

# Managing Behavioral Dyscontrol Related to Dementia

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Dementia of the Alzheimer's type involves both a cognitive and a behavioral domain. Behavioral and psychotic symptoms in dementia are defined as a heterogeneous range of psychological reactions and psychiatric symptoms and behaviors resulting from the presence of dementia. Symptoms include psychosis, agitation/aggression, anxiety, depression, apathy, and sleep disturbance. Multiple brain and neurochemical deficits may act as catalysts for these symptoms. Like other patients suffering from symptoms of aggression, patients with dementia have serotonin deficits as well as a loss of serotonin receptors in cerebrospinal fluid and the raphe nuclei. Patients with Alzheimer's type dementia additionally appear to have functionally hyperresponsive serotonin systems that likely contribute to aggressive behavior, and there is an apparent association between serotonin responsiveness and agitation in these patients. The relationship between serotonin and aggression provides a rationale for the use of serotonin antagonists to aid in the management of the behavioral and cognitive symptomatology inherent to Alzheimer's type dementia.

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**D**ementia of the Alzheimer's type was originally thought to be primarily a cognitive problem; however, in recent years it has become apparent that it involves both a cognitive domain and a behavioral domain. Behavioral and environmental paradigms have traditionally represented behavioral symptoms in Alzheimer's type dementia as resulting from the inability of patients to express their needs due to frailty and general communication impairment. In the mid-1990s, a movement began in geriatric psychiatry to identify and understand specific behavioral and psychiatric symptoms occurring in patients with Alzheimer's type dementia. This movement has since inspired psychiatrists and other physicians to begin assessing behavioral and psychotic symptoms in dementia (BPSD) in their practices.

BPSD consist of a heterogeneous range of psychological reactions and psychiatric symptoms and behaviors resulting from the presence of dementia. The symptoms include psychosis, agitation/aggression, anxiety, depres-

sion, apathy, and sleep disturbance, and the lifetime prevalence of these symptoms in patients with dementia in care environments is 70% to 80%.<sup>1,2</sup> In fact, BPSD are frequently so severe and distressing to caregivers that their inability to cope with BPSD is one of the leading reasons for nursing home placement.<sup>3</sup> Caregivers commonly report that behavioral and psychiatric symptoms are more distressing than cognitive impairment.<sup>4</sup>

Biological models portray multiple brain and neurochemical deficits as catalysts for these symptoms, portending that these symptoms are endogenously psychiatric in origin. Patients with dementia, like other patients suffering from symptoms of aggression, have a serotonin deficit as well as a loss of serotonin receptors in cerebrospinal fluid and the raphe nuclei,<sup>5,6</sup> and studies<sup>7,8</sup> indicate that a functionally hyperresponsive serotonin system may contribute to aggressive behavior in patients with Alzheimer's type dementia. The evidentiary relationship between serotonin and aggression<sup>9</sup> provides a rationale for the use of serotonin antagonists to aid in the management of the behavioral and cognitive symptoms inherent to Alzheimer's type dementia.

## SEROTONIN AND AGITATION IN ALZHEIMER'S TYPE DEMENTIA

In a 1994 study, McLoughlin et al.<sup>8</sup> conducted a fenfluramine challenge test to determine whether the central serotonin system is hyperresponsive in patients with Alzheimer's disease. Racemic fenfluramine (*dl*-fenfluramine), an indirect serotonin agonist, causes a dose-

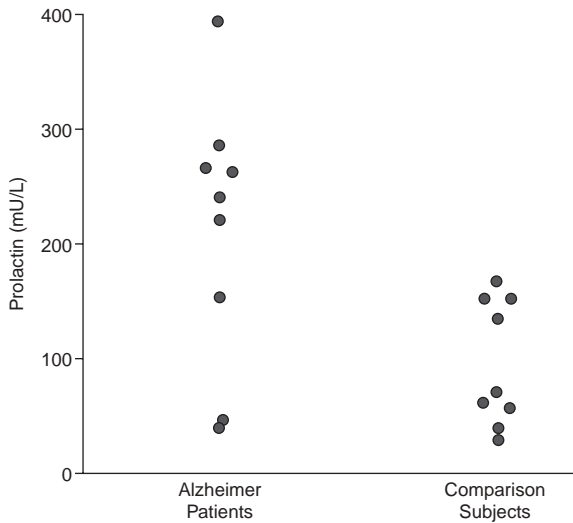
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Figure 1. Prolactin Responses to *d*-Fenfluramine (30 mg) in 9 Patients With Late-Onset Alzheimer's Disease and 9 Elderly Comparison Subjects<sup>a</sup>

