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Relapse Risk after Discontinuation of Risperidone in Alzheimer's Disease

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Abstract

BACKGROUND—Among patients with Alzheimer's disease who have had a response to antipsychotic medication for psychosis or agitation–aggression, the risk of a recurrence of symptoms after discontinuation of the medication has not been established.

METHODS—Patients with Alzheimer's disease and psychosis or agitation–aggression received open-label treatment with risperidone for 16 weeks. Those who had a response to risperidone therapy were then randomly assigned, in a double-blind fashion, to one of three regimens: continued risperidone therapy for 32 weeks (group 1), risperidone therapy for 16 weeks followed by placebo for 16 weeks (group 2), or placebo for 32 weeks (group 3). The primary outcome was the time to relapse of psychosis or agitation.

RESULTS—A total of 180 patients received open-label risperidone (mean dose, 0.97 mg daily). The severity of psychosis and agitation were reduced, although there was a mild increase in extrapyramidal signs; 112 patients met the criteria for response to treatment, of whom 110 underwent randomization. In the first 16 weeks after randomization, the rate of relapse was higher in the group that received placebo than in the groups that received risperidone (60% [24 of 40 patients in group 3] vs. 33% [23 of 70 in groups 1 and 2]; P = 0.004; hazard ratio with placebo, 1.94; 95% confidence interval [CI], 1.09 to 3.45; P = 0.02). During the next 16 weeks, the rate of relapse was higher in the group that was switched from risperidone to placebo than in the group that continued to receive risperidone (48% [13 of 27 patients in group 2] vs. 15% [2 of 13 in group 1]; P = 0.02; hazard ratio, 4.88; 95% CI, 1.08 to 21.98; P = 0.02). The rates of adverse events and

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death after randomization did not differ significantly among the groups, although comparisons were based on small numbers of patients, especially during the final 16 weeks.

CONCLUSIONS—In patients with Alzheimer's disease who had psychosis or agitation that had responded to risperidone therapy for 4 to 8 months, discontinuation of risperidone was associated with an increased risk of relapse.

Symptoms of psychosis or agitation are common in Alzheimer's disease.[1,2] These symptoms are associated with distress on the part of the patient, an increased burden on caregivers, more rapid cognitive decline, an increased likelihood of institutionalization, and increased health care costs.[3] Nonpharmacologic behavioral treatment approaches may help,[4–9] but large, controlled trials are needed to confirm the effectiveness of these strategies.

Among psychotropic medications, only antipsychotic agents show superiority over placebo for the treatment of psychosis and agitation–aggression in patients with dementia, although they are associated with only low-to-moderate efficacy.[10–12] Side effects of antipsychotic drugs include sedation, extrapyramidal signs, tardive dyskinesia, weight gain, and the metabolic syndrome.[13–15] An analysis combining data from 17 short-term trials involving patients with dementia showed that mortality among patients receiving antipsychotic medications was, on average, 1.6 to 1.7 times as high as that among patients receiving placebo — a finding that led the Food and Drug Administration to require a black-box warning for these medications.[16] Some observational studies conducted in nursing homes have not shown increased mortality with the use of antipsychotic drugs in patients with dementia.[17–19]

Even if antipsychotic drugs are effective, they are often discontinued because of concern about adverse effects and because of federal regulations that urge early discontinuation.[20] With some exceptions,[21–23] most trials of the discontinuation of antipsychotic drugs in patients with dementia[4,5,24–27] have not shown the reemergence of psychosis or agitation. These trials have important limitations: patients typically had received antipsychotic drugs for years, even though the presence of psychosis or agitation at the initiation of therapy had not been clearly established; the response of psychosis and agitation to anti-psychotic treatment was not established prospectively before discontinuation; and in each trial, more than one antipsychotic or other psychotropic drug was often discontinued in patients, limiting the assessment of relapse risk with specific medications.

In a single-site pilot study involving 20 patients with Alzheimer's disease whose symptoms of psychosis or agitation had responded to haloperidol treatment and for whom follow-up data were available, 4 of the 10 patients who continued to receive haloperidol had a relapse, as compared with 8 of the 10 who were switched to placebo.[28] These findings led to the multicenter Antipsychotic Discontinuation in Alzheimer's Disease (ADAD) trial, in which patients with psychosis or agitation–aggression initially received open-label risperidone treatment. This therapy was chosen because of studies showing the efficacy of risperidone in large samples and the absence of severe side effects at low doses.[29] Patients who had a response to this therapy were then randomly assigned to continued risperidone therapy or to discontinuation of risperidone and a switch to placebo at specified time points; the risk of relapse was then compared among the groups.

