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The Antipsychotic Discontinuation in Alzheimer Disease Trial: Clinical Rationale and Study Design

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Abstract

Objective—Research studies on the effects of discontinuing antipsychotic medications in patients with dementia have not identified specific target symptoms or response to antipsychotics prior to discontinuation. The Antipsychotic Discontinuation in Alzheimer Disease (ADAD) trial addresses these issues in a randomized, double-blind, placebo-controlled, multicenter risperidone treatment and discontinuation trial. In Phase A, AD patients with psychosis or agitation receive open treatment with risperidone for 16 weeks. Responders are randomized, double-blind, to one of three arms in Phase B: 1) continuation risperidone for the next 32 weeks, 2) risperidone for the next 16 weeks followed by placebo for 16 weeks, or 3) placebo for the next 32 weeks.

Methods—Several design features provide unique strengths to this trial: identification of target symptoms and systematic open antipsychotic treatment with only responders randomized in the discontinuation trial, use of a single antipsychotic medication, two clinically relevant time-points for discontinuation to evaluate the impact of duration of treatment on relapse, exclusion of patients at increased risk of stroke, assessment of several affected symptom domains, and state-of-the-art approaches to assess relapse and handle dropout.

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Conclusions—This study will provide clinically relevant data on the likelihood and time to relapse, and predictors of relapse, in patients switched from risperidone to placebo after response to risperidone treatment. Given the warnings about antipsychotic use in patients with dementia, studies of this type are essential to determine the optimal duration of treatment that confers the greatest benefit to risk ratio and to improve evidence-based treatment strategies.

Keywords

agitation; Alzheimer disease; antipsychotic; discontinuation trial; psychosis; risperidone

Symptoms of psychosis or agitation/aggression occur in the majority of patients with Alzheimer disease (AD) during the course of illness, are distressing to patients and increase caregiver burden, are associated with more rapid cognitive decline, and represent the most common antecedent to institutionalization.^{1–3} Data from controlled studies using behavioral interventions to treat these symptoms are sparse.^{4–7} Among the psychotropic medications studied in randomized, double-blind, placebo-controlled clinical trials, only antipsychotic medications usually show superiority to placebo to treat both psychosis and agitation, albeit with low to moderate efficacy.^{8,9} Dose comparison studies have identified the optimal dose range of haloperidol, risperidone, olanzapine, and aripiprazole in patients with dementia.^{10–14} *There is initial evidence that citalopram, an SSRI antidepressant, may show efficacy comparable to risperidone but this finding needs confirmation in additional trials.*¹⁵

Conventional antipsychotic medications, and to varying degrees atypical antipsychotic medications, are associated with sedation, motor side effects, weight gain, and the metabolic syndrome.^{16,17} Furthermore, antipsychotic medications are associated with increased mortality risk as stated in the Federal Drug Administration (FDA) black box warning: “Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients.” A few naturalistic studies in hospitals¹⁸ and long-term care facilities¹⁹ do not show an increased mortality risk with antipsychotic usage. Antipsychotic medications are widely used to treat psychosis or agitation in patients with dementia, but they are not FDA-approved for this purpose and their side-effect profile has led to regulations encouraging clinicians to discontinue them as soon as clinical necessity is no longer present.

In earlier studies on discontinuation of antipsychotic medication in dementia, concomitant educational programs or changes in nursing home structure confounded the results.^{20–23} A few studies showed increased relapse with reemergence of behavioral symptoms following antipsychotic discontinuation,^{24,25} but most placebo-controlled antipsychotic discontinuation trials conducted primarily in nursing homes showed little difference between continuation medication and placebo in relapse rates.^{22,26–28} These studies shared three limitations:

1. Most patients had received antipsychotics for long periods, often years, and many did not have target symptoms at study entry. In these patients, not surprisingly, discontinuation of these medications did not lead to emergent symptoms;
2. Response to the psychotropic medication was typically not established before discontinuation; and
3. Patients were often discontinued from different antipsychotics and other psychotropics, limiting the ability to assess relapse risk for specific antipsychotic medications.

In a recent discontinuation trial, the primary outcome was the Severe Impairment Battery that assesses cognition,²⁸ a domain where significant changes would not be expected with antipsychotic discontinuation.

