Behavioral and Psychological Symptoms in Patients With Dementia as a Target for Pharmacotherapy With Risperidone

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Objective: To examine the effect of risperidone on specific behavioral and psychological symptoms of dementia (BPSD).

Method: We conducted a post hoc exploratory analysis of an integrated database from 3 randomized, controlled trials of risperidone versus placebo in treating 1150 nursing home residents with BPSD. Changes in scores were measured for items on the Cohen-Mansfield Agitation Inventory (CMAI) and Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD).

Results: On the CMAI, risperidone was significantly more effective in treating hitting ($p = .000$), hurt self or other ($p = .005$), cursing or verbal aggression ($p = .000$), repetitive sentences or questions ($p = .001$), scratching ($p = .041$), general restlessness ($p = .001$), grabbing onto people ($p = .028$), constant request for attention ($p = .041$), pacing and aimless wandering ($p = .013$), and performing repetitious mannerisms ($p = .045$). On the BEHAVE-AD, risperidone was significantly more effective in treating physical threats and/or violence ($p = .000$), verbal outbursts ($p = .000$), other anxieties ($p = .01$), agitation ($p = .000$), tearfulness ($p = .03$), and nonparanoid delusions ($p = .02$).

Conclusions: The items from the BEHAVE-AD and CMAI that were improved with risperidone included psychotic, agitated, and aggressive symptoms. These data suggest that risperidone is more effective than placebo in treating a variety of symptoms associated with dementia.

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Behavioral and psychological symptoms in dementia (BPSD) and their treatment with atypical antipsychotic drugs are the subject of a growing body of literature. Many questions, however, remain unanswered. For instance, which specific symptoms constitute BPSD, and how does each one respond to treatment? BPSD encompass many behavioral, emotional, and psychiatric symptoms, of which only a few manifest consistently and concomitantly in the same patient.[1] Many have diverse biological underpinnings,[2,3] and the natural course of these symptoms varies, often unpredictably.[4]

Individual, clinically meaningful behaviors such as screaming, hitting, or biting may be easy to rate, but when individual scores on these behaviors are merged into and expressed as a summary score, relevant clinical information is lost. Moreover, some symptoms and behaviors, such as anxieties and phobias, directly affect the patients, whereas others, such as grabbing and trying to get to another place, mostly affect the caregivers. While all symptoms contribute to the total score, they have very different conceptual and practical implications.

Although the concept of BPSD has heuristic value, BPSD are regarded not as a single clinical syndrome, but rather as a heterogeneous group of symptoms. It has been suggested that since BPSD might be the final common

pathway of several pathophysiologic processes, there is no reason to assume that all manifestations of BPSD will respond to the same intervention.[5] As a result, it has been suggested that each symptom can be seen as a proper target for pharmacotherapy as long as the symptom manifests across different conditions (e.g., dementia, schizophrenia, or mental retardation) or that BPSD would be better defined as a syndrome.[6,7]

The current study uses data from an integrated database of 3 large trials of risperidone in elderly persons with BPSD to examine the efficacy of drug therapy at the level of single, clearly observable and identifiable behaviors (as opposed to efficacy as measured by composite scores). Because the large sample size increases the statistical power, results of this integrated database analysis can help identify, for clinical practice and for future clinical trials, the symptoms most likely to benefit from intervention with antipsychotic medication.

METHOD

Data were from 3 pivotal 12-week, randomized, placebo-controlled trials of risperidone in treating elderly nursing home residents with BPSD (N = 1150).[8–10] One trial was conducted in Australia and New Zealand,[8] another in the United States,[9] and a third in Europe and Canada.[10] All trials compared risperidone with placebo in either a fixed (0.5, 1.0, and 2.0 mg/day)[9] or a flexible (0.25–2.0 mg/day[8] or 0.25–4.0 mg/day[10]) dose, and 1 trial also included a haloperidol arm.[10]

To measure symptoms, these trials[8–10] used the Cohen-Mansfield Agitation Inventory (CMAI)[11] and the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD).[12] Information necessary for completing the scales came from the primary professional caregiver, i.e., the person most involved in the patient's day-to-day care.

The CMAI assesses agitated and disruptive behaviors and other care-related problems occurring in demented residents of nursing homes. The scale measures 29 behaviors; each is rated on a 7-point scale indicating frequency (1 = never, 2 = less than once a week, 3 = once or twice a week, 4 = a few times a week, 5 = once or twice a day, 6 = a few times a day, 7 = a few times an hour). These behaviors are organized into 4 subscales: physical/aggressive, physical/nonaggressive, verbal/aggressive, and verbal/nonaggressive.

