Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE): Alzheimer’s Disease Trial

by Lon S. Schneider, M. Saleem Ismail, Karen Dagerman, Sonia Davis, Jason Olin, Dennis McManus, Eric Pfeiffer, J. Michael Ryan, David L. Sultzer, and Pierre N. Tariot*

Abstract

This article describes the development of the protocol for the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Alzheimer’s disease trial, which was developed in collaboration with the National Institute of Mental Health to assess the effectiveness of atypical antipsychotics for psychosis and/or agitation occurring in outpatients with Alzheimer’s disease. The article provides a detailed description of the methodology used in the trial as well as the clinical outcomes and effectiveness measures incorporated into it, discussing the most salient issues encountered in developing the design of the trial, as well as the unique features of the trial.

Keywords: Alzheimer’s disease, atypical antipsychotic, psychosis, dementia, effectiveness.


This article is intended to serve as an archival published reference describing a protocol to assess the effectiveness of atypical antipsychotics for psychosis and agitation occurring in outpatients with Alzheimer’s disease (AD). The protocol was developed in response to a request from the National Institute of Mental Health (NIMH) (RFP 99–DS–0001) to examine the effectiveness of atypical antipsychotics in patients with psychosis associated with AD. A shorter prior publication also summarizes this study (Schneider et al. 2001); this report expands upon that prior article. The current report also incorporates some of the amendments to the original protocol dated September 21, 2001.

Rationale

Psychotic symptoms are common in AD throughout its clinical course (e.g., Schneider et al. 1990; Tariot et al. 1995; Devanand et al. 1997; Jeste and Finkel 2000), but essential questions remain about the nature of “psychosis” in these patients, in part because cognitive impairment limits self-report of symptoms and hence the ability to identify typical features of psychosis. In many cases, the only manifestation of psychosis is a change in behavior, such as the common co-occurrence of agitation. There are also neurobiological correlates of delusions and hallucinations, suggesting that some of these phenomena are a direct result of the disease process (e.g., Zubenko et al. 1991; Lopez et al. 1996; Sweet et al. 1997). The available evidence indicates that up to one-half of patients with AD may develop psychosis and/or agitation at some point during their illness (Paulsen et al. 2000).

There are numerous significant and morbid consequences of psychosis in dementia. Hallucinations or delusions may cause subjective distress in patients and adverse effects on caregivers. Patients under the influence of delusions or hallucinations may be disruptive, troubled, or agitated, responding to internal stimuli rather than the environment. This may lead to unsafe and violent situations where patients act on their delusions or hallucinations. These patients are at risk for being overmedicated or restrained. Those living at home or in assisted living facilities are at increased risk for institutionalization. Indeed, behavioral disruption is among the most common immediate causes for nursing home placement of dementia patients (Mittelman et al. 1996). Patients with delusions or hallucinations decline at an increased rate and have earlier nursing home placement and death (Chui et al. 1994; Stern et al. 1996). Caregivers of such patients with psychosis and dementia can experience considerable adversity, including the physical demands of constantly monitoring the patient, the emotional stress of caring for a loved one who is “out of touch,” physical illness, and depression.

Last, psychotic and/or agitated symptoms in patients with dementia have significant consequences for the health...
Design Considerations

Selecting the Setting. A major goal in the treatment of AD is to prolong the time until nursing home placement is needed. Psychosis and behavioral disruption are often proximal or immediate antecedents to placement and are potentially amenable to treatment. Ninety percent of the cost of care for AD is for nursing care, so that efforts at maintaining a person in the community will have a greater impact on community, family, quality of life, and economics than intervention in the nursing home. An effectiveness trial in nursing home patients would have only limited impact, because staffing costs are fixed, patients are severely demented and have limited expected longevity, and only limited outcomes are possible. Consequently, we decided the trial would focus on patients residing in the community.

Selecting the Medication. Conventional antipsychotics such as haloperidol have been used to manage aggression or agitation as well as to treat hallucinations and delusions (Schneider et al. 1990). The well-documented short- and long-term toxicity associated with use of these medications in patients with dementia—including central and peripheral anticholinergic effects, cardiovascular problems, and numerous forms of motor toxicity such as tardive dyskinesia (TD) (Jeste et al. 1995, 1999b; Wunder et al. 1998)—have led to a general consensus that conventional antipsychotics have been overused and misused in managing AD (Thapa et al. 1994).

Our patients need better medications. The newer atypical antipsychotics promise a lower risk for most side effects seen with conventional agents, such as TD (Jeste et al. 1999a). They are used commonly in patients with AD, but in fact the full impact of their use remains to be fully illuminated. We therefore decided to focus on the atypical antipsychotics. Because there are no randomized trials of these agents longer than 12 weeks, it is possible that some of the efficacy observed in prior trials was due to spontaneous remission in patients treated with placebo throughout the trial. A brief trial of this nature represents an artificial clinical situation that does not provide adequate information about treatment effectiveness. To address this issue, we planned a lengthy trial and included an early placebo arm. Finally, because the use of a non-atypical comparator would help inform effectiveness outcomes, we included a citalopram treatment arm in view of emerging evidence suggestive of its efficacy for agitation in dementia as well as relative safety and tolerability (Nyth and Gottfries 1990; Nyth et al. 1992; Pollock et al. 2002).