METHODS

STUDY DESIGN

The rationale, design, and methods of the ADAD trial have been published previously[30] and are described in the study protocol and statistical analysis plan, available with the full text of this article at NEJM.org. In phase A of the study, we administered open-label, flexible-dose

risperidone for 16 weeks in patients with Alzheimer's disease who had psychosis or agitation–aggression. At 16 weeks, patients who had not had a response to risperidone therapy exited the study. Patients who had a response entered phase B of the study and were randomly assigned, in a double-blind fashion, to one of three regimens: continued risperidone therapy for 32 weeks (group 1), risperidone therapy for 16 weeks followed by placebo for 16 weeks (group 2), or placebo for 32 weeks (group 3) (Fig. 1). The primary hypothesis was that in the first 16 weeks of phase B, the risk of relapse would be lower among patients who continued risperidone therapy (groups 1 and 2) than among those who received placebo (group 3). The secondary hypothesis was that in the second 16-week period of phase B, the risk of relapse would be lower among those who continued risperidone therapy (group 1) than among those who discontinued risperidone at 16 weeks and received placebo for the last 16 weeks of the study (group 2).

STUDY OVERSIGHT

The authors vouch for the completeness and accuracy of the data and analyses and for the fidelity of the study to the protocol. Janssen, a division of Johnson & Johnson, donated the risperidone tablets and matching placebo but had no role in the conduct of the study or the analysis or reporting of the data. Informed consent was obtained from each patient or from a caregiver or legal representative of the patient, as approved by the institutional review board at each participating site. Caregivers consented to participate as informants. A data and safety monitoring board monitored adverse events and study progress, and its recommendations were followed.

PARTICIPANTS

Patients were recruited from memory clinics (including Alzheimer's research centers), geriatric psychiatry clinics, and clinics at Veterans Affairs medical centers, as well as through physician referrals and advertising. Patients were eligible for participation in the study if they were outpatients or residents of assisted-living facilities or nursing homes, were 50 to 95 years of age, and met the criteria for dementia of the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV), and the criteria for probable Alzheimer's disease of the National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association.[31] In addition, eligible patients had a score on the Neuropsychiatric Inventory (NPI)[32] of 4 or more at both screening and baseline on the delusions or hallucinations subscale (psychosis score) or the agitation–aggression subscale (agitation score) (with scores on all NPI subscales ranging from 0 to 12 and higher scores indicating more pronounced symptoms) and a score of 5 to 26 on the Mini–Mental State Examination (MMSE, with scores ranging from 0 to 30 and higher scores indicating better cognition)[33] in the case of outpatients and a score of 2 to 26 in the case of nursing home residents (with the lower range reflecting the greater severity of dementia in nursing homes). Exclusion criteria were a history of stroke, transient ischemic attack, or uncontrolled atrial fibrillation.[34]

There was a 1-week washout period for psychotropic medication. If washout was not feasible (because of objections by the patient or caregiver), stable doses of selective serotonin-reuptake inhibitors or low-dose trazodone or of sedatives or hypnotic agents were permitted. Lorazepam, at a dose of 1 mg or less per day, was permitted if needed. Anticholinergic agents were not used; the dose of risperidone was lowered if extrapyramidal signs developed in the patient. Cholinesterase inhibitors and memantine at stable doses were permitted.

INTERVENTIONS

Janssen provided small tablets of risperidone, at doses of 0.25 mg, 0.5 mg, 1 mg, 2 mg, and 3 mg, and placebo — with all tablets identical in appearance. In phase A, risperidone therapy was initiated at a dose of 0.25 to 0.5 mg daily and could be increased to 3 mg daily, depending on the response and side effects. Randomization occurred at a single time point — the end of phase A. The study statistician prepared a randomized permuted-blocks procedure, with blocks of 3 or 6, to balance the group assignment in each of four (2 × 2) strata, with stratification within each site according to the presence or absence of psychosis at baseline and residence (assisted-living facility or nursing home vs. home). The central pharmacy of the New York State Psychiatric Institute maintained the assignment code, and clinicians and raters remained unaware of the group assignments of all patients during the entire study. Immediately before the end of phase A, the pharmacy dispensed prepackaged blister packs of risperidone or placebo tablets that were identical in appearance for patients eligible for randomization in phase B. The number of tablets the patient was receiving daily at the end of phase A was the number he or she received throughout phase B. In the case of patients who were receiving risperidone at a dose of 2 mg or more daily at the end of phase A, assignment to placebo in phase B required an initial 1-week tapering by means of a sequential double-blind placebo substitution (e.g., one 2-mg tablet was switched to one 1-mg tablet and then to one placebo tablet) to reduce the physical effects of the withdrawal of the antipsychotic agent. The dropout rates did not differ significantly among the randomized groups (Fig. 1).