The BEHAVE-AD is a 25-item scale that assesses the severity of behavioral disturbances in patients with dementia. The scale consists of 7 subscales: (A) paranoid and delusional ideation (7 items), (B) hallucinations (5 items), (C) activity disturbances (3 items), (D) aggressiveness (3 items), (E) diurnal rhythm disturbances (1 item), (F) affective disturbances (2 items), and (G) anxieties and phobias (4 items). Each symptom item is rated as absent (scored as 0) or present (scored as 1–3 with increasing severity: mild, moderate, and severe).

To be included in 1 of these 3 trials, nursing home residents had to be 55 years of age or older; be diagnosed with primary degenerative Alzheimer's-type dementia, vascular dementia, or mixed dementia; have no major comorbidity; and have a baseline score of ≤ 23 on the Mini-Mental State Examination.[13] They also had to have a minimum level of BPSD. In 2 of the trials,[9,10] this requirement was defined as a BEHAVE-AD[12] global rating of ≥ 1 (meaning that the patient's symptoms were at least mildly troubling to the caregiver or dangerous to the patient) and a BEHAVE-AD total score of ≥ 8. This total score is obtained if the patient scores 1 on 8 of the 25 items, 2 on 4 of the items, 3 on 2 of the items plus 2 on another item, or some other combination of the above. In the third trial,[8] the inclusion criterion was an aggression score on the CMAI of ≥ 4 on 1 aggression item, ≥ 3 on at least 2 aggression items, or ≥ 2 on at least 3 aggression items.

Data were analyzed for all patients included in the intent-to-treat placebo and risperidone samples (770 women, 380 men). The mean age for women was 83.93 years (SD = 7.09) and for men was 78.87 years (SD = 7.31; $t = 11.36$; $df = 1,148$; $p < .0001$). The diagnostic breakdown was as follows: Alzheimer's-type dementia (N = 786), mixed dementia (N = 125), and vascular dementia (N = 239).

Analytic Plan

We compared the efficacy of risperidone and placebo for each item on the CMAI and on the BEHAVE-AD, including only those patients with clinically meaningful baseline scores on a given item in the analysis of that item. On the CMAI, we defined a clinically meaningful symptom as occurring at least once a week (CMAI item score of ≥ 3), as suggested by the authors of the scale.[14] For the BEHAVE-AD, we set the clinically meaningful level at moderate (BEHAVE-AD item score of ≥ 2). We compared each item's mean change in score from baseline to endpoint between patients treated with risperidone and those treated with placebo using analysis of covariance testing for the effects of treatment while controlling for baseline levels. This let us test the efficacy of risperidone as compared to placebo in treating specific symptoms.

In addition, effect size scores of the differences between the groups were calculated using the Cohen formula,[15] which consists of subtracting the mean differences of the 2 groups and dividing by the pooled standard deviation. Cohen[15] has defined effect sizes of .20 to .50 as small, > .50 to .80 as medium, and > .80 as large. More explicitly, an effect size of .20 corresponds to the difference in heights of 15- and 16-year-old girls in the United States, an effect size of .50 corresponds to the difference in height between 14- and 18-year-old girls, and an effect size of .80 corresponds to the difference in height between

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13- and 18-year-old girls. In addition to effect sizes, the odds of at least some improvement (vs. no improvement) were also calculated using logistic regression.

Because each analysis had a different number of patients, the power of the tests varied considerably depending on how many patients had the given symptom at baseline. One group, with more than 290 patients, allowed a powerful test of even small effect sizes, while another group, with only 3 patients, was too small for any statistical inferences. In this study, we included only those symptoms manifested at baseline by at least 45 patients. This minimum number provides 80% power of finding an effect size difference of .60. Since this analysis was exploratory in nature, we did not control for multiple comparisons. Significance was set at $p \leq .05$.

RESULTS

Table 1 presents the analyzed items from the CMAI in descending order of effect size. Risperidone was significantly better than placebo in improving the following behaviors (in descending order of magnitude of effect size): hitting, hurt self or other, cursing or verbal aggression, repetitive sentences or questions, scratching, general restlessness, grabbing onto people, constant request for attention, pacing and aimless wandering, and performing repetitious mannerisms. Near statistical significance was reached on hiding things. The 3 behaviors with the highest effect sizes—hitting, hurt self or other, and cursing or verbal aggression—had odds ratios of at least 2.35, indicating that the likelihood of at least some improvement in the risperidone group was more than 2 1/3 times that of the placebo group.