Overview of Design. With these rationales in mind, we designed a trial to do the following:

1. Compare the acute efficacy and effectiveness of risperidone, olanzapine, and quetiapine using sequential treatment algorithms in outpatients with dementia complicated by agitation and/or psychosis.
2. Assess the relative effectiveness of these antipsychotics, as well as the nonantipsychotic comparator citalopram, in maintaining clinical improvement up to 36 weeks.

Hypotheses. There are two primary hypotheses to be tested for the treatment groups defined by the initial randomization:

1. The three atypical antipsychotic treatment groups, taken together, will be superior to the placebo group in terms of all-cause treatment discontinuation.
2. The three antipsychotic treatment groups will be equivalent to each other with respect to response at 12 weeks, regardless of subsequent randomizations.

Other hypotheses include the following:

1. There will be no differences among the three atypical antipsychotic treatments in side effects, tolerability, and discontinuations for the initial phase.
2. There will be no differences in costs or service utilization between the three atypical antipsychotic medications.
3. There will be no differences in efficacy between the treatment algorithms (e.g., those treated with two successive atypical antipsychotics will have
equivalent outcomes regardless of the particular medications used or their order of use).
4. Each atypical antipsychotic individually will be superior to placebo in acute phase efficacy over 2 weeks.
5. Patients with agitation will show lower response rates to atypicals than those with psychosis.
6. In phase 2, for patients originally randomized to placebo, citalopram will be equivalent to the three atypical antipsychotic groups combined with respect to overall response. (Patients with agitation may do better with citalopram, while those with psychosis may do better on a second atypical.)
7. Overall, patients who improve on any drug will have lower health services utilization than those who do not show improvement.
8. Quality of life will be better in patients whose symptoms improve.
9. Caregivers of subjects who show improvement will also show improvement.

Other hypotheses relating to effectiveness that are listed in the protocol (www.catie.unc.edu) address tolerability, discontinuations, costs, service utilization, and treatment algorithms.

Methods

Subject Selection (Table 1). Subjects are outpatients with a clinical diagnosis of dementia of the Alzheimer's type (DSM-IV) or probable AD (McKhann et al. 1984). Diagnoses of AD will be made clinically as they would be ordinarily in the community. Subjects must be able to ambulate independently or with a cane or four-point walker, or with minimal assistance, but must not be bed- or wheelchair-bound. A subject must be experiencing delusions, hallucinations, or agitation/aggression severe enough to (1) disrupt his or her functioning, and (2) justify medication treatment in the opinion of the investigator. The delusions, hallucinations, or agitation/aggression must have occurred nearly every day of the previous week, or at least intermittently over 4 weeks. The symptomaticatology must be further manifested by a score of “moderate” or greater on the Brief Psychiatric Rating Scale (Beller and Overall 1984; Overall and Beller 1984) items of conceptual disorganization, suspiciousness, or hallucinatory behavior, or by a frequency score of “often” or more frequently and a severity score of “moderate” or more on any Neuropsychiatric Inventory (Cummings et al. 1994) item from the delusion or hallucination, agitation, or aberrant motor behavior subscales, during the previous week. The allowable cognitive severity range of Mini-

Mental State Exam 5 to 26 inclusive (Folstein et al. 1975) is intended to be as broad as possible as well as sufficient to enhance the likelihood of rendering an accurate dementia diagnosis, also permitting sufficient residual cognitive function to assess for delusions and hallucinations.

Recruitment sites. Subjects are recruited from diverse study sites and may be new to the clinical site or may have been longstanding patients. Residents of assisted living facilities are candidates for this study as well. Although the enrollees will ultimately consist of samples of convenience, we expect to enhance generalizability by choosing a variety of clinical programs and requiring that potential subjects be patients of those programs. Similarly, the use of diverse clinical sites and programs will help ensure adequate representation from ethnic minority groups.

Study Design. This protocol is fundamentally a randomized-treatment assignment, parallel group, and double-blinded treatment comparing risperidone, olanzapine, quetiapine, citalopram, and placebo in AD outpatients with delusions, hallucinations, or agitation severe enough to warrant the use of antipsychotic medications. There are four phases (Figure 1).

Phase 1. In the initial treatment phase (phase 1), subjects are randomized to treatment with an atypical antipsychotic or placebo. This phase is no shorter than 2 weeks and can be as long as 36 weeks, the length determined by the investigator's assessment of adequacy of treatment intensity and effect. The investigator can advance the patient to the next treatment phase as early as week 12 whether the current medication is sufficiently optimal or whether it would be more advantageous to employ another randomized medication. If the original medication is continued at that point, the patient remains in phase 1, but if a new medication is chosen, the subject proceeds to phase 2. The intent in phase 1 is to initiate, adjust, and possibly maintain study medication as the subject responds, mirroring usual practice for this clinical problem.