The Antipsychotic Discontinuation in Alzheimer Disease (ADAD) trial, funded by the National Institute of Aging (R01 AG021488), addresses these issues in a randomized, double-blind, multicenter treatment and discontinuation trial. *The design and methods are presented here to inform clinicians and academics about the importance, need, and approach to examine antipsychotic discontinuation systematically in patients with AD. The current concerns and controversies surrounding the use of antipsychotics have created a relative mismatch between the information available from research and clinical practice, and this study's goal is to address the key concern about prescribing, continuing, and discontinuing antipsychotic medication in patients with dementia.*

METHODS

In Phase A, AD patients with psychosis or agitation receive open treatment with risperidone for 16 weeks. Responders are then randomized, double-blind, to one of three arms in Phase B: 1) continuation of risperidone for the next 32 weeks, 2) continuation of risperidone for the next 16 weeks followed by placebo for 16 weeks, or 3) continuation of placebo for the next 32 weeks (Fig. 1).

Study Design Features and Rationale

1. Patients with AD who have target symptoms of psychosis or agitation are treated with a single atypical antipsychotic, risperidone, and responders to open treatment are randomized to Phase B.
2. *Choice of a single antipsychotic medication.* Atypical antipsychotics may show differences in efficacy in the treatment of patients with dementia who develop psychosis,^{17,29} and it is possible that the likelihood of relapse after discontinuation varies between antipsychotic medications. Therefore, a single antipsychotic was chosen in preference to randomizing patients to multiple antipsychotics that may lead to differential efficacy in the initial open treatment phase and unbalance the drug versus placebo assignment in the randomized phase. Furthermore, treating patients with different antipsychotics will increase heterogeneity and possibly mask the likelihood of observing a difference between drug and placebo in the discontinuation phase. If multiple drugs were used, we would not be able to tell statistically which drug would be showing a significant difference, assuming one were found overall, without a much larger sample size than would be feasible in this trial. With a single drug, the answer for that drug would be clear.
3. *Choice of risperidone.* Among the atypical antipsychotics, risperidone has been studied the most in patients with dementia, and moderate efficacy with a generally tolerable side effect profile at low doses has been shown.^{11,12,29,30} Clinical conditions are simulated in this practical clinical trial with risperidone, which is now generic, relatively inexpensive, and widely available and is used frequently in these patients.
4. Both outpatients and nursing home/assisted living patients are eligible to increase generalizability. Several trials of antipsychotic medications in AD show similar results in outpatients^{10,11} and nursing homes/long-term care facilities.^{11–13}
5. The 16-week time-point for discontinuation is clinically relevant and consistent with U.S. regulations for discontinuation in nursing homes. At 16 weeks in Phase B, if relapse on placebo is significantly greater than on continuation of risperidone,

the question remains whether longer treatment with risperidone will decrease relapse risk after withdrawal. The second discontinuation time-point at 32 weeks partly addresses this question.

6. All statistical tests of primary and secondary null hypotheses will be conducted at the $\alpha = 0.05$, two-tailed level of significance. We next state each scientific alternative hypothesis in the specific direction expected to pertain if the null hypothesis is false.

Primary Hypothesis

1. During the first 16 weeks in Phase B, the time to relapse or death from any cause will be shorter in the immediate discontinuation (placebo) arm than in the combined risperidone continuation arms.

Secondary Hypotheses

1. During the first 16 weeks in Phase B, the proportion of patients who relapse or die will be greater in the placebo arm than in the combined risperidone continuation arms.
2. During the first 16 weeks in Phase B, the proportion of patients who move to a higher level of care or exhibit greater functional impairment will be greater for patients in the immediate discontinuation (placebo) arm than in the combined risperidone continuation arms.
3. In Phase B, patients with predominant behavioral symptoms at baseline, for example, agitation or aggression, will be more likely to relapse, and have shorter time to relapse, than patients with predominant psychotic symptoms at baseline, for example, delusions.

Exploratory analyses will examine severity of dementia and severity and type (psychosis or agitation/aggression) of target symptoms as predictors of response in Phase A and predictors of relapse in Phase B. Exploratory analyses will also examine relapse and time to relapse from 16 to 32 weeks in Phase B. Correlations between plasma concentrations of risperidone and its main metabolite with the main outcome measures will be explored.

