Behavioral and Psychological Symptoms of Dementia: Part I—Epidemiology, Neurobiology, Heritability, and Evaluation

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Introduction

Behavioral and psychological symptoms of dementia (BPSD) include noncognitive symptoms and behaviors that commonly occur in patients with dementia.[1] BPSD can be described as "a heterogeneous range of psychological reactions, psychiatric symptoms, and behaviors occurring in people with dementia of any etiology."[2] In Part I of this two-part article, we discuss the epidemiology, costs, outcomes, neurobiology, and heritability, and evaluation of BPSD. Part II of this article, which will be published in the next issue of *Clinical Geriatrics*, will review the evidence-based treatment of this important group of behaviors.

Epidemiology

Clinically significant BPSD are found in approximately one-third of community-dwelling persons with dementia.[1,3] The prevalence of BPSD increases to nearly 80% in persons with dementia residing in skilled nursing facilities.[4] BPSD symptoms tend to fluctuate, whereas cognitive symptoms of dementia, such as memory, attention, concentration, and praxis, decline over time.[5-7] Symptom clusters that emerge during the study of the psychopathology of persons with dementia include the mood disorders cluster (depression, anxiety, and apathy/indifference), psychotic cluster (delusions and hallucinations), aberrant motor behaviors cluster (pacing, wandering, and other purposeless behaviors), and inappropriate behavior cluster (agitation, disinhibition, and euphoria).[8]

In a study of 100 patients with autopsy-confirmed Alzheimer's disease (AD), Jost and Grossberg[9] documented irritability, agitation, and aggression in 81% of persons an average of 10 months after diagnosis; depression, changes in mood, social withdrawal, and suicidal ideation in 72% of persons 26.4 months before diagnosis; and hallucinations, paranoia, accusatory behavior, and delusions in 45% of persons 0.1 month after diagnosis.

Studies have reported that major and minor depressive symptoms are seen in approximately one-third to one-half of patients with dementia.[10,11] Those with a family history of depression are at increased risk for developing major depressive episodes during the course of the disease process. This association indicates that depression in dementia is genetically related to primary affective disorder.[12] Anxiety has been reported to occur in about 24% to 65% of persons with dementia and is often associated with dysphoria and agitation in these patients.[13] Apathy is the most common personality change seen in dementia and occurs in 48% to 92% of patients.[13] It tends to begin in the early stages of dementia and shows no

appreciable change during the course of the illness. Apathy is characterized by lack of interest, less affection in personal relationships, loss of enthusiasm, decreased initiative, and social withdrawal.[8,14]

Bassiony and Lyketsos[15] found that a median of 36.5% of subjects with AD presented with delusions and a median of 23% of subjects with ADpresented with hallucinations at some time during the course of their illness. Delusions that are commonly seen in persons with dementia include false beliefs of theft and infidelity, as well as misidentification syndromes such as Capgras syndrome (belief that a friend, family member, or acquaintance has been replaced by an identical-looking imposter) and phantom boarder syndrome (belief that an unseen person is living in the home).[15,16] While bothauditory and visual hallucinations have been observed in patients with dementia, visual hallucinations remain the more prominent form.[13,17] In a review of 55 studies of patients with AD, Ropacki and Jeste [17] found a median prevalence of auditory hallucinations of 9.2% as compared with a median prevalence of visual hallucinations of 18.7%. Hallucinations appear to be more common in African-American patients and in those with more severe stages of the illness, and they are associated with a more rapid rate of cognitive decline.[17]

Irritability and mood lability occur in about 35% to 54% of patients with dementia and these behaviors become more frequent as the disease progresses.[13] Pacing, wandering, rummaging, picking, and other stereotyped, purposeless behaviors, which are more common in moderate-to-severe stages of disease, are seen in 12% to 84% of patients with dementia.[13] Euphoria is less common in these patients, with a prevalence rate of approximately 3.5% to 8%.[13,18] Sleep disturbance is found in approximately 25% of patients with dementia.[19] White et al[20] reported that about 22% of patients with dementia have clinically significant weight loss, and weight loss tends to occur more frequently in patients with more severe stages of the illness. Rapid decline in cognition is associated with more pronounced weight loss.[20] Finally, disinhibition characterized by tactlessness and impulsivity occurs in 36% of patients with dementia[13] (**Table 1**).