Phase 2. Phase 2 commences if the patient is randomized to treatment with a second, different medication—that is, olanzapine, quetiapine, risperidone, or citalopram. Patients cannot be randomized to placebo in this phase. This phase can begin as early as week 2, should be no shorter than 2 weeks, and can be as long as 34 weeks. After the initial 2 weeks in phase 2, the investigator can advance the patient to the next phase because of lack of efficacy or tolerability. After the patient has received the phase 2 study drug for approximately the next 12 weeks, the investigator decides whether the cur-
Table 1. Inclusion and exclusion criteria

Inclusion criteria

- Patient must have clinical diagnosis of dementia of the Alzheimer's type (DSM-IV) or probable AD (McKhann et al. 1984).
- Patient must be an outpatient living at home, or in residential care or assisted living (not in a nursing home).
- Patient must be ambulatory—able to ambulate independently or with a cane or four-point walker, or with minimal assistance, but not bed- or wheelchair-bound.
- Patient must have Mini-Mental State Exam Scores between 5 and 26, inclusive.
- Patient must have delusions, hallucinations, or agitation/aggression severe enough to disrupt the patient's functioning and severe enough, in the opinion of the investigator, to justify medication treatment.
- The delusions, hallucinations, or agitation/aggression must have occurred nearly every day of the previous week, or at least intermittently over 4 weeks.
- The symptomatology must be further manifested by a score of "moderate" or greater on the Brief Psychiatric Rating Scale conceptual disorganization, suspiciousness, or hallucinatory behavior item, or by a frequency score of "often" or more frequently and a severity score of "moderate" or more on any Neuropsychiatric Inventory item from the delusion or hallucination, agitation, or aberrant motor behavior subscales, during the previous week.
- Onset of the psychosis or agitation/aggression must have been after the onset of cognitive and functional signs or symptoms of dementia.
- Patient taking antipsychotic medications in 2 weeks prior to randomization can be included if discontinuation of the medication is clinically warranted.
- Patient must have an informant who lives with the patient or visits the patient at least 8 hours per week over 3 to 4 days per week.
- There must be informed consent from the patient and his or her legal representative, or assent from the patient and informed consent from the responsible relative or legal representative.
- The results of laboratory screening studies must not be inconsistent with psychosis of Alzheimer's disease or agitation attributable to a medical cause. (No specific laboratory screening studies are required with respect to diagnosis and assessment.)

Exclusion criteria

- Patient must not currently be receiving and benefiting from psychotropic medication treatment.
- Patient must not fulfill criteria for schizophrenia, schizoaffective disorder, delusional disorder, or mood disorder with psychotic features.
- Patient must not fulfill criteria for delirium.
- Patient must not have a severe or unstable medical illness that requires active treatment.
- Patient must not be in need of psychiatric admission in judgment of study site or local physicians, be acutely suicidal, or have persistent suicidal intent.
- Patient must not have had previous or current treatment with any two of the three atypical antipsychotic study medications.
- Patient must not currently be receiving antidepressants or anticonvulsants as mood stabilizers.
- Patient must not be planning to start a cholinesterase inhibitor or antidepressant medication during the subsequent 24 weeks (may be currently receiving a cholinesterase inhibitor if on a stable dose for at least 4 weeks).
- Patient must not have hypersensitivity or an absolute contraindication to any of the study medications.
rent medication is sufficiently optimal or whether it would be more advantageous to attempt the next random-
ized medication. As long as the second medication is con-
tinued, the subject remains in phase 2. If a new random-
ized medication is thought to be potentially more benefi-
cial, the subject proceeds to phase 3.

**Phase 3.** In phase 3, the patient is randomized to open treatment with one of the study medications not previously received—that is, olanzapine, quetiapine, risperidone, or citalopram. That is, patients failing to respond to the second medication can be switched to a third open label treatment whose identity is revealed to the investigator. Phase 3 should be no shorter than 2 weeks, may start at any time after week 4, and is no longer than 32 weeks. During phase 3, patients are maintained on their treatments openly and managed clinically until week 36.

**Phase 4.** If the investigator determines that the subject’s response to the randomized open label medication is not sufficiently optimal, then after the first 2 weeks in phase 3, the investigator can prescribe another medication (of the investigator’s choice). In other words, the investigator can prescribe any study or nonstudy medication as clinically indicated. If this occurs, the subject is no longer taking randomized study medication and begins phase 4, the “open choice” phase. The open choice phase can be entered at any time from week 2 through week 36, and directly from any of the three phases. There are three paths to the open choice phase:

- Withdrawal from phase 1 or phase 2 if the subject or surrogate decision maker declines to proceed to the next randomized phase, permitting the investigator to prescribe an alternative medication.
- Withdrawal from phase 3.
- Withdrawal from any of the three previous phases if, in the investigator’s opinion, antipsychotic medication is no longer required.

