caregiver, as well as improving the communication between the caregiver and the dementia patient, are suggested in order to reduce behavioral disturbances. Training programs of this type that assist the caregivers in prevention, assessment, and management of BPSD could represent new first line strategies. In summary, the repurposing of already available, as well as the *de novo* development, of both pharmacologic and non-pharmacologic treatments should be considered for BPSD therapy. The therapeutic approach to neuropsychiatric symptoms for each person with dementia needs to be tailored based on the stage of dementia, main behavioral symptoms, cognitive state, comorbidities, physical fitness, as well as individual preferences. Such person-centered interventions, in addition to the caregiver-focused training and education, could be effective in management of BPSD, but will require concerted team effort.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Gerlach LB, Kales HC. Managing behavioral and psychological symptoms of dementia. Psychiatr Clin North Am. 2018;41 (1):127–139.
   • **This systematic review evaluated the available evidence for effectiveness and tolerability of pharmacologic treatments in addressing BPSD.**
2. Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. BMJ. 2015;350(mar02 7):h369.
3. Zhao QF, Tan L, Wang HF, et al. The prevalence of neuropsychiatric symptoms in Alzheimer's disease: systematic review and meta-analysis. J Affect Disord. 2016;190:264–271.
4. Magierski R, Sobow T, Schwertner E, et al. Pharmacotherapy of behavioral and psychological symptoms of dementia: state of the art and future progress. Front Pharmacol. 2020;11:1168.
   •• **This paper reviews current knowledge of the management of BPSD and its limitations and discusses ongoing clinical trials and future therapeutic options.**
5. Lim SC. Managing behavioral and psychological symptoms of dementia - from a geriatrician's perspective. J Aging Geriatr Psychiatry. 2018;21:1–7.
6. Leung DKY, Wong KKY, Spector A, et al. Exploring dementia family carers' self-initiated strategies in managing behavioral and psychological symptoms in dementia: a qualitative study. BMJ Open. 2021;11(8):e048761.
7. Finkel SI, Costa E Silva J, Cohen G, et al. Behavioral and psychological signs and symptoms of dementia: a consensus statement on current knowledge and implications for research and treatment. Int Psychogeriatr. 1996;8(Suppl 3):497–500.
8. Burley CV, Casey AN, Chenoweth L, et al. Reconceptualizing behavioral and psychological symptoms of dementia: views of people living with dementia and families/care partners. Front Psychiatry. 2021;12:710703.
9. Cloak N, Khalili YA. Behavioral and psychological symptoms in dementia. Treasure Island (FL): StatPearls Publishing; 2022.
10. Finkel SI. Behavioral and psychologic symptoms of dementia. Clin Geriatr Med. 2003 Nov;19(4):799–824.
11. Scassellati C, Ciani M, Maj C, et al. Behavioral and psychological symptoms of dementia (BPSD): clinical characterization and genetic correlates in an Italian Alzheimer's disease cohort. J Pers Med. 2020;10(3):90.
12. Kolanowski A, Boltz M, Galik E, et al. Determinants of behavioral and psychological symptoms of dementia: a scoping review of the evidence. Nurs Outlook. 2017;65(5):515–529.
13. Feast A, Orrell M, Charlesworth G, et al. Behavioral and psychological symptoms in dementia and the challenges for family carers: systematic review. Br J Psychiatry. 2016;208(5):429–434.
14. Kim B, Noh GO, Kim K. Behavioral and psychological symptoms of dementia in patients with Alzheimer's disease and family caregiver burden: a path analysis. BMC Geriatr. 2021;21(1):160.
15. Tible OP, Riese F, Savaskan E, et al. Best practice in the management of behavioral and psychological symptoms of dementia. Ther Adv Neurol Disord. 2017;10(8):297–309.
16. Van der Linde RM, Dening T, Stephan BC, et al. Longitudinal course of behavioral and psychological symptoms of dementia: systematic review. Br J Psychiatry. 2016;209(5):366–377.
17. Rabins PV, Schwartz S, Black BS, et al. Predictors of progression to severe Alzheimer's disease in an incidence sample. Alzheimers Dement. 2013;9(2):204–207.