Recruitment, Eligibility, Consent

The clinical trial is conducted at 8 sites (6 academic and 2 commercial, Table 1). Patients are recruited from memory clinics including Alzheimer Research Centers, geriatric psychiatry clinics, Veterans Administration geriatric clinics, primary care referrals, and advertising.

Informed consent, which includes a description of the major side effects and the FDA boxed warning about mortality risk, is obtained from the patient and surrogate/caregiver or authorized legal representative as approved by the sites' institutional review boards, in accordance with local law. Caregivers also give consent to participate as informants.

Inclusion/exclusion criteria are described in Table 2. Patients need to have symptoms of psychosis or agitation of at least moderate severity. Cholinesterase inhibitors and memantine are permitted at stable doses during the study. Patients with a history of stroke, transient ischemic attack, or uncontrolled atrial fibrillation are excluded because early reports³⁰ indicated that atypical antipsychotic medications may be associated with cerebrovascular adverse events (Table 2). The study begins with a 1-week "lead in" washout period for psychotropic medications (3 weeks for fluoxetine and monoamine oxidase inhibitors). Stable doses of SSRIs that cannot be washed out and low dose lorazepam p.r.n. are permitted (Table 2; 31). No anticholinergic agents are used to treat EPS. If EPS develops, the

risperidone dose is lowered. *Lewy body dementia is excluded on the basis of consensus clinical diagnostic criteria.*³¹ *Extensive neuropsychological and neuroimaging assessment may improve diagnostic accuracy for Lewy body dementia*³² *but this type of assessment is not feasible in the study sample with psychosis or agitation that comprises a large proportion with severe dementia. The evaluation for Lewy body dementia is an important issue because the clinical diagnosis is not always consistent with autopsy findings.*³¹

Treatment Regimen

In Phase A, risperidone is administered at doses of 0.25 to 3 mg daily.^{11,12,17} After the starting risperidone oral dose of 0.25 to 0.5 mg daily, subsequent increases of 0.25 mg to 0.5 mg daily occur at consecutive visits until the optimal tradeoff between efficacy and side effects is reached.

At the start of Phase B, to avoid rapid withdrawal effects in patients randomized to placebo, there is a 1- to 2-week tapering period with sequential double-blind placebo substitution of tablets, keeping the total number of tablets constant. Patients on 3 mg daily switch to 2 mg daily for 1 week, then 1 mg daily for 1 week, and then placebo (if assigned to placebo). Patients on 2 mg daily switch to 1 mg daily for 1 week and then placebo. Patients who receive 0.5 mg or 1 mg at end-Phase A switch directly to placebo without a taper. A similar procedure is used at 16 weeks into Phase B (Fig. 1). For patients randomized to continuation risperidone, the dose at end-Phase A is kept constant throughout Phase B. Clinicians provide psychosocial support and usual clinical care throughout the study.

Randomization and Masking

At 12 weeks in Phase A, and in ambiguous cases at 14 weeks as well, assessments determine response and likely eligibility for randomization at 16 weeks. If there is clinical fluctuation or uncertainty about responder status at 16 weeks, this time-point is extended to 18 weeks with reassessment to finalize eligibility for randomization.

For Phase B, randomization is stratified by site, nursing home/outpatient status, and presence/absence of psychosis (Table 1). A randomized permuted block procedure with blocks of length 3 or 6 is used (varying the block size further reduces the risk of unblinding raters) to balance treatment arm assignment in each stratum.³³

Response and Relapse Criteria

In Phase A, response requires a minimum 30% reduction in the sum of Neuropsychiatric Inventory (NPI) scores (severity $\times$ frequency scores) for agitation/aggression, hallucinations, and delusions (NPI core score) from baseline to week 16, and a score of 1 (very much improved) or 2 (much improved) on the Clinical Global Impression of Change (CGI-C) (1–7 scale). In Phase B, relapse requires a minimum 30% increase or a minimum 5-point increase in NPI core scores from end-Phase A (week 16), and a score of 6 (much worse) or 7 (very much worse) on the CGI-C.