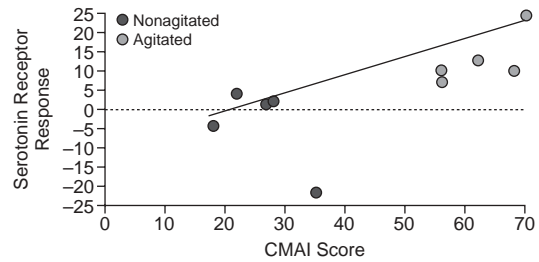


<sup>a</sup>Reprinted with permission from McLoughlin et al.<sup>8</sup>

dependent increase in plasma prolactin levels of healthy people. The dextrorotatory isomer of fenfluramine (*d*-fenfluramine) specifically affects the serotonin synapse, increasing the release and inhibiting the reuptake of serotonin and indirectly stimulating all postsynaptic serotonin receptors. *d*-Fenfluramine dose-induced prolactin secretion, therefore, provides researchers a probe to assess net central serotonin responsivity.<sup>10</sup> In the study,<sup>8</sup> 9 healthy controls and 9 patients with late-onset Alzheimer's disease were given 30 mg of *d*-fenfluramine, and blood samples were collected to measure prolactin levels at baseline and 60, 120, 180, 240, and 300 minutes after *d*-fenfluramine was administered. At baseline, prolactin values were not significantly different between the 2 groups ( $p = .66$ ). At endpoint, results revealed significant ( $p = .04$ ) differences in prolactin levels between the controls and the patients with Alzheimer's disease (Figure 1) and indicated no significant correlation between prolactin and duration of illness. Researchers concluded that a functionally hyperresponsive serotonin system might contribute to the cognitive disturbances typically attributed to cholinergic disruptions in patients with Alzheimer's disease and postulated that serotonin antagonists might be beneficial in the management of behavioral and cognitive symptoms in these patients.

Mintzer et al.<sup>7</sup> conducted a similar study using the fenfluramine challenge test to explore whether hyperresponsivity of the serotonin system is involved in the pathophysiology of agitated patients by comparing prolactin excretion in agitated and nonagitated patients who met the DSM-III-R and the National Institute of Neurological

Figure 2. Correlation Between Postsynaptic Serotonin Receptor Response and Total CMAI Score<sup>a</sup>



<sup>a</sup>Reprinted with permission from Mintzer et al.<sup>7</sup>  
Abbreviation: CMAI = Cohen-Mansfield Agitation Inventory.

and Communicative Disorders and Stroke-Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria for Alzheimer's disease. Researchers compared prolactin levels in 5 agitated patients with those of 5 nonagitated patients, after each was administered 60 mg of *dl*-fenfluramine. Levels of prolactin were obtained at baseline and 2 and 3 hours after the administration of the *dl*-fenfluramine. The Cohen-Mansfield Agitation Inventory (CMAI) was used to measure aggression as a function of the number of episodes exhibited over a period of a week. Three hours after *dl*-fenfluramine was administered, prolactin levels were significantly ( $p = .022$ ) greater among agitated patients than nonagitated patients. Additionally, there appeared to be a significant ( $p = .01$ ) positive correlation between the change in prolactin levels from baseline and level of agitation (Figure 2). Researchers concluded not only that patients with Alzheimer's type dementia appear to have functionally hyperresponsive serotonin systems but that there is an association between serotonin responsiveness and agitation in these patients.

### TREATMENT OPTIONS FOR BPSD

BPSD in patients with Alzheimer's type dementia were traditionally managed by means of physical restraint. In an attempt to determine whether using mechanisms of physical restraint would lead to a decrease or an increase in agitation, Werner and colleagues<sup>11</sup> observed agitated nursing home residents and recorded aggressive behavior. They determined that nursing home residents exhibited either equal or higher levels of agitation when restrained and suggested that the act of restraining a patient may contribute to the manifestation of agitated behavior. For example, they reported that on average, a patient who had been behaving aggressively 5% of the time prior to restraint displayed aggressive behavior 20% of the time while restrained. Furthermore, patients were often kept in restraint until the agitated behavior decreased, but agitation levels typically decreased only to levels that were equal to the

**Table 1. Pharmacologic Treatments for Behavioral and Psychological Symptoms of Dementia**

Antipsychotics
Haloperidol
Olanzapine
Quetiapine
Risperidone
Mood stabilizers
Carbamazepine
Divalproex
Cholinesterase inhibitors
Donepezil
Galantamine
Metrifonate
Physostigmine
Rivastigmine

level of agitation prior to the restraint, so no improvement was accomplished. In the nursing home setting, medication is more effective than physical restraint in controlling BPSD.

