Behavioral and psychological symptoms are present in most patients with Alzheimer disease (AD) and contribute significantly to increasing the cost of care, deteriorating the quality of life of patients and caregivers, and increasing the caregiver burden and suffering, being the principal predictors of the need for premature placement of the patient in a geriatric nursing home. The importance of behavioral and psychological symptoms of dementia (BPSD) is increasing because most of these symptoms can be treated effectively with drug measures and behavior modification techniques. In the present study, the possible pathophysiological mechanisms of BPSD as well as the relationship of these symptoms with the patient’s cognitive and functional deterioration, the caregiver’s burden, and currently available therapies are discussed.

Key words: Alzheimer’s disease, cognitive impairment, behavioral and psychological symptoms, burden, treatment.

Actas Esp Psiquiatr 2010;38(4):212-222

INTRODUCTION

Patients with Alzheimer disease (AD) have a high prevalence of neuropsychiatric symptoms that occur in conjunction with the two other main characteristics of dementia: cognitive alterations and difficulties in carrying out the activities of daily life. This type of AD manifestations was at first considered less important than cognitive symptoms and for some time this masked the association of behavioral disorders with other aspects of AD. However, numerous studies have shown important relations between AD, its clinical manifestations and neurobiology, as well as its impact on the family members and informal caregivers of patients.

Consensus was developed by the International Psychogeriatric Association, which recommended calling these manifestations behavioral and psychological signs and symptoms in dementias (BPSD) and defined them as disorders of perception, thought content, mood, or behavior that frequently occur in patients with dementia.

BPSD cause a great deal of suffering to the patient and to the people related with the patient, increased costs of care, premature nursing home placement, and a significant loss of quality of life of the patient, family members, and caregivers. The presence of BPSD is associated with more psychopharmaceutical use and physical restriction of the patient.
Neuropsychiatric and behavioral symptomatology in Alzheimer disease

J.M. García-Alberca, et al

Actas Esp Psiquiatr 2010;38(4):212-222

10–20%. Delusions and hallucinations are present less frequently, occurring in 11 to 73% and 3 to 67%, respectively. In contrast, euphoria is the least common symptom among patients with AD (Table 1). Alterations of sleep and appetite are not mentioned, although this is unnecessary.

ETIOPATHOGENESIS

Neuropathologic, neurochemical, and neuroimaging studies, as well as the possible genetic factors that could be involved, support the idea that BPSD are a primary manifestation of AD. BPSD could originate from genuinely cortical alterations or a combination of cortico-cortical and cortico-subcortical alterations. Neuropathologic and neuroimaging studies, for example, suggest that interruption of the fronto-subcortical circuits has a decisive role in the development of BPSD symptoms in both demented and non-demented patients, especially with regard to the presence of depressive symptoms, impulsivity, disinhibition, and disturbed executive functions.

Neuropathology and cerebral circuits

In AD, it has been suggested that the fronto-temporal cortex may play a decisive role in the etiology of psychotic processes. The results of SPECT studies seem to confirm this pattern with the finding of hypoperfusion of the frontal or temporal lobes in patients with delusional thoughts and hallucinations. Studies made with PET indicate the association between the presence of paranoid thoughts and hallucinations with fronto-temporal cortex dysfunction. In particular, hypometabolism of the right prefrontal cortex could be associated with delusional ideas. On the other hand, psychotic disorders have been associated with a significant increase in senile plaques in the prosubiculum and neurofibrillary tangles in the medial frontal cortex. Likewise, patients with AD and delusions are characterized by a specific pattern of abnormal symmetry of the frontal and temporal cerebral atrophy as opposed to the symmetrical pattern of patients who do not present delusions.

The convergence of the neuropathologic and neuroradiologic data seems to indicate that major depression in AD could be associated with fronto-subcortical dysfunction, with the involvement of aminergic nuclei and the anterior cingulate cortex, as well as temporal dysfunction. This suggests that a broader limbic disorder (fronto-temporal) is necessary to cause depression. In this sense, studies carried out with SPECT have demonstrated that patients with AD and depression have a lower cerebral blood flow in the left temporoparietal region than patients without depression, as well as cerebral hypoperfusion of the left prefrontal area. Studies made with PET have demonstrated that patients with AD and major depression have more hypometabolism in the bilateral parietal regions, bilateral superior frontal regions, and left cingulate cortex.

