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## Effectiveness of Atypical Antipsychotic Drugs in Patients with Alzheimer's Disease

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### ABSTRACT

#### BACKGROUND

Second-generation (atypical) antipsychotic drugs are widely used to treat psychosis, aggression, and agitation in patients with Alzheimer's disease, but their benefits are uncertain and concerns about safety have emerged. We assessed the effectiveness of atypical antipsychotic drugs in outpatients with Alzheimer's disease.

#### METHODS

In this 42-site, double-blind, placebo-controlled trial, 421 outpatients with Alzheimer's disease and psychosis, aggression, or agitation were randomly assigned to receive olanzapine (mean dose, 5.5 mg per day), quetiapine (mean dose, 56.5 mg per day), risperidone (mean dose, 1.0 mg per day), or placebo. Doses were adjusted as needed, and patients were followed for up to 36 weeks. The main outcomes were the time from initial treatment to the discontinuation of treatment for any reason and the number of patients with at least minimal improvement on the Clinical Global Impression of Change (CGIC) scale at 12 weeks.

#### RESULTS

There were no significant differences among treatments with regard to the time to the discontinuation of treatment for any reason: olanzapine (median, 8.1 weeks), quetiapine (median, 5.3 weeks), risperidone (median, 7.4 weeks), and placebo (median, 8.0 weeks) ( $P=0.52$ ). The median time to the discontinuation of treatment due to a lack of efficacy favored olanzapine (22.1 weeks) and risperidone (26.7 weeks) as compared with quetiapine (9.1 weeks) and placebo (9.0 weeks) ( $P=0.002$ ). The time to the discontinuation of treatment due to adverse events or intolerability favored placebo. Overall, 24% of patients who received olanzapine, 16% of patients who received quetiapine, 18% of patients who received risperidone, and 5% of patients who received placebo discontinued their assigned treatment owing to intolerability ( $P=0.009$ ). No significant differences were noted among the groups with regard to improvement on the CGIC scale. Improvement was observed in 32% of patients assigned to olanzapine, 26% of patients assigned to quetiapine, 29% of patients assigned to risperidone, and 21% of patients assigned to placebo ( $P=0.22$ ).

#### CONCLUSIONS

Adverse effects offset advantages in the efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with Alzheimer's disease. (ClinicalTrials.gov number, NCT00015548.)

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**D**ELUSIONS, HALLUCINATIONS, AGGRESSION, and agitation affect more than half of patients with Alzheimer's disease and related dementias.<sup>1-4</sup> Antipsychotic drugs are used to treat these behaviors and symptoms and are among the most frequently used psychotropic drugs in Alzheimer's disease.<sup>5,6</sup>

Second-generation (atypical) antipsychotic drugs have been considered to be at least as effective as conventional antipsychotic agents such as haloperidol, with a lower risk of most adverse effects,<sup>7</sup> and are used as first-line pharmacologic treatments for patients with dementia.<sup>5,8</sup> However, there is a dearth of placebo-controlled and active-drug-controlled, randomized trials and longer-term data from controlled trials regarding the effectiveness of atypical antipsychotic drugs. Moreover, the available data on efficacy have been inconsistent, rates of response to placebo have been high, and patients have been required to receive drugs for the 6-week to 12-week study periods, whether or not they benefited, an artificial situation that does not address effectiveness.<sup>9</sup>

New safety issues have emerged with respect to atypical antipsychotic drugs. Increased risks of cerebrovascular adverse events<sup>10-12</sup> and death<sup>13,14</sup> have complicated their use. Antidepressant medications such as citalopram have been suggested as alternatives to antipsychotic drugs,<sup>15</sup> at least for aggression or agitation,<sup>16</sup> despite the lack of data from adequate trials.<sup>17</sup>

We conducted a double-blind, placebo-controlled trial to determine the effectiveness of olanzapine, quetiapine, and risperidone as compared with placebo in outpatients with Alzheimer's disease and psychosis, aggression, or agitation.

## METHODS

### STUDY SETTING AND DESIGN

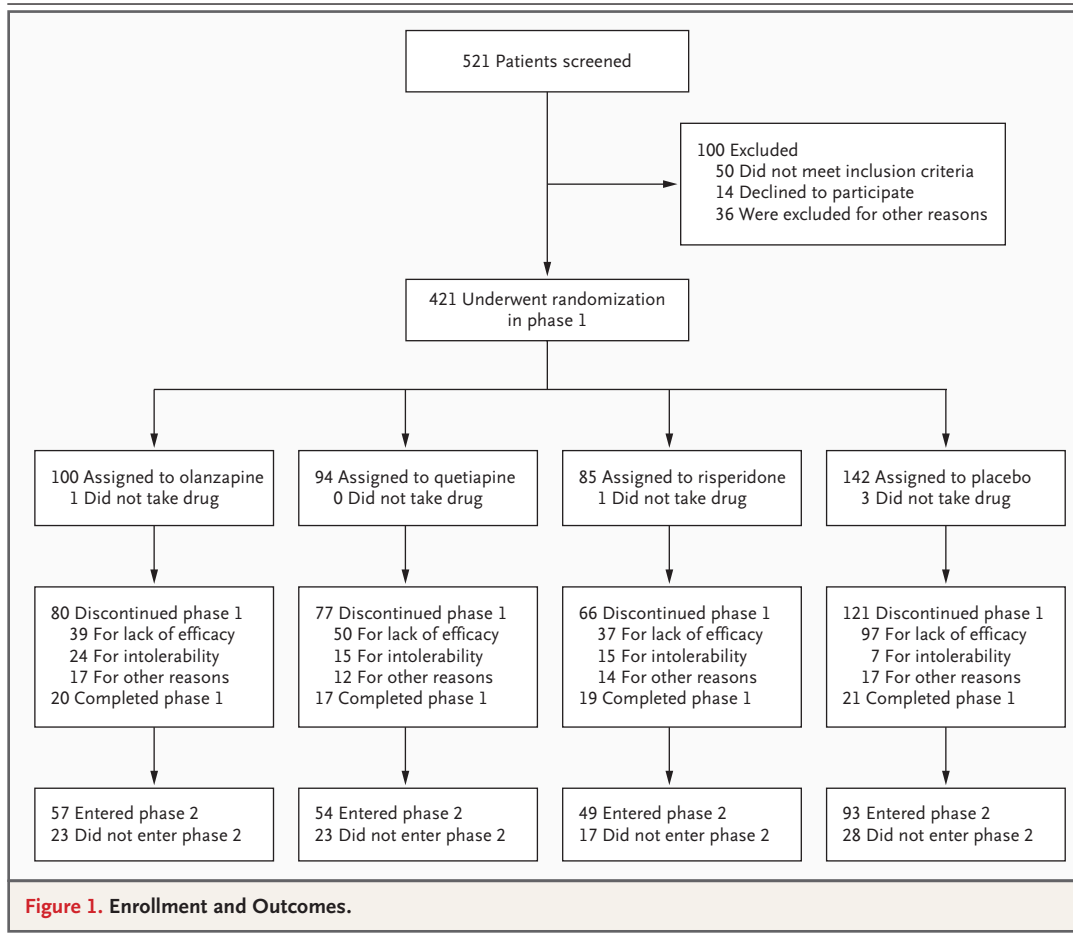
The trial was part of the National Institute of Mental Health (NIMH) Clinical Antipsychotic Trials of Intervention Effectiveness. Such trials address broad outcomes in settings and with interventions that reflect usual practices. The rationale, design, and methods of this study — Clinical Antipsychotic Trials of Intervention Effectiveness—Alzheimer's Disease (CATIE-AD) — have been described previously.<sup>18</sup> The trial was conducted between April 2001 and November 2004 at 45 sites in the United States (26 univer-

sity clinics, 7 Veterans Affairs medical centers, and 12 private-practice sites [3 sites did not randomly assign any patients]).