18. Wancata J, Windhaber J, Krautgartner M, et al. The consequences of non-cognitive symptoms of dementia in medical hospital departments. Int J Psychiatry Med. 2003;33(3):257–271.
19. Resnick B, Galik E, Kolanowski A, et al. Gender differences in presentation and management of behavioral and psychological symptoms associated with dementia among nursing home residents with moderate to severe dementia. J Women Aging. 2020;33(1):1–18.
20. Cipriani G, Lucetti C, Danti S, et al. Apathy and dementia. Nosology, assessment and management. J Nerv Ment Dis. 2014;202 (10):718–724.
21. Fauth EB, Gibbons A. Which behavioral and psychological symptoms of dementia are the most problematic? Variability by prevalence, intensity, distress ratings, and associations with caregiver depressive symptoms. Int J Geriatr Psychiatry. 2014;29(3):263–271.
22. García-Alberca JM, Lara Muñoz JP, Berthier Torres M. Neuropsychiatric and behavioral symptomatology in Alzheimer disease. Actas Esp Psiquiatr. 2010;38(4):212–222.
23. Tampi RR, Williamson D, Muralee S, et al. Behavioral and psychological symptoms of dementia: part I—epidemiology, neurobiology, heritability, and evaluation. Clin Geriatr. 2011;19(5):41–46.
24. Van der Linde RM, Stephan BCM, Savva GM, et al. Systematic reviews on behavioral and psychological symptoms in the older or demented population. Alzheimers Res Ther. 2012;4(4):28.
25. Fuh JL. Study of behavioral and psychological symptoms of dementia in Taiwan. Acta Neurol Taiwan. 2006;15(3):154–160.
26. Huang S, Wang WF, Liao YC. Severity and prevalence of behavioral and psychological symptoms among patients of different dementia stages in Taiwan. Arch Clin Psychiatry. 2017;44(4):89–93.
27. Ismail Z, Smith EE, Geda Y, et al. Neuropsychiatric symptoms as early manifestations of emergent dementia: provisional diagnostic criteria for mild behavioral impairment. Alzheimers Dement. 2016;12(2):195–202.
28. Mortby ME, Ismail Z, Anstey KJ. Prevalence estimates of mild behavioral impairment in a population-based sample of pre-dementia states and cognitively healthy older adults. Int Psychogeriatr. 2018;30(2):221–232.
29. Hashimoto M, Yatabe Y, Ishikawa T, et al. Relationship between dementia severity and behavioral and psychological symptoms of dementia in dementia with lewy bodies and Alzheimer's disease patients. Dement Geriatr Cogn Dis Extra. 2015;5(2):244–252.
30. Cerejeira J, Lagarto L, Mukaetova-Ladinska EB. Behavioral and psychological symptoms of dementia. Front Neurol. 2012;3:73.
31. Rockwell E, Choure J, Galasko D, et al. Psychopathology at initial diagnosis in dementia with Lewy bodies versus Alzheimer disease: comparison of matched groups with autopsy-confirmed diagnoses. Int J Geriatr Psychiatry. 2000;15(9):819–823.
32. Ikeda M, Brown J, Holland AJ, et al. Changes in appetite, food preference, and eating habits in frontotemporal dementia and Alzheimer's disease. J Neurol Neurosurg Psychiatry. 2002;73 (4):371–376.
33. Engelborghs S, Maertens K, Nagels G, et al. Neuropsychiatric symptoms of dementia: cross-sectional analysis from a prospective, longitudinal Belgian study. Int J Geriatr Psychiatry. 2005;20(11):1028–1037.
34. Chiu MJ, Chen TF, Yip PK, et al. Behavioral and psychologic symptoms in different types of dementia. J Formos Med Assoc. 2006;105 (7):556–562.
35. Liu S, Jin Y, Shi Z, et al. The effects of behavioral and psychological symptoms on caregiver burden in frontotemporal dementia, Lewy body dementia, and Alzheimer's disease: clinical experience in China. Aging Ment Health. 2017;21(6):651–657.