Sample Estimates

Of 200 recruited patients, 110 are expected to respond in Phase A. Of these 110 responders, 102 patients are expected to enter one of three arms ($N = 34$ in each arm) in Phase B (double-blind phase). Therefore, in the first 16 weeks in Phase B, 68 patients continue to receive risperidone and 34 patients are switched to placebo.

Dropout

We expect 20 dropouts (10%) in Phase A open treatment (16 weeks). During Phase B, we estimate 6 dropouts (10% of approximately 60 patients who do not relapse).

End of Study Treatment

Patients who relapse during Phase B, or end-Phase B without relapse, exit the protocol and receive open treatment (off-study).

Procedure for Unblinding

The blind is maintained after study exit to avoid biasing raters. A code-break is authorized only if needed in cases of overdose or medical emergency.

Discontinuation From the Study

The patient exits the study if consent or assent is withdrawn or a major protocol violation precludes study continuation. Development of an intolerable adverse event or hospitalization may lead to study discontinuation or the patient may go on an interruption of therapy (medication withdrawn but procedures continue) if the patient and patient representative are willing to continue the study. All end-of-trial procedures are completed at the patient's final study visit, adverse events (if any) are recorded and the Protocol Exit form is completed.

Outcome Measures and Data Collection Schedule

The efficacy outcomes are based on informant interview supplemented by direct patient observation. The time-points of scale administration are specified in Table 3.

Efficacy Measures

Primary Efficacy Measure—NPI sum score of delusions, hallucinations, and agitation/aggression, which are three of 12 domains in the NPI.³⁴ The NPI is the most widely used of such instruments, has high reliability and validity, and has shown sensitivity to change in several clinical trials in dementia.^{13,35} Raters are certified on the NPI training Web site before study initiation.

Secondary Efficacy Measures—The Clinical Global Impression of Change with semi-structured probes³⁶ is a global measurement of change in the patient's condition (range: 1–7). The CGI-C rating here focuses on target symptoms and not the patient's cognitive or functional status. At baseline, for each patient the three most prominent target symptoms of psychosis or behavioral disturbance on a 1–7 scale are identified. The mean score is a secondary outcome measure.

Side-Effect Measures

Vital signs include assessment for orthostatic hypotension at every visit. The Treatment Emergent Symptom Scale (TESS) is used for general somatic side effects, EPS is monitored by the Simpson-Angus Scale (SAS);³⁷ and TD is assessed by the Abnormal Involuntary Movement Scale (AIMS).

Other Measures

Functioning is assessed by the Physical Self Maintenance Scale (PSMS), a structured interview with the caregiver (items rated on a 1–5 scale). Quality of life is assessed by the Alzheimer's Disease-Related Quality of Life Scale.¹⁷ To assess cognition, the 30-item Mini-Mental State Exam (MMSE)³⁸ is primary and the ADAS-cog is secondary.

Blood Samples

Plasma to assess risperidone levels of parent drug and the major pharmacologically active metabolite, 9-hydroxy-risperidone, are obtained at 16 weeks in Phase A and at 16 and 32 weeks in Phase B. In exploratory analyses plasma concentrations are correlated with change in NPI core scores.

Data Safety and Monitoring Board

A Data Safety and Monitoring Board, approved by NIA, receives study updates and meets or teleconferences annually to monitor the safety and course of the study.

Statistical Analyses, Sample Size, and Power Calculations

Outcome Measures—The primary efficacy measure is the NPI core score in Phase A, and the primary outcome in Phase B is time to relapse or death from any cause, measured in weeks from randomization. The primary side-effect measures are total scores for somatic side effects (TESS), EPS (SAS), TD (AIMS), daily functioning (PSMS), and cognition (MMSE).

Primary Hypothesis Tests—The test of the primary hypothesis of a difference in survival functions between the immediate discontinuation and risperidone continuation arms is the stratified log-rank statistic (equivalent to a Mantel-Haenszel procedure³⁹), using the randomization strata of site, psychosis (yes/no), and nursing home versus outpatient status as stratification variables. Supplementary estimates of the log relative hazard ratio for the two groups use discrete-time maximum partial likelihood methods. Kaplan-Meier (product-limit) estimates of the survival functions are compared.