In phase 1 of the study, patients were randomly assigned under double-blind conditions to receive olanzapine, quetiapine, risperidone, or placebo in a 2:2:2:3 ratio. Doses were adjusted as clinically indicated by study physicians. If the physicians judged that the patient's response was not adequate at any time after the first 2 weeks, then treatment could be discontinued. Patients with an adequate response continued treatment for up to 36 weeks. Patients whose initial treatment was discontinued during phase 1 could be enrolled in phase 2 and randomly assigned under double-blind conditions to receive one of the antipsychotic drugs to which they were not initially assigned or to receive citalopram.<sup>18</sup> This report is limited to phase 1 results.

### PARTICIPANTS

Eligible participants fulfilled criteria for dementia of the Alzheimer's type (according to the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition)<sup>19</sup> or probable Alzheimer's disease<sup>20</sup> on the basis of the history, physical examination, results of structural brain imaging, and the score on the Mini-Mental State Examination (MMSE)<sup>21</sup>; the MMSE score had to be between 5 and 26 (on a scale from 0 to 30, with lower scores indicating poorer performance). To be eligible, patients had to be ambulatory and living at home or in an assisted-living facility. Eligible patients had delusions, hallucinations, aggression, or agitation that developed after the onset of dementia and was severe enough to disrupt their functioning and, in the opinion of the study physicians, to justify treatment with antipsychotic drugs. Signs and symptoms of psychosis, aggression, or agitation had to have occurred nearly daily during the previous week or at least intermittently for 4 weeks. During the week before they were randomly assigned to treatment, eligible patients also had a severity rating of at least "moderate" for conceptual disorganization, suspiciousness, or hallucinatory behavior on the Brief Psychiatric Rating Scale (BPRS).<sup>22</sup> Alternatively, a frequency rating of "often" or "more frequently" and a severity rating of at least "moderate" were required for delusions, hallucinations, agitation, or "aberrant motor behavior" in the Neuropsychiatric Inventory.<sup>23</sup>



A study partner or caregiver who had regular contact with the patient was required to participate in the assessments.<sup>18</sup>

Patients were excluded if they had received a diagnosis of a primary psychotic disorder (e.g., schizophrenia), delirium, other dementia such as vascular dementia<sup>24</sup> or Lewy-body dementia,<sup>25</sup> or psychosis, agitation, or aggression that could be better accounted for by another medical condition, medication, or substance abuse. Patients were also excluded if they required psychiatric admission, were suicidal, were going to receive treatment with a cholinesterase inhibitor or antidepressant medication, had previously been treated with two of the three atypical antipsychotic drugs under study, or had contraindications to any of the study drugs.

The study was approved by the NIMH data and safety monitoring board and by the institutional review board at each site. Written informed consent was obtained from the patients or their

legally authorized representatives and from the partners or caregivers who participated with the patients.

**INTERVENTIONS**

The trial design encouraged prescribing that reflected clinical practice while maintaining the randomized and double-blind treatment assignment. The study physicians determined the starting doses and adjusted the doses on the basis of their clinical judgment and patients' responses. Medications were dispensed at each visit in the form of identically appearing small and large capsules containing lower and higher doses of olanzapine (Zyprexa, Eli Lilly; 2.5 mg or 5.0 mg), quetiapine (Seroquel, AstraZeneca; 25 mg or 50 mg), risperidone (Risperdal, Janssen Pharmaceutica; 0.5 mg or 1.0 mg), or placebo.

To treat difficult behaviors during the trial, study physicians could increase the dose of the

**Table 1.** Baseline Characteristics of Patients Who Underwent Randomization.\*

| Characteristic                                     | Olanzapine Group<br>(N=100) | Quetiapine Group<br>(N=94) | Risperidone Group<br>(N=85) | Placebo Group<br>(N=142) | Total<br>(N=421) |
|--|-----------------------------|----------------------------|-----------------------------|--------------------------|------------------|
| <b>Demographic</b>                                 |                             |                            |                             |                          |                  |
| Age — yr   | 78.8±7.3                    | 77.3±8.7                   | 78.4±7.1                    | 77.3±7.1                 | 77.9±7.5         |
| Female sex — no. (%)                               | 55 (55)                     | 50 (53)                    | 49 (58)                     | 81 (57)                  | 235 (56)         |
| Race — no./total no. (%)†                          |                             |                            |                             |                          |                  |
| White  | 80/99 (81)                  | 76/94 (81)                 | 68/85 (80)                  | 107/141 (76)             | 331/419 (79)     |
| Black  | 14/99 (14)                  | 15/94 (16)                 | 15/85 (18)                  | 31/141 (22)              | 75/419 (18)      |
| Other  | 5/99 (5)                    | 3/94 (3)                   | 2/85 (2)                    | 3/141 (2)                | 13/419 (3)       |
| <b>Education — no. (%)</b>                         |                             |                            |                             |                          |                  |
| Did not complete high school                       | 28 (28)                     | 21 (22)                    | 15 (18)                     | 37 (26)                  | 101 (24)         |
| General equivalency diploma or high-school diploma | 35 (35)                     | 33 (35)                    | 28 (33)                     | 46 (32)                  | 142 (34)         |
| <4 yr of college                                   | 16 (16)                     | 16 (17)                    | 22 (26)                     | 36 (25)                  | 90 (21)          |
| ≥4 yr of college                                   | 15 (15)                     | 21 (22)                    | 17 (20)                     | 20 (14)                  | 73 (17)          |
| Unknown  | 6 (6)                       | 3 (3)                      | 3 (4)                       | 3 (2)                    | 15 (4)           |
| Married — no. (%)                                  | 63 (63)                     | 56 (60)                    | 49 (58)                     | 81 (57)                  | 249 (59)         |
| <b>Residence — no. (%)</b>                         |                             |                            |                             |                          |                  |
| Own home   | 77 (77)                     | 69 (73)                    | 61 (72)                     | 100 (70)                 | 307 (73)         |
| Family's home                                      | 11 (11)                     | 13 (14)                    | 14 (16)                     | 28 (20)                  | 66 (16)          |
| Assisted-living facility                           | 9 (9)                       | 10 (11)                    | 10 (12)                     | 12 (8)                   | 41 (10)          |
| Other  | 3 (3)                       | 2 (2)                      | 0                           | 2 (1)                    | 7 (2)            |

study medication or prescribe a benzodiazepine or oral or parenteral haloperidol.