36. Mukherjee A, Biswas A, Roy A, et al. Behavioral and psychological symptoms of dementia: correlates and impact on caregiver distress. Dement Geriatr Cogn Dis Extra. 2017;7(3):354–365.
37. Majer R, Simon V, Csiba L, et al. Behavioral and psychological symptoms in neurocognitive disorders: specific patterns in dementia subtypes. Open Med (Wars). 2019;14(1):307–316.
38. Köhler CA, Magalhaes TF, Oliveira JM, et al. Neuropsychiatric disturbances in mild cognitive impairment (MCI): a systematic review of population-based studies. Curr Alzheimer Res. 2016;13(10):1066–82.39.
39. Modrego PJ, Ferrandez J. Depression in patients with mild cognitive impairment increases the risk for developing dementia of Alzheimer type: A prospective color study. Arch Neurol. 2004;61 (8):1290–1293.
40. Brodaty H, Heffernan M, Draper B, et al. Neuropsychiatric symptoms in older people with and without cognitive impairment. J Alzheimers Dis. 2012;31(2):411–420.

41. Diniz BS, Butters MA, Albert SM, et al. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. Br J Psychiatry. 2012;202(5):329–335.
42. Palmer K, Berger AK, Monastero R, et al. Predictors of progression from mild cognitive impairment to Alzheimer disease. Neurology. 2007;68(19):1596–1602.
43. Palmer K, Di Iulio F, Varsi AE, et al. Neuropsychiatric predictors of progression from amnestic-mild cognitive impairment to Alzheimer's disease: the role of depression and apathy. J Alzheimers Dis. 2010;20(1):175–183.
44. Lee J, Lee KJ, Kim H. Gender differences in behavioral and psychological symptoms of patients with Alzheimer's disease. Asian J Psychiatr. 2017;26:124–128.
45. Hsieh SW, Chen CH, Huang LC, et al. Gender differences in presentation of behavioral and psychological symptoms in Alzheimer's disease in Taiwan. Aging Ment Health. 2020;24(8):1342–1347.
46. Mao Y, Fisher DW, Yang S, et al. Protein-protein interactions underlying the behavioral and psychological symptoms of dementia (BPSD) and Alzheimer's disease. PLoS One. 2020;15(1):e0226021.
47. Zaudig M. Assessing behavioral symptoms of dementia of the Alzheimer type: categorical and quantitative approaches. Int Psychogeriatr. 1996;8(S2):183–200.
48. De Deyn PP, Wirshing WC. Scales to assess efficacy and safety of pharmacologic agents in the treatment of behavioral and psychological symptoms of dementia. J Clin Psychiatry. 2001;62:19–22.
49. Auer SR, Monteiro IM, Reisberg B. The empirical behavioral pathology in Alzheimer's disease (E-BEHAVE-AD) rating scale. Intl Psychogeriatr. 1996;8(2):247–266.
50. Reisberg B, Auer SR, Monteiro IM. Behavioral pathology in Alzheimer's disease (BEHAVE-AD) rating scale. Int Psychogeriatr. 1996;8:301–308.
51. Reisberg B, Borenstein J, Franssen E, et al. BEHAVE-AD: a Clinical Rating Scale for the Assessment of Pharmacologically Remediable Behavioral Symptomatology in Alzheimer's Disease. In: Alzheimer's Disease: Problems, Prospects, and Perspectives, editor. Altman HJ. 1987;pp. 1–16. Boston, MA: Springer.
52. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology. 1994;44(12):2308–2314.
53. Cummings JL. The Neuropsychiatric Inventory: assessing psychopathology in dementia patients. Neurology. 1997;48(5):S10–16.
54. Kaufer DI, Cummings JL, Ketchel P. Validation of the NPI-Q, a brief clinical form of the Neuropsychiatric Inventory. J Neuropsychiatry Clin Neurosci. 2000;12(2):233–239.
55. Wood S, Cummings JL, Hsu MA, et al. The use of the Neuropsychiatric Inventory in nursing home residents: characterization and measurement. Am J Geriatr Psychiatry. 2000;8(1):75–83.