OUTCOME MEASURES

In phase A, patients were considered to have had a response if they had a reduction of 30% or more from baseline on the NPI core score (the sum of the subscale scores for agitation–aggression, hallucinations, and delusions) and a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Impression of Change (CGI-C) scale (which ranges from 1 to 7, with higher scores indicating less improvement) for overall psychosis or agitation. In phase B, patients were considered to have had a relapse if they had an increase in the NPI core score of 30% or more, or a 5-point increase from the score at the end of phase A, and a score of 6 (much worse) or 7 (very much worse) on the CGI-C. At any phase B study visit, if the criteria for relapse were met on the basis of scores on the NPI and CGI-C during the preceding 2 weeks, end-of-study procedures were completed, and the patient exited the study to receive open-label treatment.

For the primary hypothesis, the primary end point was the time to relapse during weeks 0 to 16 of phase B. For the secondary hypothesis, the end point was the time to relapse during weeks 17 to 32 of phase B.

Secondary outcome measures included assessments of extrapyramidal signs, with the use of the Simpson–Angus scale (which ranges from 0 to 40, with higher scores indicating more extrapyramidal signs); tardive dyskinesia, with the use of the Abnormal Involuntary Movement Scale (AIMS; which ranges from 0 to 35, with higher scores indicating more severe symptoms); general somatic symptoms developing during treatment, as assessed with the use of the Treatment Emergent Symptoms Scale (TESS; which ranges from 0 to 26, with higher scores indicating more somatic symptoms); cognitive status, as assessed with the use of the MMSE and the Alzheimer's Disease Assessment Scale (ADAS)–cognitive score (which ranges from 0 to 70, with higher scores indicating worse cognition); and physical function, as assessed with the use of the Physical Self-Maintenance Scale (PSMS; which ranges from 1 to 30, with higher scores indicating worse functioning). A more detailed description of each outcome measure and its scoring range is provided in the protocol.

STATISTICAL ANALYSIS

The primary hypothesis of a difference in the hazard ratio for relapse over the first 16 weeks of phase B between the group receiving placebo (group 3) and the groups that continued to receive risperidone (groups 1 and 2) was tested in the primary analysis with the use of the stratified log-rank statistic. The stratification variables were the presence or absence of psychosis and residence in an assisted-living facility or nursing home versus residence at home; there were no other covariates. Kaplan–Meier estimates of the risk of relapse were prepared for visual comparison. For descriptive purposes, the overall rate of relapse was assessed as the number of patients who had a relapse per patient-week of follow-up or, for secondary interpretive support, as a simple proportion of patients entering a 16-week period. In secondary analyses, the proportions of patients who had a relapse were compared with the use of the Mantel–Haenszel chi-square procedure. Similar analyses were used to test the secondary hypothesis of a difference in the risk of relapse in weeks 17 to 32 of phase B between the patients who continued to receive risperidone (group 1) and the patients who discontinued risperidone at week 16 and were switched to placebo (group 2). Patients who died and those in whom a relapse was considered to be imminent (as adjudicated by an independent research psychiatrist who was unaware of the group assignments) before they dropped out of phase B were classified in the analyses as having had a relapse (Fig. 1). Secondary outcomes were analyzed according to the intention-to-treat principle, with the last-observation-carried-forward method used for patients who dropped out of the study. P values for the secondary outcome measures were prepared with the use of one-way analysis of variance for continuous measures and chi-square tests for categorical variables. All hypothesis tests were conducted at a two-tailed alpha level of significance of 0.05. P values have not been adjusted for multiple comparisons.

The trial was designed to observe approximately 48 events (relapses) to test the primary hypothesis. A description of statistical power considerations has been published previously[30] and is also provided in the study protocol and statistical analysis plan.