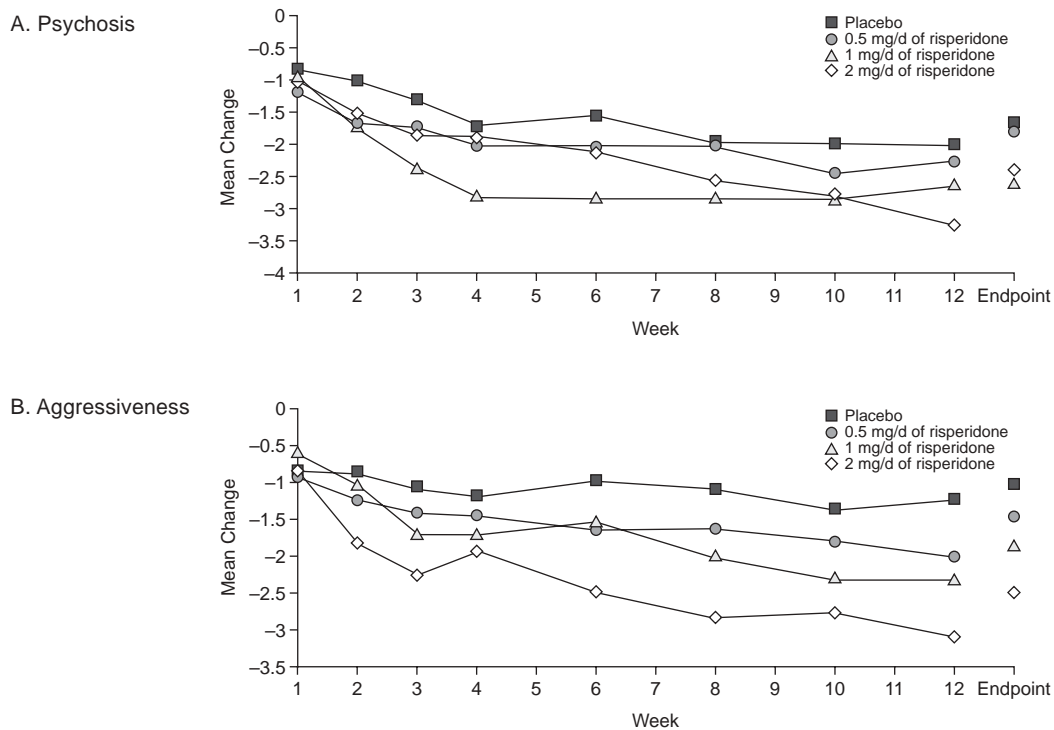
Numerous pharmacologic agents are currently being used to treat BPSD (Table 1). Antipsychotics are well-established treatments for the behavioral symptoms of dementia, but typical antipsychotics carry with them the risk of reversible drug-induced movement disorders and tardive dyskinesia, and elderly patients are especially susceptible to these side effects. Atypical antipsychotics, unlike typical agents, affect both dopamine and serotonin and may be effective for both psychosis and aggression in these patients. Another benefit of atypical antipsychotics is that they carry a lower risk of motor side effects such as extrapyramidal symptoms and tardive dyskinesia compared with typical agents such as haloperidol, and they work in this population at relatively low doses.<sup>12-15</sup>

**Atypical Antipsychotics**

Katz et al.<sup>15</sup> conducted the first large, double-blind, placebo-controlled study to evaluate the efficacy of the atypical antipsychotic risperidone in the treatment of behavioral and psychotic symptoms in Alzheimer’s disease. All of the 625 participants were residing in a nursing home or a chronic disease hospital at the time of the study, and 73% had been diagnosed with DSM-IV Alzheimer’s disease, 15% with vascular dementia, and 12% with a combination of the two. To participate in the study, all of the patients were required to have scored a total of ≥ 8 and a global rating of ≥ 1 on the Behavioral Pathology in Alzheimer’s Disease (BEHAVE-AD) rating scale, indicating substantial psychotic and behavioral symptoms. Patients were randomly assigned to receive placebo (N = 163), 0.5 mg/day of risperidone (N = 149), 1 mg/day of risperidone (N = 148), or 2 mg/day of risperidone (N = 165) for 12 weeks, and the BEHAVE-AD was used as an outcome measure. Of the 70% of patients who completed the study, more than 95% had scored 6 or 7 on the Baseline Functional Assessment Staging scale before the study, indi-

cating severe dementia. By endpoint, patients receiving 1 mg/day and 2 mg/day of risperidone had significantly (p = .005 and p < .001, respectively) greater reductions in BEHAVE-AD total scores and psychosis and aggressiveness subscale scores than patients receiving placebo (Figure 3A). Patients receiving 0.5 mg/day of risperidone had significantly (p = .02) greater reductions in BEHAVE-AD aggression scores than those receiving placebo at week 12 (Figure 3B). Additionally, tardive dyskinesia emerged in only 1 participant receiving placebo and in none of the patients exposed to risperidone. Although the 2-mg/day group improved the most over the placebo group, patients receiving 2 mg/day of risperidone reported more adverse events than did patients in all the other groups. The most common dose-related adverse events were somnolence, extrapyramidal symptoms, and mild peripheral edema. Extrapyramidal symptoms were reported with equal frequency in patients receiving 1 mg/day of risperidone and patients receiving placebo. Due to increased adverse effects in the 2-mg/day group, researchers recommended 1 mg/day of risperidone as an appropriate and efficacious dose for most elderly patients with dementia.