56. De Medeiros K, Robert P, Gauthier S, et al. The Neuropsychiatric Inventory-Clinician rating scale (NPI-C): reliability and validity of a revised assessment of neuropsychiatric symptoms in dementia. Int Psychogeriatr. 2010;22(6):984–994.
57. Cohen-Mansfield J, Marx M, Rosenthal A. A description of agitation in a nursing home. J Gerontol. 1989;44(3):M77–M84.
58. Kupeli N, Vickerstaff V, White N, et al. Psychometric evaluation of the Cohen-Mansfield Agitation Inventory in an acute general hospital setting. Int J Geriatr Psychiatry. 2018;33(1):e158–e165.
59. Bessey LJ, Walaszek A. Management of behavioral and psychological symptoms of dementia. Curr Psychiatry Rep. 2019;21(8):66.
•• **The paper examines methods for BPSD assessment and evidence for interventions, focusing on recent findings and innovations, and recommends an algorithm for management of BPSD.**
60. Prior J, Abraham R, Nicholas H, et al. Are premorbid abnormal personality traits associated with behavioral and psychological symptoms in dementia? Int J Geriatr Psychiatry. 2016;31(9):1050–1055.
61. Zilkens RR, Bruce DG, Duke J, et al. Severe psychiatric disorders in mid-life and risk of dementia in late-life (age 65–84 years): a population based case-control study. Curr Alzheimer Res. 2014;11(7):681–693.
62. Ambrogio F, Martella LA, Odetti P, et al., Behavioral disturbances in dementia and beyond: time for a new conceptual frame. Int J Mol Sci. 2019;20(15):3647.
• **This paper provides an update of evidence on the behavioral patterns associated with different dementia subtypes and offers a potential future perspective for the development of new translational studies in the BPSD field.**
63. Kazui H, Yoshiyama K, Kanemoto H, et al. Differences of behavioral and psychological symptoms of dementia in disease severity in four major dementias. PLoS One. 2016;11(8):e0161092.
64. Minger SL, Esiri MM, McDonald B, et al. Cholinergic deficits contribute to behavioral disturbance in patients with dementia. Neurology. 2000;55(10):1460–1467.
65. Engelborghs S, Vloeberghs E, Le Bastard N, et al. The dopaminergic neurotransmitter system is associated with aggression and agitation in frontotemporal dementia. Neurochem Int. 2008;52(6):1052–1060.
66. Herrmann N, Lanctôt KL, Khan LR. The role of norepinephrine in the behavioral and psychological symptoms of dementia. J Neuropsychiatry Clin Neurosci. 2004;16(3):261–276.
67. Flirski M, Sobow T, Kloszewska I. Behavioral genetics of Alzheimer´s disease: a comprehensive review. Arch Med Sci. 2011;7(2):195–210.
68. Ballard CG, Gauthier S, Cummings JL, et al. Management of agitation and aggression associated with Alzheimer disease. Nat Rev Neurol. 2009;5(5):245–255.
69. Clare L, Wilson BA, Carter G, et al. Depression and anxiety in memory clinic attenders and their carers: implications for evaluating the effectiveness of cognitive rehabilitation interventions. Int J Geriatr Psychiatry. 2002;17(10):962–967.
70. De Vugt ME, Nicolson NA, Aalten P, et al. Behavioral problems in dementia patients and salivary cortisol patterns in caregivers. J Neuropsychiatry Clin Neurosci. 2005;17(2):201–207.
71. Smith M, Hall GR, Gerdner L, et al. Application of the progressively lowered stress threshold model across the continuum of care. Nurs Clin North Am. 2006;41(1):57–81.
72. Zuidema SU, de Jonghe JF, Verhey FR, et al. Environmental correlates of neuropsychiatric symptoms in nursing home patients with dementia. Int J Geriatr Psychiatry. 2010;25(1):14–22.
73. Kunik ME, Snow AL, Davila JA, et al. Consequences of aggressive behavior in patients with dementia. J Neuropsychiatry Clin Neurosci. 2010;22(1):40–47.