All patients and caregivers were given basic information about Alzheimer's disease.<sup>26</sup> Caregivers were offered two counseling sessions during the first 18 weeks and could speak with staff members as needed.

#### OUTCOMES

The primary outcome measure was the time until discontinuation of treatment for any reason in phase 1. This outcome integrates the judgments of patients, caregivers, and clinicians regarding efficacy, safety, and tolerability into a global measure of effectiveness that reflects therapeutic benefits in relation to undesirable effects.

The two primary hypotheses in phase 1 were, first, there would be pairwise differences between the three groups given atypical antipsychotic agents and the placebo group in the time until discontinuation of treatment for any reason, and second, that among those antipsychotic drugs that were found to be different from placebo, none would be inferior to the others.

The main secondary outcome measure was the attainment of minimal or greater improvement on the Clinical Global Impression of Change (CGIC)<sup>27</sup> scale at week 12 while the patients continued to receive the phase 1 drug. The other secondary outcomes were the time to the discontinuation of treatment in phase 1 because of lack of efficacy and the time to the discontinuation of treatment because of adverse events, intolerability, or death. Safety was assessed by eliciting information about the occurrence of adverse events. The patients' weight and prolactin, glucose, cholesterol, and triglyceride levels were measured at weeks 12, 24, and 36.

#### STATISTICAL ANALYSIS

Patients who underwent randomization and received at least one dose of the study medication were included in the intention-to-treat sample. Randomization was performed with the use of permuted blocks of nine per site without stratification and was implemented with the use of an interactive voice-response telephone system.

A total of 421 patients underwent randomiza-

**Table 1. (Continued.)**

| Characteristic   | Olanzapine Group<br>(N=100) | Quetiapine Group<br>(N=94) | Risperidone Group<br>(N=85) | Placebo Group<br>(N=142) | Total<br>(N=421) |
|--|-----------------------------|----------------------------|-----------------------------|--------------------------|------------------|
| <b>Clinical</b>  |                             |                            |                             |                          |                  |
| MMSE total score   | 15.0±5.4                    | 14.9±6.1                   | 15.7±6.1                    | 14.7±5.8                 | 15.0±5.8         |
| Alzheimer's Disease Assessment Scale (cognitive) total score               | 34.6±12.7                   | 36.1±13.6                  | 31.1±13.6                   | 35.7±13.2                | 34.6±13.3        |
| Criteria met for psychosis of Alzheimer's disease — no./total no. (%)      | 73/100 (73)                 | 73/93 (79)                 | 71/85 (84)                  | 106/142 (75)             | 323/420 (77)     |
| BPRS total score   | 27.0±11.8                   | 28.0±12.3                  | 27.7±13.6                   | 28.2±12.0                | 27.8±12.3        |
| NPI total score‡   | 31.8±16.3                   | 37.6±18.4                  | 38.3±20.2                   | 39.1±17.8                | 36.9±18.3        |
| Delusions — no./total no. (%)  | 77/98 (79)                  | 76/93 (82)                 | 74/84 (88)                  | 112/140 (80)             | 339/415 (82)     |
| Hallucinations — no./total no. (%)   | 41/98 (42)                  | 47/93 (51)                 | 47/83 (57)                  | 67/139 (48)              | 202/413 (49)     |
| Agitation or aggression — no./total no. (%)                                | 82/98 (84)                  | 80/93 (86)                 | 71/83 (86)                  | 125/140 (89)             | 358/414 (86)     |
| Depression — no./total no. (%)   | 55/98 (56)                  | 58/93 (62)                 | 51/83 (61)                  | 88/140 (63)              | 252/414 (61)     |
| Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory | 39.4±17.4                   | 39.0±17.8                  | 40.0±18.1                   | 38.2±16.3                | 39.0±17.2        |
| <b>Medications — no. (%)§</b>  |                             |                            |                             |                          |                  |
| Antidepressant or antipsychotic  | 27 (27)                     | 19 (20)                    | 23 (27)                     | 35 (25)                  | 104 (25)         |
| Antidepressant   | 19 (19)                     | 9 (10)                     | 18 (21)                     | 18 (13)                  | 64 (15)          |
| Conventional antipsychotic   | 5 (5)                       | 7 (7)                      | 1 (1)                       | 6 (4)                    | 19 (5)           |
| Atypical antipsychotic   | 11 (11)                     | 7 (7)                      | 10 (12)                     | 16 (11)                  | 44 (10)          |
| Cholinesterase inhibitor   | 67 (67)                     | 54 (57)                    | 50 (59)                     | 82 (58)                  | 253 (60)         |
| Mean weight — lb¶  | 148.9±36.6                  | 153.3±30.5                 | 151.7±31.4                  | 148.3±28.0               | 150.3±31.4       |
| Mean body-mass index   | 25.3±5.7                    | 25.5±3.9                   | 25.9±4.8                    | 25.2±4.0                 | 25.4±4.6         |

\* Plus-minus values are means ±SD. MMSE scores range from 0 to 30, with higher scores indicating better mental status; scores on the Alzheimer's Disease Assessment Scale range from 0 to 70, with lower scores indicating milder disease; BPRS scores range from 0 to 108, with lower scores indicating milder symptoms; scores on the Neuropsychiatric Inventory (NPI) range from 0 to 144, with lower scores indicating milder symptoms; and scores on the Alzheimer's Disease Cooperative Study—Activities of Daily Living Inventory range from 0 to 78, with higher scores indicating better functioning. Because of rounding, percentages may not total 100. Treatment groups were compared for baseline differences with the use of analysis of variance or chi-square tests.

† 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%).

‡ P=0.02 for the overall comparison of the treatment groups.

§ Trazodone accounted for 47% of antidepressant use, and donepezil accounted for 72% of cholinesterase-inhibitor use.

¶ To convert values to kilograms, divide by 2.2.

|| The body-mass index is the weight in kilograms divided by the square of the height in meters.

tion (from a target sample of 450 patients), yielding a statistical power of 99% to identify a difference of 33% in the rates of discontinuation of treatment by 36 weeks between any one of the drugs and placebo and a power of 80% to detect a difference of 20%, assuming a 60% rate of discontinuation in the placebo group.

We used Kaplan–Meier survival curves to estimate the time to the discontinuation of treatment for all patients in the intention-to-treat population. The treatment groups were compared with the use of Cox proportional-hazards regression models,<sup>28</sup> stratified according to site. Sites with 17 or

fewer patients were grouped according to the size and type of site (i.e., university clinic, private practice, or Veterans Affairs medical center) for a total of 15 sites (8 pooled and 7 with 18 or more randomly assigned patients).