Table 2 presents a similar analysis of the treatment effects on the items of the BEHAVE-AD. Risperidone was statistically better than placebo in improving the following behaviors (in descending order of magnitude of effect size): physical threats and/or violence, verbal outbursts, other anxieties, agitation, tearfulness, and nonparanoid delusions. Near statistical significance was reached on wandering and anxiety regarding upcoming events. Of the items that had a statistically significant difference when analyzed as continuous variables, the most statistically significant odds of at least some improvement was 2.03 on physical threats and/or violence, with 70.9% of risperidone patients showing at least some improvement compared with 54.5% of the placebo patients showing at least some improvement.

DISCUSSION

The results of this exploratory post hoc analysis of specific manifestations of BPSD as measured by 2 assessment scales suggest that risperidone is effective in treating many of these disturbing symptoms. Risperidone's greatest effects were on symptoms related to aggressive and agitated behaviors. The concept of BPSD may be useful in describing and cataloging neuropsychiatric symptoms occurring in Alzheimer's disease and other dementias. However, because this concept encompasses many behaviors and emotions, of which only a few manifest consistently, clinical and academic investigators and regulatory agencies consider it too ambiguous and broad to constitute a true syndrome.[6,7] In these analyses, due to the large sample size afforded by the integrated database, we were able to examine specific symptoms in contrast to having to assess BPSD at the syndrome level.

The results of these analyses help to identify which behavioral and psychological symptoms are most common in the population of nursing home residents suffering from dementia and which symptoms respond best to treatment with risperidone. Typically, drug trials examine selected populations and differences in scores on aggregate scales. These scales comprise many items in which small improvements on many items can together result in a significant difference. Our finding of significant differences on single items is thus notable because such differences are often very subtle. However, findings derived from post hoc analysis can not be useful in clinical practice or even in research until confirmed in prospective studies.

Psychotic symptoms were not abundant in the patients included in these studies. This is due, at least in part, to the fact that the inclusion criteria in these studies did not require patients to be psychotic. As a result, some psychotic symptoms could not be adequately tested, and for others, testing was not optimal due to low power. For example, auditory hallucinations were not included in our analysis, as they afflicted only 59 risperidone-treated patients and 35 placebo-treated patients, which affords only a 64% chance of finding a statistically significant medium effect size difference. However, it should be noted that there was a trend toward a significant difference in auditory hallucinations in favor of risperidone. A further difficulty in examining psychotic symptoms is that such symptoms among persons with dementia are different from those associated with schizophrenia, perhaps since they might have a different biological substrate and do not have identical manifestations.

Some caution in viewing and interpreting these results is warranted. The integrated database came from trials with some design variations. In addition, these were exploratory analyses in which many comparisons were made with no controls for multiple comparisons. It should be noted, however, that the major differences between risperidone and placebo were of sufficient magnitude that they would still be significant even after controlling for multiple comparisons.

Another limitation of this study and similar studies is the lack of a clear hierarchy of symptoms. Scales sum individual items, giving each item equal weight.[16] For ex-

Table 1. Improvement in Cohen-Mansfield Agitation Inventory Score for Patients With a Symptom Frequency of "Once or Twice a Week" at Baseline Ordered by Effect Size