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<tr>
<th>Table 1</th>
<th>BPSD in a sample of 125 patients with Alzheimer disease*</th>
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<td>Apathy</td>
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<td>Irritability</td>
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<td>Depression</td>
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<td>Agitation</td>
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<td>Anxiety</td>
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<td>Sleep disorders</td>
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<td>Disinhibition</td>
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<td>Appetite disorders</td>
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<td>Hallucinations</td>
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<td>Euphoria</td>
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* García-Alberca et al, 2008
** The sum of the percentages is more than 100% because all the patients presented various BPSD

The prevalence rates of BPSD in AD vary between studies, ranging from 61 to 100% in patients living at home, 29 to 90% in patients placed in nursing homes, and 95% in patients with long-term hospitalization. Most patients exhibit various BPSD, which may occur at any stage of dementia; the frequency of BPSD increases with the severity of dementia (Table 1).

Most studies coincide in citing apathy as the most common symptom, being observed in 50 to 100% of patients. Agitation, irritability, and aberrant motor activity are also common and become more evident as the disease progresses, attaining a prevalence of 3 to 66%. Symptoms of anxiety and depression are present in 0 to 86% of patients, although the frequency of major depression is

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The presence of agitation has been related with frontal lobe dysfunction in such a way that this dysfunction predisposes patients with AD to experience agitation as an exaggerated response to multiple environmental stimuli.49

Fronto-subcortical and temporal dysfunctions are associated with the presence of apathy in patients with AD.40,50,51 Aside from reduced metabolic activity in the bilateral anterior cingulate cortex and medial orbito-frontal cortex, apathy could also be associated with reduced medial thalamus activity.52 These results reinforce the conjunction of evidence that suggests medial frontal dysfunction and certain neuronal circuits are involved in the neurobiology of apathy in AD.52 Recently, dysfunction of the cerebral dopaminergic compensation circuits has also been associated with the presence of apathy in AD,53 whereas excessive amygdalar activity has been correlated with the presence and severity of symptoms of irritability and agitation in AD. These functional alterations of the amygdala could be a physiological marker of certain neuropsychiatric manifestations in AD.54

AD is a proteinopathy with anomalies of the tau proteins and ß-amyloid peptide, manifesting a complex behavioral phenotype. Evidence of the association of these anomalies with the presence of BPSD has been found. Thus, the greater density of neurofibrillary tangles in the orbito-frontal cortex has been correlated with the presence of agitation and aberrant motor activity, whereas increased neurofibrillary pathology in the anterior cingulate correlates with apathy.55 In contrast, patients with alpha-synuclein alterations would be especially predisposed to hallucinations and delusions. This molecular approach to neuropsychiatry can help to understand the mechanisms of degenerative diseases, providing knowledge of the pathophysiology of BPSD and contributing to the development of disease course-modifying therapies.56

The results of a recent study indicate that suffering an anterior cerebrovascular accident at the onset of AD is associated with greater risk of presenting delusions, depression, and apathy. The presence of arterial hypertension is associated with an increased risk of delusions, anxiety, and agitation/aggression. No association was observed between diabetes, hyperlipidemia, heart attack, and the presence of BPSD in AD. These results suggest that a history of cerebrovascular accident or arterial hypertension may alter specific cerebral circuits of certain brain areas involved in the occurrence of BPSD.52

**Neurotransmission**

The cholinergic system plays a fundamental role not only in the cognitive processes of dementia, but also in BPSD. Alterations in the cholinergic system can originate symptoms such as apathy, affective disorders, psychomotor agitation, and psychosis58-60 in patients with AD, vascular dementia, dementia with Lewy bodies, and dementia associated with Parkinson disease. This fact is corroborated by clinical experience that demonstrates the efficacy of anti-cholinesterase drugs in the reduction of BPSD, especially apathy, agitation, and psychosis (particularly hallucinations). Thus, progressive neuronal deficit, diminished cholinergic function, and consequent diffuse cerebral atrophy may be key characteristics in the appearance of both cognitive and behavioral symptomatology. The functionality of the cholinergic system may be lessened as a result of the reduction in the number of post-synaptic nicotinic receptors and the disappearance of pre-synaptic muscarinic receptors in the late phases of the disease.61,62

