Behavioral and Psychological Symptoms in Dementia: The Role of Atypical Antipsychotics

Brian A. Lawlor M.D., Ph.D.

Although cognitive dysfunction is the hallmark of dementia, behavioral and psychological symptoms of dementia (BPSD), such as psychosis, aggression, sleep disturbance, agitation, and mood disorders, develop in most elderly patients at some stage. These symptoms pose major difficulties in the day-to-day care of patients and are likely to impair the quality of life of both patient and caregiver. Patients exhibiting BPSD should be assessed in a detailed clinical interview to establish symptoms causing distress to the patient and/or caregiver. Several mood and behavior scales with good psychometric properties are available for patient evaluation. Initial intervention should focus on nonpharmacologic measures, and the quality of patient care should be optimized with potential physical, environmental, social, and psychiatric triggers being addressed where possible. Caregiver education, support, and behavioral training can also be effective in alleviating BPSD. However, pharmacologic intervention is necessary in many cases and includes use of antidepressants for mood disorders, anticonvulsants for nonpsychotic agitation, and antipsychotics for aggression, agitation, and psychotic symptoms. Conventional antipsychotics have shown modest benefit over placebo in the treatment of psychosis and agitation in dementia patients; however, they are associated with treatment-emergent side effects, particularly extrapyramidal symptoms (EPS). Atypical antipsychotics such as risperidone, olanzapine, and quetiapine are at least as effective as conventional antipsychotics, are better tolerated, and have a lower propensity for EPS. There are, however, significant differences between atypical agents with regard to receptor affinities and, therefore, side effect profiles. Patients' vulnerability to these side effects should be considered when making individual treatment decisions.

(J Clin Psychiatry 2004;65[suppl 11]:5–10)

Behavioral and psychological symptoms of dementia (BPSD) is a descriptive term that embraces a heterogeneous group of noncognitive symptoms and behaviors occurring in patients with dementia. BPSD is not a diagnostic entity but rather describes an important clinical dimension of dementia that has until recently gained little attention from both a research and a therapeutic point of view. The management of BPSD represents a significant part of the day-to-day workload of clinicians dealing with dementia patients and their families in hospital, institutional, and community settings. Improving our recognition and management of BPSD can impact positively on the quality of life of our patients and caregivers and potentially delay the transition from home to institutional care settings. This article describes the concept of BPSD, discusses why BPSD are an important therapeutic target, and outlines the role of atypical antipsychotic treatment within the broader framework of management strategies for BPSD.

REDEFINING THE BEHAVIORAL DIMENSION OF DEMENTIA

One approach to the description of BPSD is the use of a list of observed behaviors (e.g., wandering, agitation, sexually inappropriate behaviors) and elicited psychological symptoms (e.g., depression, anxiety, delusions).[1] This approach fails to take into account the fact that many so-called elicited symptoms also represent observed behaviors (e.g., "looks depressed," "acts as though hallucinating or deluded") and that most of these symptoms and behaviors do not occur in isolation but tend to occur together in clusters or syndromes. For example, delusions have been associated with agitation, aggression, and insomnia[2,3]; depression has been associated with psychotic symptoms[4]; and sleep disturbance correlates with aggression.[5]

From Mercer's Institute for Research on Ageing, St. James's Hospital and Trinity College, Dublin, Ireland.

Presented at the satellite symposium "Clinical Effectiveness of Atypical Antipsychotics in Dementia," which was held on August 18, 2003, in Chicago, Ill. This symposium was held in conjunction with the 11th International Congress of the International Psychogeriatric Association, August 17–22, 2003, in Chicago, Ill., and was supported by an unrestricted educational grant from AstraZeneca Pharmaceuticals, Wilmington, Del.

Corresponding author and reprints: Brian A. Lawlor, M.D., Ph.D., Mercer's Institute for Research on Ageing, St. James's Hospital and Trinity College, James's Street, Dublin 8, Ireland (e-mail: balawlor@indigo.ie).