74. Clyburn LD, Stones MJ, Hadjistavropoulos T, et al. Predicting caregiver burden and depression in Alzheimer's disease. J Gerontol B Psychol Sci Soc Sci. 2000;55(1):S2–13.
75. Brown SL, Smith DM, Schulz R, et al. Caregiving behavior is associated with decreased mortality risk. Psychol Sci. 2009;20(4):488-494.
76. Kasuya RT, Polgar-Bailey P, Takeuchi R. Caregiver burden and burnout. A guide for primary care physicians. Postgrad Med. 2000;108(7):119–123.
77. Campbell P, Wright J, Oyebode J, et al. Determinants of burden in those who care for someone with dementia. Int J Geriatr Psychiatry. 2008;23(10):1078–1085.
78. Volicer L. Caregiver burden in dementia care: prevalence and health effects. Curr Psychos Ther Reports. 2005;3:20-25.
79. Vellone E, Piras G, Sansoni J. Stress, anxiety, and depression among caregivers of patients with Alzheimer's disease. Ann Ig. 2002;14(3):223-232.
80. Vitaliano PP, Zhang J, Scanlan JM. Is caregiving hazardous to one's physical health? A meta-analysis. Psychol Bull. 2003;129(6):946-972.
81. Lou Q, Liu S, Huo YR, et al. Comprehensive analysis of patient and caregiver predictors for caregiver burden, anxiety and depression in Alzheimer's disease. J Clin Nurs. 2015;24(17–18):2668-2678.
82. Isik AT, Soysal P, Solmi M, et al., Bidirectional relationship between caregiver burden and neuropsychiatric symptoms in patients with Alzheimer's disease: a narrative review. Int J Geriatr Psychiatry. 2019;34(9):1326–1334.

•• **The aim of this review is to make a state of the art of the potential influence of neuropsychiatric symptoms (NPs) on caregiver stress and vice versa.**

83. Baiyewu O, Smith-Gamble V, Akinbiyi A, et al. Behavioral and caregiver reaction of dementia as measured by the neuropsychiatric inventory in Nigerian community residents. Int Psychogeriatr. 2003;15(4):399–409.
84. Von Känel R, Mills PJ, Mausbach BT, et al. Effect of Alzheimer caregiving on circulating levels of C-reactive protein and other biomarkers relevant to cardiovascular disease risk: a longitudinal study. Gerontology. 2012;58(4):354-365.
85. Steinberg M, Hess K, Corcoran C, et al. Vascular risk factors and neuropsychiatric symptoms in Alzheimer's disease: the Cache County Study. Int J Geriatr Psychiatry. 2014;29(2):153–159.
86. Bruce DG, Paterson A. Barriers to community support for the dementia carer: a qualitative study. Int J Geriatr Psychiatry. 2000;15(5):451–457.
87. Davidsdottir SR, Snaedal J, Karlsdottir G, et al. Validation of the Icelandic version of the Neuropsychiatric Inventory with caregiver distress (NPI-D). Nord J Psychiatry. 2012;66(1):26–32.
88. Kosberg JI, Kaufman AV, Burgio LD, et al. Family caregiving to those with dementia in rural Alabama: racial similarities and differences. J Aging Health. 2007;19(1):3–21.
89. Waite A, Bebbington P, Skelton-Robinson M, et al. Social factors and depression in carers of people with dementia. Int J Geriatr Psychiatry. 2004;19(6):582–587.
90. Riello R, Geroldi C, Zanetti O, et al. Caregiver's distress is associated with delusions in Alzheimer's patients. Behav Med. 2002;28(3):92-98.
91. Connors MH, Ames D, Woodward M, et al. Psychosis and clinical outcomes in Alzheimer disease: a longitudinal study. Am J Geriatr Psychiatry. 2017;26(3):304-313.
92. McCurry SM, Logsdon RG, Teri L, et al. Characteristics of sleep disturbance in community-dwelling Alzheimer's disease patients. J Geriatr Psychiatry Neurol. 1999;12(2):53–59.
93. Canevelli M, Lucchini F, Garofalo C, et al. Inappropriate sexual behaviors among community-dwelling patients with dementia. Am J Geriatr Psychiatry. 2017;25(4):365-371.
