

# Treatment of the Neuropsychiatric Symptoms in Alzheimer's Disease

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## IMPORTANCE OF TREATING BEHAVIORAL DISTURBANCES IN ALZHEIMER'S DISEASE

Behavioral symptoms are common in Alzheimer's disease (AD) and represent a major source of the disease morbidity. Neuropsychiatric disturbances have been associated with more rapid cognitive decline,<sup>1</sup> increased caregiver burden,<sup>2,3</sup> increases in patient care costs as a result of earlier institutionalization of the patient with AD, greater medication use and more adverse side effects, and more extensive institutional staffing needs.<sup>4,5</sup> Kaufer and colleagues<sup>6</sup> reported a strong correlation between the amount of neuropsychiatric disturbance as measured by the Neuropsychiatric Inventory (NPI) and the degree of caregiver distress with little relationship between the degree of impairment on the Mini-Mental State Exam (MMSE)<sup>7</sup> and the degree of caregiver distress. In addition, in a recent cost analysis, it was shown that patients with AD with higher NPI scores (worse psychopathology) had formal costs between \$3162 and \$5919 higher than those with low NPI scores, and the total direct costs were between \$10,670 and \$16,141 higher, depending on the severity of cognitive impairments.<sup>8</sup>

Clinical research on the treatment of these noncognitive symptoms has only recently become a subject of major investigation. Clinical drug trials of new therapeutic agents for patients with AD are beginning to regularly include specific scales to measure potential changes in behavioral symptoms with respect to their therapeutic interventions. In addition, an increasing number of randomized, placebo-controlled clinical trials of a wide variety of psychotropic medications to treat significant behavioral disturbances in dementia are beginning to emerge. The successful management of troublesome behaviors associated with AD can significantly improve the overall quality of life for patients and their caregivers and could result in significant relevant benefit.

## THE PREVALENCE OF BEHAVIORAL SYMPTOMS IN ALZHEIMER'S DISEASE

A wide spectrum of behavioral changes occurs throughout the course of AD with the prevalence of certain behaviors varying widely across studies. In general, behavioral disturbances are extremely common in patients with AD with

overall prevalence estimates between 60% and 80% and a lifetime risk of 90% or greater.<sup>9,10</sup> In one cross-sectional analysis, Mega and colleagues<sup>11</sup> examined the occurrence of certain common symptoms in patients with AD across disease severity, which included changes such as personality alterations, mood disturbances, perceptual disturbances (delusions and hallucinations), vegetative symptoms, and aberrant motor disturbances (Table 1).

Nearly all patients with AD develop neuropsychiatric symptoms sometime during the course of their illness with estimates of disruptive agitated behaviors ranging from 70% to 90%.<sup>1,12</sup> In a longitudinal study by Devandand and colleagues, the authors found that of 235 patients with early AD, only 8.5% remained free of psychopathology during the first 3 years of follow up. It is also not uncommon for multiple behavioral symptoms to coexist simultaneously.<sup>13,14</sup>

In addition, many of these behavioral disturbances are episodic and, in some cases, could precede the diagnosis of AD.<sup>15,16</sup> However, although behavioral symptoms can fluctuate, once they are present, they tend to recur. This is supported by a longitudinal assessment of 181 outpatients with AD and psychosis and/or aggression by Levy and colleagues,<sup>13</sup> in which they found 95% of patients with psychosis, 93% with agitation, and 85% with depression exhibited a recurrence of those symptoms during the following year. Devanand and colleagues also conducted a longitudinal study of 235 patients with early AD and followed them every 6 months for 5 years; they found that 80% of patients who exhibited behavioral disturbances at one visit manifested them at the next visit.<sup>17</sup>

## THE CHOLINERGIC DEFICIT IN ALZHEIMER'S DISEASE AND NEUROPSYCHIATRIC SYMPTOMATOLOGY

Many studies have focused on the relationship between the cholinergic deficit and cognitive impairment; however, evidence is emerging relating the cholinergic abnormalities to some of the neuropsychiatric manifestations of AD as well (see Table 2).