If there are any major imbalances in potential prognostic variables across treatment conditions (0.01 level of significance, unlikely because of the stratified randomization), Cox models⁴⁰ will be used to model the log relative hazard ratio as a function of treatment group, adjusting for potential prognostic variables as the primary analysis.

Secondary Hypotheses Tests

The Mantel-Haenszel one degree of freedom chi-squared procedure, stratified by site, psychosis (yes/no), and nursing home versus outpatient status will be used to test the secondary hypotheses involving proportions. The log-rank statistic, stratified by treatment arm and nursing home versus outpatient status, will be used to compare the time-to-event distributions for the behavioral versus psychosis subgroups.

Handling of Dropouts and Other Forms of Noncompliance

In Phase B, follow-up continues until relapse or end of study in patients who do not relapse. Closeout from the protocol due to relapse or death, that is, a primary endpoint, is *not* a loss to follow-up. Intent-to-treat analyses are used for all protocol violations such as adherence failures or interruptions of therapy.

Relapse and Dropout

All failures of treatment, including all-cause mortality, are counted as relapse. For all other losses to follow-up, a blinded expert will review the case report forms and classify them into one of three categories. Category 1 (endpoint imminent): clinical signs indicating a worsening condition, inability to participate due to other conditions related to AD, or other failures of treatment. Category 1 losses to follow-up will have a primary endpoint imputed as their study outcome at the date of loss to follow-up. A loss to follow-up will qualify as Category 2 (independent censoring) if the reasons stated are considered to be statistically

independent of the likely time of primary endpoint. Losses to follow-up in Category 2 will be treated as right-censored observations, without incurring bias. All other losses to follow-up will be considered nonignorable missing data (Category 3). For Category 3 losses to follow-up, Rubin's multiple imputation method will be used to impute (repeatedly) different times to relapse under the null hypothesis based on treatment-blinded (pooled) complete data from the trial.

Power Analysis

The size of the study entry sample was predicated on providing adequate power to test the primary null hypothesis. During the first 16 weeks in Phase B ($N = 102$), two-thirds of the sample ($N = 68$) receive risperidone, and one-third of the sample receive placebo ($N = 34$). The power of the log-rank statistic depends on the number of events and the treatment allocation ratio.²⁹ Given the 2:1 allocation ratio, a total of 33.4 events (relapses) would be needed for 80% power. In fact, we estimate that 75% of patients will relapse on placebo compared to 35% on risperidone during the first 16 weeks of Phase B, which would yield 48 primary endpoints, thus providing more than adequate power for the primary hypothesis test.

The detectable effect size (at 80% power, $\alpha = 0.05$ two-tailed) with 48 events and a 2:1 allocation ratio is 0.857 (log relative hazard ratio). The corresponding hazard ratio is 2.36. For a constant hazard rate of 0.0866, or 8.66 relapses per 100 patient-weeks, the detectable hazard rate is $0.0866/2.36 = 0.0367$, or 3.67 relapses per 100 patient-weeks, corresponding to a cumulative 16-week relapse proportion of 44.4%. Therefore, the trial will have very good power for the primary analysis even if the hazard rate varies, as long as the expected number of events is observed.

For the secondary hypotheses involving the proportion of patients who relapse, the power for a wide range of possible relapse proportions is listed in Table 4. For the estimated relapse proportion of 75% on placebo and 35% on risperidone, the power is 0.966 (or 96.6%), which provides more than sufficient power to test this hypothesis. The detectable difference in relapse proportions (with 80% power, $\alpha = 0.05$, two-tailed) is between 30 and 35 percentage points.

For the exploratory analyses covering the second 16 weeks of Phase B, we will compare the survival functions of patients discontinued after the first 16 weeks of Phase B with patients continued on risperidone to 32 weeks. The analysis group will be those still in follow-up and at risk after 16 weeks in Phase B. A log-rank test of significance for the difference in conditional survival functions will be prepared with zero weight over the first 16-week period because there is identical treatment for these two groups in this period. We do not expect sufficient numbers of participants in the third arm discontinued at end-Phase A for meaningful statistical comparisons. They will be followed until they reach an endpoint or end of the study to collect valuable information out to 32 weeks in Phase B.