The investigator may switch a patient to a new phase at any time throughout the 36-week study, but the general intent is to maintain treatment with each randomized medication for a minimum of 2 weeks, while adjusting dosage. Patients not taking study medications or those who have been prescribed medications within the open choice phase are considered enrolled for the 36-week period and need assessments as defined in the study protocol. Patients are in only one phase at a time and are always in one of the four phases described above during these 36 weeks.

**Treatment Group Assignments**

**Phase 1.** Subjects in phase 1 are randomized to treatment with risperidone, olanzapine, quetiapine, or placebo in a 1:1:1:1 allocation ratio. The investigator has a choice of two capsule strengths: risperidone 0.5 mg, 1.0 mg; olanzapine: 2.5 mg, 5.0 mg; quetiapine 25 mg, 50 mg; or placebo. Placebo treatment occurs in only phase 1. The daily medication dose is adjusted upward or downward by the investigator until acceptable clinical response is achieved or the investigator concludes that the phase 1 treatment is ineffective, at which point the treatment is switched as described above. Patients who initially respond but then relapse are typically treated with the randomized alternative treatment, thus beginning phase 2, except for the rare instance where the decision is made to advance to open choice treatment (phase 4).

**Phase 2.** If the subject had initially been assigned to receive placebo treatment in phase 1, then phase 2 double-blind treatment assignments occur in 1:1:1:3 allocation ratios to one of the four medications that the subject has not received yet, ensuring that 50 percent of patients in this arm receive citalopram. If the subject had initially been assigned to receive treatment with an antipsychotic, then phase 2 double-blind treatment assignments occur in 3:3:2 allocation ratios so that patients have a 75 percent chance of receiving one of the two antipsychotic medications that they have not received and a 25 percent chance of receiving citalopram. As in phase 1, the investigator has a choice of two dosing strengths (now including citalopram at 10 mg or 20 mg).

**Phase 3.** Phase 3 assignments are randomized in equal allocation ratios to one of the two (or three, if the subject initially received placebo in phase 1) remaining medications that the subjects have not received. Unlike in the preceding phases, the medication is administered in an open fashion.

**Phase 4.** During this open choice phase of the study, the investigator has the option of treating the subject with any psychotropic and at any dose deemed appropriate.

**Treatment Algorithms.** An important aspect of the algorithms is that treatment duration may vary considerably among patients, even though the order of medications may be the same. For example, one patient may be switched from risperidone to olanzapine at 2 weeks, and then 2 weeks later be switched to quetiapine. Another may be maintained on risperidone for 12 weeks, then switched to olanzapine for an additional 12 weeks, prior to being switched to quetiapine. As such, both the order and the timing of switches will be taken into account in the effectiveness analysis.

**Medication Dosages.** The pharmaceutical manufacturers have provided medication tablets and capsules. Medication has been prepared into identically appearing “lower strength” capsules containing risperidone 0.5 mg,
olanzapine 2.5 mg, quetiapine 25 mg, citalopram 10 mg, or placebo, or “higher strength” capsules containing 1 mg, 5 mg, 50 mg, 20 mg, or placebo, respectively, in order to preserve the blind. These dosages were chosen because they are available on the market (except for quetiapine 50 mg, which is formulated into one capsule) and the closest we could determine for equivalency based on the risperidone and olanzapine nursing home studies, the most extensive clinical trials of these agents in dementia thus far. We acknowledge that estimates of effective and equivalent quetiapine dosages are not as well established as those for the other antipsychotics in the population of interest. The best evidence comes from a year-long open trial in the elderly, in which the median dose was 137.5 mg/day (Tariot et al. 2000). Citalopram doses were selected based on those used in previous trials in the elderly in general and patients with dementia specifically (Nyth and Gottfries 1990; Nyth et al. 1992; Pollock et al. 2002).

Concomitant Medications. The following medications are allowed on an “as needed” basis for treating difficult behaviors: (1) an increased dose of study medication; (2) benzodiazepines delivered orally or, in extreme circumstances, parenterally for acute behavioral agitation; and (3) haloperidol or parenteral haloperidol HCl (not decanoate) for emergencies when the study clinician believes that an antipsychotic is the preferred emergency treatment.

Because this effectiveness study attempts to represent ordinary community-dwelling patients and clinical practice, the use of a wide variety of other medications is permissible. Cholinesterase inhibitors are allowed if the dose has been stable for the previous 4 weeks, there is no intention to change dosage or discontinue medication, and the clinician believes that these medications are not contributing to the patient’s psychosis or agitation. To make the acute effectiveness comparison as straightforward as possible, anticonvulsants (as mood stabilizers), antidepressants (except for subjects randomized to citalopram and trazodone on a p.r.n. basis for sleep), and regularly prescribed benzodiazepines are not allowed during the first two randomized phases. Anticonvulsants used to treat seizure disorders are allowed. During the third phase after randomized open label treatment assignment, it is recognized that some clinicians may wish to add a second medication in the hopes of better treating the patient. This is permissible within the protocol.