TABLE 1

Behavioral and Psychological Symptoms of Dementia[a]

Agitation/irritability/mood lability
Anxiety
Apathy
Delusions
Depressive symptoms
Disinhibition
Euphoria
Hallucinations
Loss of appetite
Sleep disturbances
Stereotyped behaviors (eg, pacing/wandering, rummaging, picking)

[a] *Contains information from references 10-20.*

Costs

BPSD adds significantly to the direct and indirect costs of care, even after adjusting for the severity of cognitive impairment and other comorbidities.[21]A 2002 study by Beeri et al [22] reported that the annual indirect cost of managing BPSD in a patient with AD was about $2665, which is over 25% of the total annual indirect cost of caring for a patient with AD ($10,520). In addition, the authors reported that the annual direct cost of BPSD was approximately $1450, which is over 35% of the total annual direct cost of caring for a patient

with AD ($3900).

Caregiver and Patient Outcomes

The development of BPSD is a major risk factor for caregiver burden and depression. [23,24] Paranoia, aggression, incontinence, and sleep-wake cycle disturbances in patients appear to be particularly important factors in increasing caregiver burden and institutionalization of patients,[25] and the development of BPSD is often the triggering event for the recognition of dementia and the referral of these patients to a specialist service.[1] For patients, BPSD is associated with worse quality of life,[3] greater impairment in activities of daily living, [26] and more rapid cognitive decline.[27-30]

Neurobiology and Heritability

Available data indicate that BPSD occurs due to both anatomical and biochemical changes within the brain.[31] Psychological factors such as premorbid neuroticism and low frustration tolerance appear to predispose individuals to develop BPSD.[32,33] Pathological changes in the cholinergic system cause BPSD via the denervation of the frontal and temporal cortices.[8] Alterations in adrenergic and serotonergic systems also contribute to the development of these symptoms.[8] Higher levels of norepinephrine in the substantia nigra and lower levels of serotonin in the presubiculum are seen in patients with BPSD.[34,35]

Some neuropathologic changes that contribute to the development of BPSD include the presence of neuritic plaques and tangles in the frontal and temporal lobes of persons with dementia.[34,36,37] It has been shown in metabolic and perfusion imaging studies that psychosis in AD correlates well with frontal, temporal, and parietal lobe dysfunction.[38-42] In a study of delusional misidentification symptoms (DMS; where patients believe that the identity of a person, object, or place has somehow changed or has been altered) in AD, persons with DMS showed increased electroencephalogram delta power over the right hemisphere, and their computed tomography scans demonstrated more severe right frontal lobe atrophy.[43] In addition, the number of pyramidal cells in area CA1 in patients with DMS was lower than in patients without DMS.

Studies of genetic risk factors for BPSD indicate that patients with AD who have depression had significantly more first-degree relatives with depression as compared with patients with AD who did not have depression.[12,44-46] A case-control study by Sweet et al [47] found a significantly increased risk for AD with psychosis among probands who had family members with AD and concomitant psychosis, demonstrating familial aggregation; however, the correlation among siblings for AD with psychosis status was modest. Another study demonstrated that estimated heritability for late-onset AD with psychosis was 30%, as defined by any occurrence of psychotic symptoms, and 61%, as defined by multiple psychotic symptoms.[48]

Studies indicate that patients with AD and the apolipoprotein E (ApoE) 3/4 genotype had higher rates of depression and psychosis when compared with patients with the ApoE 3/3 genotype or with control subjects.[49,50] One study showed that frequency of the ApoE epsilon

2 allele was significantly lower in the depressive illness group as compared with the control group, and was associated with a later mean age at onset of symptoms.[51] Another study showed that the presence of the ApoE epsilon 4 allele was associated with an earlier age at onset of the illness and that the presence of the ApoE epsilon 2 allele was associated with depressive symptoms in late-onset AD.[52] In a study by Cacabelos, [53] disorientation, agitation, and motor disorders were slightly more frequent in patients with dementia who were homozygous for ApoE epsilon 4 allele, while anxiety and sleep disorders appeared more frequently in patients who had ApoE epsilon 3 allele, although behavioral changes and psychotic symptoms did not show any clear association with specific ApoE subtypes.[53]

