

Cost-Benefit Analysis of Second-Generation Antipsychotics and Placebo in a Randomized Trial of the Treatment of Psychosis and Aggression in Alzheimer Disease

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Context: Second-generation antipsychotics (SGAs) are prescribed for psychosis, aggression, and agitation in Alzheimer disease (AD).

Objective: To conduct a cost-benefit analysis of SGAs and placebo (taken to represent a “watchful waiting” treatment strategy) for psychosis and aggression in outpatients with AD.

Design: Randomized placebo-controlled trial of alternative SGA initiation strategies.

Setting: Forty-two outpatient clinics.

Participants: Outpatients with AD and psychosis, aggression, or agitation (N=421).

Intervention: Participants were randomly assigned to treatment with olanzapine, quetiapine fumarate, risperidone, or placebo with the option of double-blind randomization to another antipsychotic or citalopram hydrobromide or open treatment over 9 months.

Main Outcome Measures: Monthly interviews documented health service use and costs. The economic perspective addressed total health care and medication costs. Costs of study drugs were estimated from wholesale prices with adjustment for discounts and rebates. Quality-

adjusted life-years (QALYs) were assessed with the Health Utilities Index Mark 3 and were supplemented with measures of functioning, activities of daily living, and quality of life. Primary analyses were conducted using all available data. Secondary analyses excluded observations after the first medication change (ie, phase 1 only). Cost-benefit analysis was conducted using the net health benefits approach in a sensitivity analysis in which QALYs were valued at \$50 000 per year and \$100 000 per year.

Results: Average total health costs, including medications, were significantly lower for placebo than for SGAs, by \$50 to \$100 per month. There were no differences between treatments in QALYs or other measures of function. Phase 1-only analyses were broadly similar. Net-benefit analysis showed greater net health benefits for placebo as compared with other treatments, with probabilities ranging from 50% to 90%.

Conclusions: There were no differences in measures of effectiveness between initiation of active treatments or placebo (which represented watchful waiting) but the placebo group had significantly lower health care costs.

Trial Registration: clinicaltrials.gov Identifier: NCT00015548.

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ALZHEIMER DISEASE (AD) IS A costly and debilitating illness that affects an estimated 5 to 8 million Americans.¹ In 2000, Medicare spending to treat 4.5 million Americans with AD totaled \$62 billion, or 34% of all Medicare spending, with an additional government expenditure of \$19 billion through Medicaid.² Psychotic symptoms and agitation complicate the course of AD in about half of all cases.^{3,4} In recent years, second-generation antipsychotics (SGAs) have become the first-line pharmacological treat-

ments for psychosis or agitation associated with dementia, in part because they have been perceived as more effective and safer than older antipsychotic medications.^{5,6} Some studies have shown reduced risk of neurological adverse effects relative to older antipsychotics.^{7,8} The few controlled trials of these drugs in AD have been mainly in nursing home patients⁹ where safety issues have emerged concerning risk for cerebrovascular adverse events^{10,11} and death.¹¹ Antidepressants, such as citalopram hydrobromide, have been suggested as alternatives to antipsychotics.^{12,13}

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Group Information: The CATIE-AD study group is listed on page 1266.

To further evaluate the effectiveness of these agents in the treatment of patients with AD, the National Institute of Mental Health (NIMH) initiated the Clinical Antipsychotic Trial of Intervention Effectiveness—AD Trial (CATIE-AD). CATIE-AD used an experimental study design to compare the effectiveness of SGAs (olanzapine, risperidone, and quetiapine fumarate) that were available in the United States in January 2001 and commonly used in patients with dementia and placebo.¹⁴ The primary clinical outcome from this study was time to discontinuation for any cause from the initial randomly assigned drug or placebo,¹⁵ an outcome that integrated outcomes for efficacy, safety, and tolerability into a global measure of effectiveness that reflects therapeutic benefits in relation to undesirable effects. No differences were found between treatments on this measure, although time to discontinuation specifically because of lack of efficacy favored olanzapine and risperidone over placebo, and time to discontinuation specifically because of adverse events or intolerability favored placebo over the 3 SGAs.¹⁵ The current article presents results from CATIE-AD on measures of health care costs and health-related quality of life. It also presents a cost-benefit analysis using the net health benefit approach¹⁶ in which quality-adjusted life-years (QALYs) are given a range of plausible monetary values from which health care costs are subtracted, yielding a dollar-based estimate of net health benefits on which treatments can be compared.

METHODS

STUDY DESIGN

The background, rationale, and methods of CATIE-AD have been presented in detail previously.¹⁴ The trial was conducted between April 2001 and November 2004 at 45 clinical sites in the United States.

Participants were initially randomly assigned to receive olanzapine, quetiapine, risperidone, or placebo under double-blind conditions in a 2:2:2:3 allocation ratio (phase 1). Those whose initial assigned treatments were discontinued (end of phase 1) could be randomly and double-blindly assigned to receive treatment with 1 of the 2 SGAs that they were not initially assigned to or with citalopram (phase 2). Participants receiving placebo in phase 1 received citalopram or 1 of the 3 SGAs in a 3:1:1:1 ratio in phase 2. Participants whose phase 2 treatments were discontinued could then be randomly assigned to open-label treatment with one of the active agents not yet received (phase 3). Patients could be shifted at any time to open treatment with the physician's choice of medication and continue data collection.