In the Cox model, the overall difference among the treatment groups was evaluated with the use of a test with 3 degrees of freedom. If the difference was significant at a P value of less than 0.05, then each drug was compared with placebo by means of a Hochberg adjustment for multiple comparisons.<sup>29</sup>

Any antipsychotic drug found to be signifi-

**Table 2. Medication Doses and Outcomes in the Intention-to-Treat Sample.\***

| Dose and Outcome   | Olanzapine Group<br>(N=99) | Quetiapine Group<br>(N=94) | Risperidone Group<br>(N=84) | Placebo Group<br>(N=139) | P Value<br>(Overall<br>Comparison) <sup>†</sup> |
|--|----------------------------|----------------------------|-----------------------------|--------------------------|---|
| <b>Medication dose</b>   |                            |                            |                             |                          |   |
| Initial dose — mg per day  |                            |                            |                             |                          |   |
| Mean   | 3.2                        | 34.1                       | 0.7                         |                          |   |
| Range  | 0–10                       | 0–100                      | 0.5–2.5                     |                          |   |
| Last dose — mg per day   |                            |                            |                             |                          |   |
| Mean   | 5.5                        | 56.5                       | 1.0                         |                          |   |
| Range  | 0–17.5                     | 0–200                      | 0–2.0                       |                          |   |
| Discontinuation of treatment for any reason<br>— no. of patients (%)                 | 79 (80)                    | 77 (82)                    | 65 (77)                     | 118 (85)                 |   |
| Kaplan–Meier estimate of time to<br>discontinuation — wk                             |                            |                            |                             |                          | 0.52 <sup>†</sup>                               |
| 50th percentile  | 8.1                        | 5.3                        | 7.4                         | 8.0                      |   |
| 95% CI   | 5.1–11.6                   | 3.6–8.1                    | 5.0–12.0                    | 5.0–9.3                  |   |
| Comparison with placebo  |                            |                            |                             |                          |   |
| Hazard ratio   | 0.83                       | 1.01                       | 0.88                        | —                        |   |
| 95% CI <sup>†</sup>  | 0.62–1.11                  | 0.75–1.36                  | 0.64–1.20                   |                          |   |
| P value for test of a difference   | 0.21                       | 0.95                       | 0.41                        |                          |   |
| Discontinuation of treatment because<br>of lack of efficacy — no.<br>of patients (%) | 39 (39)                    | 50 (53)                    | 37 (44)                     | 97 (70)                  |   |
| Kaplan–Meier estimate of time to dis-<br>continuation — wk                           |                            |                            |                             |                          | 0.002 <sup>†</sup>                              |
| 50th percentile  | 22.1                       | 9.1                        | 26.7                        | 9.0                      |   |
| 95% CI   | 12.1– <sup>‡</sup> ∞       | 7.0–21.6                   | 8.1– <sup>‡</sup> ∞         | 6.4–11.6                 |   |
| Comparison with placebo  |                            |                            |                             |                          |   |
| Hazard ratio   | 0.51                       | 0.81                       | 0.61                        |                          |   |
| 95% CI   | 0.35–0.74                  | 0.57–1.15                  | 0.41–0.89                   |                          |   |
| P value for test of a difference   | <0.001 <sup>§</sup>        | 0.24                       | 0.01 <sup>§</sup>           |                          |   |
| Comparison with quetiapine   |                            |                            |                             |                          |   |
| Hazard ratio   | 0.63                       |                            | 0.75                        |                          |   |
| 95% CI   | 0.41–0.96                  |                            | 0.49–1.16                   |                          |   |
| P value for test of superiority <sup>¶</sup>   | 0.02 <sup>  </sup>         |                            | 0.10                        |                          |   |
| Comparison of olanzapine with risperidone  |                            |                            |                             |                          |   |
| Hazard ratio   | 0.84                       |                            |                             |                          |   |
| 95% CI   | 0.53–1.32                  |                            |                             |                          |   |
| P value for test of noninferiority   |                            |                            |                             |                          |   |
| Olanzapine vs. risperidone   | <0.001 <sup>  </sup>       |                            |                             |                          |   |
| Risperidone vs. olanzapine   | 0.01 <sup>  </sup>         |                            |                             |                          |   |

cantly better than placebo was then tested for noninferiority to the other antipsychotic agents. Noninferiority was concluded when the P value was less than 0.025 from a one-sided test with a margin of 2.0 (i.e., the upper limit of the 95% confidence interval [CI] for the hazard ratio was <2.0).

Two atypical antipsychotic drugs were considered to be equivalent if the CI was contained within 0.5 and 2.0 (i.e., each drug was noninferior to the other); this was a broad equivalence margin for noninferiority.

Finally, any antipsychotic drug found to be non-

**Table 2. (Continued.)**

| Dose and Outcome  | Olanzapine Group<br>(N=99)                      | Quetiapine Group<br>(N=94) | Risperidone Group<br>(N=84)      | Placebo Group<br>(N=139) | P Value<br>(Overall<br>Comparison) <sup>†</sup> |
|---|---|----------------------------|----------------------------------|--------------------------|---|
| Discontinuation of treatment because of intolerance, adverse events, or death — no. of patients (%) | 24 (24)   | 15 (16)                    | 15 (18)                          | 7 (5)                    |   |
| Kaplan–Meier estimate of time to discontinuation — wk <sup>**</sup>                                 |   |                            |                                  |                          | 0.009 <sup>†</sup>                              |
| 25th percentile   | 13.7  | 29.4                       | 20.1                             | ?                        |   |
| 95% CI  | 6.1–?   | 5.6–?                      | 9.6–?                            | ?–?                      |   |
| Comparison with placebo   |   |                            |                                  |                          |   |
| Hazard ratio  | 4.32  | 3.58                       | 3.62                             |                          |   |
| 95% CI  | 1.84–10.12                                      | 1.44–8.91                  | 1.45–9.04                        |                          |   |
| P value for test of a difference  | <0.001 <sup>§</sup>                             | 0.006 <sup>§</sup>         | 0.006 <sup>§</sup>               |                          |   |
| Comparison with quetiapine  |   |                            |                                  |                          |   |
| Hazard ratio  | 1.21  |                            | 1.01                             |                          |   |
| 95% CI  | 0.62–2.36                                       |                            | 0.49–2.11                        |                          |   |
| P value for test of noninferiority  | olanzapine vs. quetiapine: 0.07                 |                            | risperidone vs. quetiapine: 0.04 |                          |   |
|   | quetiapine vs. olanzapine: 0.005 <sup>  </sup>  |                            | quetiapine vs. risperidone: 0.03 |                          |   |
| Comparison of olanzapine with risperidone   |   |                            |                                  |                          |   |
| Hazard ratio  | 1.19  |                            |                                  |                          |   |
| 95% CI  | 0.61–2.32                                       |                            |                                  |                          |   |
| P value for test of noninferiority  | olanzapine vs. risperidone: 0.06                |                            |                                  |                          |   |
|   | risperidone vs. olanzapine: 0.005 <sup>  </sup> |                            |                                  |                          |   |
| Response based on CGIC score at 12 wk — no. of patients (%) <sup>††</sup>                           | 32 (32)   | 24 (26)                    | 24 (29)                          | 29 (21)                  | 0.22  |
| Comparison with placebo   | P=0.05  | P=0.37                     | P=0.21                           |                          |   |
| Change in score at 12 wk — change (no. of patients) <sup>‡‡</sup>                                   |   |                            |                                  |                          |   |
| CGIC <sup>§§</sup>  | 2.9±1.3 (40)                                    | 2.7±1.1 (31)               | 2.6±1.5 (33)                     | 3.3±1.5 (48)             |   |
| BPRS total score  | -7.4±9.8 (40)                                   | -7.4±9.8 (30)              | -8.5±12.2 (32)                   | -3.9±9.8 (48)            |   |
| NPI total score   | -14.0±18.7 (40)                                 | -16.6±18.3 (31)            | -16.4±15.0 (32)                  | -9.0±20.6 (47)           |   |