Protocol Noncompliance. All randomized subjects are considered “in the study” and followed at the predetermined intervals over 36 weeks, regardless of whether they receive study medication. Only patients and caregivers who withdraw their consent are considered “dropouts.” If patients or caregivers/informants cannot come to the study site, the site will attempt home visits to obtain study-related and clinical information.
Subject Retention. The investigators have been allowed significant discretion in individualizing dosage and making adjustments to and switching medications. Even if an investigator or patient cannot fully comply or requests open treatment, the intent is to continue to follow patients and perform assessments, making home visits if necessary. This method allows the acquisition of important (and nearly complete) utilization and services data, and thus reduces the biases and threats to validity inherent in this study.

Psychosocial Interventions. In an effort to model good clinical practice, optimize patient care, and reduce variability due to nonpharmacological factors, all patients and caregivers/informants receive basic information and education about AD, its clinical course, cognitive and behavioral problems, symptomatic behaviors, management approaches, and expectations for medication effects. It has been shown that even a simple psychosocial intervention may prolong patients' survival in the community (Mittelman et al. 1996). The New York University model was selected for implementation because it is simple to apply, is of low intensity, has established validity and efficacy, and closely reflects the kind of counseling that might be expected in the community (Mittelman et al. 1996). Caregivers receive two voluntary counseling sessions in the first 18 weeks, after which they may speak with a counselor on an as-needed basis.

Clinical Outcomes and Effectiveness Measures (Table 2). Efficacy measures are those related to the direct, expected effects of the medication and include the investigator's "global" assessment of clinical response, systematic assessment of psychotic signs and symptoms through interview examination of both subjects and informants, and other clinical neuropsychiatric findings. Safety and tolerability measures are those medical or behavioral signs or symptoms that occur after randomization as a result of using one of the medications. The effectiveness-related outcomes help describe the aspects associated with treatment, such as its acceptability, effects on quality of life, effects on other activities, and services utilization.

Efficacy.
- Clinical response based on a global assessment
- Changes in frequency or severity of signs and symptoms
- Subject (interview based)
- Informant (interview based)
- Clinically significant endpoints (e.g., nursing home placement, death, serious comorbid illness, change in medication, significant cognitive worsening, episodes of psychiatric hospitalization, disabling extrapyramidal side effects, falls, gait difficulties)

Safety.
- Treatment-emergent effects
- Treatment-emergent effects that are of particular concern when they occur in the elderly: falls, syncope, fractures, anorexia, weight changes
- "Serious adverse effects"—as defined in U.S. Food and Drug Administration regulations
- Adverse events particularly associated with the medications, as determined from the drug monographs

Process and effectiveness-related outcomes.
- Compliance, medication and plasma levels, and treatment assessment
- Concomitant or treatment-emergent medical illnesses, changes in medical burden

Economic and services utilization outcomes.
- Services utilization, direct and indirect costs
- Cost-benefit, cost-effectiveness, and quality-adjusted life years (QALYs)

Caregiving indexes.
- Depression, caregiver burden, caregiver activity

The specific outcome measures are listed in table 3.

Cognitive assessments (tables 2 and 3). A cognitive advisory group was selected in concert with NIMH and the external scientific advisory board to ensure consensus in the selection of tests. This issue is of particular importance given that independent investigators may desire access to the neurocognitive data base in the future, and that the choice of tests is often controversial. The rationale for and limitations of these tests are described further in the protocol (www.catie.unc.edu).

Medication adherence—plasma levels. Because of the wide interindividual variation due to aging, genetics, or interacting medications, plasma-level monitoring may provide more accurate information about dosage groups or at least explain outlier responses.

Health services and cost-effectiveness. The Service Use and Resources Form—Alzheimer's disease (SURF-AD) is a multi-item, caregiver-completed report form that comprehensively documents use of health services, including the number and duration of contacts and the specific agencies from which services were obtained. It also documents nonhealth resource consumption, such as public support payments, involvement with the criminal justice system, and productivity (a negative cost).

The Health Utilities Index (Feeny et al. 1996) is a general health-related quality of life measure that documents health-related impairment. It is standardized to measures of preference-based utilities and thus assesses

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Table 2. Schedule of assessments

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<tr>
<th>Assessment</th>
<th>Visit 1</th>
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<td>AIMS (Guy 1976)/Barnes (Barnes 1989)/Simpson-Angus (Tracy et al. 1997)</td>
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<td>Neurocognitive battery, MMSE, ADAS</td>
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<td>ADCS Activities of Daily Living Inventory (Galasko et al. 1997)</td>
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<td>Dependence Scale (Stern 1994)</td>
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### Alzheimer's Disease Trial

**Schizophrenia Bulletin, Vol. 29, No. 1, 2003**

#### Data Acquisition, Statistical Methods, and Analytic Plan

**Health States in QALYs, the cardinal measure of health outcomes.**

To evaluate the possible effects on weight gain and glucose and lipid metabolism, waist-hip ratio and body mass indexes are obtained.

**Safety and Tolerability.** These assessments include physical examinations, vital signs, laboratory evaluations, electrocardiograms, monitoring of concurrent medication records, and maintenance of concurrent medication records.