A study by Holmes et al [54] of subjects with late-onset AD found an association between serotonin receptor polymorphism and BPSD. The presence of the C102 allele was associated with visual and auditory hallucinations, and the presence of the Ser23 allele was associated with visual hallucinations.[54] A case-control study of patients with AD and aggressive behavior found that the presence of the long variant (*L) of an identified biallelic polymorphism of the serotonin transporter promoter region (5-HTTPR) *L/*L genotype was significantly associated with aggression in patients with AD.[55] Another study found that both psychosis and aggression were significantly associated with the 5-HTTPR II genotype and with an increased I allele frequency in patients with AD.[56] Persons with the combined behavioral phenotype of AD plus psychosis and aggression had the highest rate of II genotype and the highest I allele frequency. Researchers concluded that the 5-HTTPR I allele appears to be associated with the risk of the combined AD plus psychosis and aggressive behavior phenotype.[56]

A study by Borroni et al [57] examining the relationship between ApoE and behavioral disturbances in AD and genetic variations in dopamine- or serotonin-related genes, such as catechol-O-methyltransferase or 5-HTT gene-linked promoter region (5-HTTLPR), found that 66.4% of patients showed more than one behavioral symptom. A study by Sweet et al[58] examining the association between selected polymorphisms in the dopamine receptor genes DRD1, DRD2, DRD3, and DRD4 and the presence of psychosis or aggressive behavior in persons with AD found that psychosis and aggression were both significantly more frequent in DRD1 B2/B2 homozygotes ($P < .02$) among white subjects; psychosis was significantly more frequent in DRD3 1/1 or 2/2 homozygotes ($P < .05$). In another study, investigators found an association between the presence of psychotic symptoms and aggressive behavior and the DRD1 polymorphism. They also noted an association between the presence of psychosis, but not aggression, and the DRD3 polymorphism.[9] Specifically, carriers of the DRD1 B2 allele were more likely to be aggressive or experience hallucinations, whereas homozygous carriers of the DRD3 1 allele were more likely to experience delusions.

These studies indicate that BPSD develop due to the neurodegenerative disease process that manifests after a certain period, when the genetic factors assume greater significance in the brain.[12,31,44-58]

Evaluation

Clinicians should always include an inquiry about the presence of BPSD during an assessment of a patient with dementia (**Figure**[30,60-65]). Early detection of BPSD will enable the clinician to treat problem behaviors earlier, thereby reducing undue suffering in the patient and preventing caregiver burnout and irreversible damage to the patient's social support structure. A comprehensive evaluation of patients with BPSD must assess the presence of all possible behavioral problems [60]and determine whether symptoms are acute or chronic and if they tend to fluctuate or remain stable over time. This assessment should consider the points of view and observations of, as well as collateral information from, the patient, his or her caregiver(s), and the healthcare professional(s) involved in the care of the patient. Factors to consider include the impact of the patient's behavior on the caregiver; the impact of the caregiver's characteristics, including neuroticism, extraversion, and agreeableness, on the development of BPSD; and overall caregiver burden.[61]