Depression in AD has been related with neuronal loss in the locus coeruleus, substantia nigra, and dorsal nucleus of the raphe, which would have the consequence of reducing the serotoninergic and noradrenergic function, with relative preservation of acetyl-choline transferase function.63,64 These findings suggest that two neuroanatomical systems are affected in some patients with AD and depression: on the one hand, the structures of the medial temporal lobe and cholinergic neurotransmission systems that mainly affect cognition and, on the other hand, brainstem structures and aminergic systems, which affect mood.

Most studies report a loss of 5-HT$_{1A}$ serotoninergic receptors in AD and venture that this receptor could be important in the development of behavioral symptoms.65 The different 5-HT$_{1A}$ serotoninergic receptors are also involved in the psychobehavioral disturbances (all of them).65,66 Specifically, the 5-HT$_{1A}$ receptor is related with anxiety, whereas the 5-HT$_{2A}$ receptor is associated with depression, sleep disorders, and hallucinations. There is apparently a greater loss of 5-HT$_{2A}$ than 5-HT$_{1A}$ receptors. These findings suggest that the balance between the cholinergic and serotoninergic systems could be responsible for both cognitive deterioration and BPSD associated with AD.67

Patients with AD and psychotic symptoms have higher norepinephrine levels in the substantia nigra and lower serotonin levels in the prosubiculum than patients without psychotic symptoms,62 which suggests that a minimum threshold of norepinephrine is necessary for psychotic manifestations to occur. In this sense, recent postmortem studies have found that the adrenergic system can be an important therapeutic target.58

Although a reduction in the D$_2$ dopaminergic receptors has been observed, it has not been possible to demonstrate a direct relation between abnormal dopamine levels and the BPSD of AD.69 Consequently, the dopaminergic system is relatively well preserved in AD, in contrast with what occurs in other dementias. There is no clear evidence of a possible implication of GABA and neuropeptides, such as the
neurotrophic factors, somatostatin and neuropeptide Y, in the BPSD of AD,^{70,71} although recent studies suggest that changes in the GABAergic system may contribute to the presence of apathy and depression in terminal stages of AD.^{72}

Postmortem studies demonstrate that agitated and aggressive patients have a better preserved substantia nigra than patients who are not aggressive, which has been attributed to alterations in the serotoninergic nuclei in the context of relatively well preserved dopaminergic brain areas.^{73,74}

Genetic factors

Some genetic studies are beginning to show an influence of genetic factors in the expression of BPSD and indicate that a genetic predisposition for BPSD may exist in AD. Patients homozygous for the D1 B2/B2 dopaminergic receptor have been found to have a greater risk of developing aggressiveness and psychosis in the course of the disease, whereas patients homozygous for the D1 1/1 and 2/2 dopaminergic receptor had a greater risk for developing psychosis alone.^{75} Some studies have shown a relation between the C102 allele of the 5-HT2A serotoninergic receptor and the presence of visual and auditory hallucinations.^{76} An association has also been found between the Ser23 allele of the 5-HT2C serotoninergic receptor and visual hallucinations.^{76} These studies may indicate a genetic predisposition for the development of BPSD that becomes evident once the neurodegenerative process starts.

A recent study showed how the ε4 genetic type of APOE modifies the behavioral and neuropsychiatric phenotype in AD. In particular, delusions, agitation, and aggressiveness are more common and serious among APOE ε4 homozygotes than among APOE ε4 heterozygotes or negative subjects.^{77}

Definitively speaking, all of these observations together suggest that the BPSD of AD are primary manifestations of the underlying neurobiological changes. The presence of these symptoms would be determined by the different brain areas affected at different times of the disease.