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<th>Visit 6</th>
<th>Visit 7</th>
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**Note.**—ADAS = Alzheimer's Disease Assessment Scale; AIMS = Abnormal Involuntary Movement Scale; ADCS = Alzheimer's Disease Cooperative Study; CGIC = Clinical Global Impression of Change; MMSE = Mini-Mental State Exam; NYU = New York University; SURF-AD = Service Use and Resources Form—Alzheimer's disease.
Table 3. Outcome instruments, scales and assessments

CGIC

- ADCS-CGIC

Measures used to assess psychosis

- NPI (delusion and hallucination scales)
- BPRS (conceptual disorganization and unusual thought content items)
- Target symptoms

Measures used to assess agitation (in the absence of psychosis)

- NPI (agitation and aberrant motor behavior scales)
- BPRS

Functional assessments

- ADCS-ADL Inventory
- Dependence Scale (Stern 1994; rates degree of dependence or assistance needed by a patient; was sensitive to medication effects in a previous study [Sano et al. 1997] and as a predictor of nursing home placement [Stern et al. 1997])

Quality of life

- Alzheimer's Disease Related Quality of Life (addresses concepts and domains most important to family caregivers and clinicians who provide care to people with Alzheimer's disease and to detect change in health-related quality of life over time; as a proxy-based measure of health-related quality of life, is administered to caregivers, who are asked to identify recently observed behaviors that reflect aspects of that person's health-related quality of life)

Cognitive assessments

- Mini-Mental State Exam
- ADAS-Cog (Mohs et al. 2001)
- Neurocognitive battery
  - Category Instances (verbal fluency)
  - Trailmaking A
  - Finger Tapping (Reitan 1969) (motor function)
  - Letter Cancellation or Either of Two Numbers Cancellation Test (Mohs et al. 2001) (attention)
  - Dot Test of Visuospatial Working Memory

Side effects/safety

- AIMS
- Barnes Akathisia Scale
- Simpson-Angus Scale

Health care

- Health Utilities Index
- Service Utilization and Resources Form-Alzheimer's disease
- General Medical Health Rating

Caregiver assessments/interventions

- Beck Depression Inventory
- Burden Interview
- Caregiver Activity Survey
- Cornell Scale for Depression in Dementia
- NYU Caregiver Intervention

Note.—ADCS = Alzheimer's Disease Cooperative Study; ADL = Activities of Daily Living; AIMS = Abnormal Involuntary Movement Scale; BPRS = Brief Psychiatric Rating Scale; CGIC = Clinical Global Impression of Change; NPI = Neuropsychiatric Inventory.
these parameters with a goal of generating important new clinical hypotheses. Statistical significance of all exploratory analyses will be evaluated relative to \( p = 0.05 \), with no adjustment for multiple comparisons. Initial analyses will be based on the phase 1 antipsychotic treatment assignment in an intent-to-treat fashion. Additional analyses will adjust for subsequent rerandomizations and other covariates.

Time to all-cause treatment discontinuation and time to permanent nursing home placement will be analyzed via survival methods. Equivalence criteria of [0.8, 1.25] will be evaluated relative to 95 percent CIs for the estimated Cox proportional hazards ratio. Continuous outcomes will be assessed via linear models. In addition, repeated measures analyses will be conducted to further explore treatment differences during the course of the study via generalized estimating equation methods (Diggle et al. 1994). Citalopram will be compared to the combined phase 2 atypical antipsychotics using similar methods.

**Health Services and Effectiveness Analyses.** Because atypical antipsychotic medications are 15 to 20 times more expensive than conventional medications, a central policy question is, Is the expenditure on these agents justified by either (1) the savings the medication generates in other health care or non–health care costs, or (2) the improvements it yields in the well-being of patients, their families, and/or the communities in which they live? Cost analyses will be conducted from the perspective of society and will include the cost of medications and all other health care costs. Secondary analyses will be used to identify distributional effects across different payers.

Costs will be measured as the product of the units of service times the cost per unit and will be assessed through the SURF. We will rely on administrative cost data from Medicare and from the Market Scan Data Base to generate sets of unit costs for a series of sensitivity analyses using different unit cost estimates. Medication costs will be based on the specific dosing of all agents to each patient.

Effectiveness will be evaluated in two ways. First, we will use the utilities generated by the Health Utilities Index, which will be measured in QALYs. Second, we will combine other quality of life and symptom measures and scale them to generate disease-specific QALYs using methods developed elsewhere (Rosenheck et al. 1998). Sensitivity analysis will be conducted using both measures of effectiveness.

Initially, costs and effectiveness measures will be examined separately. If total costs are lower for atypical antipsychotics (i.e., the increased medication costs are offset by reduced service use) and outcomes are superior, then they will emerge as dominant choices and further analysis will not be necessary. If both costs and benefits increase with atypical antipsychotics, further analysis will be undertaken using cost-effectiveness acceptability curves (Van Hout et al. 1994). These curves take into consideration various estimates of the monetary value of a QALY and estimate the probability of achieving various cost-effectiveness ratios.