Anticholinergic toxicity is commonly accompanied by delirium with delusions and is reversible with physostigmine, a short-acting acetylcholinesterase inhibitor (AChEI). Treatment with physostigmine on psychotic symptoms was compared with haloperidol in a pilot double-blind, crossover trial involving patients with probable AD.<sup>18</sup> Reductions in psychotic symptoms were similar with the 2 drugs. Tacrine, another AChEI and the first drug approved for the symptomatic treatment of AD was shown in 2 subsequent studies to also have a beneficial effect on behavioral symptomatology. In an open-label study of 28 patients with probable AD, the

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**Table 1.** Spectrum of Neuropsychiatric Symptoms in Alzheimer's Disease

Behavior	Mild %	Moderate %	Severe %
Delusions	12	25	31
Hallucinations	12	15	8
Agitation	47	55	85
Dysphoria	12	45	62
Anxiety	24	65	54
Euphoria	18	0	8
Apathy	47	80	92
Disinhibition	35	40	54
Irritability	35	40	54
Aberrant motor	12	30	84

Adapted from Mega et al. *Neurology* 1996.

authors evaluated the effects of tacrine on behavioral symptoms and found a significant reduction in behavioral symptoms as measured by the NPI in response to therapy at the 120-mg/day and 160-mg/day doses. This was particularly true for symptoms of disinhibition, anxiety, and apathy.<sup>6</sup> In a post-hoc analysis of the randomized, double-blind, placebo-controlled clinical trial data with tacrine, Raskind and co-workers<sup>19</sup> reported on the results of one of the secondary outcome measures in that study, the Alzheimer Disease Assessment Scale, noncognitive subscale (ADAS-noncog), and found that treatment resulted in stabilization or improvement in the scores for delusions, pacing, and cooperation.

In 1999, Cummings and colleagues<sup>20</sup> reported the results of a retrospective analysis of 86 patients with AD treated with open-label donepezil and found behavioral improvement in 41%, which included a beneficial effect on delusions, agitation, anxiety, disinhibition, and irritability. McRae and colleagues<sup>21</sup> also reported the results of another open-label study using donepezil to treat 275 patients with AD and coexisting behavioral problems for 20 weeks. These investigators found a significant improvement in overall NPI scores. More recently, the effects of donepezil on behavioral aspects of AD was evaluated as part of a 24-week, multicenter, randomized, double-blind, placebo-controlled clinical trial involving patients with moderate to severe AD.<sup>22</sup> This study involved 290 subjects with MMSE scores ranging from 5–17 and found significant improvement in those subjects treated with donepezil compared with placebo in the primary outcome measure, the Clinician's Interview-Based Impression of Change with

**Table 2.** Neuropsychiatric Symptoms and the Cholinergic Deficit in Alzheimer's Disease (AD)

Anticholinergic medications produce similar neuropsychiatric symptoms.
Anticholinergic agents worsen AD.
Neuropsychiatric symptoms in AD are more marked in patients with AD with more severe cholinergic deficits.
Neuropsychiatric symptoms in AD reflect frontal and temporal lobe dysfunction.

caregiver input (CIBIC Plus), as well as in measures of cognitive function, behavior, and activities of daily living. The behavioral symptoms as measured by the NPI improved from baseline with donepezil by 4.6 points. Individual item analysis at week 24 showed a significant difference in depression/dysphoria, anxiety, and apathy.

Galantamine, a newer FDA-approved ChEI, has also been found in a randomized, double-blind, placebo-controlled clinical trial in outpatients with mild to moderate AD to have a beneficial effect on neuropsychiatric symptoms.<sup>23</sup> The total NPI score was improved in the group of subjects receiving galantamine compared with placebo; and the specific neuropsychiatric symptoms of anxiety, disinhibition, hallucinations, and aberrant motor behavior were significantly improved and the degree of caregiver distress reduced ( $P < 0.05$ ).

Rivastigmine, another FDA-approved AChEI, has also been reported to benefit the behavioral symptoms in a multicenter study of open-label rivastigmine in 173 patients with AD residing in nursing homes. Cummings and colleagues<sup>24</sup> found that 58% demonstrated improvement in behavioral problems, which included significant responses for irritability, aberrant motor behavior, apathy, hallucinations, disruptive nighttime behavior, agitation, and delusions. In another study of rivastigmine, researchers examined the effects of this compound on behavioral symptoms found in patients with dementia with Lewy bodies (DLB), another common cause of dementia with many similar features to AD.<sup>25</sup> This placebo-controlled, double-blind, multicenter study of 120 patients with DLB was conducted in Europe. Doses of rivastigmine up to 12 mg/day were compared with placebo for 20 weeks and neuropsychiatric assessments were performed using the NPI. Rivastigmine at 6 to 12 mg/day produced statistically and clinically significant behavioral effects showing at least a 30% improvement from baseline and was well tolerated.