If improvements in aggressive behavior with atypical antipsychotics are related to the serotonin system, then in higher doses these improvements should disappear because as the dose increases the relative serotonin effect of a compound diminishes. Improvements did decrease in patients receiving higher doses of the atypical antipsychotic olanzapine in a 6-week, double-blind, placebo-controlled trial conducted by Street et al.<sup>13</sup> The study sample consisted of 206 elderly nursing care residents who met the NINCDS-ADRDA criteria for possible or probable Alzheimer’s disease and scored 3 or higher on any of the agitation/aggression, hallucinations, or delusions items of the Neuropsychiatric Inventory-Nursing Home version (NPI/NH). Following a single-blind, placebo lead-in, participants were given 5, 10, or 15 mg/day of olanzapine or placebo. Those receiving 10 or 15 mg/day were titrated by 5 mg/day every 7 days to the target dose. As expected, low-dose olanzapine (5 and 10 mg/day) produced significant improvements compared with placebo (p < .001). Patients in the lower dose groups demonstrated a 50% mean improvement in NPI/NH core total scores, while NPI/NH core total improvement in patients receiving 15 mg/day was not significantly greater than placebo (p = .24). Patients in the 5- and 10-mg/day groups each had significantly greater reductions in mean scores compared with placebo on the secondary efficacy measures of agitation/aggression (p = .01 and p = .02, respectively) and psychosis total (p = .001 and p = .04, respectively). The higher dose of 15 mg/day of olanzapine demonstrated a negative effect on tolerability and was associated with a greater incidence of somnolence, extrapyramidal symptoms, and peripheral edema than either of the lower doses. Overall, somnolence was more common in patients re-

Figure 3. Mean Changes From Baseline in BEHAVE-AD Scores<sup>a</sup>

<sup>a</sup>Adapted with permission from Katz et al.<sup>15</sup>

Abbreviation: BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease rating scale.

ceiving olanzapine than placebo, and gait disturbance occurred in 19.6% of patients receiving 5 mg/day and in 17% of patients receiving 15 mg/day of olanzapine. Researchers concluded that low-dose olanzapine (5 and 10 mg/day) was effective in reducing behavioral and psychotic symptoms in patients with Alzheimer's disease, with the lowest dose of 5 mg/day showing the greatest benefit.

De Deyn et al.<sup>16</sup> conducted a study comparing the tolerability of risperidone with placebo and haloperidol and the efficacy of risperidone with placebo in treating patients with dementia for aggression and other behavioral symptoms. In this 13-week, double-blind study, 344 patients who had been diagnosed with primary degenerative Alzheimer's type dementia, vascular dementia, or mixed dementia according to DSM-IV criteria were randomly assigned to receive placebo (N = 114) or a flexible dose (0.5–4.0 mg/day) of risperidone (N = 115) or haloperidol (N = 115). Behavioral symptoms were assessed using the BEHAVE-AD, CMAI, and the Clinical Global Impressions scale (CGI). A total of 223 patients completed the trial, and of those who dropped out, 50.4% did so due to adverse effects and 43.8% due to lack of efficacy. Reductions in the BEHAVE-AD total score were significantly ( $p = .05$ ) greater for patients receiving risperidone than placebo by week 12 (Table 2). Risperidone also showed significantly greater improvement than placebo in

BEHAVE-AD and CMAI aggression cluster scores by week 12 ( $p = .0002$  and  $p = .02$ , respectively), and a post hoc analysis showed significantly ( $p = .05$ ) greater reductions in the BEHAVE-AD aggressiveness scores with risperidone than haloperidol at week 12. CGI scores were significantly ( $p < .05$ ) lower for patients receiving risperidone compared with placebo at week 12 and endpoint. Adverse events were reported in 76.5% of patients receiving risperidone compared with 80% of patients receiving haloperidol, and somnolence occurred in more patients receiving haloperidol (18.3%) than risperidone (12.2%). There were no significant differences between groups in the occurrence of serious adverse events. Researchers of this study concluded that low-dose risperidone (mean = 1.1 mg/day) was a well-tolerated treatment associated with reductions in the severity and frequency of behavioral symptoms, particularly aggression, in elderly patients with dementia.