The objective of the cost-benefit component of CATIE-AD was to compare alternative treatment initiation strategies in an intention-to treat (ITT) analysis (ie, to determine whether choice of one of the SGAs as the first treatment in the CATIE-AD algorithm led to superior health and cost outcomes as compared with the other SGAs or placebo, which we take herein to represent an initial strategy of "watchful waiting"). Secondary cost-benefit analysis compared treatments exclusively during the period on the initially assigned condition (phase 1—only analysis). Although placebo is not a real-world treatment, it is a relevant experimental condition for this cost-benefit analysis inasmuch as it represents an approach to agitation and psychosis in AD involving general support without active pharmacotherapy. Watchful waiting has become an increasingly

important clinical option in diseases such as prostate¹⁷ and other forms of cancer¹⁸⁻²⁰ and depression^{21,22} as well as in surgical conditions such as abdominal aortic aneurysm²³ and inguinal hernia.²⁴ It can only be subject to double-blind experimental evaluation through a "placebo" control.

PARTICIPANTS

Eligible participants had dementia of the Alzheimer type (DSM-IV)²⁵ and Mini-Mental State Examination²⁶ scores from 5 to 26 and were ambulatory outpatients living at home or in assisted living. They had clinically severe delusions, hallucinations, aggression, or agitation, occurring after the onset of symptoms of dementia. A score of "moderate" or greater was required during the week prior to randomization on the Brief Psychiatric Rating Scale²⁷ and a severity score of "moderate" or more was required on the delusion, hallucination, agitation, or "aberrant motor behavior" items of the Neuropsychiatric Inventory.²⁸ A study partner or caregiver who lived with or visited the prospective participant at least 8 hours per week and 3 days per week was required to contribute to the assessments.

Participants were excluded if they had schizophrenia, schizoaffective disorder, delirium, or probable vascular dementia (by Association Internationale pour la Recherche et l'Enseignement en Neurosciences—National Institute of Neurological Disorders and Stroke criteria).²⁹ Other exclusion criteria were described previously.¹⁵ Participants were allowed to continue to receive stable doses of various medications, including cholinesterase inhibitors, memantine, antihypertensives, anti-inflammatory drugs, anticoagulants, laxatives, and diuretics. Concurrent use of antipsychotics, antidepressants, anticonvulsants as mood stabilizers, or regularly prescribed benzodiazepines was prohibited.

The study was reviewed and approved by the NIMH data safety and monitoring board and the institutional review board for each site. Written informed consent was obtained from participants or their legally authorized representatives and from the study partners.

INTERVENTIONS

The trial was designed to encourage prescribing as close as possible to typical clinical practices, allowing flexibility of dosing while maintaining the randomized (phases 1-3) and double-blinded treatment assignment (phases 1-2) of a clinical trial. Study physicians adjusted dosages based on their clinical judgments and participants' responses to treatment.¹⁵

PSYCHOSOCIAL INTERVENTION

All participants and caregivers were given basic information and education about AD, its course, clinical problems, and management. Caregivers were offered 2 counseling sessions during the first 18 weeks and could speak with staff members as needed.^{30,31}

MEASURES

Costs

The economic perspective addressed comprehensive health care costs, which were estimated by multiplying the number of units of each type of service received by the estimated local unit cost of that service and then summing the products across different services.³²

Service use was documented every month through a questionnaire completed by the caregiver that recorded 5 kinds of

hospital stays across 6 different types of facilities, nights spent in nursing homes, halfway houses, board and care homes, and respite care programs. Use of 18 types of outpatient services or community supports commonly used by patients with AD³³ and 14 types of outpatient mental health care, including psychiatric and psychosocial rehabilitation services, were documented along with 7 different types of medical or surgical outpatient visits and use of both psychiatric and medical emergency department services.

Unit costs of these services were estimated from published reports and administrative data sets (data available on request). Antipsychotic medication costs were based on published wholesale prices for the specific capsule strengths used in CATIE,³⁴ adjusted downward for discounts and rebates affecting patients whose medication costs would have been paid by Medicaid (with costs about 25% less than wholesale prices)³⁵ or by the Department of Veterans Affairs (40% less than wholesale prices).³⁶ Costs of more than 200 different ancillary medications were estimated on the basis of average daily medication costs for specific agents in the 2002 MarketScan data set, representing typical medication costs for privately insured patients.³⁷

Quality of Life

Cost-benefit analysis requires a single measure of health-related quality of life that reflects both health gains and health losses due to adverse effects. The Public Health Service Task Force on Cost-Effectiveness in Health and Medicine³² specifically recommended that health states be expressed as quality-adjusted life-years (QALYs), a year of life rated on a cardinal scale from 0 (worst possible health) to 1 (perfect health), as evaluated by members of the general public.