\* Plus-minus values are means ±SD. Question marks denote 95% CI limits that could not be estimated because of low event rates.  
<sup>†</sup> Hazard ratios are based on a Cox proportional-hazards regression model. The P value for the overall treatment group comparison is from a test with 3 degrees of freedom. A ratio of less than 1 indicates a longer time to the discontinuation of the first treatment listed. A 95% CI between 0.5 and 2.0 indicates equivalence of treatments. A test of noninferiority compares the upper limit of the 95% CIs with 2.0. A test of superiority compares the upper limit of the 95% CI with 1.0.  
<sup>‡</sup> The upper confidence limit of the Kaplan–Meier 50th percentile for discontinuation of treatment because of lack of efficacy could not be estimated because of low event rates in the olanzapine and risperidone groups.  
<sup>§</sup> The P value for comparison with placebo is significant at 0.05 in accordance with the Hochberg adjustment for multiple comparisons.  
<sup>||</sup> Olanzapine and risperidone were both noninferior to quetiapine (P<0.001).  
<sup>|||</sup> The P value, which is significant at 0.025, is applicable to one-sided tests of noninferiority or superiority.  
<sup>\*\*</sup> The Kaplan–Meier 25th percentile for discontinuation of treatment owing to adverse events, intolerable side effects, or death could not be estimated in the placebo group because of low event rates. The upper confidence limit of the active-treatment groups could not be calculated because of low event rates in the placebo group.  
<sup>††</sup> A response was defined as continued treatment with the original phase 1 study drug and at least minimal improvement on the CGIC.  
<sup>‡‡</sup> Statistical testing is not presented for the subgroup of patients who remained in phase 1 for 12 weeks.  
<sup>§§</sup> CGIC scores are as follows: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; and 7, very much worse. For the BPRS and the Neuropsychiatric Inventory, decreases in scores indicate decreases in the severity of symptoms.

inferior to the other antipsychotic drugs was tested for superiority on the basis of a one-sided test with a P value of less than 0.025. Discontinuation of treatment for a specific reason was analyzed in the same way, except that the data for patients who discontinued treatment for a different reason were censored at the time of discontinuation.

Patients who had a response to the assigned study drug were defined as those who were still in phase 1 and who had a CGIC score indicating at least minimal improvement at 12 weeks; all patients who had discontinued medications or who did not have minimal improvement on the CGIC scale were classified as not having a response. Groups were compared with the use of a nonparametric analysis of covariance,<sup>30</sup> stratified according to the type of site and adjusted for the following baseline covariates: age, sex, MMSE score, and total BPRS score. Statistical testing followed the same strategy as for time to discontinuation of treatment, with equivalence defined as a 95% CI of  $-0.20$  to  $0.20$  for the difference between response rates.

The study was funded by the NIMH. The pharmaceutical companies whose drugs were included in the study donated drug supplies; they were not involved in the design of the study, analyses, or interpretation of results. The authors and a protocol committee (see the Appendix) designed the trial. The site investigators gathered the data, and one of the authors analyzed the data. The manuscript was written by the authors, who vouch for the completeness and veracity of the data and data analyses.

## RESULTS

### PATIENTS, CAREGIVERS, AND MEDICATION DOSES

A total of 521 patients were screened and 421 underwent randomization and received at least one dose of medication (Fig. 1). Eighty-two percent of patients discontinued their initially assigned medication (i.e., during the 36-week follow-up period).

Clinical characteristics of the patients are shown in Table 1. Fifty-seven percent required a level of care equivalent to that given in assisted-living facilities, and 17% needed the equivalent of nursing home care.<sup>31</sup> At baseline, 46% were receiving antihypertensive drugs, 24% cholesterol-lowering drugs, 16% antiinflammatory drugs, and 30% vitamin E.

Fifty-two percent of caregivers were spouses, and 33% were children or sons-in-law or daughters-in-law. The mean ages of caregivers were 73.5 years for spouses and 51.2 years for children or their spouses; 71% were women.<sup>31</sup> They spent a mean ( $\pm$ SD) of  $5.2\pm 4.0$  hours per day in specific caregiving activities.<sup>32</sup>

The mean initially prescribed doses were 3.2 mg of olanzapine per day, 34.1 mg of quetiapine per day, and 0.7 mg of risperidone per day. The last prescribed mean dose in phase 1 was 5.5 mg of olanzapine per day, 56.5 mg of quetiapine per day, and 1.0 mg of risperidone per day. The mean number of capsules prescribed was similar for all treatment groups: 0.7 large or 1.4 small capsules per day initially, and 1.1 large or 2.2 small capsules per day for the last prescribed dose in phase 1.

### OUTCOMES

There were no significant overall differences among treatment groups with regard to the time to discontinuation of treatment for any reason (Table 2 and Fig. 2A). The median time to discontinuation of treatment ranged from 5.3 weeks with quetiapine to 8.1 weeks with olanzapine.

The median time to discontinuation of treatment because of lack of efficacy was longer in the olanzapine group (22.1 weeks) and the risperidone group (26.7 weeks) than in the placebo group (9.0 weeks) (Table 2 and Fig. 2B). The hazard ratio for the discontinuation of treatment because of lack of efficacy was 0.51 ( $P<0.001$ ) for olanzapine as compared with placebo, and 0.61 ( $P=0.01$ ) for risperidone. The time to discontinuation of treatment with quetiapine owing to lack of efficacy (median, 9.1 weeks) did not differ significantly from that for placebo. For the discontinuation of treatment, olanzapine and risperidone were equivalent to each other (hazard ratio, 0.84; 95% CI, 0.53 to 1.32), and olanzapine was significantly superior to quetiapine (hazard ratio, 0.63; 95% CI, 0.41 to 0.96;  $P=0.02$ ).

The time to discontinuation of treatment owing to intolerance of the study drug, adverse effects, or death favored placebo, with discontinuation rates of 24% for patients who received olanzapine, 16% for patients who received quetiapine, and 18% for patients who received risperidone, as compared with 5% for patients who received placebo (Table 2 and Fig. 2C). All three groups of patients who received an atypical antipsychotic drug were sig-

nificantly more likely to discontinue treatment than were those who received placebo (hazard ratio for olanzapine, 4.32; 95% CI, 1.84 to 10.12; for quetiapine, 3.58; 95% CI, 1.44 to 8.91; and for risperidone, 3.62; 95% CI, 1.45 to 9.04).