There is a paucity of data examining the safety and effects of quetiapine in treating patients with dementia. No double-blind trials have been reported. An open-label, 52-week, multicenter trial<sup>14</sup> was conducted in 151 patients who had a concomitant diagnosis of Parkinson's disease and a DSM-IV diagnosis for one of a variety of disorders that included idiopathic psychoses and organic psychoses. The primary outcome measures were the 18-item Brief



**Table 2. Mean Baseline Scores and Mean Shifts at Endpoint and at Week 12 in BEHAVE-AD and CMAI<sup>a</sup>**

Measure	Risperidone	Haloperidol	Placebo	p Value, Risperidone vs Placebo
	Mean	Mean	Mean	
<b>BEHAVE-AD</b>				
Total				
Baseline	16.3	16.5	16.6	
Endpoint	-5.2	-6.6	-4.2	.19
Week 12	-8.6	-7.5	-6.2	.05
Aggressiveness				
Baseline	5.0	4.7	5.0	
Endpoint	-1.7	-1.6	-0.8	.004
Week 12	-2.9	-1.8	-1.5	.002
<b>CMAI</b>				
Total aggressive				
Baseline	25.6	26.3	27.5	
Endpoint	-3.9	-3.3	-1.6	.01
Week 12	-8.3	-3.6	-4.9	.02
Physical aggressive				
Baseline	18.9	19.3	19.7	
Endpoint	-2.7	-2.3	-0.7	.01
Week 12	-5.9	-2.8	-3.5	.04
Verbal aggressive				
Baseline	6.8	7.0	7.7	
Endpoint	-1.2	-1.0	-0.8	.01
Week 12	-2.5	-0.8	-1.4	.01

<sup>a</sup>Reprinted with permission from De Deyn et al.<sup>16</sup>

Abbreviations: BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease rating scale, CMAI = Cohen-Mansfield Agitation Inventory.

Psychiatric Rating Scale (BPRS) and the CGI, both of which mainly report adverse events. The median dose was 100 mg/day of quetiapine, and an interim analysis was performed at 12 weeks, at which time researchers reported that the most common side effects were somnolence (32%), dizziness (14%), postural hypotension (13%), and agitation (11%). According to their findings, BPRS total and CGI-Severity of Illness scores revealed significant ( $p < .0001$  and  $p < .01$ , respectively) improvement at endpoint. Quetiapine appeared to be well-tolerated and associated with improved symptoms in patients.

### Mood Stabilizers

Mood stabilizers may also be efficacious in treating BPSD, especially agitation. In a study by Tariot et al.,<sup>17</sup> patients treated with carbamazepine experienced a dramatic decrease in agitation and hostility as well as a decrease in demand on staff time because of agitation. In this 6-week, randomized, multisite, parallel-group study, 51 patients with possible or probable Alzheimer's disease based on DSM-III-R criteria were given 100 mg/day of carbamazepine that was increased by 50 mg/day until a serum level of 5 to 8 µg/mL was achieved. For patients who exhibited toxicity at lower doses, the highest subtoxic dose was used. Primary outcome measures were the BPRS and CGI scales, and researchers reported that over 6 weeks, the mean total BPRS scores decreased 7.7 points for the carbamazepine group compared with 0.9 for the placebo group. Further, CGI ratings improved in 77% of

patients receiving carbamazepine compared with only 21% of those receiving placebo. According to secondary analyses, the positive changes were primarily due to decreased agitation and aggression.

Divalproex also decreased agitation, but this agent was associated with severe side effects such as respiratory problems and somnolence.<sup>18</sup> Portsteinsson et al.<sup>18</sup> assessed the efficacy, tolerability, and safety of divalproex in the treatment of agitation associated with dementia in a 6-week, randomized study of 56 patients with probable or possible Alzheimer's disease, vascular dementia, or mixed dementia as determined by DSM-IV and NINCDS-ADRDA criteria. Participants were treated with either placebo or individualized doses of divalproex and were blinded to treatment with the exception of a physician monitor and a pharmacist. The CMAI revealed that 68% of patients treated with divalproex experienced reduced agitation compared with 52% of patients given placebo ( $p = .006$ ). Side effects occurred in 68% of patients treated with divalproex compared with 33% of placebo patients and were generally mild.