The effects of the irreversible acetylcholinesterase inhibitor, metrifonate, on behavioral symptoms in patients with AD were evaluated prospectively in 2 randomized, placebo-controlled clinical trials of 672 patients. This AChEI demonstrated significant improvements in behavioral disturbances in patients with AD as measured by the NPI showing particular benefit of symptoms of hallucinations, aggression, agitation, and aberrant motor behavior.<sup>26,27</sup> An application to the U.S. Food and Drug Administration for metrifonate, however, was withdrawn in 2000 as a result of side effects of the drug.

In a recent meta-analysis of the published literature on the effects of ChEI on behavioral symptoms, Trinh and colleagues<sup>28</sup> reviewed the published literature on the topic from 1966 through 2001 and reported on the 29 parallel-group or crossover, randomized, double-blind, placebo-controlled trials of outpatients with mild to moderate AD treated for at least 1 month with a ChEI; 16 trials included evaluations of neuropsychiatric symptoms. A small, but statistically significant, improvement was seen with ChEI use.

In addition to the cholinesterase inhibitors, the selective muscarinic agonist, xanomeline tartrate, has been shown to improve the behavioral symptoms of AD in a randomized, double-blind, placebo-controlled trial involving 343 patients with mild to moderate AD. Dose-dependent reductions were

noted in symptoms such as vocal outbursts, suspiciousness, delusions, agitation, hallucinations, wandering, fearfulness, compulsiveness, tearfulness, mood swings, and threatening behavior.<sup>29</sup>

Although the precise neurobiology of the neuropsychiatric disturbances in patients with AD is not fully understood, cholinergic systems appear to play a role in some of the noncognitive manifestations of the illness. In addition, there are known alterations in several other neurotransmitter systems (such as noradrenergic, serotonergic, cholinergic, and dopaminergic), which have also been implicated in the pathobiology of anxiety, mood disorders, and psychosis. Alterations in these other transmitter systems in patients with AD could contribute in an important way to behavioral disturbances in these patients and could be a further target for improved therapies.

### **EVALUATING BEHAVIORAL DISTURBANCES IN PATIENTS WITH DEMENTIA**

Critical to the initial management of these disturbances is a search for any contributing medical, medication-related, or social/environmental factors. Superimposed delirium as a cause of behavioral deterioration should always be considered. Patients with dementia are more likely than nondemented elderly patients to develop an acute confusional state with toxic or metabolic insults. There should be a high index of suspicion of the presence of delirium with any acute alteration in behavior, sleep patterns, or attention, or with the onset of motor restlessness or increase in visual hallucinosis.<sup>30</sup> Understanding the patient's underlying needs or motivation can lead to creative interventions that diminish disturbed behaviors without drugs.<sup>31</sup> If these approaches are not successful and behavioral disorders are severe enough to interfere with normal functioning, pharmacologic therapy should be considered (see Table 3).

### **NONPHARMACOLOGIC BEHAVIORAL INTERVENTIONS**

Behavior modification treatment involves identification of the specific problem behavior and assessment of environmental factors that precipitate or reinforce the undesired behavior. The environment and actions of others are then modified to extinguish undesirable behaviors and increase desired behaviors. Operant techniques and environmental manipulation have been used to successfully reduce wandering behavior, verbal and physical aggression, and depressive behaviors and to increase self-care skills, appropriate ambulation, and socialization.<sup>32</sup> Caregivers and family members can benefit from education regarding the expected changes in memory, language skills, cognition, and behavior during the progressive course of AD.