RESULTS

PHASE A

Figure 1 shows the numbers of patients who underwent screening, enrollment in phase A, randomization in phase B, and follow-up. At baseline, nearly half the sample resided in assisted-living facilities or nursing homes; 80% had psychosis and 81% had agitation–aggression (Table 1; and Table S1 in the Supplementary Appendix, available at NEJM.org). A total of 11 patients completed a washout of antipsychotic medications before phase A. During phase A, in which all patients received open-label risperidone treatment, 112 of 180 (62%) met the criteria for a response. The NPI core score and the NPI total score decreased significantly from baseline ($P<0.001$ for both comparisons), indicating a reduction in symptoms of psychosis and agitation–aggression. Scores on the Simpson–Angus scale increased by an average of 0.7 points, indicating more extrapyramidal (parkinsonian) signs ($P = 0.009$), but there was no significant change in AIMS scores for tardive dyskinesia. General physical symptoms, as reflected by the TESS score, decreased from baseline ($P<0.001$), and physical self-maintenance, as reflected by the PSMS score, worsened ($P<0.001$). The global score for cognition on the MMSE was, on average, 0.5 points lower at the end of phase A than at baseline ($P = 0.007$), but there was no significant change in the ADAS-cognitive score in the total sample (Table 1) or in patients with a baseline score of 10 or more on the MMSE.

As compared with the 68 patients who did not have a response in phase A, the 112 who did have a response had had, at baseline, significantly higher MMSE scores, lower TESS scores,

and lower scores on the Simpson–Angus scale, but there was no significant difference between these two groups with respect to the percentage of patients with baseline psychosis or agitation–aggression (Table 1).

PHASE B

At 16 weeks, 110 of the 112 patients who had a response to risperidone (mean [±SD] daily dose, 0.97±0.74 mg) in phase A underwent randomization. Demographic characteristics and efficacy and side-effect variables at the time of randomization did not differ significantly among groups 1, 2, and 3 (Table 1).

Stratified Cox analyses showed that during the first 16-week period of phase B, the group that was randomly assigned to receive placebo (group 3), as compared with the groups that continued to receive risperidone (groups 1 and 2), had an increased risk of relapse (hazard ratio with placebo, 1.94; 95% confidence interval [CI], 1.09 to 3.45; P = 0.02). Figure 2 shows the Kaplan–Meier curves. A total of 24 of 40 patients (60%) in group 3 had a relapse, as compared with 23 of 70 (33%) in groups 1 and 2 (P = 0.004), with crude (unstratified) rates of 6.5 and 3.0 relapses per 100 patient-weeks of follow-up, respectively.

For the second 16-week period of phase B, stratified Cox analyses showed that the group that discontinued risperidone at 16 weeks and was switched to placebo (group 2), as compared with the group that continued to receive risperidone (group 1), had an increased risk of relapse (hazard ratio with placebo, 4.88; 95% CI, 1.08 to 21.98; P = 0.02). A total of 13 of 27 patients (48%) in group 2 had a relapse, as compared with 2 of 13 (15%) in group 1 (P = 0.02), with crude (unstratified) rates of 4.3 and 1.1 relapses per 100 patient-weeks of follow-up, respectively.

The results for both comparisons were in the same direction within each of the four strata analyzed (presence or absence of psychosis and residence in an assisted-living facility or nursing home vs. residence at home). There were no significant interactions between treatment and psychosis, treatment and nursing home status, or treatment and baseline MMSE score in the primary comparison between the groups receiving risperidone (groups 1 and 2) and the group receiving placebo (group 3) during the first 16 weeks of phase B. The mean total NPI score was 36 (indicating severe symptoms) at baseline (Table 1) and decreased to 9 (indicating minimal or mild symptoms) at the time of randomization; neither score predicted a relapse during the first 16 weeks of phase B.

ADVERSE EVENTS

In the first 16-week period of phase B, there were no significant differences in adverse events as defined by increases above prespecified thresholds in Simpson–Angus, AIMS, TESS, ADAS-cognitive, or PSMS scores or decreases in MMSE scores between patients receiving risperidone (groups 1 and 2) and those receiving placebo (group 3), after adjustment for each corresponding value at randomization (Table 2). In the second 16-week period of phase B, there were no significant differences in such adverse events between patients who continued to receive risperidone (group 1) and those who discontinued risperidone and were switched to placebo (group 2), after adjustment for each corresponding value at randomization (Table 2).