EVALUATION AND DIAGNOSIS

Different instruments are available for the evaluation of BPSD in AD. Some of these instruments are used to conduct unidimensional evaluations: Hamilton Depression Rating Scale,^{78} Cornell Scale for Depression in Dementia,^{79} Geriatric Depression Scale,^{80} or the Cohen-Mansfield Agitation Inventory.^{81} Others, in contrast, are used for multidimensional examinations: BEHAVE-AD,^{82} Neurobehavior Rating Scale,^{83} CUSPAD,^{84} Behavioral Rating Scale for Dementia,^{85} non-cognitive subscale of the Alzheimer Disease Assessment Scale,^{86} and the Neuropsychiatric Inventory.^{87}

The BEHAVE-AD is used to evaluate delusions, hallucinations, anomalous motor activity, aggressiveness, diurnal rhythm disorders, depression, anxiety, and phobias. However, it cannot be used to evaluate other types of behavior, such as apathy, disinhibition, or irritability, which are frequent in AD. In addition, it only registers measures of severity for the symptoms evaluated. The Neurobehavior Rating Scale, which was initially developed for the evaluation of behavior changes after head injury, is also used to evaluate BPSD in dementia and to differentiate the behavioral alterations of AD from those of vascular dementia.^{88} Its principal drawback is that it is a time-consuming instrument to administer, making it difficult to use routinely in clinical practice. CUSPAD is used to evaluate a narrower range of behavior than other instruments and has less capacity for differential diagnoses.

The NPI is presently the instrument most often used in the evaluation of BPSD. It is specifically prepared for the assessment of the presence of psychopathology in patients with AD and other dementias. The NPI is a structured interview based on the responses provided by the patient’s primary caregiver. It consists of 12 subscales that are used to evaluate the psychobehavioral changes that occur most commonly in patients with dementia: delusions, hallucinations, agitation/aggressiveness, depression, anxiety, euphoria, apathy/indifference, disinhibition, irritability/emotional lability, anomalous motor activity, sleep disorders, and appetite disorders.

The symptomatology collected refers to the changes that appear when the disease starts and continue in the month prior to the examination. On each subscale, if a disorder is present the caregiver assigns it a score of 1 to 4 according to frequency and a score of 1 to 3 for severity. A compound score, of a maximum of 12 points, is obtained for each subscale by multiplying frequency by severity. The total NPI score obtained refers to the frequency (maximum 48 points), severity (maximum 36 points), and compound scores (maximum 144 points).

With regard to the psychometric properties of the instrument, in its original version it has demonstrated an interobserver reliability of 93.6 to 100% for different behaviors. The overall test-retest reliability was 0.79 for frequency and 0.86 for severity. Likewise, a high content validity and an acceptable level of concurrent validity were demonstrated compared to standard instruments. The NPI has been adapted to Spanish and has been shown to be reliable and valid.^{89}

BPSD AND THE SEVERITY OF AD

Numerous studies have reported that the frequency and intensity of BPSD increase as AD advances in stage.^{2,24,30-92}
whereas other authors have not found this relation.\textsuperscript{51} If this association is confirmed, BPSD could serve as a marker of the stage of progress of AD and may be considered as indicators of a more serious and advanced state of dementia.\textsuperscript{24}

Psychotic symptoms are usually more common in moderate or severe phases of the disease.\textsuperscript{95-98} The relation between depression and disease stage is less clear: There have been reports of an association between depression and mild stages of dementia,\textsuperscript{99-100} an inverse relation between depression and dementia,\textsuperscript{24,101} and some authors have not found any relation at all.\textsuperscript{102,103} These variations in results are probably due to differences between studies in methodology and patient selection criteria. It also is possible that the lower frequency of depression in advanced stages of AD is due more to the difficulty of detecting depression in a patient with cognitive deterioration than to a true reduction in prevalence. On the other hand, depressive symptoms vary over time\textsuperscript{104} and long-term follow-up studies show that depression persists throughout the course of AD.\textsuperscript{105} However, most studies coincide in reporting that apathy, agitation, aggressive behavior, irritability, and aberrant motor activity tend to increase in frequency as AD becomes more severe.\textsuperscript{24,25,49,98} In contrast, the presence of disinhibition is usually associated to the initial phases of the disease.\textsuperscript{24}