								Some Improvement in Either Group[e]						
	Risperidone		Placebo		ANCOVA[c]			Risperidone Improved		Placebo Improved		Comparison of Group Improvement Rates		
Behavior[a]	Mean (SD)[b]	N	Mean (SD)[b]	N	F	p Value[d]	ES	N/N	(%)	N/N	(%)	OR	95% CI	p Value[d]
Hitting	–2.60 (1.87)	171	–1.70 (1.95)	94	12.757	.000	–0.46	140/171	(81.9)	60/94	(63.8)	2.56	1.44 to 4.54	.001
Hurt self or other	–3.38 (1.97)	73	–2.47 (2.22)	49	8.313	.005	–0.43	65/73	(89.0)	38/49	(77.6)	2.35	0.87 to 6.36	.086
Cursing or verbal aggression	–2.21 (2.01)	279	–1.38 (1.96)	199	20.57	.000	–0.41	208/279	(74.6)	108/199	(54.3)	2.47	1.68 to 3.64	.000
Repetitive sentences or questions	–2.03 (2.20)	321	–1.39 (1.99)	184	11.241	.001	–0.30	207/321	(64.5)	101/184	(54.9)	1.49	1.03 to 2.16	.033
Kicking	–2.94 (2.00)	79	–2.40 (2.18)	50	2.412	.123	–0.26	64/79	(81.0)	38/50	(76.0)	1.35	0.57 to 3.18	.495
Scratching	–2.23 (2.13)	167	–1.69 (2.06)	104	4.199	.041	–0.26	120/167	(71.9)	62/104	(59.6)	1.73	1.03 to 2.90	.037
General restlessness	–1.77 (2.15)	459	–1.25 (1.96)	284	12.100	.001	–0.25	293/459	(63.8)	137/284	(48.2)	1.89	1.40 to 2.56	.000
Hiding things	–2.95 (2.12)	92	–2.41 (2.13)	61	3.393	.067	–0.25	73/92	(79.3)	48/61	(78.7)	1.04	0.47 to 2.30	.922
Grabbing onto people	–2.16 (1.97)	232	–1.69 (2.14)	142	4.844	.028	–0.23	164/232	(70.7)	84/142	(59.2)	1.67	1.08 to 2.58	.022
Constant request for attention	–2.18 (2.27)	222	–1.67 (2.32)	141	4.204	.041	–0.22	139/222	(62.6)	76/141	(53.9)	1.43	0.93 to 2.20	.100
Pacing, aimless wandering	–1.48 (2.05)	374	–1.05 (1.90)	220	6.25	.013	–0.21	211/374	(56.4)	99/220	(45.0)	1.58	1.13 to 2.21	.007
Strange noises	–2.45 (2.34)	119	–1.94 (2.44)	93	2.446	.119	–0.21	81/119	(68.1)	52/93	(55.9)	1.68	0.96 to 2.95	.069
Pushing	–2.83 (1.99)	123	–2.47 (2.06)	87	1.696	.194	–0.18	99/123	(80.5)	62/87	(71.3)	1.66	0.87 to 3.17	.120
Negativism	–2.58 (2.23)	175	–2.19 (2.21)	112	2.488	.116	–0.17	127/175	(72.6)	76/112	(67.9)	1.25	0.75 to 2.10	.392
Trying to get to a different place	–2.27 (2.22)	252	–1.95 (2.20)	164	2.108	.147	–0.14	178/252	(70.6)	103/164	(62.8)	1.43	0.94 to 2.16	.096
Hoarding things	–2.82 (2.16)	90	–2.51 (2.17)	57	.957	.330	–0.14	69/90	(76.7)	45/57	(78.9)	0.88	0.39 to 1.96	.747
Performing repetitious mannerisms	–2.11 (2.29)	290	–1.89 (2.27)	179	4.025	.045	–0.1	193/290	(66.6)	109/179	(60.9)	1.28	0.87 to 1.88	.214
Inappropriate dressing or disrobing	–2.39 (1.99)	137	–2.30 (1.98)	92	.070	.791	–0.05	105/137	(76.6)	69/92	(75.0)	1.09	0.59 to 2.03	.775
Complaining	–2.36 (2.20)	199	–2.29 (2.22)	117	.087	.768	–0.03	139/199	(69.8)	83/117	(70.9)	0.95	0.58 to 1.57	.838
Handling things inappropriately	–2.49 (2.33)	113	–2.41 (2.31)	86	.150	.699	–0.03	79/113	(69.9)	62/86	(72.1)	0.9	0.48 to 1.67	.737

[a]The following items were not included due to small group sizes of fewer than 45 patients in either the risperidone or the placebo group (risperidone treated, placebo treated): intentional falling (12,9); making verbal sexual advances (17,11), eat/drink inappropriate substances (19,16); making physical sexual advances (27,8); biting (27,12); throwing things (39,27); spitting (include at meals) (55,22); tearing and destroying (35,27); screaming (68,31).
[b]Difference from baseline.
[c]Controlling for baseline.
[d]Significance was set at $p < .05$.
[e]From logistic regression analysis.
Abbreviations: ANCOVA = analysis of covariance, ES = effect size (change in risperidone – change in placebo)/pooled standard deviation, OR = odds ratio.