Table 1. Symptom Clusters in Behavioral and Psychological Symptoms of Dementia[a]

Study	Rating Scale	Symptom Clusters
Haupt et al[7]	BEHAVE-AD/ DMAS	Depression, psychosis/aggression, misidentification/agitation, apathy
Frisoni et al[8]	NPI	"Mood," psychosis, "frontal"
Hope et al[9]	PBE	Psychosis, aggressive behavior, "overactivity"
Mack et al[10]	BRSD	Depressive symptoms, psychosis, vegetative symptoms, irritability/aggression, behavioral dysregulation, inertia
Devanand et al[11]	BSSD	Depression, aggression, apathy
Sultzer et al[12]	NRS	Depression, psychosis, motor hyperactivity, apathy
Lyketsos et al[13]	NPI	Depressive symptoms, "psychotic features," agitation/aggression

[a]Reprinted with permission from Lawlor and Ni Bhriain.[6]
Abbreviations: BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease Rating Scale, BRSD = Behavior Rating Scale for Dementia, BSSD = Behavioral Syndromes Scale for Dementia, DMAS = Dementia Mood Assessment Scale, NPI = Neuropsychiatric Inventory, NRS = Neurobehavioral Rating Scale, PBE = Present Behavioral Examination.

The concept of symptom clusters refers to the fact that different behavioral symptoms in patients with dementia tend to occur together and are highly intercorrelated. A particular symptom may appear in a number of clusters and any one patient may have a number of different clusters of behavioral symptoms. The concept of syndromes is somewhat different in that it implies the existence of behavioral subgroups within dementia. In this situation, individuals may belong to only 1 particular subgroup. Different statistical methods have been applied to symptom behavioral rating scales to try to identify clusters or syndromes within BPSD. The advantage of identifying clusters or syndromes is that it may help in the targeting of therapeutic interventions and also aid in the understanding of the neurobiological underpinnings of behavioral change in dementia.

A number of symptom clusters have been consistently produced by factor analysis using a variety of behavioral rating scales: depressive, psychotic, aggressive, apathetic, and overactivity/agitation clusters (Table 1).[6–13] Using latent class analysis to detect subgroups of patients with Alzheimer's disease on the basis of the pattern of their behavioral symptoms, 2 studies have reported different findings. In one large-scale community study using the Neuropsychiatric Inventory (NPI), 3 subgroups were determined: an affective syndrome subgroup, a psychotic symptom subgroup, and a group with no neuropsychiatric disturbance.[14] In a second clinic-based study, 3 groups were identified: a low symptom prevalence subgroup, an anxiety/depressive subgroup, and an aggressive subgroup.[15] Although there is some disagreement and inconsistency regarding the cluster and syndrome approach of BPSD, it is still a useful framework in terms of conceptualizing the issue from a phenomenologic point of view and, in particular, defining a target for therapeutic intervention. Further research is required to determine whether the subgroups or syndromes as defined have biological or treatment predictive validity.

Both depression and psychosis are included as descriptors in the DSM-IV criteria[16] for Alzheimer's disease, and, more recently, diagnostic criteria for a distinct syndrome of psychosis of Alzheimer's disease and related dementias has been developed.[17] Provisional criteria for depression in Alzheimer's disease have also been recently proposed.[18] The agitation cluster is more poorly defined, and it is unclear whether aggression and sleep-wake cycle disturbances are part of agitation or represent further distinct syndromes. It is likely that diagnostic criteria for other behavioral syndromes of dementia will also be developed in the near future and this will facilitate recognition and future therapeutic targeting of more specific aspects of BPSD.