A wide variety of nonpharmacologic interventions such as sensory intervention, environmental interventions, structured activities, and behavioral therapy have been looked at for their effect on unwanted behavioral symptoms in patients with dementia. For an excellent review of the literature, the reader is referred to Cohen-Mansfield.<sup>33</sup>

In a large-scale, multicenter, randomized, parallel-group,

placebo-controlled trial sponsored by the Alzheimer's Disease Cooperative Study Group (ADCS), the results of a behavioral intervention (behavior management techniques (BMT) with 2 common pharmacologic interventions used at the time (trazodone and haloperidol) versus placebo for treating agitation in patients with AD was studied.<sup>34</sup> The results suggested that improvement rates were similar in all 3 groups (BMT = 32%, haloperidol = 32%, trazodone = 41%, and placebo 31%), and there were no differences in efficacy or dropout rates. There was less bradykinesia and Parkinsonism in the behavioral management arm. It has been argued that one potential reason for the lack of superiority of the pharmacologic interventions could have been the result of a "floor effect" with fewer patients exhibiting significant behavioral disturbances in this outpatient population compared with the more typically, acutely agitation inpatients with more advanced disease in which most of the efficacy data has been reported. Also, newer atypical antipsychotic agents have since become available, which appear to be better tolerated and possibly more efficacious.

### **PHARMACOLOGIC INTERVENTIONS**

#### *Treatment of Psychosis and Agitation*

Psychosis (delusions and/or hallucinations) is not uncommon in patients with dementia and represents a distinct clinical syndrome that could be responsive to appropriate directed pharmacologic therapy. A working definition for this has been put forth by Jeste and Finkel (see Table 4), and more recent clinical trials in patients with dementia are now being conducted using this definition.

#### *Atypical Neuroleptics*

Although the use of typical and atypical neuroleptics in the demented elderly patient has been widely studied, many investigations have been limited by methodologic flaws (ie, heterogeneous patient populations, inadequate definition and measurement of target symptoms, lack of randomization, inadequate controls, and lack of double-blind assessment methods). In a statistical meta-analysis of controlled trials of neuroleptic treatment of agitation in patients with a primary diagnosis of dementia, Schneider and colleagues<sup>36</sup> found that 18% of patients with dementia derived benefit from neuroleptic treatment beyond response attributable to placebo. The placebo response was significant in many studies, varying from 0% to 67%. Kindermann and colleagues<sup>37</sup> conducted another recent review of the published literature from 1960 to 2000 on the treatment of psychosis, agitation, and aggression in patients with dementia. Forty-eight studies meeting their selection criteria were identified from Medline and Science Citation Index. The authors found that antipsychotic medication was generally effective for the treatment of psychosis and agitation in elderly patients with dementia; and in double-blind, placebo-controlled trials in this population, mean improvement rates were 61% with antipsychotics and 35% with placebo. The placebo effect was still significant, but more recent studies used atypical antipsychotic agents, which appear to have a more favorable side effect profile in this patient population.

**Table 3.** Neuropsychiatric Symptom Cluster in Dementia and Class of Psychopharmacologic Agent

Drug	Trade Name	Starting Dose	Maximum Dose
<b>Psychosis</b>			
Atypical Antipsychotic			
Risperidone	Risperdal	0.5 mg/d	1–2 mg/d
Olanzapine	Zyprexa	2.5 mg/d	5–10 mg/d
Quetiapine	Seroquel	12.5–25 mg/d	50–150 mg/d
Clozapine	Clozaril	6.25–12.5 mg/d	25–100 mg/d
Drug	Trade Name	Starting Dose	Maximum Dose
<b>Agitation/Aggression</b>			
Antipsychotics (same as listed above)			
Anticonvulsant			
Divalproex	Depakote	125 twice a day	1500–2000 mg/d
Carbamazepine	Tegretol	50–100 mg/d	500–800 mg/d
Antidepressant			
Trazadone	Deseryl	25–50 mg/d	200–300 mg/d
Paroxetine	Paxil	5–10 mg/d	40 mg/d
Sertaline	Zoloft	25–50 mg/d	150–200 mg/d
Citalopram	Celexa	10–20 mg/d	40 mg/d
Anxiolytic			
Buspirone	Buspar	5 mg twice a day	45 mg/d
Lorazepam	Ativan	0.5 mg/d	4–6 mg/d
Other			
Propranolol	Inderal	10 mg twice a day	50–240 mg/d
Drug	Trade Name	Starting Dose	Maximum Dose
<b>Depression</b>			
Selective Serotonin Reuptake Inhibitor			
Fluoxetine	Prozac	10 mg/d	20–40 mg/d
Paroxetine	Paxil	5–10 mg/d	40 mg/d
Sertaline	Zoloft	25–50 mg/d	150–200 mg/d
Citalopram	Celexa	10–20 mg/d	40 mg/d
Fluvoxamine	Luvox	50 mg/d	300 mg/d
(Tricyclic)			
Nortriptyline	Pamelor	10 mg/d	50–100 mg/d
Desipramine		50 mg/d	150 mg/d
(Other)			
Nefazodone	Serzone	150 mg twice a day	600 mg/d
Venlafaxine	Effexor	37.5 mg/d	375 mg/d
Mirtazapine	Remeron	15 mg/d	90 mg/d
Drug	Trade Name	Starting Dose	Maximum Dose
<b>Anxiety</b>			
Buspirone	Buspar	5 mg/d	30–45 mg/d
Lorazepam	Ativan	0.5 mg/d	2–6 mg/d
Oxazepam		10 mg/d	30 mg/d
Drug	Trade Name	Starting Dose	Maximum Dose
<b>Sleep Disturbance</b>			
Trazadone	Deseryl	50 mg/d	300 mg/d
Zolpidem	Ambien	5–10 mg/d	10 mg/d
Temazepam	Restoril	15 mg/d	30 mg/d
Zaleplon	Sonata	5–10 mg/d	10 mg/d