There were no significant differences between patients who received risperidone continuously for 32 weeks (group 1) and those who received placebo continuously for 32 weeks (group 3) with respect to the prespecified changes in Simpson–Angus, AIMS, TESS, ADAS-cognitive, PSMS or MMSE scores or increases in body weight, after adjustment for each corresponding value at randomization. These two groups did not differ significantly with respect to adverse events, serious adverse events, or deaths. A total of 11 serious

adverse events occurred during phase B, with no significant between-group differences during either 16-week period. Three deaths occurred during phase A in the total cohort of 180 patients, and 3 deaths (2 in patients receiving risperidone and 1 in a patient receiving placebo) occurred during phase B in the cohort of 110 patients who had undergone randomization, with no pattern observed with respect to the cause of death.

DISCUSSION

Among patients with Alzheimer's disease whose symptoms of psychosis or agitation had decreased while they were receiving risperidone, the time to a relapse was shorter among those who discontinued risperidone and received placebo during the first 16 weeks after randomization than among those who continued to receive risperidone, and the risk of relapse was nearly double (60% vs. 33%). These findings were corroborated in the second 16-week period after randomization. Therefore, among patients who had a sustained response to risperidone for 4 to 8 months, subsequent discontinuation was associated with an increased risk of relapse for at least another 4 months.

Although discontinuation of risperidone resulted in an increased risk of relapse, risperidone was not highly effective in achieving and maintaining a reduction in symptoms of psychosis and agitation in patients with Alzheimer's disease. Among patients who had had a response in phase A and continued to receive risperidone in phase B, a large proportion had a relapse or dropped out. The rates of discontinuation of risperidone treatment for any reason were 38% in the total cohort during phase A, 68% in group 1 during the 32 weeks of phase B, and 29% in group 2 during the 16 weeks in phase B in which they received risperidone. In contrast, the rate of discontinuation of initial risperidone treatment for any reason during an average of 7.4 weeks in the Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease (CATIE-AD) study was 77%.[14]

In trials of both short-term discontinuation[27] and long-term discontinuation[23] involving several antipsychotic drugs, increased baseline psychopathologic symptoms were associated with worsening condition when the patients discontinued the drug and were switched to placebo. However, in the current study, neither increased NPI scores at baseline or randomization nor the presence of psychosis at baseline or randomization predicted a relapse after discontinuation of risperidone and the switch to placebo in phase B.

During 4 months of initial open-label risperidone treatment, somatic side effects diminished, body weight did not change substantially, and extrapyramidal signs increased to some degree. In phase B, somatic side effects did not differ significantly between patients who continued to receive risperidone and those who were switched to placebo — even between patients who received risperidone for the entire 32-week period (group 1) and those who received placebo for the entire 32-week period (group 3), a finding that may be attributable to the low doses of risperidone used.[23] In CATIE-AD, risperidone was not associated with weight gain or with the metabolic syndrome to the same extent as were olanzapine and quetiapine.[15] In our study, progression of disease may underlie the small but significant decline in MMSE scores during the open-label treatment period (phase A), and the ADAS-cognitive score did not change significantly during this period. The change in MMSE scores did not differ significantly between patients who received risperidone and those who received placebo for the entire 8-month period after randomization. There is limited evidence that short-term exposure to antipsychotic drugs may worsen cognition,[23,35] but long-term deleterious effects on cognition have not been established. Antipsychotic drugs with strong anticholinergic effects, such as olanzapine and clozapine, theoretically may worsen cognition, but data from patients with dementia are limited.[36–39]

The ADAD trial had some limitations. The sample size was inadequate to evaluate between-group differences in serious adverse events and mortality. Comparisons of adverse events in phase B were limited by the small sample and the truncated observation period for side effects in the case of patients who had an early relapse. The identification of predictors of relapse after discontinuation of risperidone treatment was limited by the small sample.