94. Hamel M, Gold DP, Andres D, et al. Predictors and consequences of aggressive behavior by community-based dementia patients. Gerontologist. 1990;30(2):206-211.
95. Preuss UW, Wong JWM, Koller G. Treatment of behavioral and psychological symptoms of dementia: a systematic review. Psychiatr Pol. 2016;50(4):679–715.
96. De Oliveira AM, Radanovic M, Cotting Homem de Mello P, et al. Nonpharmacological interventions to reduce behavioral and psychological symptoms of dementia: a systematic review. Biomed Res Int. 2015;2015:218980.
97. Lowery D, Cerga-Pashoja A, Iliffe S, et al. The effect of exercise on behavioral and psychological symptoms of dementia: the EVIDEM-E randomized controlled clinical trial. Int J Geriatr Psychiatry. 2014;29(8):819–827.
98. Abraha I, Rimland JM, Trotta FM, et al. Systematic review of systematic reviews of non-pharmacological interventions to treat behavioral disturbances in older patients with dementia. The SENATOR-OnTop series. BMJ Open. 2017;7(3):e012759.
99. Scales K, Zimmerman S, Miller SJ. Evidence-based nonpharmacological practices to address behavioral and psychological symptoms of dementia. Gerontologist. 2018;58(suppl_1):S88–S102.

• **This review aims to identify, describe, and critique nonpharmacological practices to address BPSDs and provide evidence-based recommendations for dementia care.**

100. Mascherona I, Ferretti M, Soldini E, et al. Essential oil therapy for the short-term treatment of behavioral and psychological symptoms of dementia: a monocentric randomized pilot study. Aging Clin Exp Res. 2021;33(8):2251–2259.
101. Press-Sandler O, Freud T, Volkov I, et al. Aromatherapy for the treatment of patients with behavioral and psychological symptoms of dementia: a descriptive analysis of RCTs. J Altern Complement Med. 2016;22(6):422–428.
102. Raglio A, Bellelli G, Traficante D, et al. Efficacy of music therapy in the treatment of behavioral and psychiatric symptoms of dementia. Alzheimer Dis Assoc Disord. 2008;22(2):158–162.
103. Ueda T, Suzukamo Y, Sato M, et al. Effects of music therapy on behavioral and psychological symptoms of dementia: a systematic review and meta-analysis. Ageing Res Rev. 2013;12(2):628–641.
104. Olazarán J, Reisberg B, Clare L, et al. Nonpharmacological therapies in Alzheimer's disease: a systematic review of efficacy. Dement Geriatr Cogn Disord. 2010;30(2):161–178.
105. Dyer SM, Harrison SL, Laver K, et al. An overview of systematic reviews of pharmacological and non-pharmacological interventions for the treatment of behavioral and psychological symptoms of dementia. Int Psychogeriatr. 2018 Mar;30(3):295–309.
106. Zhou T, Wang J, Xin C, et al. Effect of memantine combined with citalopram on cognition of BPSD and moderate Alzheimer's disease: a clinical trial. Exp Ther Med. 2019;17(3):1625–1630.
107. Carotenuto A, Rea R, Traini E, et al. The effect of the association between donepezil and choline alphoscerate on behavioral disturbances in Alzheimer's disease: interim results of the ASCOMALVA trial. J Alzheimers Dis. 2017;56(2):805–815.
108. Chen R, Chan PT, Chu H, et al. Treatment effects between monotherapy of donepezil versus combination with memantine for Alzheimer's disease: a meta-analysis. PLoS One. 2017;12(8):e0183586.
109. Savaskan E, Mueller H, Hoerr R, et al. Treatment effects of Ginkgo biloba extract EGb 761® on the spectrum of behavioral and psychological symptoms of dementia: meta-analysis of randomized controlled trials. Int Psychogeriatr. 2018;30(3):285–293.
110. Ohno Y, Kunisawa N, Shimizu S. Antipsychotic treatment of behavioral and psychological symptoms of dementia (BPSD): management of extrapyramidal side effects. Front Pharmacol. 2019;10:1045.