Potential side effects also include sedation, orthostatic hypotension, central and peripheral anticholinergic effects, and extrapyramidal symptoms (EPS; akathisia, Parkinsonism, tardive dyskinesia, neuroleptic malignant syndrome) resulting from dopamine blockade. All of these side effects appear to occur with increased frequency and at lower dosage levels in

elderly patients.<sup>38</sup> The one exception is neuroleptic malignant syndrome, which is more common among younger patients. There is an increased incidence and severity of tardive dyskinesia with advancing age.<sup>39</sup> Excessive sedation can potentially cause increased confusion and agitation. More serious consequences (eg, hip fracture) can result from falls in

**Table 4.** *Jeste and Finkel Criteria for Psychosis in Alzheimer's Disease (AD)*<sup>35</sup>

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Characteristic symptoms: delusions or auditory/visual hallucinations
Primary diagnosis of AD
Chronology of onset of symptoms of dementia versus psychosis
Duration >1 month; severity: functional disruption
Exclusion of schizophrenia, delirium, and other causes of psychosis

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elderly patients. Elderly patients are more likely to have preexisting medical conditions such as cardiac disease or prostatic hypertrophy, increasing the risk of adverse peripheral anticholinergic effects. Patients with AD might be more susceptible to central anticholinergic cognitive effects given the widespread cortical cholinergic deficit present in patients with AD. Neuroleptic-induced akathisia can increase pacing and other repetitive nonaggressive behaviors.

The use of the atypical neuroleptics in the treatment of behavioral problems in patients with dementia has been gaining more widespread approval. In a randomized, placebo-controlled trial comparing 0.5, 1.0, and 2.0 mg per day of risperidone to placebo in treating psychosis and aggressive behavior in 625 elderly institutionalized patients with dementia, the authors found significant reductions in these behaviors as measured by the BEHAVE-AD.<sup>40</sup> Seventy percent of patients completed the study, and more side effects were seen in the 2-mg/day versus the 1-mg/day dose of risperidone.<sup>41</sup> Another study in 344 nursing home patients found slightly less robust results, but efficacy was clearly demonstrated. DeDeyn and coworkers<sup>42</sup> also reported on a double-blind, randomized trial of 12 weeks' duration of risperidone versus haloperidol in a nursing home dementia population showing an antiaggressive effect in treated patients and a superiority of risperidone over haloperidol in terms of tolerability. A more recent randomized, placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis in dementia was conducted in 337 elderly nursing home patients with dementia. Treatment with low-dose risperidone (mean, 0.95 mg/day) resulted in significant reduction in aggressive behavior, agitation, and psychosis compared with placebo.<sup>43</sup> Risperidone was generally well tolerated with no increase seen in EPS, but somnolence and urinary tract infection was more common in the treated group.

Olanzapine, another newer atypical antipsychotic agent, has also been recently shown to improve psychotic and behavioral symptoms in patients with AD in nursing care facilities. In a 6-week, double-blind, randomized, placebo-controlled trial with 206 patients, which used as the primary efficacy measure the sum of the agitation/aggression, hallucinations, and delusions items of the NPI-Nursing Home version, a validated scale for use in this patient population, significant behavioral improvement was demonstrated.<sup>44</sup> The 5-mg/day and 10-mg/day doses of olanzapine produced signif-

icant improvement compared with placebo in these core symptoms, but somnolence was significantly more common among treated patients and gait disturbance occurred in 19.6% and 17.0% of the 5-mg/day and 15-mg/day doses, respectively.