**Sample size.** The phase 1 sample size of 150 patients receiving placebo and 300 patients randomized to receive one of the three atypical antipsychotic treatments combined provides 97 percent power to detect a 20 percent difference in all-cause treatment discontinuation rate. Within the phase 1 atypical treatment groups, 100 patients per group provide 92 percent power to detect equivalence in response rate between any pair of treatments, assuming a response rate of 66 percent and an equivalence limit of \pm 20\% percent. There is 85 percent power to detect equivalence between the three atypical treatments in a pairwise fashion. In phase 2, we expect that approximately 100 patients from the phase 1 placebo group will be rerandomized to either citalopram \((n = 50)\) or one of the three atypical antipsychotics \((n = 50)\). There is 78 percent power to show equivalence in response rates between citalopram and the antipsychotics, under the same assumptions.

**Human Subjects Considerations.** A comprehensive plan was developed to ensure that all institutional, National Institutes of Health, and Federal regulations concerning informed consent are fulfilled. The plan includes careful assessment of risks and benefits, review by the CATIE protocol and ethics committees, and review by the NIMH Data Safety and Monitoring Board.

**Discussion**

An important goal of this trial is to model clinical practice so that outcomes can be translated into clinical benefits for "real world" patients who currently receive these treatments in the community. In a typical clinical practice, significant delusions, hallucinations, and agitation are treated with individualized dosing of medication. Once patients have a significant response, they are usually maintained on medication for a reasonable period (many experts recommend 2–4 months [Alexopoulos et al. 1998]). In this trial, several treatment periods can be conceptualized to reflect typical clinical practice where improvement is expected within days to 2 weeks at an appropriate dose. The design allows the study physicians to adjust, switch, or discontinue medications as they might do in practice. Subjects who do not respond to their originally assigned medication
may be randomly switched to one of the other medications and included in the analyses of the treatment algorithms. The sequential "hybrid" design combines elements of randomized efficacy trials with effectiveness trials to assess the comparative outcomes of risperidone, olanzapine, and quetiapine, and, at a second level, the likelihood of response to a subsequent antipsychotic or to citalopram in patients who did not respond to initial treatment. Its design takes advantage of the uncertainty principle and the concept of clinical equipoise in assessing the nonsuperiority of the intervention algorithms. We believe that the design will yield results that can inform clinical practice.

The trial encourages active participation by clinicians to constantly monitor clinical response and to adjust the dose or change medications because of lack of response or intolerable side effects. In this regard, it is important to note that initial dosage range in protocol is suggested as a guide and there is no maximum dose. The effective doses of risperidone and olanzapine conceptualized from recent studies of older nursing home patients may provide some guidance. On the other hand, effective doses of quetiapine and citalopram are not as well demonstrated because of lack of satisfactory placebo-controlled evidence. Physicians in this trial will individualize dosages of study medications on the basis of clinical response, although they will remain blind to the actual medications assigned.

During this trial, all randomized subjects are followed for 36 weeks, whether or not they comply with the protocol. If they withdraw consent for study medication treatment, they are asked to agree to evaluation at protocol-designated intervals, providing further followup and outcomes information, and allowing formal intent-to-treat analyses. This approach enhances the value and validity of the data. In addition, information obtained about subjects' various clinical courses can generate further hypotheses and serve as a basis for ancillary clinical investigations. The decision not to require a longer period of placebo treatment during this trial was based on the concern that a prolonged mandatory period of placebo treatment might be unacceptable to treating physicians or families and cause unnecessary discomfort to patients. We felt that it was necessary to include at least some exposure to placebo, however. Initial placebo treatment provides assay sensitivity, in that any improvements noted after treatment with the atypical antipsychotics are directly comparable to any improvements with placebo treatment. In addition, it was essential that there be an initial randomization possibility to placebo treatment in order to assess any significant improvement in psychosis or agitation with general psychosocial management. The risk of placebo exposure for patients who are not responding is limited, as study physicians are able to adjust and change medications in this trial, based on their clinical assessments.

There are several reasons for not using haloperidol as a comparator in this trial. Despite being efficacious for behavioral disruption in dementia, haloperidol has a low therapeutic index. The known efficacious doses of haloperidol of 2 to 3 mg/day are at the levels that cause toxicity (Devanand et al. 1998). The risk of TD with haloperidol use in elderly patients is well known, with as many as 25 to 30 percent developing TD within 1 year (Jeste et al. 1995; Woerner et al. 1998). A minority of dementia patients also show exquisite sensitivity to haloperidol, developing muscular rigidity or temperature dysregulation. For these reasons, haloperidol was not considered a "best practice" with regard to antipsychotic prescription for patients with dementia. Further, the use of haloperidol might not have been acceptable to investigators, and many indicated that they would not participate in a long-term study that included a haloperidol arm. This phenomenon would have hampered recruitment, and the sample would have been less representative of patients in general. The option of using a different conventional antipsychotic, such as thioridazine or perphenazine, would not have been useful either, because of a paucity of data regarding risks and benefits, because of concerns about safety, and because so few physicians prescribe these other antipsychotics that results would not be meaningful.