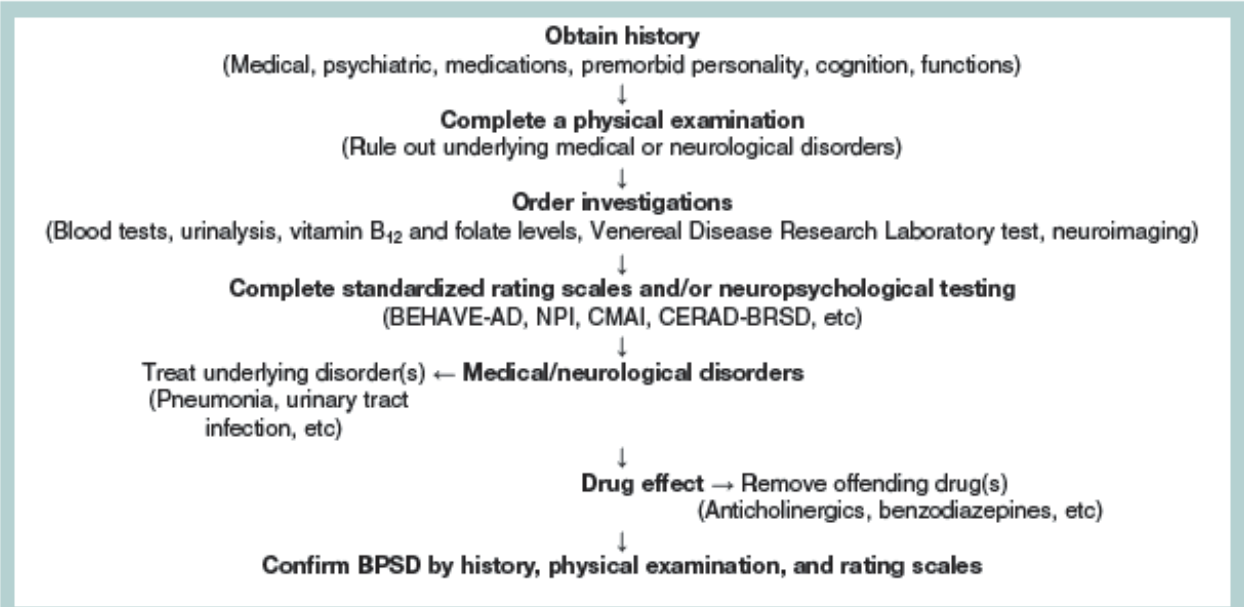

Figure. Algorithm for the assessment of BPSD.

Abbreviations: BEHAVE-AD, Behavioral Pathology in Alzheimer's Disease Rating Scale; BPSD, behavioral and psychological symptoms of dementia; CERAD-BRSD, Consortium to Establish a Registry for Alzheimer's Disease Behavior Rating Scale for Dementia; CMAI, Cohen-Mansfield Agitation Inventory; NPI, Neuropsychiatric Inventory.

Contains information from references 30, 60–65.

Identification of underlying medical conditions, especially pain syndromes, will prevent the use of inappropriate treatments and undue suffering in the patient. Assessments should include a complete evaluation of all changes in the clinical condition of the patient, such as pain, fever, anxiety, and drug treatments or withdrawal. It is also important to identify psychosocial or environmental triggers for the behaviors.[60] Assessments of patients with BPSD should not only include an objective evaluation of their cognitive and behavioral profile, but also an assessment of their global functional status.[30]Evaluations should ideally include standardized assessment scales such the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD), the Neuropsychiatric Inventory (NPI), the Consortium to Establish a Registry for Alzheimer's Disease Behavior Rating Scale for Dementia (CERAD-BRSD), the Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD), and the Cohen-Mansfield Agitation Inventory (CMAI).[62,63] The Cornell Scale for Depression in

Dementia (CSDD)[64] and the Apathy Inventory[65] are some examples of instruments developed for the assessment of specific behaviors (**Table 2**[62-65]). The use of standardized instruments with other collateral sources of information will better help to qualify and quantify BPSD, and to understand their impact on the life of patients and their caregivers.

TABLE 2

Common Scales Used in the Assessment of Behavioral and Psychological Symptoms of Dementia[a]

Scale	Time for Completion (minutes)	Score Range	Higher Score Means
Apathy Inventory (Clinician Version)	5	0-12	Greater apathy
Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD)	20	0-75	Greater severity of behavioral symptoms
Columbia University Scale for Psychopathology in Alzheimer's Disease (CUSPAD)	25	0-51	Greater severity of behavioral symptoms
Consortium to Establish a Registry for Alzheimer's Disease Behavior Rating Scale for Dementia (CERAD-BRSD)	30	0-148	Greater severity of behavioral symptoms
Cohen-Mansfield Agitation Inventory (CMAI)	15	29-203	Greater severity of behavioral symptoms
Cornell Scale for Depression in Dementia (CSDD)	30	0-38	Greater severity of depression
Neuropsychiatric Inventory (NPI)	20	1-144	Greater severity of behavioral symptoms

[a] Contains information from references 62-65.

Conclusion

BPSD are an important group of noncognitive symptoms that occur commonly in patients with dementia. They include psychotic symptoms, mood symptoms, aberrant motor behaviors, and inappropriate behaviors. These symptoms occur due to both anatomical and biochemical changes within the brain. BPSD are also heritable, with certain symptoms occurring more frequently in family members with dementia. BPSD are often associated with increased morbidity, increased cost of caring for the patient, and poorer quality of life for the patient and his or her caregiver(s). A prompt and comprehensive evaluation of these behaviors will help in making the diagnosis of BPSD and in planning appropriate treatments, (the latter of which will be discussed in Part II of this article), thereby reducing undue suffering in patients and their families.

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