Quetiapine was evaluated in a prospective, open-label, 12-week pilot study in outpatients with probable AD with psychosis or aggressive behaviors. This study found that in doses ranging from 50 to 150 mg, patients given quetiapine showed a significant decrease in delusions, aggression, and overall behaviors based on NPI scores at 6 and 12 weeks.<sup>45,46</sup> Larger, multicenter, placebo-controlled trials in AD are in progress.

Ziprasidone and aripiprazole are the newest atypical antipsychotics available in the United States, but there is limited data regarding their use in the elderly and no reports regarding use in patients with dementia.

Important side effects can occur with the atypical antipsychotics and include extrapyramidal symptoms, tardive dyskinesia, sedation, orthostatic hypotension, falls, metabolic (weight change, hyperglycemia, dyslipidemia), QT prolongation, and cognitive toxicity, including delirium and impaired activities of daily living.

A major limitation in many of the current studies using antipsychotics in treating behavioral disturbances in patients with dementia is the lack of randomized trials that extend beyond 12 weeks, and long-term controlled data is lacking. To address this issue, a large, multicenter, randomized, controlled study of the use of antipsychotics in patients with AD sponsored by the National Institute of Mental Health is currently underway known as the Clinical antipsychotic Trials of Intervention Effectiveness (CATIE). Information from this study will provide useful data on many of the effectiveness of these compounds in this patient population with evaluation of more prolonged exposure.<sup>47</sup>

In general, atypical antipsychotics are more useful than typical antipsychotics but have their own limitations, and patients with AD need lower doses than elderly patients with schizophrenia.

## ANTICONSULSANTS

Divalproate sodium is an anticonvulsant, which works by enhancing the release of the primarily inhibitory neurotransmitter, gaba-butyric acid (GABA). It has been shown to be effective in managing agitation and aggression in patients with dementia in a number of open trials.<sup>48,49</sup> In a small, controlled pilot study with 16 subjects, divalproate sodium was used for the treatment of agitation in patients with dementia with good efficacy and tolerability.<sup>50</sup> The doses were gradually titrated from 500 to 2000 mg/day. More recently, Porsteinsson and colleagues<sup>51</sup> reported the results of a 6-week, placebo-controlled study of divalproex sodium for agitation in dementia in 56 nursing home patients. The Brief Psychiatric Rating Scale (BPRS) was used as the primary outcome measure in this study and has been validated for use in this setting. They found that the agitation score on the BPRS was reduced in the treated patients compared with placebo and this was statistically significant. Similarly, the Clinical Global Impression scale also showed a trend toward improvement in the

treated group ( $P = 0.06$ ). In general, divalproate sodium is well tolerated in the elderly but can cause gastrointestinal side effects as well as a benign tremor and sedation. Liver function tests should also be monitored.

Currently, the Alzheimer's Disease Cooperative Study Group is investigating the potential role of valproate in potentially delaying or preventing the onset of agitation in a group of patients with AD and further investigating a potential neuroprotective effect.<sup>52</sup>

Carbamazepine, an anticonvulsant with psychotropic properties found to be effective in bipolar disorder, has also been reported to reduce emotional lability, aggression, and socially inappropriate behaviors in various brain disorders.<sup>53</sup> Small, controlled clinical trials in patients with dementia have found it efficacious in reducing irritability, hostility, agitation, and combativeness in patients with AD.<sup>54,55</sup> Carbamazepine can be started as low as 50 mg twice daily and slowly titrated upward to avoid oversedation and ataxia.<sup>56</sup> Daily dosages used in patients with possible AD have ranged from 100 to 1000 mg, and clinical improvement usually occurs within 2 to 4 weeks.<sup>57</sup> Central nervous system side effects of carbamazepine are dose-related and include sedation and ataxia. Baseline complete blood count and routine liver function tests should be obtained. Monthly measurements are recommended for the first 6 months, with measurements repeated at 3- to 12-month intervals thereafter.