The results from the flexible dose clinical trial in which risperidone was compared to haloperidol and placebo are notable. Haloperidol was found to be comparable in efficacy to risperidone with respect to the primary endpoint, while side effects in the haloperidol group were only somewhat greater than in the risperidone group (De Deyn et al. 1999). Secondary measures of behavior indicated superior efficacy of risperidone. In the aggregate, however, we concluded that the available data point toward superior tolerability of atypicals compared with haloperidol in this patient population, a conclusion that finally determined key aspects of the trial design.

While the primary comparison at the beginning of this trial is among antipsychotics and placebo, citalopram is one of the randomly assigned medications after the first phase. This permits an assessment of the potential effectiveness of citalopram in comparison to a second antipsychotic should the first antipsychotic (or placebo) fail. A majority of the protocol committee favored the introduction of citalopram as a blinded treatment to allow assessment of whether a nonantipsychotic might be effective when an antipsychotic is not. Use of a nonantipsychotic comparator provides "added value" in an effectiveness study of antipsychotics by providing information about a different class of agents. Further, some patients have agitation without psychosis and might respond to nonantipsychotics, and/or some patients might not respond to any antipsychotic. Recent evidence regarding the relative effi-
cacy and safety of citalopram compared to a conventional antipsychotic in inpatients (Pollock et al. 2002), as well as data from previous Scandinavian trials suggesting that citalopram might be efficacious (Nyth et al. 1992), supported the decision to include citalopram. The committee considered the use of other nonantipsychotic comparators such as anticonvulsants and anxiolytics but felt that there was insufficient evidence to warrant inclusion of these medications in a multicenter trial of treatment of agitation/psychosis. As a practical matter, dosing, titration, and monitoring issues posed feasibility barriers to the incorporation of anticonvulsants as well.

To achieve generalizability and representation of a more typical group of patients, the individual inclusion and exclusion criteria (table 1) are intended to be as broad, typical, and inclusive as possible. Inclusion of a representative sample was also a priority in the selection process for participating sites. A site selection committee developed criteria for individual site participation. Sites were identified based on their geographic diversity, minority recruitment potential, and type of clinical service. Study site nominations were also solicited by public announcements. Each site was asked to complete a study site questionnaire that elicited its experience in conducting trials, its patient population, and its role in the community.

From a public health perspective, a major focus of treatment is to maintain patients in the community and to delay the time until nursing home placement becomes unavoidable. Psychosis and behavioral disruption are often antecedents to nursing home placement. Patients in nursing homes have severe dementia, limited longevity, and limited expected outcomes, and staffing costs for their care are fixed. In contrast to an intervention in nursing home patients, outpatient management of potentially treatable symptoms can have a greater impact on the community, family, quality of life, and economics. With this perspective in mind, the outcome variables used in this trial were selected on the basis of their relevance and meaningfulness to the clinical symptoms and progression of AD in community-dwelling patients. These outcomes address the cognitive, functional, and behavioral domains affected in AD patients as well as their ability to live in the community. The outcomes have been used frequently enough in previous studies that the medical community recognizes them, and the results of this trial can be compared with those of previous and ongoing trials. Further, they have established validity and good interrater and test-retest reliabilities. The endpoints used in survival analyses were chosen because they represent clinical progression of the illness and not a fluctuating or reversing condition (Sano et al. 1997). In this trial, nursing home placement, hospitalization, and death are considered clinically important markers for quality of life and function over the morbid period.

An important goal of this study will be to establish a cohort that can be followed for a longer period than the protocol-specified 36 weeks. This allows for controlled observation of long-term safety and future treatments and for greater understanding of patients who do not respond to treatment, how services are utilized, and how the illness progresses clinically.

Summary

The goal of the CATIE AD trial is to assess the effectiveness of commonly used treatments in a vulnerable population. We believe that such a protocol is a step forward in understanding several ways in which treatment may benefit patients who actually receive them. The CATIE AD protocol blends a public health model of interventions research, focusing on effectiveness and broader measures of outcome, with a design that also addresses efficacy. Key protocol features characteristic of effectiveness trials include use of medications in a manner approximating their use in community practice; measurement of a broad range of outcomes, such as compliance, residual disability, recovery, daily and social functioning, quality of life, and cost-effectiveness; and the impact of external factors on treatment delivery, compliance, and eventual outcomes. Because a major goal of such a trial is broader generalizability, inclusion criteria are such that subjects will be representative of those requiring therapy of this nature and not excluded because of comorbid psychiatric disorders, drug abuse, or medical illness, as is the custom in efficacy studies. Further, the protocol emphasizes demographic and geographic diversity of subjects as well as use of research settings that represent usual loci of care. In view of the breadth of objectives and desire for generalizability, the trial results are expected to be heavily descriptive and generate hypotheses for future studies. Last, the trial aims to develop a network of sites and investigators for future treatment effectiveness research in dementia in the event that the NIMH pursues similar research agendas in the future.

References


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