One possible explanation for these contradictory results could lie in the fact that most studies use MMSE scores to classify patients into different stages of AD. It has been demonstrated that studies of the progression of AD based exclusively on measures of cognitive functioning are less exact than studies that use instruments that evaluate functional capacities, as functional capacities have been shown to be strong markers of the progress of the disease.\textsuperscript{106,107}

**BPSD AND COGNITIVE DETERIORATION**

Different studies\textsuperscript{4,108,109} have shown the existence of a relation between degree of cognitive deterioration and the frequency and severity of the BPSD, at least for some individual BPSD. In this sense, the natural history of the disease reveals, for example, that patients with psychotic symptoms present more rapid cognitive deterioration.\textsuperscript{110,111} The findings of other studies support the association between the deterioration of executive functions and BPSD,\textsuperscript{4,112,113} especially with regard to apathy, agitation, and disinhibition; other cognitive deficits, such as memory, language, and visual-spatial functions, are independent.

**BPSD AND FUNCTIONAL DETERIORATION**

Although some studies\textsuperscript{114,115} suggest that BPSD overall do not have a substantial impact on the capacity of patients to carry out the activities of daily life (ADL) and that disability depends more on the extension of cognitive deterioration than on the degree of behavioral alterations present, most studies report a significant association between the presence of BPSD and a greater degree of functional deterioration.\textsuperscript{4,116} In this sense, the presence of specific BPSD can lead to a reduction in the independence of patients with AD, as such patients may have lower levels of ADL functionality than other patients with a similar level of cognitive deterioration, but no behavioral manifestations.\textsuperscript{117,118}

**BPSD AND THE CAREGIVER BURDEN**

There is sufficient empirical evidence on the negative impact of BPSD on caregivers.\textsuperscript{8,119,120} The overall burden experienced by caregivers of patients with AD has several dimensions, including physical, social, economic, and psychological aspects.\textsuperscript{121} The international literature identifies caregivers of people with AD as being among the caregivers at greatest risk of experiencing stress-related problems, including anxiety and depression.\textsuperscript{122,123} The subjective feelings of caregivers are directly associated with the perceived burden, and the reaction of caregivers to problematic behaviors is one of the strongest predictors of eventual nursing home placement.\textsuperscript{124,125} Consequently, the care of patients with AD entails a high risk for the physical and mental health of caregivers.\textsuperscript{126,127}

The presence of BPSD is associated with more caregiver overload. Both the frequency and severity of BPSD correlate with different measures of the caregiver burden and suffering. Most of these studies use a measure of the overall burden, such as the Caregiver Burden Interview (CBI),\textsuperscript{18} which offers information about different aspects of the caregiver burden: physical, emotional, and economic. Other studies have reported high levels of anxiety and depression among caregivers,\textsuperscript{19} as well as more consumption of psychopharmaceuticals\textsuperscript{10} and worse self-perceived health.\textsuperscript{127} Sharing the same residence\textsuperscript{129} and prolongation of the need for care\textsuperscript{130} potentiate the impact on the caregiver’s health.

**TREATMENT**

BPSD are one of the main therapeutic objectives in the comprehensive treatment of AD. The approach to BPSD contemplates the use of both pharmacologic and non-pharmacologic measures.\textsuperscript{131}

**Pharmacologic treatment**

The pharmacologic treatment of BPSD is based on the use of anti-dementia drugs such as acetyl-cholinesterase inhibitors (ACI), galantamine and memantine, as well as some...
antidepressants and atypical antipsychotics. Anxiolytics, hypnotics, or anticonvulsants are used less frequently. In any case, the drug therapy of BPSD should be considered prudently and with full information. Patients should be started initially with low doses, which should be increased slowly and carefully, closely monitoring for the possible occurrence of adverse effects.\(^{132,133}\) It must always be kept in mind that the use of multiple drugs in this type of patients, who may experience negative consequences due to the interaction of antipsychotics with other concomitant medications that could inhibit their metabolism, could excessively enhance the pharmacological effect of the antipsychotics.\(^{134,135}\)