Gabapentin is a novel anticonvulsant that acts on the GABA system to help control seizures and has little if any drug-drug interactions. It has gained widespread off-label clinical use for a variety of conditions and is being explored as a potential useful agent in controlling difficult behavior in patients with dementia. One open-label pilot study of 12 patients has been reported<sup>58</sup> with modest effectiveness and other studies are planned.

## TRAZODONE

Several case reports and small, uncontrolled series have shown that trazodone, a serotonin reuptake inhibitor, can effectively control agitation in dementia. The mechanism of the antiagitation effect is unknown but appears to be unrelated to antidepressant or sedative properties and could be associated with calming effects observed in animal models after blockade of serotonin reuptake.<sup>57</sup> Serotonin deficiency was shown by one group of investigators to be particularly severe in the frontal lobes in patients with AD, and it was suggested that this neurotransmitter deficiency contributes significantly to aggressive behavior in patients with AD.<sup>59</sup> Adverse effects of trazodone include sedation, hypotension, ventricular arrhythmias, and priapism.

## BENZODIAZEPINES

Benzodiazepines are effective for reducing anxiety and agitation, but not psychotic symptoms. Neuroleptics have been shown to have greater efficacy than benzodiazepines in controlled trials of treatment of agitation. This superiority was most evident with increasing severity of dementia and agitation.<sup>55</sup> Side effects of benzodiazepines include sedation, cognitive impairment, paradoxical disinhibition, amnesic effects,

tolerance, and withdrawal syndromes. Short-acting agents such as lorazepam or oxazepam are preferred in elderly patients to minimize drug accumulation and drug interactions. Very small doses can be used intermittently for treatment of anxiety and mild agitation in patients with mild AD with close monitoring of behavior and function. The literature does not support the use of benzodiazepines for agitation in patients with more severe dementia for whom atypical neuroleptics, or possibly an anticonvulsant, could be more efficacious.<sup>60,61</sup>

## BUSPIRONE

Buspirone is a nonbenzodiazepine anxiolytic agent whose mechanism of action is unknown. There are a few case observations supporting the use of buspirone to treat agitation in patients with AD. The binding of the drug to central dopamine receptors has raised concern about possible EPS. There have been a few open series and case reports of its effectiveness in dementia populations.<sup>62-64</sup>

## BETA-ADRENERGIC RECEPTOR-BLOCKING AGENTS

In a few small clinical series, propranolol at doses ranging from 60 to 560 mg/day was successful in improving aggressive and agitated behavior in patients with dementia.<sup>59</sup> Other beta-blockers have not been extensively studied. Cardiovascular side effects can limit the use of these agents in elderly patients. Concomitant conditions such as chronic obstructive lung disease and diabetes also can preclude use of these agents in some geriatric patients. Blood pressure and pulse should be monitored closely in any patient with dementia receiving beta-adrenergic-blocking agents.

In summary, treatment of agitation in patients with AD must be individualized. Agitation should be approached initially by investigation of potentially reversible causes such as physical discomfort or environmental factors. Acute management can include sedation with atypical and typical neuroleptics or short-acting benzodiazepines. Severe adverse effects and limited efficacy make these agents less useful for the management of chronic agitation. Low-dose neuroleptic therapy is, however, indicated for agitation related to psychotic symptomatology. Other available agents reported to be effective in some clinical studies are divalproate sodium and carbamazepine. Antidepressants like the selective serotonin reuptake inhibitors (SSRIs), which are generally well tolerated, can be helpful in treating both depressive symptoms and agitation in patients with dementia, but further studies are needed. Propranolol could also be helpful for aggressive, impulsive behaviors and is used frequently in patients with behavioral disturbances resulting from head trauma. These drugs, however, need to be used with care in the elderly because they are associated with common side effects. Therapeutic approaches must be strongly influenced by consideration of potential side effects in the individual patient, and patients must be closely monitored for adverse effects. Periodic attempts should be made to reduce or discontinue any therapeutic agent.