### Cholinesterase Inhibitors

Cholinesterase inhibitors appear to inhibit behavioral symptoms in patients with Alzheimer's type dementia but often cause severe side effects. The effectiveness and safety of controlled-release physostigmine was evaluated<sup>19</sup> in 475 patients with probable Alzheimer's disease of mild to moderate severity in a prospective, 24-week, randomized, multicenter, double-blind, parallel-group study. Patients were randomly assigned to receive 30 mg/day (N = 176) or 36 mg/day (N = 182) of physostigmine or placebo (N = 117) for 24 weeks. Primary outcome measures were the Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) and the Clinician's Interview-Based Impression of Change-Plus with caregiver input (CIBIC+). Significant improvements were evident in ADAS-cog ( $p = .002$ ) and CIBIC+ ( $p = .048$ ) scores of both physostigmine treatment groups compared with placebo. However, discontinuation rates were high due primarily to adverse effects—only 210 patients completed the study. Gastrointestinal side effects included nausea, vomiting, diarrhea, anorexia, dyspepsia, and abdominal pain and were prevalent in patients treated with either dose of physostigmine. In fact, vomiting eventually proved to be so prevalent in patients treated with physostigmine that the Food and Drug Administration did not approve the drug to be sold in the United States.

An open-label study conducted by Mega et al.<sup>20</sup> examined the efficacy of donepezil in 86 patients with Alzheimer's disease treated with a flexible dose of donepezil. To determine whether pretreatment behavior can help predict patient response to treatment, researchers divided patients into 3 groups—responder, unchanged, and nonresponder—based on patients' previous double-blind,

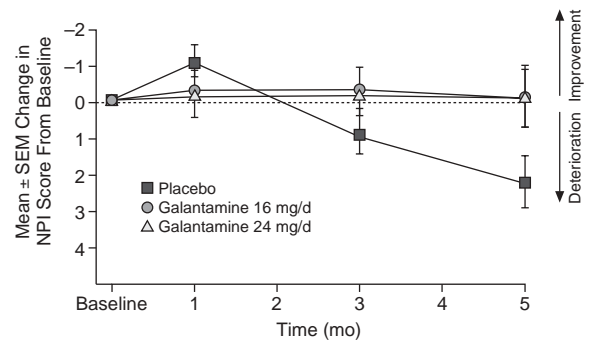
placebo-controlled experiences with the NPI. Researchers reported that overall behavioral improvement was seen in 35 patients (48%), worsening in 24 (28%), and no change in 27 (31%). Responders demonstrated considerable improvement from baseline on NPI scores compared with nonresponders in delusions ( $p = .04$ ), agitation ( $p = .04$ ), depression ( $p = .006$ ), anxiety ( $p = .02$ ), apathy ( $p = .003$ ), disinhibition ( $p = .02$ ), and irritability ( $p < .001$ ). Behavioral changes were dose-dependent. Donepezil appeared to have psychotropic properties, and pretreatment behavior appeared to be relevant in predicting patient response to treatment; however, no placebo-control group was utilized, and adverse events were not assessed.

Gauthier et al.<sup>21</sup> conducted a subanalysis of a double-blind, placebo-controlled trial to determine the efficacy of donepezil on behavioral symptoms in 290 patients with moderate-to-severe Alzheimer's disease. Participants were randomly assigned to receive once-daily doses of 5 mg/day of donepezil for 24 weeks and 10 mg/day thereafter, depending on the clinician's judgment ( $N = 144$ ), or placebo ( $N = 146$ ). The primary outcome measure was the NPI. Baseline demographics were similar between treatment groups, and the most common symptoms were apathy/indifference (67%), aberrant motor behavior (53%), depression/dysphoria (52%), anxiety (49%), and agitation/aggression (45%). Using the last-observation-carried-forward analysis at week 24, NPI scores showed significant benefits with donepezil treatment compared with placebo for all items. Significant ( $p < .05$ ) treatment differences were present for depression/dysphoria, anxiety, and apathy/indifference, and significant ( $p < .05$ ) improvements in symptoms from baseline for donepezil-treated patients compared with placebo-treated patients were evident for anxiety, apathy/indifference, and irritability/lability. Additionally, when patients who had not been receiving psychoactive medications at baseline were analyzed separately, improvements in NPI scores for patients receiving donepezil remained.

The effects of rivastigmine on behavioral symptoms of 92 patients with dementia with Lewy bodies were assessed using the NPI as a primary outcome measure in a prospective, double-blind, randomized, placebo-controlled exploratory study.<sup>22</sup> This multicenter international study was conducted at various sites in the United Kingdom, Spain, and Italy. Participants received rivastigmine for 20 weeks and were tested prior to dosing and at weeks 12, 20, and 23. The effects were large in magnitude, revealing substantial improvements in NPI scores in the rivastigmine-treated patients that lasted the duration of the study.