At 12 weeks, 32% of patients in the olanzapine group had a response (i.e., a CGIC score indicating at least minimal improvement with continued use of the phase 1 study medication), as compared with 26% in the quetiapine group, 29% in the risperidone group, and 21% in the placebo group; these rates were not significantly different ( $P=0.22$ ). The overall rate of discontinuation of treatment at 12 weeks was 63%.

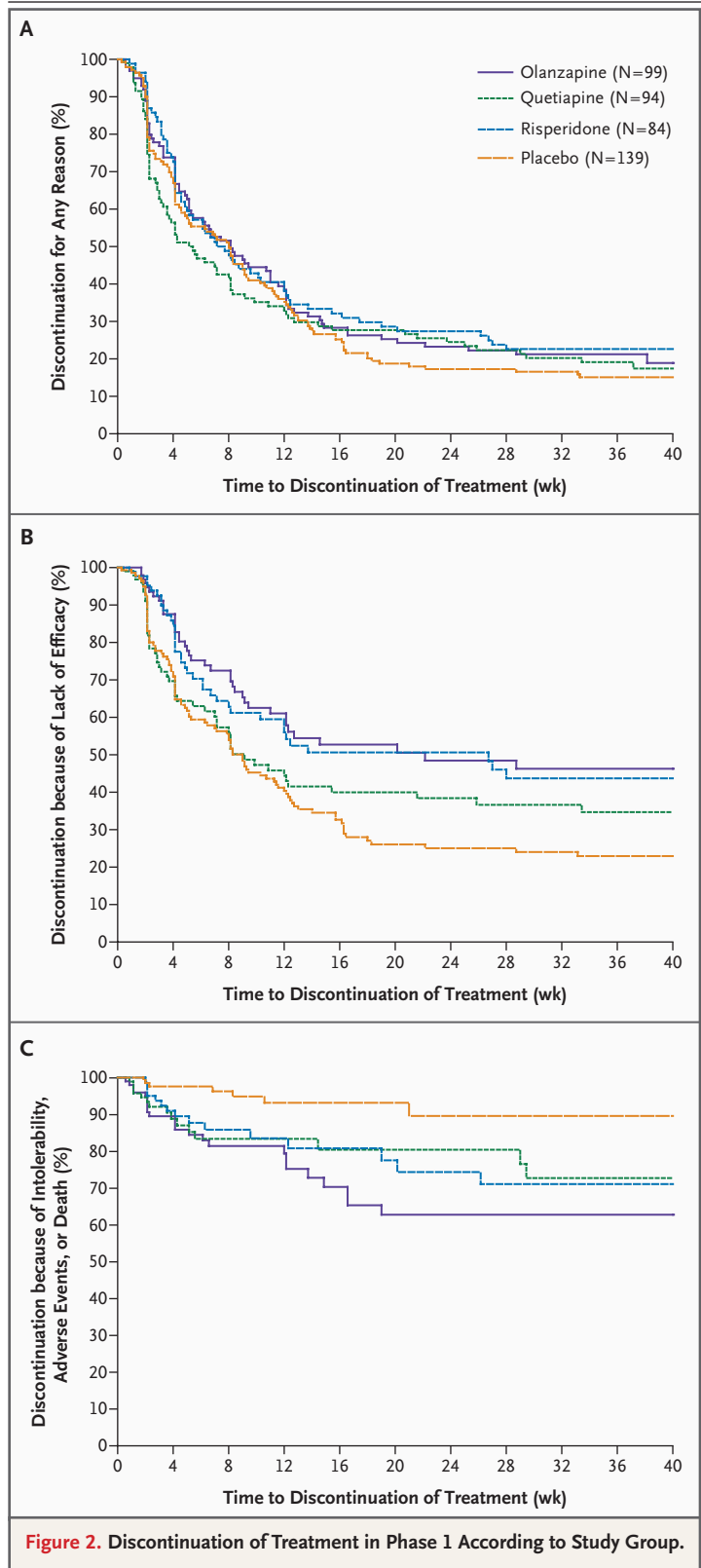
**ADVERSE EVENTS**

There were no significant differences among the groups with regard to the proportion of patients who had at least one serious adverse event and the proportion who had any adverse event (Table 3). There were higher rates of parkinsonism or extrapyramidal signs in the olanzapine and risperidone groups (12% in each) than in the quetiapine group (2%) or the placebo group (1%). Correspondingly, the proportion of patients with a score of 1 or more on the Simpson–Angus scale (on a scale of 0 to 4, with 1 indicating mild extrapyramidal signs, and 4 the most severe signs) was higher with olanzapine (14%) and risperidone (11%) than with placebo (2%).

Sedation occurred more commonly with the three drugs (reported in 15 to 24% of patients) than with placebo (5%), and confusion or changes in mental status occurred more commonly with olanzapine (18%) and risperidone (11%) than with placebo (5%). Both cognitive disturbances and psychotic symptoms were more common with olanzapine (5% and 7%, respectively) than with the other medications or placebo (0 to 2%).

The body weight and body-mass index (BMI) of patients increased with antipsychotic drugs (by 0.4 to 1.0 lb [0.18 to 0.45 kg] per month and 0.2 BMI unit) and decreased slightly with placebo (by -0.9 lb [0.41 kg] per month and -0.2 BMI unit). Prolactin levels at week 12 were markedly elevated in the risperidone group only.

Ten patients entered nursing homes during phase 1 (two patients receiving olanzapine, four patients receiving quetiapine, three patients receiving risperidone, and one patient receiving placebo).