111. Wolinsky D, Drake K, Bostwick J. Diagnosis and management of neuropsychiatric symptoms in Alzheimer´s disease. Curr Psychiatry Rep. 2018;20(12):117.
112. Lanctôt KL, Herrmann N, Rothenburg L, et al. Behavioral correlates of GABAergic disruption in Alzheimer's disease. Int Psychogeriatr. 2007;19(1):151–158.
113. Lin CH, Lane HY. The role of N-methyl-D-aspartate receptor neurotransmission and precision medicine in behavioral and psychological symptoms of dementia. Front Pharmacol. 2019;10:540.
114. Garcia-Alloza M, Tsang SW, Gil-Bea FJ, et al. Involvement of the GABAergic system in depressive symptoms of Alzheimer's disease. Neurobiol Aging. 2006;27(8):1110–1117.
115. Lin CH, Yang HT, Chen PK, et al. Precision medicine of sodium benzoate for the treatment of behavioral and psychological symptoms of dementia (BPSD). Neuropsychiatr Dis Treat. 2020;16:509–518.
116. Lin CH, Chen PK, Wang SH, et al. Effect of sodium benzoate on cognitive function among patients with behavioral and psychological symptoms of dementia: secondary analysis of a randomized clinical trial. JAMA Network Open. 2021;4(4):e216156.
117. Nowrangi MA, Lyketsos CG, Rosenberg PB. Principles and management of neuropsychiatric symptoms in Alzheimer's dementia. Alzheimers Res Ther. 2015;7(1):1–10.
118. Rapp MA, Schnaider-Beeri M, Grossman HT, et al. Increased hippocampal plaques and tangles in patients with Alzheimer disease with a lifetime history of major depression. Arch Gen Psychiatry. 2006;63(2):161–167.
119. Rapp MA, Schnaider-Beeri M, Purohit DP, et al. Increased neurofibrillary tangles in patients with Alzheimer's disease with comorbid depression. Am J Geriatr Psychiatry. 2008;16(2):168–174.
120. Korczyn AD, Halperin I. Depression and dementia. J Neurol Sci. 2009;283(1–2):139–142.
121. Lanari A, Amenta F, Silvestrelli G, et al. Neurotransmitter deficits in behavioral and psychological symptoms of Alzheimer's disease. Mech Aging Dev. 2006;127(2):158–165.
122. Zubenko GS, Moossy J, Martinez AJ, et al. Neuropathologic and neurochemical correlates of psychosis in primary dementia. Arch Neurol. 1991;48(6):619–624.

123. Bergener M, Finkel SI. Treating Alzheimer´s and other dementias: clinical application of recent research advances. New York (NY): Springer; 1995. Chapter 6, Biochemical, Neuropathological, and Clinical Correlations of Neurofibrillary Degeneration in Alzheimer's Disease; p. 57–80.
124. Förstl H, Burns A, Levy R, et al. Neuropathological correlates of psychotic phenomena in confirmed Alzheimer's disease. Br J Psychiatry. 1994;165(1):53–59.
125. Farber NB, Rubin EH, Newcomer JW, et al. Increased neocortical neurofibrillary tangle density in subjects with Alzheimer disease and psychosis. Arch Gen Psychiatry. 2000;57(12):1165–1173.
126. Sweet RA, Panchalingam K, Pettegrew JW, et al. Psychosis in Alzheimer disease: postmortem magnetic resonance spectroscopy evidence of excess neuronal and membrane phospholipid pathology. Neurobiol Aging. 2002;23(4):547–553.
127. Pinto T, Lanctôt KL, Herrmann N. Revisiting the cholinergic hypothesis of behavioral and psychological symptoms in dementia of the Alzheimer's type. Aging Res Rev. 2011;10(4):404–412.
128. Ismail Z, Nguyen MQ, Fischer CE, et al. Neurobiology of delusions in Alzheimer's disease. Curr Psychiatry Rep. 2011;13(3):211–218.
129. Tsang SW, Francis PT, Esiri MM, et al. Loss of [3 H]4-DAMP binding to muscarinic receptors in the orbitofrontal cortex of Alzheimer's disease patients with psychosis. Psychopharmacology (Berl). 2008;198(2):251–259.