## Treatment of Anxiety

Anxiety is common in patients with AD, reported in approximately 40%.<sup>66</sup> In patients with AD, anxiety is inversely related to MMSE score (ie, worse with more severe dementia), appears to be more prevalent in younger-onset patients, and correlates with disability.<sup>67</sup> However, no results from any large-scale, well-designed, placebo-controlled trials for treatment of anxiety in this population are currently available. The treatment of anxiety with standard benzodiazepine anxiolytic agents is problematic, as discussed earlier, and use of benzodiazepines must be accompanied by ongoing assessment of the risk-benefit ratio. Shorter-acting benzodiazepine agents (eg, lorazepam, oxazepam) are preferable in elderly patients. Buspirone, a nonbenzodiazepine anxiolytic that is generally well tolerated, can be effective in the treatment of anxiety in nondemented elderly patients. Because it does not appear to adversely affect cognition in young healthy persons, this agent may be helpful for the treatment of anxiety in patients with AD,<sup>60</sup> but well-controlled studies are needed.

## TREATMENT OF INSOMNIA

Sleep disturbance is common in patients with AD. The disturbance is characterized by reduced depth and efficiency as well as increased fragmentation of sleep. With progression of the disease, disruption of the normal circadian rhythm is observed, with multiple periods of sleeping and waking, daytime naps, and sundowning (nocturnal agitation, confusion, and wandering). This disruption of the normal sleep-wake cycle in patients with AD could be related to degeneration of the suprachiasmatic nucleus. The cholinergic system is important in the generation of REM sleep, and cholinergic dysfunction in patients with AD is likely related to sleep disturbances.<sup>68</sup> Poor nocturnal sleep can reduce daytime alertness, aggravating cognitive impairment in patients with AD and further increasing caregiver stress.

A randomized, double-blind, placebo-controlled crossover trial was undertaken to test the hypothesis that 6 mg slow-release exogenous melatonin improves sleep for people with dementia. Serfaty et al.<sup>69</sup> examined 44 subjects with dementia and sleep disturbance for 7 weeks using wrist actigraphy. They found no evidence that 2 weeks of exogenous melatonin is effective in improving sleep in people with dementia.

Nonpharmacologic management includes optimizing sleep hygiene by limiting time in bed to 6.5 to 7 hours per night, reducing daytime naps, establishing a consistent morning awakening time, and reducing evening fluids to prevent awakening for micturition.<sup>70</sup> The use of light therapy has also been shown to be of some benefit in patients with dementia. Potentially useful medications include trazodone, temazepam, chloral hydrate, and zolpidem (Sonata). Both temazepam and chloral hydrate are associated with tolerance and withdrawal syndromes.

## SEXUAL BEHAVIOR

Alteration in sexual relationships can be a cause of distress for the caregiver, and these concerns should be frankly addressed. There are variable changes in libido among patients with AD, ranging from loss of interest in sexual activity to

increased sexual drive and disinhibition in a minority of cases. Relational changes can also make continued sexual activities distasteful to the caregiver spouse. Suggestions for redirecting undesired sexual attention or encouraging desirable physical affection can be beneficial.

## CAREGIVER SUPPORT

Experience with care of patients with dementia has shown that the needs of the patient cannot be addressed in isolation from those of his or her family. Caregivers have been found to have poorer overall physical health, increased use of psychotropic medications, and more depressive symptomatology than age-matched control subjects.<sup>71</sup> The proportion of caregivers with clinically significant depression is not known, but one study found that 55% of family caregivers of patients with AD had symptoms of depression.<sup>72</sup> Caregivers should be assessed for depressive symptomatology and referred for individual therapy or medication if indicated. Participation in support groups, group therapy, or family therapy can ameliorate depressive symptoms. There is evidence that caregiver training directed at improving coping strategies and reducing psychologic distress and isolation could delay nursing home placement of persons with dementia.<sup>73</sup>

The clinician should educate the caregiver regarding AD so that he or she can better understand the disease and adjust to progressive changes in the patient's behavior and care needs.<sup>74</sup> Several support organizations, web sites, and books are available to help family members understand the nature and course of AD. These include *The 36-Hour Day*<sup>75</sup> and *Understanding Alzheimer's Disease*.<sup>76</sup> Some of these issues are covered in the chapter by Morrison and Rabins in this issue. Caregiver support groups are also an excellent source of information. They can increase informal support networks, enhance feelings of competence in the caregiver role, and improve psychologic functioning.<sup>77</sup>

In summary, mood and behavioral symptoms are frequently the most distressing aspects of AD for the caregiver, and finding effective therapies to significantly reduce these symptoms is likely to have an important impact on patient care, caregiver distress, and the rate of institutionalization. Use of specific class of agents can be matched to particular target behavioral symptom clusters (Table 4).<sup>35</sup>

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