**Table 3. Adverse Events and Other Safety Outcomes in Phase 1.\***

| Variable   | Olanzapine Group<br>(N=100) | Quetiapine Group<br>(N=94) | Risperidone Group<br>(N=85) | Placebo Group<br>(N=142) | P Value (Overall<br>Comparison) |
|--|-----------------------------|----------------------------|-----------------------------|--------------------------|---------------------------------|
| <b>Adverse event — no. (%)</b>   |                             |                            |                             |                          |                                 |
| Any serious adverse event†   | 14 (14)                     | 17 (18)                    | 9 (11)                      | 19 (13)                  | 0.35                            |
| Cerebrovascular accident or transient<br>ischemic attack               | 2 (2)                       | 1 (1)                      | 1 (1)                       | 1 (1)                    | 0.92                            |
| Death  | 1 (1)                       | 3 (3)                      | 1 (1)                       | 3 (2)                    | 0.68                            |
| Any severe adverse event   | 17 (17)                     | 24 (26)                    | 12 (14)                     | 21 (15)                  | 0.11                            |
| Any adverse event  | 71 (71)                     | 59 (63)                    | 62 (73)                     | 83 (58)                  | 0.84                            |
| Parkinsonism or extrapyramidal<br>signs                                | 12 (12)                     | 2 (2)                      | 10 (12)                     | 1 (1)                    | <0.001                          |
| Gait disturbance   | 4 (4)                       | 3 (3)                      | 1 (1)                       | 3 (2)                    | 0.66                            |
| Sedation   | 24 (24)                     | 21 (22)                    | 13 (15)                     | 7 (5)                    | <0.001                          |
| Dizziness  | 6 (6)                       | 6 (6)                      | 4 (5)                       | 9 (6)                    | 0.96                            |
| Headache   | 5 (5)                       | 1 (1)                      | 5 (6)                       | 2 (1)                    | 0.10                            |
| Motor disturbance or dyskinesia  | 3 (3)                       | 2 (2)                      | 3 (4)                       | 4 (3)                    | 0.98                            |
| Cognitive disturbance  | 5 (5)                       | 0                          | 1 (1)                       | 1 (1)                    | 0.03                            |
| Seizures   | 3 (3)                       | 1 (1)                      | 0                           | 0                        | 0.07                            |
| Agitation or aggression  | 7 (7)                       | 11 (12)                    | 5 (6)                       | 14 (10)                  | 0.30                            |
| Psychotic symptoms   | 7 (7)                       | 0                          | 0                           | 3 (2)                    | 0.004                           |
| Confusion or mental-status change                                      | 18 (18)                     | 6 (6)                      | 9 (11)                      | 7 (5)                    | 0.03                            |
| Sleep disturbance  | 5 (5)                       | 5 (5)                      | 4 (5)                       | 5 (4)                    | 0.90                            |
| Depression   | 4 (4)                       | 2 (2)                      | 0                           | 2 (1)                    | 0.25                            |
| Anxiety  | 3 (3)                       | 0                          | 0                           | 3 (2)                    | 0.21                            |
| Fatigue or weakness  | 3 (3)                       | 4 (4)                      | 3 (4)                       | 2 (1)                    | 0.53                            |
| Falls, fractures, or injuries  | 17 (17)                     | 7 (7)                      | 10 (12)                     | 21 (15)                  | 0.16                            |
| <b>Neurologic effects — no./total no. (%)‡</b>                         |                             |                            |                             |                          |                                 |
| AIMS global severity score ≥2  | 1/73 (1)                    | 2/55 (4)                   | 2/64 (3)                    | 1/96 (1)                 | 0.62                            |
| Barnes Akathisia Rating Scale global<br>score ≥3                       | 1/73 (1)                    | 1/55 (2)                   | 0/64                        | 0/96                     | 0.33                            |
| Simpson–Angus Extrapyramidal Signs<br>Scale mean score ≥1              | 10/73 (14)                  | 5/54 (9)                   | 7/64 (11)                   | 2/94 (2)                 | 0.03                            |
| P value for comparison with placebo                                    | 0.02                        | 0.10                       | 0.04                        |                          |                                 |
| <b>Specific reasons for discontinuation<br/>of treatment — no. (%)</b> |                             |                            |                             |                          |                                 |
| Intolerability, adverse effects, or death                              | 24 (24)                     | 15 (16)                    | 15 (18)                     | 7 (5)                    | <0.001                          |
| Sedation   | 6 (6)                       | 3 (3)                      | 3 (4)                       | 1 (1)                    | 0.10                            |
| Extrapyramidal signs   | 6 (6)                       | 1 (1)                      | 4 (5)                       | 1 (1)                    | 0.03                            |
| Dizziness  | 1 (1)                       | 4 (4)                      | 1 (1)                       | 1 (1)                    | 0.20                            |
| Cerebrovascular adverse event  | 1 (1)                       | 1 (1)                      | 1 (1)                       | 2 (1)                    | 1.0                             |
| Confusion  | 3 (3)                       | 1 (1)                      | 3 (4)                       | 0                        | 0.07                            |
| Other  | 7 (7)                       | 5 (5)                      | 3 (4)                       | 2 (1)                    | 0.13                            |
| <b>Weight change from baseline to last<br/>observation</b>             |                             |                            |                             |                          |                                 |
| Weight gain >7% — no./total no. (%)                                    | 10/90 (11)                  | 5/80 (6)                   | 8/75 (11)                   | 4/128 (3)                | 0.10                            |

**Table 3. (Continued.)**

| Variable   | Olanzapine Group<br>(N=100) | Quetiapine Group<br>(N=94) | Risperidone Group<br>(N=85) | Placebo Group<br>(N=142) | P Value (Overall<br>Comparison) |
|--|-----------------------------|----------------------------|-----------------------------|--------------------------|---------------------------------|
| Weight change — lb/mo of treatment   | 1.0±0.4                     | 0.4±0.6                    | 0.7±0.4                     | -0.9±0.3                 | 0.003                           |
| P value for comparison with placebo  | 0.001                       | 0.03                       | 0.008                       |                          |                                 |
| <b>Change in body-mass index from baseline to last observation</b>               |                             |                            |                             |                          |                                 |
| Change   | 0.3±0.1                     | 0.2±0.1                    | 0.3±0.1                     | -0.2±0.1                 | 0.001                           |
| P value for comparison with placebo  | 0.001                       | 0.02                       | 0.001                       |                          |                                 |
| <b>Change in laboratory values from baseline to last observation<sup>§</sup></b> |                             |                            |                             |                          |                                 |
| Glucose — mg/dl  | 11.2±5.7                    | 2.5±6.4                    | 5.6±6.0                     | -1.2±5.0                 | 0.28                            |
| Total cholesterol — mg/dl  | -11.3±4.6                   | -1.9±5.2                   | -7.5±4.9                    | -7.5±4.2                 | 0.67                            |
| Triglycerides — mg/dl  | 20.1±10.2                   | 16.0±11.5                  | 1.3±10.9                    | 11.9±9.4                 | 0.40                            |
| Prolactin — mg/dl  | 4.1±3.6                     | -4.4±4.2                   | 44.5±3.7                    | -4.6±3.4                 | <0.001                          |
| <b>Electrocardiographic findings</b>   |                             |                            |                             |                          |                                 |
| Change in corrected QT interval from baseline to last observation — msec         | -6.1±5.5                    | -0.1±4.4                   | 5.1±4.7                     | 4.8±4.9                  | 0.27                            |
| Prolonged corrected QT interval — no./total no. (%)                              | 0/37                        | 3/31 (10)                  | 1/32 (3)                    | 4/52 (8)                 | 0.19                            |
| <b>New cataracts — no./total no. (%)</b>   | 0/99                        | 0/94                       | 0/83                        | 1/142 (1)                | 1.0                             |
| <b>Medications added — no. (%)</b>   |                             |                            |                             |                          |                                 |
| Any psychotropic drug <sup>¶</sup>   | 5 (5)                       | 10 (11)                    | 7 (8)                       | 15 (11)                  | 0.41                            |
| Antidepressant or antipsychotic agent  | 1 (1)                       | 3 (3)                      | 4 (5)                       | 8 (6)                    | 0.27                            |
| Benzodiazepine   | 3 (3)                       | 8 (9)                      | 3 (4)                       | 7 (5)                    | 0.35                            |
| Conventional antipsychotic agent   | 0                           | 0                          | 1 (1)                       | 2 (1)                    | 0.55                            |
| Atypical antipsychotic agent   | 0                           | 1 (1)                      | 1 (1)                       | 4 (3)                    | 0.32                            |
| Cholinesterase inhibitor   | 1 (1)                       | 1 (1)                      | 4 (5)                       | 1 (1)                    | 0.17                            |
| Antihypertensive agent   | 2 (2)                       | 6 (6)                      | 4 (5)                       | 4 (3)                    | 0.37                            |
| Gastrointestinal medication  | 6 (6)                       | 1 (1)                      | 2 (2)                       | 5 (4)                    | 0.28                            |