U.S. federal regulations for nursing homes strongly urge discontinuation of antipsychotic drugs after 3 to 6 months of treatment.[20] Evidence from controlled trials in support of this long-standing regulation is very limited. Our findings suggest that patients with psychosis or agitation–aggression who have a sustained response to antipsychotic treatment for 4 to 8 months have a significantly increased risk of relapse for at least 4 months after discontinuation, and this finding should be weighed against the risk of adverse effects with continued antipsychotic treatment. Additional long-term, controlled trials of antipsychotic treatment and prospective, controlled trials of discontinuation of treatment among patients who have had a response to antipsychotic drugs are needed to inform current regulations that govern clinical practice.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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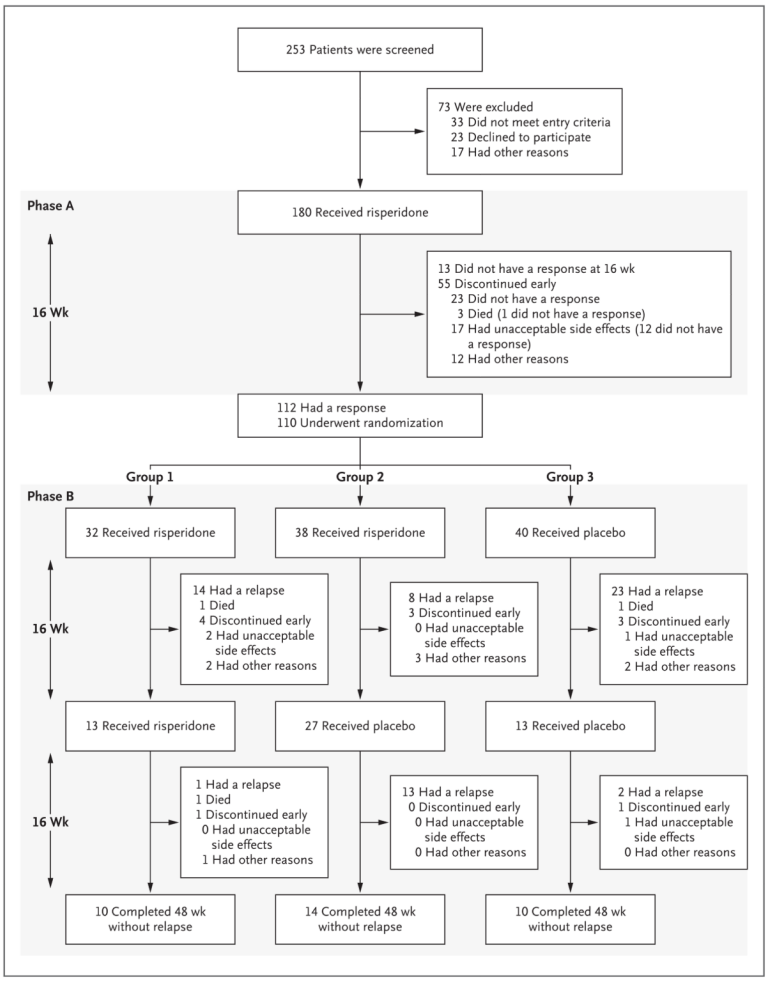

Figure 1. Screening, Enrollment in Phase A, Randomization in Phase B, and Outcomes

A total of 12 patients discontinued the study after phase A and before randomization for reasons other than a lack of response, death, or unacceptable side effects; these other reasons included withdrawal of consent (7 patients), a move away from the study center (3), nonadherence to medication (1), and a medical illness (1). In the first 16-week period of phase B, 1 patient in group 1, 1 patient in group 2, and 2 patients in group 3 in whom a relapse was considered to be imminent (as assessed by an independent psychiatrist, who was unaware of the group assignments) were classified as having had a relapse.