Galantamine data suggest a behavioral benefit in patients with Alzheimer's type dementia, as well.<sup>23</sup> Tariot et al.<sup>23</sup> investigated the efficacy and tolerability of galantamine in 978 patients with mild to moderate Alzheimer's disease in a 5-month, placebo-controlled, double-blind trial using a slow dose-escalation schedule of up to 8

Figure 4. Galantamine Behavioral Results Over 5 Months Versus Placebo<sup>a</sup>



<sup>a</sup>Adapted with permission from Tariot et al.<sup>23</sup>  
Abbreviation: NPI = Neuropsychiatric Inventory.

weeks. Patients were randomly assigned to receive placebo or galantamine escalated to final maintenance doses of 8, 16, or 24 mg/day. Outcome measures included the ADAS-cog and the NPI. After 5 months, ADAS-cog scores for 16- and 24-mg/day galantamine-treated patients improved significantly ( $p < .001$  for both groups). Results of the NPI also indicated a significant beneficial effect of galantamine on behavioral symptoms (Figure 4). By the end of the study, total NPI scores for both 16- and 24-mg/day galantamine-treated groups were significantly ( $p < .05$ , both groups) better than those in the placebo group; NPI total scores of patients treated with placebo or 8 mg/day of galantamine deteriorated compared with baseline ( $p < .05$ , both groups). The majority of adverse events were gastrointestinal and were mild in severity. Dropout rates due to adverse events in galantamine-treated patients and placebo-treated patients were similar. Overall, galantamine was efficacious in delaying increasing behavioral and cognitive symptomatology in patients with Alzheimer's disease.

### Combination Treatments

Because the majority of patients with Alzheimer's disease type dementia display behavioral disturbances in addition to cognitive impairment, many of these patients will be treated concomitantly with antipsychotic drugs and cholinesterase inhibitors. Combination treatments for BPSD may be efficacious, but this combination may also increase the risk of reversible drug-induced movement disorders; therefore, safety is of concern, particularly in the elderly. Using an atypical antipsychotic in combination with a cholinesterase inhibitor may decrease this risk.

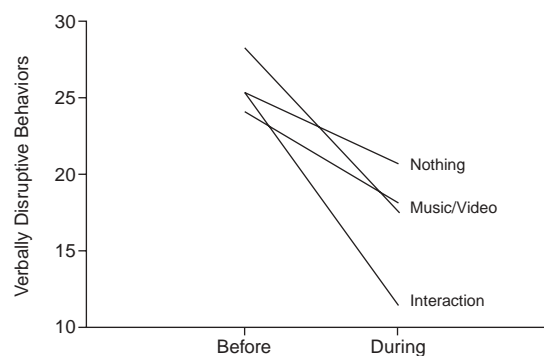
Zhao et al.<sup>24</sup> tested for possible changes in the steady-state pharmacokinetic profiles of donepezil-risperidone combination treatment. Donepezil and risperidone are both metabolized through cytochrome P450 2D6 and 3A4, which raises the possibility that a drug interaction might occur with combination therapy and that extrapyramidal

symptoms may increase. In their open-label, 3-way cross-over study, 24 healthy men were randomly assigned to receive 0.5 mg of risperidone twice daily, 5 mg/day of donepezil, or both drugs for 14 days, followed by a 21-day washout period. Researchers determined that no significant pharmacokinetic differences occurred in risperidone-active moiety or donepezil in patients either receiving each agent alone or in combination. Furthermore, adverse events were mild and comparable for all treatment groups. While this trial revealed that no clinically meaningful drug interactions occurred between donepezil and risperidone, additional studies are warranted to evaluate the potential for interactions in elderly patients who may eliminate drugs more slowly than younger subjects, and thus may be more vulnerable to clinical drug interactions.

A randomized, open-label trial<sup>25</sup> was conducted in 90 patients with Alzheimer's disease (N = 75), vascular dementia (N = 10), or both (N = 15) to examine the effects of 0.5 to 2.0 mg/day of risperidone in patients already being treated with 3 to 12 mg/day of rivastigmine and the effects of 3 to 12 mg/day of rivastigmine in patients being treated with 0.5 to 2.0 mg/day of risperidone. Patients were randomly assigned to open-label rivastigmine and risperidone for 20 weeks, and adverse effects caused by coadministration were assessed. Researchers concluded that by the end of the 20 weeks, although adverse effects (primarily somnolence, vomiting, and weakness) were reported in approximately 5% of patients, no clinically relevant adverse interactions were observed, indicating that rivastigmine and risperidone can be safely coadministered.