Consensus exists that antidepressant drugs improve the mood of patients with dementia,\(^{136,137}\) although there is little evidence of their efficacy.\(^{138}\) Selective serotoninergic reuptake inhibitors (SSRI) are probably the most interesting antidepressants for the treatment of depression in patients with AD due to the good adverse effect profile of the SSRIs and lower risk with the use of high doses.\(^{139,140}\) Although their degree of efficacy diminishes in advanced phases of AD. In contrast, tricyclic antidepressants are not recommended due to the high risk of side effects in older adults. Dual-action antidepressants, which act on both serotonin and norepinephrine, are also useful and well tolerated.\(^{141}\)

Despite having demonstrated their efficacy against psychotic symptoms and other behavioral disorders in AD, the use of conventional antipsychotics is not recommended because they are often associated with the presentation of tardive dyskinesia, extrapyramidal symptoms, diminished cognitive performance, and cardiovascular adverse effects. In contrast, the so-called atypical antipsychotics have also demonstrated their efficacy in the control of various BPSD, principally delusions, hallucinations, anxiety, agitation, and aggressiveness, but with a lower rate of side effects. The two most used and evaluated are olanzapine and risperidone.\(^{142-144}\) Risperidone is the only product in Spain with an indication for the treatment of BPSD. Olanzapine and risperidone are used at low or moderate dose and have moderate efficacy in the control of some BPSD. The use is associated with higher rates of mortality and vascular stroke, and their concomitant administration with ACI can intensify extrapyramidal symptoms, which sustains an ongoing debate for and against using these drugs.\(^{145,146}\) Other atypical antipsychotics, such as quetiapine, ziprasidone, and amisulpride can also be somewhat useful, especially for the control of psychotic symptoms in AD.

ACI drugs, donepezil, rivastigmine, and galantamine, as well as memantine, have demonstrated their efficacy in the control of certain BPSD, especially apathy\(^{147,148}\) and psychotic symptoms.\(^{149,150}\) Some studies\(^{151}\) suggest that galantamine, in addition to being effective in anomalous motor activity, could have a preventive effect on the occurrence of behavioral symptoms. A meta-analysis of 29 clinical trials in relation to the efficacy of ACI in the treatment of BPSD concludes that these drugs have a beneficial effect on this type of symptoms.\(^{152,153}\) Memantine, for its part, has been demonstrated to be effective in the improvement of agitation, aggressiveness, and irritability.\(^{151}\)

**Non-pharmacologic treatment**

Various psychological techniques have been proposed for the non-pharmacologic approach to BPSD: behavior modification strategies, cognitive intervention and psycho-stimulation, interventions on the physical surroundings, and caregiver support programs.

The behavior modification techniques are aimed at controlling and containing non-cognitive symptoms. They have obtained positive results in the treatment of apathy, depression, agitation, aggressions, laziness, or repetitive questions.\(^{154}\) Behavior modification centers on contingency management, parting from an analytical model in which the problem is clearly identified (how, when, where, in the presence of whom it occurs, with what frequency, etc.), which is used to prepare an action plan for the behavioral disorder identified.

Cognitive intervention and comprehensive psycho-stimulation allow direct treatment of the patient and indirect management of the BPSD. Intervention on the physical surroundings and the control of the temporal surroundings using alarms, visual barriers, or the establishment of routines provide indirect treatment of the patient and direct treatment of non-cognitive symptoms.

Finally, support measures for family members and caregivers, psychoeducational programs, self-help groups, or psychotherapy makes indirect intervention on the patient possible, with all the parties involved working to develop containment or minimization strategies.\(^{155,156}\)

**CONCLUSIONS**

BPSD occur with high frequency in AD, which suggests that they are part of the physiopathogenesis of the dementia syndrome per se. Alterations in the functioning of cortical (frontal and temporal) and subcortical areas are related with most behavioral manifestations in AD. Although the relation between the cognitive and non-cognitive aspects of AD is not exactly known, evidence is growing that both types of symptoms mutually influence the course of the dementia. Consequently, more studies are needed to obtain more exact knowledge about the pathophysiological mechanisms involved in BPSD and their relation with the other manifestations of AD. The presence of BPSD accentuates the deterioration of patients and the burden of caregivers.
favoring premature placement in a nursing home, so the evaluation and treatment of BPSD are essential for the well-being of patients and the people who care for them.

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