DISCUSSION

Several design features distinguish this study from other antipsychotic discontinuation trials, help to address the limitations of published studies, and reflect an advantageous design for future discontinuation trials.

Identification of Target Symptoms and Systematic Open Treatment Prior to Discontinuation

The design ensures that only patients who can benefit from risperidone treatment enter the study. Selecting target symptoms specific to each patient addresses the diverse nature of behavioral complications in dementia and permits an individualized evaluation of treatment

response. The 16-week open treatment phase allows for clinically relevant adjustments in dose and assessment of tolerability, ensuring that adequate response is clearly established before randomization.

Response Required Prior to Randomization

Assessment of relapse is meaningful after response to open treatment is established. Only patients who meet response criteria in Phase A are eligible to be randomized in Phase B. This criterion represents an advantage over essentially all prior published studies that did not establish that the patient had responded to antipsychotic treatment before discontinuation was attempted.

Use of a Single Antipsychotic Medication

The design lends itself to the interpretation of risperidone's singular effects in open treatment followed by discontinuation. Several prior studies discontinued patients off a variety of antipsychotics,^{22,28} and in some instances benzodiazepines as well,²⁶ making it difficult to identify the likely risk of relapse for specific medications.

Two Clinically Relevant Time-Points for Discontinuation

The Phase B branch points are at 16 weeks and 32 weeks in Phase B. There are advantages to include two time-points for discontinuation, which is novel in antipsychotic discontinuation trials in dementia. The 16-week time-point is clinically relevant and consistent with the OBRA (Omnibus Budget Reconciliation Act) regulation requiring written physician justification to continue antipsychotics after 3 months. The 32-week time-point addresses the concern that if the study were restricted to discontinuation (continuation risperidone versus placebo) at a single time-point (16 weeks), if relapse on placebo is significantly greater than that on continuation risperidone, it raises the question of whether longer treatment decreases relapse risk. However, there are disadvantages to having this second time-point: 1) a slight reduction in power for the Phase B comparison for the first 16 weeks that now involve 102 patients randomized 2:1 risperidone versus placebo rather than 1:1 risperidone versus placebo and 2) likely inadequate power for the comparison from 16 to 32 weeks in Phase B. The clinical relevance of two time-points rather than one time-point for discontinuation weighed in the choice of study design.

Short-Term Versus Long-Term Antipsychotic Use Before Discontinuation

The initial open treatment phase for 16 weeks before randomization is relatively a short-term antipsychotic treatment. This is a clinically relevant time-point in nursing homes as well as outpatients. Furthermore, because symptoms of psychosis and agitation are known to fluctuate over time during the course of AD, it remains unclear whether patients need to be maintained on antipsychotic treatment for an extended period. Therefore, a discontinuation trial after relatively short-term open treatment is justified. The use of two time-points of study discontinuation for a total 48-week trial duration allows for an extended period to evaluate the risk of relapse.

Assessment of Several Affected Domains

As in recent trials of psychosis/agitation¹⁷ and depression⁴¹ in patients with AD, the assessment battery spans the symptoms of psychopathology, somatic and neurological side effects, cognition, function, and quality of life.

Assessing Relapse and Handling Dropouts

The assessment of relapse using strict, clinically relevant, operational criteria strengthens the design. The rigorous classification of type of dropout in this study to improve the statistical

analyses has been used in trials of cardiac disease and stroke,⁴² but hitherto has not been used in any trials of psychotropic medications in dementia.

Follow-Up of Early Dropouts in Phase B

Following recommended procedures in studies that adopt the intent-to-treat analytic approach, all early dropouts in Phase B will be followed until the end of the entire study period, whenever feasible.

CONCLUSION

These features strengthen the design and are important to consider when designing a study of antipsychotic discontinuation in patients with dementia. Given the warnings about antipsychotic use in patients with dementia, studies of this type are essential to optimize treatment and to minimize adverse outcomes with the goal of generating a strong foundation for evidence-based treatment strategies in dementia. Future studies may require similar, relatively complex, designs to determine the most judicious use of these medications and to best understand the precise duration of use that confers the greatest benefit to risk ratio.