Cummings et al.<sup>26</sup> conducted a double-blind crossover study involving 2 patients to compare the antidelusional efficacy of physostigmine with haloperidol. Both patients met the criteria of the NINCDS-ADRDA for probable Alzheimer's disease. The delusion scale of the BEHAVE-AD was used as an outcome measure along with various subscales of the BEHAVE-AD measuring other aspects of psychopathology such as hallucinations, activity disturbances, aggressiveness, and anxieties and phobias. Both patients were drug-free at the beginning of the study, and both had initially received variable doses of haloperidol. The first patient experienced a 75% decrease in the delusion score and a 50% reduction of the combined delusion and hallucination score of the BEHAVE-AD with 3 mg/day of haloperidol. Physostigmine (increased to 6 mg/day) was added after 4 weeks, and delusions and hallucinations were clinically undetectable until the physostigmine was discontinued and the delusions and hallucinations returned. The second patient initially reached an optimal dose of 3 mg/day of haloperidol and evidenced a 60% reduction in delusions as measured by the BEHAVE-AD, from a score of 8 to a score of 3. The patient's wife discontinued the haloperidol after 2 weeks and the delusions increased. After a 30-day drug-free period, physostigmine was initiated and increased to 4 mg/day, at which time the patient's

Figure 5. Change in Verbally Disruptive Behaviors and Type of Intervention Based on Observational Measures<sup>a</sup>



<sup>a</sup>Reprinted with permission from Cohen-Mansfield and Werner.<sup>28</sup>

delusion score decreased again from 6 to 1. The primary adverse effect was parkinsonism, which occurred in the second patient during treatment with haloperidol. When the physostigmine was discontinued, both patients declined until it was added a second time when they again improved, suggesting that cholinergic deficiency may contribute to the occurrence of delusions in Alzheimer's disease, and that cholinergic therapy may aid in the treatment of delusional symptoms. The parkinsonism adverse events were a cause for concern, however.

**Other Considerations**

The correlates of BPSD are important to consider because, in addition to pharmacologic agents, improving variables such as pain, social contact, and sleep may also decrease BPSD in patients with Alzheimer's disease type dementia.<sup>27</sup> Cohen-Mansfield et al.<sup>27</sup> reported the results of 2 studies concerning screaming in the nursing home. One of the reviewed studies revealed that, of 408 nursing home residents, 25% screamed at least 4 times a week, and that screaming was associated with depressed affect, social networks of poor quality, cognitive impairment, and severe impairment in the performance of daily activities. The second study reviewed observed 5 nursing home residents who frequently screamed. This study reported a positive correlation between screaming and being alone, suggesting that screaming may be a response to social isolation.

In a separate study by Cohen-Mansfield and Werner,<sup>28</sup> 3 interventions designed to manage verbally disruptive behaviors in nursing home residents were compared with a control no-intervention phase. The interventions consisted of playing a videotape of a family member talking, initiating in person social interaction, and playing music for the patient. Researchers found that the verbally disruptive behaviors decreased by 56% during the social interaction, 46% during the videotape, 31% during the music, and 16% during no-intervention (Figure 5). This study underscored the importance of providing stimulating activities,

increasing social interactions, and providing a richer environment for functionally and cognitively impaired nursing home residents to aid in minimizing BPSD.

### SUMMARY

While pharmacologic agents have ameliorated the disease process and accompanying symptomatology of Alzheimer's disease type dementia in some patients, many other patients experience little or no benefit from these agents. This varied treatment response is partially attributable to individual genetic differences in humans. Physicians need to be better equipped to accurately identify which patients will and will not respond to treatment. Pharmacogenomics has the potential to alter the current approach to drug treatment by changing the treatment paradigm from drug development based on populations to drug development that takes into account intrinsic variation between individuals—from undifferential treatment to differential treatment. Pharmacogenomics has the potential to correlate genotypes with disease progression and subsequently with drug efficacy and metabolism which would enable physicians to provide cost-effective health care management for patients by equipping physicians with the ability to select patients most suited for specific therapies. Indications suggest that some compounds may be more specific to one subset than others, so while many compounds today appear to be relatively safe and effective in improving the symptomatology of Alzheimer's disease type dementia, physicians still need help in clinically differentiating which patient will respond to what agents.

*Drug names:* carbamazepine (Tegretol and others), divalproex (Depakote and others), donepezil (Aricept), galantamine (Reminyl), haloperidol (Haldol), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), rivastigmine (Exelon).

*Disclosure of off-label usage:* Dr. Mintzer has determined that, to the best of his knowledge, carbamazepine, divalproex, haloperidol, olanzapine, quetiapine, risperidone, fenfluramine, physostigmine, and metrifonate are not approved by the U.S. Food and Drug Administration for the treatment of Alzheimer's disease, agitation, and behavioral and psychotic symptoms in dementia (BPSD); donepezil and galantamine are not approved for the treatment of BPSD; and rivastigmine is not approved for the treatment of agitation and BPSD.

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