Table 2. Improvement in BEHAVE-AD Score for Patients With a Symptom Severity of at Least "Moderate" vs. Less Troubling Several Times a Week at Baseline Ordered by Effect Size

								Some Improvement in Either Group[e]						
	Risperidone		Placebo		ANCOVA[c]			Risperidone Improved		Placebo Improved		Comparison of Group Improvement Rates		
Behavior[a]	Mean (SD)[b]	N	Mean (SD)[b]	N	F	p Value[d]	ES	N/N	(%)	N/N	(%)	OR	95% CI	p Value[d]
Physical threats and/or violence	–1.45 (1.20)	320	–0.87 (1.17)	187	30.42	.000	–0.48	227/320	(70.9)	102/187	(54.5)	2.03	1.40 to 2.96	< .000
Verbal outbursts	–1.13 (1.28)	489	–0.65 (1.09)	292	31.05	.000	–0.39	278/489	(56.9)	124/292	(42.5)	1.79	1.33 to 2.39	< .000
Anxiety regarding upcoming events	–1.62 (1.01)	90	–1.25 (1.12)	59	3.09	.08	–0.35	76/90	(84.4)	41/59	(69.5)	2.38	1.08 to 5.28	.03
Other anxieties[f]	–1.32 (1.05)	188	–0.98 (1.03)	117	7.08	.01	–0.32	138/188	(73.4)	77/117	(65.8)	1.43	0.87 to 2.37	.16
Agitation (other)	–1.16 (1.21)	413	–0.81 (1.08)	260	15.07	.000	–0.3	255/413	(61.7)	141/260	(54.2)	1.36	1.00 to 1.87	.05
Tearfulness	–1.46 (1.09)	123	–1.11 (1.20)	92	5.06	.03	–0.3	93/123	(75.6)	58/92	(63.0)	1.82	1.01 to 3.28	.05
Delusions, nonparanoid	–1.46 (1.10)	191	–1.15 (1.11)	106	5.73	.02	–0.28	141/191	(73.8)	69/106	(65.1)	1.51	0.91 to 2.53	.11
Visual hallucinations	–1.48 (1.22)	99	–1.21 (1.18)	63	1.04	.31	–0.22	72/99	(72.7)	41/63	(65.1)	1.43	0.72 to 2.83	.30
Suspicious/paranoia (other)	–1.48 (1.02)	187	–1.28 (1.14)	111	2.18	.14	–0.19	147/187	(78.6)	77/111	(69.4)	1.62	0.95 to 2.77	.07
Fear of being left alone	–1.07 (0.95)	100	–0.91 (1.10)	68	0.96	.33	–0.16	65/100	(65.0)	40/68	(58.8)	1.3	0.69 to 2.45	.42
Inappropriate activity	–1.28 (1.14)	135	–1.14 (1.21)	94	1.4	.24	–0.12	96/135	(71.1)	62/94	(66.0)	1.27	0.72 to 2.24	.41
Wandering	–0.90 (1.11)	269	–0.79 (1.10)	167	3.2	.07	–0.1	160/269	(59.5)	87/167	(52.1)	1.35	0.92 to 1.99	.13
Purposeless activity	–0.91 (0.97)	188	–0.86 (0.97)	134	0.63	.43	–0.05	113/188	(60.1)	80/134	(59.7)	1.02	0.65 to 1.60	.94
Day/night disturbance	–1.33 (1.06)	151	–1.30 (0.99)	91	0.05	.82	–0.03	114/151	(75.5)	69/91	(75.8)	0.98	0.54 to 1.80	.95
"People are stealing things" delusion	–1.49 (1.03)	133	–1.48 (1.14)	79	0.49	.49	–0.01	99/133	(74.4)	56/79	(70.9)	1.2	0.64 to 2.23	.57
"One's house is not one's home" delusion	–1.24 (1.10)	121	–1.52 (1.09)	63	1.3	.26	0.25	85/121	(70.2)	47/63	(74.6)	0.8	0.40 to 1.60	.53

[a]The following items were not included due to small group sizes of fewer than 45 patients in either the risperidone or the placebo group (risperidone treated, placebo treated): olfactory hallucinations (2,3); haptic hallucinations (15,11), other hallucinations (23,10); other phobias (44,36); "delusion of infidelity" (78,38); "spouse (or other caregiver) is an impostor" delusion (70,42); "delusion of abandonment" (59,25); auditory hallucinations (59,35); depressed mood: other (38,23).
[b]Difference from baseline.
[c]Controlling for baseline.
[d]Significance was set at $p \leq .05$.
[e]From logistic regression analysis.
[f]Other than regarding upcoming events and fear of being left alone.
Abbreviations: ANCOVA = analysis of covariance, BEHAVE-AD = Behavioral Pathology in Alzheimer's Disease Rating Scale, ES = effect size (change in risperidone – change in placebo)/pooled standard deviation, OR = odds ratio.