PREVALENCE OF BPSD

The prevalence of BPSD in both community and clinical settings is very high. It has been estimated from studies in clinic populations that almost all elderly patients with dementia will develop BPSD at some point. In community-dwelling patients with dementia, more than 80% exhibit some BPSD from the onset of cognitive impairment, with apathy (45.3%), depression (43.6%), and agitation/aggression (40.1%) showing the highest cumulative prevalence.[19] For up to 60% of these patients, the level of BPSD will be in the clinically significant range.[19] The prevalence of clinically significant BPSD rises to almost 80% for patients with dementia who reside in care environments.[20]

Prevalence estimates for BPSD vary widely because of the heterogeneity of patient populations studied in terms of setting and type of dementia and the different definitions used for BPSD. The recent application of standardized and validated assessment instruments is resulting in more consistent data for community and clinic-based populations. Three population-based studies, 2 from the United States[13,19] and 1 from the United Kingdom,[21] show similar prevalence figures of about 20% for BPSD in people with Alzheimer's disease. Unlike the cognitive dysfunction in dementia, which becomes progressively worse over time, many BPSD tend to fluctuate, with psychomotor agitation being the most persistent over time.[22] Further research is needed regarding the natural history and longitudinal course of BPSD to better inform clinicians regarding the appropriate duration of pharmacologic interventions and what advice and information should be given to families distressed by these symptoms and behaviors. More recently, the focus of therapeutic intervention has shifted to mild dementia and mild cognitive impairment. It would appear that there is also a high prevalence of neuro-

Table 2. Dementia-Specific Rating Scales and Their Characteristics

Characteristic	Rating Scale							
	BEHAVE-AD	NPI	PBE	NRS	DBRI	CERAD	CUSPAD	MOUSEPAD
Parameter measured								
Frequency	–	+	–	–	+	+	–	–
Severity	+	+	+	–	–	–	–	+
Duration	–	–	–	–	–	+	–	+
Caregiver impact	+	+	–	–	+	–	–	–
Patient category								
Outpatient (community)	+	+	+	+	+	+	+	+
Inpatient (hospital/ nursing home)	–	+	–	–	–	–	–	–
Rater category								
Observer	–	–	–	+	–	–	–	–
Proxy (usually a caregiver/family member)	+	+	+	–	+	+	+	+
Requires training	+	+	+	+	+	+	+	+

Abbreviations: BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease Rating Scale, NPI = Neuropsychiatric Inventory, PBE = Present Behavioral Examination, NRS = Neurobehavioral Rating Scale, DBRI = Dysfunctional Behavior Rating Instrument, CERAD = Consortium to Establish a Registry for Alzheimer's Disease, CUSPAD = Columbia University Scale for Psychopathology in Alzheimer's Disease, MOUSEPAD = Manchester and Oxford Universities Scale for Psychopathological Assessment of Dementia.
Symbols: + = yes, – = no.

psychiatric symptoms in mild cognitive impairment. A total of 50% of people with mild cognitive impairment showed some form of BPSD, and 29% of these were in the clinically significant range.[19]

IMPACT OF BPSD

The development of BPSD is often the triggering event for recognition and referral of patients with dementia to primary care and specialist services. Severity of dementia, functional impairment, and the presence of BPSD are the key factors in recognition of dementia by a family member.[23] The development of BPSD is a major risk factor for caregiver burden[24] and patient institutionalization[25] and is more important in this regard than are the cognitive deficits of the disease process.[26] All aspects of BPSD can be associated with caregiver burden, but paranoia, aggression, and incontinence appear to be particularly important drivers of caregiver burden and patient institutionalization.[25] The development of BPSD is also associated with a poorer prognosis, a more rapid rate of cognitive decline, illness progression,[27,28] greater impairment in activities of daily living,[29] and diminished quality of life,[30] and it adds significantly to the direct and indirect costs of care.[31] Expert assessment and targeted treatment of BPSD can alleviate patient suffering and promote caregiver well-being but will be less effective if interventions occur after the support system has been disturbed.

MANAGEMENT APPROACHES

In the assessment of individuals with dementia at all stages of the illness, care must be taken to establish the presence of BPSD. The emphasis must be to detect and deal with BPSD before caregiver "burnout" and irretrievable damage to the support environment occurs. Just as the collateral history and the use of an objective performance-based test is part of any comprehensive cognitive assessment, so too should the history and assessment focus on BPSD, given their high frequency and impact on both patient and caregiver quality of life.