\* Plus-minus values are means ±SE. Comparisons of treatment groups are based on an overall test with 3 degrees of freedom and are presented for descriptive purposes. For percentages, tests are based on a Poisson regression with adjustment for different exposure times or Fisher's exact test in the case of rates based on small numbers.<sup>33</sup> Comparisons for continuous measures are based on an analysis of covariance (ANCOVA) with adjustment for the duration of exposure. Laboratory values were tested with the use of ranked ANCOVA to account for skewed distributions.

† A serious adverse event is any adverse drug-related event that results in any of the following outcomes: death, a life-threatening condition, hospital admission or prolongation of a hospital stay, a persistent or clinically significant disability or incapacity, or a congenital anomaly or birth defect.<sup>34</sup> The classification of an adverse event as severe was based on the judgment of the investigator.

‡ A global severity score of 2 or more on the Abnormal Involuntary Movement Scale (AIMS) indicates at least mildly abnormal movements. A score of 3 or more for the global clinical assessment of the Barnes Akathisia Rating Scale indicates at least moderate severity. A score of 1 or more on the Simpson-Angus Extrapyramidal Signs Scale indicates at least mild extrapyramidal signs (range, 0 to 4). For all three outcomes, percentages are based on the number of patients who did not meet the criteria at baseline and who underwent at least one post-baseline measurement in phase 1.

§ Laboratory values are adjusted for duration of medication exposure. To convert values for blood glucose to millimoles per liter, multiply by 0.05551. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

¶ This category includes antipsychotic agents, antiepileptic agents, hypnotics and sedatives, psychostimulants and nootropic agents, and antidepressants.

## DISCUSSION

In this study, we randomly assigned patients with Alzheimer's disease and psychosis, aggression, or agitation to placebo or one of three atypical antipsychotic medications. The median time to discontinuation of treatment for any reason ranged from 5 to 8 weeks, with no significant differences among the four groups. The study physicians discontinued the study drugs within 8 weeks after the start of treatment in about half the patients. This practice was consistent with the opinions of expert clinicians who have recommended discontinuing or switching antipsychotic treatment after 2 to 4 weeks in patients who are not benefiting from it.<sup>5,8</sup> The time to discontinuation of treatment, due to lack of efficacy, favored olanzapine and risperidone but was offset by the increased rates of discontinuation of these drugs due to adverse events. Because the study was designed to allow patients who discontinued a study medication in phase 1 to enter phase 2 and be randomly assigned to a different study drug, expectations that the phase 2 treatments might be more effective may have increased the likelihood of earlier discontinuation of treatment during phase 1.

The study physicians increased the initial medication doses from an average of 1.4 small capsules to an average of 2.2, equivalent to approximately 1.0 mg of risperidone, 5.5 mg of olanzapine, and 57.0 mg of quetiapine. The risperidone and olanzapine doses were both within the ranges recommended by experts<sup>5</sup> and used in previous trials.<sup>9</sup> The quetiapine dose, however, was half to a quarter that used in two nursing home trials.<sup>9</sup>

The protocol committee was unwilling to use a higher minimum starting dose of quetiapine or a larger incremental dose because of the possibility of excess sedation, but the committee expected that physicians would determine dosing individually for each patient. The rates of adverse events were similar among the drugs, however, so the apparent reluctance to increase the dose may have been related to observed adverse events or concern that adverse events would occur with higher doses of risperidone or olanzapine. Nevertheless, the decision not to increase the dose in the face of an inadequate response limits some conclusions about efficacy and adverse effects.

Sedation was more likely with all of the anti-

psychotic drugs than with placebo and was particularly likely with olanzapine, which was also associated with increased confusion. Although worsening of cognition has been observed in other trials of antipsychotic medications for the treatment of dementia,<sup>9</sup> MMSE scores did not worsen in our trial. Extrapyramidal signs and symptoms with both risperidone and olanzapine were common reasons for the discontinuation of treatment. The clinical significance of the expected hyperprolactinemia with risperidone is uncertain. Patients gained weight with olanzapine and risperidone and lost weight with placebo; the possibility that antipsychotic drugs cause the metabolic syndrome in the elderly requires further investigation.

The key enrollment criterion — the physician's assessment that an antipsychotic drug was the appropriate pharmacologic therapy — helped to ensure clinical equipoise. The patient population was broad and representative in terms of age, race, ethnic group, level of disability, and extent of cognitive impairment. The level of psychopathology was moderate to severe, which is similar to that in studies of patients in nursing homes. Approximately 75% of the patients required a level of care at least equivalent to that given in assisted-living facilities.<sup>31</sup> Most of the patients in our study required a level of care equivalent to that given in an assisted-living facility, and 17% needed the equivalent of nursing home care.<sup>31</sup> Washout from previous treatment and run-in periods were not used because of the patients' acute clinical symptoms; instead, the study design allowed for rapid assignment and initiation of treatment to be consistent with clinical practice. Specifically, 14% percent of the patients were receiving antipsychotic medications within 2 weeks before randomization (5% risperidone, 4% haloperidol, 3% quetiapine, and 2% olanzapine). The use of cholinesterase inhibitors did not influence outcomes.

We used the discontinuation of treatment for any reason as a pragmatic measure of outcomes for individual patients rather than means for scores on rating scales because the discontinuation of treatment incorporates the judgments of patients, caregivers, and clinicians regarding efficacy, safety, and tolerability and reflects therapeutic benefits in relation to undesirable effects. Previous trials compared mean scores on rating

scales according to group at the end of 6 to 12 weeks without regard to tolerability and did not address the outcomes among individual patients. Our results are consistent with those of the few previous outpatient trials of atypical antipsychotic medications,<sup>9</sup> which showed modest trends or no significant effects on symptom ratings.

Overall, the rates of discontinuation of treatment among the four study groups ranged from 77 to 85%. Although the differences among the groups may have been significant in a larger trial, our findings suggest that there is no large clinical benefit of treatment with atypical antipsychotic medications as compared with placebo.

Physicians were likely to switch medications quickly in the face of lack of efficacy or adverse effects. Although the atypical antipsychotic drugs were more effective than placebo, adverse effects limited their overall effectiveness, and their use may be restricted to patients who have few or no side effects and for whom benefits can be discerned. Clinicians, patients, and family members must consider both risks and benefits in order to optimize a patient's care.

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#### APPENDIX

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