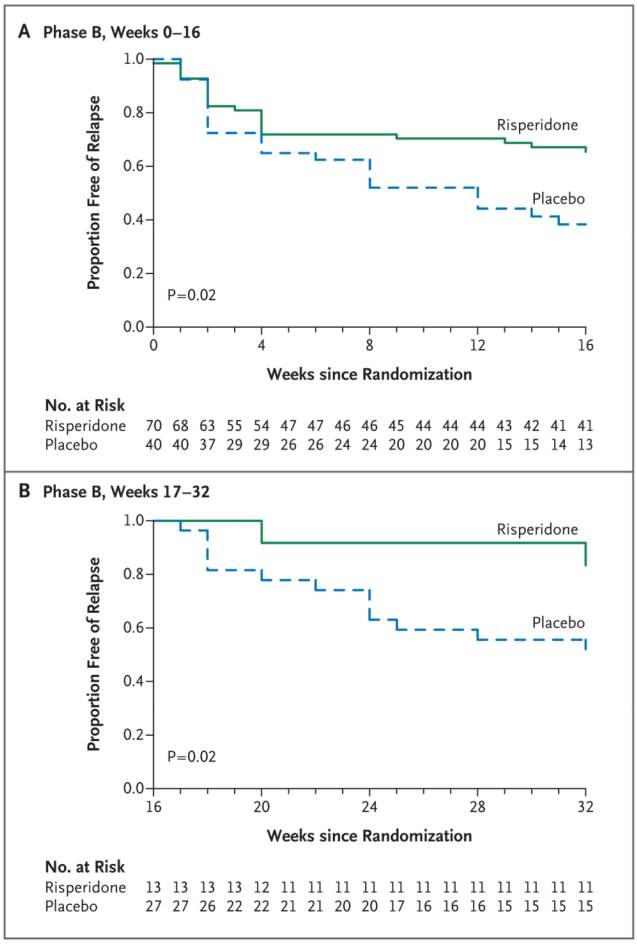

Figure 2. Time from Randomization to Relapse among Patients Receiving Risperidone and Those Receiving Placebo

Panel A shows Kaplan–Meier curves for the risk of relapse during the first 16-week period of phase B (weeks 16 to 32 of the study) among the 70 patients who were randomly assigned to continue to receive risperidone (groups 1 and 2) and the 40 patients who were assigned to be withdrawn from risperidone at the end of phase A and switched to placebo (group 3). Panel B shows Kaplan–Meier curves for the risk of relapse during the second 16-week period of phase B (weeks 33 to 48 of the study) among the 13 patients who continued to receive risperidone (group 1) and the 27 patients who were switched to placebo at the end of the first 16-week period (group 2).

Table 1

Characteristics of the Patients at Baseline and at the Time of Randomization for Phase B.*

Characteristic	Baseline (N = 180)	Randomization for Phase B (N = 110)		
		Group 1 (N = 32)	Group 2 (N = 38)	Group 3 (N = 40)
Age (yr)	79.6±7.6	80.7±7.9	79.1±8.0	80.3±7.7
Education (yr)	12.0±3.7	12.6±4.2	12.0±2.7	12.0±3.2
Female sex (%)	59	69	53	60
Race (%)†				
White	72	81	74	70
Black	21	16	18	22
Other	8	3	8	8
Residence (%)				
Home	56	44	55	52
Assisted-living facility or nursing home	44	56	45	48
Concomitant drugs (%)				
Cholinesterase inhibitor	62	59	68	65
Memantine	35	34	34	25
Anxiolytic or hypnotic‡	17	28	16	20
Antidepressant‡	24	16	26	28
Target symptoms (%)				
Psychosis	80	12	8	15
Agitation–aggression	81	9	19	18
NPI score§				
Total	36.1±17.0	9.6±7.8	9.7±10.4	7.9±7.3
Core	16.9±7.3	2.7±3.4	2.4±3.2	3.0±3.5
Simpson–Angus score¶	2.5±3.5	4.4±4.7	3.2±4.6	2.4±2.6
AIMS score‖	0.2±0.6	0.2±0.4	0.2±0.7	0.1±0.4
MMSE score**	13.9±6.4	13.4±6.6	13.6±6.7	15.5±6.6
ADAS-cognitive score††	42.4±15.7	43.7±15.0	40.9±16.4	39.9±13.8
TESS score‡‡	6.2±4.6	3.8±2.7	3.4±2.5	2.8±2.1

Characteristic	Baseline (N = 180)	Randomization for Phase B (N = 110)		
		Group 1 (N = 32)	Group 2 (N = 38)	Group 3 (N = 40)
PSMS score§§	12.6±5.8	15.1±7.1	12.7±4.7	12.4±4.9

* Plus–minus values are means ±SD. A total of 180 patients entered the study (baseline); during the 16-week phase A, all patients received open-label risperidone. Of 112 patients who had a response to risperidone in phase A, 110 were randomly assigned for the 32-week phase B to receive risperidone for the entire 32-week period (group 1), risperidone for 16 weeks followed by placebo for 16 weeks (group 2), or placebo for the entire 32-week period (group 3). Analyses of variance did not reveal any significant differences in measures of symptoms and side effects at the time of randomization among groups 1, 2, and 3. For an expanded version of this table that shows the baseline characteristics of patients according to whether they ultimately had a response to risperidone in phase A, see Table S1 in the Supplementary Appendix.

† Race was reported by the patient or caregiver. “Other” includes Native American or Native Alaskan (<1% of patients), Asian (2%), Native Hawaiian or other Pacific Islander (<1%), and more than one race (2%).