130. Ballard C, Piggott M, Johnson M, et al. Delusions associated with elevated muscarinic binding in dementia with Lewy bodies. Ann Neurol. 2000;48(6):868–876.
131. Teaktong T, Piggott MA, Mckeith IG, et al. Muscarinic M2 and M4 receptors in anterior cingulate cortex: relation to neuropsychiatric symptoms in dementia with Lewy bodies. Behav Brain Res. 2005;161(2):299–305.
132. Garcia-Alloza M, Gil-Bea FJ, Diez-Ariza M, et al. Cholinergic-serotonergic imbalance contributes to cognitive and behavioral symptoms in Alzheimer's disease. Neuropsychologia. 2005;43(3):442–449.
133. Borroni B, Grassi M, Agosti C, et al. Genetic correlates of behavioral endophenotypes in Alzheimer disease: role of COMT, 5-HTTLPR and APOE polymorphisms. Neurobiol Aging. 2006;27(11):1595–1603.
134. Angelucci F, Bernardini S, Gravina P, et al. Delusion symptoms and response to antipsychotic treatment are associated with the 5-HT2A receptor polymorphism (102 T/C) in Alzheimer's disease: a 3-year follow-up longitudinal study. J Alzheimers Dis. 2009;17(1):203–211.
135. Di Maria E, Bonvicini C, Bonomini C, et al. Genetic variation in the G720/G30 gene locus (DAOA) influences the occurrence of psychotic symptoms in patients with Alzheimer's disease. J Alzheimers Dis. 2009;18(4):953–960.
136. Proitsi P, Lupton MK, Reeves SJ, et al. Association of serotonin and dopamine gene pathways with behavioral subphenotypes in dementia. Neurobiol Aging. 2012;33(4):791–803.
137. Mitchell RA, Herrmann N, Lanctôt KL. The role of dopamine in symptoms and treatment of apathy in Alzheimer's disease. CNS Neurosci Ther. 2011;17(5):411–427.
138. Massimo L, Powers C, Moore P, et al. Neuroanatomy of apathy and disinhibition in frontotemporal lobar degeneration. Dement Geriatr Cogn Disord. 2009;27(1):96–104.
139. Rosen HJ, Allison SC, Schauer GF, et al. Neuroanatomical correlates of behavioral disorders in dementia. Brain. 2005;128(11):2612–2625.
140. Tekin S, Mega MS, Masterman DM, et al. Orbitofrontal and anterior cingulate cortex neurofibrillary tangle burden is associated with agitation in Alzheimer disease. Ann Neurol. 2001;49(3):355–361.
141. Matthews KL, Chen CP, Esiri MM, et al. Noradrenergic changes, aggressive behavior, and cognition in patients with dementia. Biol Psychiatry. 2002;51(5):407–416.
142. Yesavage JA, Friedman L, Ancoli-Israel S, et al. Development of diagnostic criteria for defining sleep disturbance in Alzheimer's disease. J Geriatr Psychiatry Neurol. 2003;16(3):131–139.
143. Sagud M, Nikolac Perkovic M, Vuksan-Cusa B, et al. A prospective, longitudinal study of platelet serotonin and plasma brain-derived neurotrophic factor concentrations in major depression: effects of vortioxetine treatment. Psychopharmacol (Berl). 2016;233(17):3259–3267.
144. Bishop MM, Fixen DR, Linnebur SA, et al. Cognitive effects of vortioxetine in older adults: a systematic review. Ther Adv Psychopharmacol. 2021;11:20451253211026796.
145. Scuteri D, Corasaniti MT, Tonin P, et al. New trends in pharmacological control of neuropsychiatric symptoms of dementia. Curr Opin Pharmacol. 2021;61:69–76.
•• **This review sheds light on the most recent advances and novel paths for the pharmacological treatment of NPSs during dementia.**
146. Kwon CY, Lee B. Herbal medicine for behavioral and psychological symptoms of dementia: a systematic review and meta-analysis. Front Pharmacol. 2021;12:713287.