ample, the CMAI gives equal weight to repetitive sentences and hitting. Clearly the former is a nuisance for the caregiver, whereas the latter is a major concern in managing the patient. Similarly, on the BEHAVE-AD, tearfulness has the same weight as physical threats and/or violence. While both have an impact on the patient's well-being and require attention, their relevance and required intervention are different. Additionally, it is important to add that not all of these symptoms necessarily require pharmacologic treatment simply because they are improved with risperidone. For example, constant request for attention may represent an unmet medical or social need. Some of these symptoms may better respond to nonpharmacologic intervention. To best address a patient's needs and to take advantage of the benefits offered by the intervention, consideration must be given to some kind of differential weighting in scoring so that the instruments measure the impact of treatment based on the severity and relevance of symptoms. Work is needed to enhance existing scales and possibly to create new ones to better capture the relevant symptoms.

In summary, this post hoc exploratory analysis of an integrated database from 3 randomized controlled trials of risperidone versus placebo, which focused on differences in response on individual symptom items, found more improvement with risperidone in psychotic, agitated, and aggressive symptoms. These data suggest that risperidone is more effective than placebo in treating a variety of specific symptoms associated with dementia, which should be further assessed in prospective trials.

Drug names: haloperidol (Haldol and others), risperidone (Risperdal).

REFERENCES

1. Tractenberg RE, Patterson M, Weiner MF, et al. Prevalence of symptoms on the CERAD behavior rating scale for dementia in normal elderly subjects and Alzheimer's disease patients. J Neuropsychiatry Clin Neurosci 2000;12:472–479
2. Mintzer JE. Underlying mechanisms of psychosis and aggression in patients with Alzheimer's disease. J Clin Psychiatry 2001;62(suppl 21): 23–25
3. Sweet RA, Pollock BG, Sukonick DL, et al. The 5-HTTPR polymorphism confers liability to a combined phenotype of psychotic and aggressive behavior in Alzheimer disease. Int Psychogeriatr 2001; 13:401–409
4. Schneider L. Assessing outcomes in Alzheimer disease. Alzheimer Dis Assoc Disord 2001;15(suppl 1):S8–S18
5. Lanctot KL, Herrmann N, van Reekum R, et al. Gender, aggression and serotonergic function are associated with response to sertraline for behavioral disturbances in Alzheimer's disease. Int J Geriatr Psychiatry 2002;17:531–541
6. Cummings JL. Written Statement for FDA Advisory Committee Meeting on Drug Development for Treating Psychiatric Disturbances Associated With Dementias. Washington, DC: Food and Drug Administration; 2000
7. Laughren T. A regulatory perspective on psychiatric syndromes in Alzheimer disease. Am J Geriatr Psychiatry 2001;9:340–345
8. Brodaty H, Ames D, Snowdon J, et al. A randomized placebo-controlled trial of risperidone for the treatment of aggression, agitation, and psychosis of dementia. J Clin Psychiatry 2003;64:134–143
9. Katz IR, Jeste DV, Mintzer JE, et al, for the Risperidone Study Group. Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial. J Clin Psychiatry 1999;60:107–115
10. De Deyn PP, Rabheru K, Rasmussen A, et al. A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. Neurology 1999;53:946–955
11. Cohen-Mansfield J, Marx MS, Rosenthal AS. A description of agitation in a nursing home. J Gerontol 1989;44:M77–M84
12. Reisberg B, Borenstein J, Salob SP, et al. Behavioral symptoms in Alzheimer's disease: phenomenology and treatment. J Clin Psychiatry 1987;48(suppl 5):9–15
13. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198
14. Cohen-Mansfield J, Werner P, Watson V, et al. Agitation among elderly persons at adult day-care centers: the experiences of relatives and staff members. Int Psychogeriatr 1995;7:447–458
15. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Hillsdale, NJ: Erlbaum; 1976
16. Perrault A, Oremus M, Demers L, et al. Review of outcome measurement instruments in Alzheimer's disease drug trials: psychometric properties of behavior and mood scales. J Geriatr Psychiatry Neurol 2000;13:81–96