‡ Percentages indicate patients who took the medication at baseline (i.e., no washout before phase A).

§ The total score on the Neuropsychiatric Inventory (NPI) ranges from 0 to 144. The NPI comprises 12 subscales. Scores on each subscale range from 0 to 12, with the scores derived by multiplying the frequency of symptoms, on a scale of 0 to 4, by the severity of symptoms, on a scale of 0 to 3; higher scores indicate more frequent and more severe symptoms. Patients were considered to have psychosis if they had a score of 4 or higher on the subscale for delusions or hallucinations and were considered to have agitation–aggression if they had a score of 4 or higher on the subscale for agitation–aggression. The NPI core score is the sum of scores on the subscales for delusions, hallucinations, and agitation–aggression (with the core score ranging from 0 to 36).

¶ The Simpson–Angus scale assesses extrapyramidal signs. Scores range from 0 to 40, with higher scores indicating more extrapyramidal signs.

‖ The Abnormal Involuntary Movement Scale (AIMS) assesses tardive dyskinesia. Scores range from 0 to 35, with higher scores indicating more severe tardive dyskinesia.

** The Mini–Mental State Examination (MMSE, Folstein version) assesses cognition. Scores range from 0 to 30, with higher scores indicating better cognition.

†† The Alzheimer’s Disease Assessment Scale (ADAS)-cognitive assesses cognition. Total scores range from 0 to 70, with higher scores indicating worse cognition. The ADAS-cognitive score was assessed in 166 of the 180 patients at baseline.

‡‡ The Treatment Emergent Symptoms Scale (TESS) assesses 26 somatic symptoms. Total scores range from 0 to 26, with a score of 0 or 1 for each symptom. Higher scores indicate more somatic symptoms.

§§ The Physical Self-Maintenance Scale (PSMS) assesses physical functioning. Scores range from 1 to 30, with higher scores indicating worse functioning.

Table 2

Adverse and Serious Adverse Events in Phase A and Phase B.*

Event	16-Wk Phase A (N = 180)	32-Wk Phase B				
		Wk 0–16		Wk 17–32		
		Groups 1 and 2 (N = 70)	Group 3 (N = 40)	Group 1 (N = 13)	Group 2 (N = 27)	Group 3 (N = 13)
		number of patients (percent)				
Serious adverse events†						
Death	3 (2)	1 (1)	1 (2)	1 (8)	0	0
Cardiovascular event	5 (3)	1 (1)	1 (2)	1 (8)	0	0
Neurologic event	5 (3)	0	1 (2)	0	0	0
Agitation–aggression	2 (1)	0	2 (5)	0	0	0
Pulmonary event	2 (1)	1 (1)	1 (2)	0	0	0
Fall or fracture	3 (2)	0	0	0	0	0
Other	5 (3)	2 (3)	2 (5)	0	0	0
Adverse events‡						
Extrapyramidal signs	30 (17)	13 (19)	4 (10)	4 (31)	4 (15)	2 (15)
Akathisia or restlessness	12 (7)	4 (6)	6 (15)	1 (8)	3 (11)	1 (8)
Sedation	20 (11)	7 (10)	5 (12)	1 (8)	1 (4)	1 (8)
Insomnia	4 (2)	3 (4)	1 (2)	0	1 (4)	0
Confusion	11 (6)	4 (6)	4 (10)	1 (8)	3 (11)	1 (8)
Agitation–aggression	8 (4)	1 (1)	1 (2)	0	1 (4)	1 (8)
Fall	10 (6)	2 (3)	1 (2)	0	0	0
Nausea or vomiting	11 (6)	2 (3)	2 (5)	2 (15)	0	1 (8)

[*] All serious adverse events are included here; adverse events are listed if they occurred in more than 5% of patients in any group. For an expanded version of this table that lists all adverse events, see Table S2 in the Supplementary Appendix.

[†] A serious adverse event was an adverse drug-related event that resulted in any of the following outcomes: death, a life-threatening condition, hospital admission or prolongation of a hospital stay, or an unexpected event leading to clinically significant disability or incapacity. The classification of an adverse event as serious was based on the judgment of the investigator and the study medical monitor.

[‡] An adverse event was either a report of a clinically significant new adverse event or a worsening of a symptom from baseline to a moderate or severe level, as assessed by means of the TESS. Extrapyramidal signs and akathisia or restlessness were considered to be adverse events if there was an average increase from baseline of more than 1 point on the Simpson–Angus scale.