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FIGURE 1.
Flow Sheet for Study

TABLE 1

Summary of Study Design (Clinical trials.gov identifier NCT00417482)

Objectives
To conduct an open treatment trial with risperidone in patients with AD who have target symptoms of psychosis or agitation of sufficient intensity to require treatment, after which responders are randomized to continuation medication or placebo to compare the likelihood of relapse and time to relapse.
Type of trial
Open clinical trial (Phase A) followed by a randomized clinical trial (Phase B)
Multicenter (8)
Masked (double-blind)
Phase B: 2:1 assignment ratio (risperidone:placebo) followed by 1:1:1 (risperidone:placebo:placebo)
Study sample (projected)
200 patients entering Phase A open treatment
110 responders to Phase A, of whom 102 patients are randomized in Phase B
Sites
New York State Psychiatric Institute/Columbia University: central coordinating site
Medical University of South Carolina
University of Iowa
VA Medical Center, Tuscaloosa, Alabama
VA Medical Center Brentwood, Los Angeles
Mount Sinai Medical Center, New York, NY
Global Research and Consulting, Buffalo, NY
Research Center for Clinical Studies, Inc, Norwalk, CT
Sample size and power calculations
Two-sided alpha = 0.05
Power = 96.6% for relapse rates, 75% on placebo, and 35% on risperidone, power = 90% for relapse rates, 70% on placebo and 35% on risperidone
Estimated 15% nonadherence (10% Phase A and 10% Phase B; Phase B comprises half the Phase A sample)
Treatments
Phase A: flexible dose risperidone 0.25 to 3 mg per day
Phase B: responders to risperidone are randomized, double-blind, to one of three arms in Phase B: 1) continuation risperidone for the next 32 weeks, 2) risperidone for the next 16 weeks followed by placebo for 16 weeks, or 3) placebo for the next 32 weeks.
Stratification
Stratification by three factors: site, presence or absence of psychosis, outpatient versus nursing home/assisted living
Masking
Treatment assignment masked to patients, caregivers, and all evaluators and raters at all sites
Adherence
If pill counts are $\geq 25\%$ above the prescribed level at any two visits within a phase, the patient is rated as nonadherent. Nonadherent patients who continue in the protocol are retained, and statistical analyses are conducted both including, and excluding, nonadherent patients.
Criterion for study treatment discontinuation
The patient exits the study if consent or assent is withdrawn or a major protocol violation precludes study continuation. Development of an intolerable adverse event or hospitalization may lead to study discontinuation or the patient may go on an interruption of therapy.
Study visits

In Phase A, assessments take place at study entry (0 weeks), 2, 4, 8, 12, and 16 weeks, and at the time of protocol exit for dropouts. In Phase B, assessments take place at 0 weeks (same as end-16 weeks in Phase A), and at 2, 4, 8, 16, 18, 20, 24, 28, and 32 weeks, and at the time-point of relapse or dropout in such participants.	
Outcomes	
Primary efficacy measure:	<i>NPI sum score of delusions, hallucinations, and agitation/aggression.</i>
Secondary efficacy measure:	CGI-C scored on target symptoms only.
Side-effect measures.	Somatic side effects: TESS; Extrapyrimalidal Signs: Simpson-Angus Scale; Tardive dyskinesia: AIMS.
Cognition:	30-item MMSE and modified ADAS-cog.
Quality of life:	PSMS.