Recognition of BPSD is the first and most important step in devising a management plan and will be facilitated by the use of standardized assessment scales (Table 2). The most commonly used and cited instruments are the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD)[32] and NPI.[33] The characteristics of the behavior or symptoms together with the frequency, severity, and impact on the patient and caregiver must be identified before formulating a tailored and targeted plan of action that is likely to involve a combination of nonpharmacologic and pharmacologic interventions.

The plan should consider the severity and pervasiveness of the behavior and whether it warrants nonpharmacologic intervention only or is severe enough to require combined pharmacologic and psychological interventions. The identification of target syndromes in the patient is useful: is this primarily a psychotic syndrome (hallucinations or delusions) or is the main problem psychomotor agitation and sleep disturbance? The context of the behavior or symptom and its impact are also key elements in assessment. Aggressive resistance when a personal activity is being carried out with the patient may not warrant first-line pharmacologic intervention. Also, misidentification of symptoms as part of a psychotic syndrome can be more distressing to caregivers than patients and in such instances requires education of family members rather than drug treatment.

Nonpharmacologic Treatments

Nonpharmacologic treatments are recommended as first line for BPSD and include interventions with both the patient and caregiver. There is a dearth of controlled

Table 3. Occurrence of Somnolence, EPS, and Gait Disturbance in Double-Blind, Placebo-Controlled Studies of Quetiapine, Risperidone, and Olanzapine in Patients With Dementia

		Frequency of Side Effect[a]			
Study	Drug, mg/day	Somnolence	Gait Disturbance	EPS	Comment
Tariot et al[46]	Quetiapine, 113.0[b]	25[c]	3	11	EPS (including gait disturbance) no different from placebo for quetiapine
	Haloperidol, 2.0[b]	36[c]	10[c]	35[c]	
	Placebo	4	3	12	
Katz et al[47]	Risperidone				EPS included gait disturbance; dose-dependent increases in somnolence and EPS
	0.5,	10	…	7	
	1.0,	17	…	13	
	2.0, or	28	…	21[c]	
	vs Placebo[46]	8	…	7	
Brodaty et al[48]	Risperidone, 0.95[b]	37	6	23	EPS no different from placebo; somnolence more common with risperidone than with placebo
	Placebo	25	1.2	16	
De Deyn et al[49]	Risperidone, 1.1[b]	12	…	15	EPS no different from placebo for risperidone
	Haloperidol, 1.2[b]	18	…	22[c]	
	Placebo	4	…	11	
Street et al[50]	Olanzapine				EPS no different from placebo for all doses of olanzapine (gait disturbance excluded)—data not presented
	5,	25[c]	20[c]	…	
	10,	26[c]	14	…	
	15, or	36[c]	17[c]	…	
	vs Placebo	6	2	…	

[a]As a percentage of patients.
[b]Mean dose.
[c]Statistically significantly greater than placebo.
Abbreviation: EPS = extrapyramidal symptoms.

evidence for the effectiveness of psychological interventions in BPSD. Individualized music therapy, bright light treatment, and aromatherapy have been found to improve certain problematic behavioral symptoms under controlled conditions in dementia patients,[34] but more evidence is required in this area.

Interventions for the Caregiver

Improving caregiver support, increasing "time for self," and providing caregiver education and training in the management of BPSD can be effective in lowering burden level and modifying its impact on the caregiver.[35] Interventions with caregivers may not only decrease caregiver burden and improve the tolerability of the particular BPSD[36] but can also impact in a positive way on patient behavior[37] and possibly delay institutionalization.[38,39]

Pharmacologic Treatments

Drug treatments in BPSD should be evidence-based and targeted to specific syndromes that are clinically significant because of their frequency, pervasiveness, or impact. Appropriate pharmacotherapies for persistent and moderate to severe BPSD include antidepressants for mood disorders, anticonvulsants for nonpsychotic agitation, and antipsychotics for aggression, agitation, and psychosis.

Antipsychotics. Antipsychotics remain the most widely prescribed drug treatment for BPSD. In the past, antipsychotic use in dementia has been excessive, inappropriate, and poorly monitored. However, if appropriately targeted, antipsychotic treatment can significantly improve the quality of life of both the patient and the caregiver. The goal of antipsychotic therapy must be the improvement in a specific target behavioral syndrome without impairing other aspects of dementia such as cognition, function, and quality of life.

Conventional antipsychotics, such as haloperidol, have shown modest benefit over placebo in the treatment of psychosis and agitation in patients with dementia[40]; however, they are associated with treatment-emergent side effects, even at modest doses. This is a potentially serious obstacle to treatment, as elderly patients, particularly those with dementia, are more sensitive than are younger patients to medication side effects such as orthostatic hypotension and extrapyramidal symptoms (EPS) including tardive dyskinesia.[41,42] In addition to the distress such side effects cause, they also increase the risk of falls and consequent fragility fractures in the elderly.[43] Of most concern are EPS such as parkinsonism and tardive dyskinesia.

When compared with conventional agents, atypical antipsychotics such as risperidone, olanzapine, and quetiapine are at least as effective in treating psychotic symptoms, are better tolerated, and have a lower propensity to cause EPS.[44,45] There are, however, significant differences between atypical agents with regard to receptor affinities and, therefore, side effect profiles. Table 3 summarizes the common atypical antipsychotic side effects, somnolence and EPS, and their frequency in the double-blind, placebo-controlled studies of quetiapine, risperidone, and olanzapine in patients with dementia.[46–50] In these studies,

somnolence was a side effect of both olanzapine and quetiapine.[46,50] Risperidone was associated with EPS and somnolence at higher doses,[47] and gait disturbance occurred with olanzapine.[50] Of the 3 atypical antipsychotics, quetiapine appears to be the least likely to cause EPS or gait disturbance in elderly patients with dementia.

The overall benefit of both conventional and atypical antipsychotics above that of placebo is modest (approximately 20%), and the placebo response rate is high. However, targeting the more severe cases is likely to improve the treatment response rate by decreasing the likelihood of treating patients who will improve spontaneously and in whom, therefore, pharmacologic treatment is not appropriate.

Nonantipsychotic treatments. Anticonvulsants have been used to treat nonpsychotic agitation in dementia. Carbamazepine has demonstrated modest efficacy over placebo in the treatment of agitation in nursing home patients,[51] but the placebo-controlled evidence for valproate is weak.[52,53] For depression in dementia, although there is little placebo-controlled evidence to guide practice, clinical experience indicates that selective serotonin reuptake inhibitors are safe and effective. A recent placebo-controlled trial with sertraline for major depression in Alzheimer's disease demonstrated superior efficacy over placebo, with an associated improvement in behavioral disturbance, activities of daily living, and caregiver distress.[54] Placebo-controlled studies suggest that cholinesterase inhibitors improve the apathetic syndrome in Alzheimer's disease and also decrease psychotic symptoms, particularly hallucinations, in Alzheimer's disease and dementia with Lewy bodies.[55,56]

CONCLUSIONS

BPSD are now accepted as an important therapeutic target in dementia. Management strategies, including pharmacologic and nonpharmacologic treatments, together with caregiver-focused training and education approaches, can be effective in decreasing BPSD. Although mild forms of BPSD may respond to simple environmental and psychosocial interventions, drug therapy is often required for the more severe psychotic, aggressive, and agitated presentations. If optimally selected, dosed, and monitored, atypical antipsychotics can improve these symptoms and have a positive impact on quality of life for both the patient and the caregiver.

Drug names: carbamazepine (Tegretol, Epitol, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft).

Disclosure of off-label usage: The author has determined that, to the best of his knowledge, carbamazepine, haloperidol, olanzapine, quetiapine, risperidone, sertraline, and valproate are not approved by the U.S. Food and Drug Administration for the treatment of behavioral and psychological symptoms in dementia.

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