TABLE 2

Inclusion/Exclusion Criteria

Inclusion Criteria	
1	Meets DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) criteria for dementia, either sex, age 50–95 years.
2	Meets NINCDS-ADRDA criteria for probable Alzheimer disease (McKhann et al, 1984).
3	Intellectual impairment present for at least 6 months.
4	Availability of informant who has had contact with the patient for an average of at least once every week during the 3 months prior to study entry.
5	Informed consent by patient and/or family member (or other informant) as per institutional review board procedures and local law.
6	Meets criteria for either 1) psychosis in AD as defined by the presence of a hallucination or delusion on the CUSPAD, and threshold cutoff scores on the NPI (score ≥ 4 on either delusions or hallucinations), or 2) criteria for behavioral dyscontrol as identified by a minimum NPI threshold cutoff score ≥ 4 on agitation/aggression.
7	For outpatients, Mini Mental Status Examination score ≥ 5 to ≤ 26 . For nursing home patients, MMSE score ≥ 2 to ≤ 26 .
8	Able to mobilize independently (if wheelchair-bound, the subject must be able to self-propel).
9	Negative on a stroke screening scale, or if positive, score of 0 on the NIH Stroke Scale.
10	Expected to complete the study (including all efficacy evaluations) and without major sensory impairment that would prevent participation in any aspect of the study.
Exclusion Criteria	
1	Meets <i>DSM-IV</i> criteria for any persistent major Axis I disorder predating onset of AD. Presence of disorders that remitted prior to onset of AD, e.g., major depression or panic disorder, is permitted.
2	Currently, or within the past year, meets <i>DSM-IV</i> criteria for substance abuse or dependence.
3	Dementia due to head trauma. Remote history of head trauma without cognitive sequelae is not exclusionary.
4	History of allergy or intolerance to risperidone.
5	Diffuse Lewy body disease by McKeith et al (1996) criteria.
6	History of seizure disorder, infectious encephalitis, Parkinson's disease, CNS neoplasm, tardive dyskinesia, stroke, transient ischemic attack or uncontrolled atrial fibrillation.
7	Untreated or incompletely treated hypothyroidism based on serum T4 and TSH at screening.
8	Active, unstable medical condition that requires active medication adjustment or surgery.
9	Currently at risk for suicide or homicide, or at risk for harm to themselves or others as a result of randomization to placebo.
10	Use of monoamine oxidase inhibitors and be unable to undergo 3-week washout. Patients also may not take monoamine oxidase inhibitors for 2 weeks after completing the study. Treatment with a) depot antipsychotic within 2 weeks of the screening visit; b) any other psychotropic medications within a period of less than five times the half life of the drug (if the five half lives period is longer than the 1-week planned "wash out") and is unable to tolerate 1-week washout. The primary approach is to wash out all antidepressant medications. However, if the patient is on a stable dose of antidepressant medication of any type for at least 3 months, the patient can be included if the antidepressant dose will not be changed during the study. Otherwise, patients should be free of psychotropic medication (or able to tolerate washout) for at least 1 week prior to study entry. Lorazepam (or benzodiazepine equivalent) 0.25 to 0.5 mg p.r.n. up to a maximum of 1.5 mg daily and 5 mg weekly will not require washout and will be permitted as rescue medication during the trial.
11	Need for concomitant psychotropic medications, other than zolpidem, zaleplon, or trazodone for insomnia, or antidepressants as noted under item 10 above, or ECT.

TABLE 3

Schedule of Assessments During Phase A

	Screen	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16/Early Termination
Visit	1	2	3	4	5	6	7
Informed consent	X						
Inclusion/exclusion criteria	X						
Medical history/demography	X						
Psychiatric history	X						
Physical/neuro examination		X			X		X
CUSPAD	X						
NPI	X	X	X	X	X	X	X
Target symptoms		X	X	X	X	X	X
CGI/CGI-C		X	X	X	X	X	X
AIMS		X	X	X	X	X	X
SAS		X	X	X	X	X	X
ECG	X						X
Labs	X						X
Risperidone level							X
Vital signs	X	X	X	X	X	X	X
MMSE	X						
PSMS		X			X		X
ADRRQL		X			X		X
TESS		X	X	X	X	X	X
Dispense meds		X	X	X	X	X	X
Monitor adherence			X	X	X	X	X

Note. Screening and Baseline can occur on the same day or separate days. An identical schedule of assessments takes place in the first 16 weeks of Phase B and the final 16 weeks of Phase B.

TABLE 4

Sample Power Analysis Based on Relapse Rates in the First 16 Weeks of Phase B.

	Relapse Rate on Risperidone (N = 68)					
	0.25	0.30	0.35	0.40	0.45	
Relapse Rate on Placebo (N = 34)	0.80	0.999	0.998	0.993	0.971	0.918
	0.75	0.999	0.992	0.966	0.905	0.792
	0.70	0.992	0.965	0.897	0.776	0.608
	0.65	0.966	0.895	0.767	0.593	0.404
	0.60	0.901	0.768	0.587	0.395	0.230