Quality-adjusted life-years were assessed in CATIE-AD using the Health Utilities Index Mark 3,³⁸ a generic utility measure that has been used in previous studies of AD.^{39,40} The Health Utilities Index was supplemented by 3 disease-specific measures: (1) the Alzheimer's Disease Related Quality of Life Scale,^{41,42} (2) the Alzheimer's Disease Cooperative Study Activities of Daily Living Scale (ADCS-ADL),⁴³ and (3) the AD Dependence Scale,^{44,45} which rates the degree of dependence or assistance needed by a patient. All of these measures were administered to caregivers who were asked to rate recently observed behaviors.

STATISTICAL METHODS

The overall difference among the treatment groups was evaluated using a test with 3 *df*. If the difference was significant at $P \leq .05$, then each drug was compared with placebo/watchful waiting by means of a Hochberg adjustment for multiple comparisons⁴⁶ in which the largest pairwise *P* value was considered statistically significant at $P = .05$ and the smallest was compared with $P = .017$ ($P = .05/3$). The SGAs were tested with each other with a 2-*df* test. If that test was significant at $P < .05$, then each pair was compared at $P = .05$.

Average monthly costs during 9 months were compared across treatment groups in an ITT analysis using all available data with a mixed model including terms representing the baseline value of the dependent cost variable, time (treated as a classification variable for months 1-9), pooled site, and baseline \times time interactions. Dropouts and patients who died were not included in these. The baseline \times time term adjusts for baseline differences in characteristics of participants who dropped out early and thus are less well represented at later points. A random subject effect and a first-order autoregressive covariance structure were used to adjust standard errors for the correlation of observations from the same individual.

Because of the skewed distribution of nondrug cost data, statistical tests for health care costs and total costs including medications were conducted on log-transformed data. Adjusted average monthly log-transformed costs were then re-transformed into average monthly costs using the "smearing estimation" method of Duan,⁴⁷ after testing the data for heteroscedasticity.⁴⁸ Median costs and winsored mean cost (in which the top and bottom 3% of observations are set to the value of the third and 97th percentiles, respectively⁴⁹) are also presented. The same ITT analytic model was used for quality-of-life outcomes based on scores averaged across the 3-, 6-, and 9-month observations, again using a random subject effect and a first-order autoregressive covariance structure.

In addition to the primary analysis, in which all data were used and observations were classified according to the initial randomization, a secondary analysis was also conducted excluding observations after participants discontinued the initially assigned treatment (ie, limited to phase 1 of the trial). Since 63% of the patients had discontinued treatment in phase 1 by 3 months (when the first quality-of-life assessments were made) the phase 1 analysis of quality-of-life outcomes is limited to the subset of patients still in phase 1 by 3 months. Approximately 80% of patients discontinued taking phase 1 medication before 9 months. The repeated-measures model estimates the missing values due to discontinuation based on the correlations between points for patients who did not discontinue treatment and assumes that the loss of data caused by a patient's discontinuing medication use during the phase is missing at random. Mixed-model results limited to phase 1-only assessments should therefore be viewed cautiously.

Post hoc power analysis, using the actual standard errors of mean differences between pairs of drugs from this study,⁵⁰ showed that in the primary analysis there was 80% power to detect differences of 0.22 SD for log-transformed cost measures, 0.28 SD for QALYs, and 0.26 to 0.28 SD for other outcomes. For the phase 1-only analysis, there was 80% power to detect differences of 0.31 SD for cost, 0.47 SD for QALYs, and 0.33 to 0.49 SD for other outcomes. We thus had adequate power to detect small to moderate differences between groups in the primary analysis but limited power to detect small effects that might be clinically meaningful.

COST-BENEFIT ANALYSIS

In the cost-benefit analysis, treatments were compared using the method of net health benefits.¹⁶ In this approach, a range of conventional estimates for the dollar value of a QALY are multiplied by the QALY estimate for each patient at each point to estimate the monetized value of his or her health status at each observation. Following conventions used in policy making,⁵⁰ we used estimates of \$50 000 per QALY per year (\$4167 per QALY per month) and \$100 000 per QALY per year (\$8333 per QALY per month) in a sensitivity analysis.

Monthly health care costs were then subtracted from the estimated monthly health benefits to generate an estimate of net health benefits for each patient for each month. Finally, we used mixed-model regression analyses of the type described earlier to compare mean differences between the groups on net health benefits using monthly net health benefits estimates from all points. Following the method proposed by Hoch et al,⁵¹ which uses linear regression to make these comparisons. The probability that the treatment with the greatest net benefits is superior to the others at each of the 2 estimated values of a QALY was estimated in a 1-tailed test based on the significance of differences between the least square means as $1 - p/2$.⁵²

Table 1. Patient Characteristics at the Time of Random Assignment by Initial Treatment

Characteristic	Mean (SD)				
	Total Sample (n = 421)	Olanzapine (n = 100)	Risperidone (n = 85)	Quetiapine (n = 94)	Placebo (n = 142)
Age, y	77.9 (7.5)	78.8 (7.3)	78.4 (7.1)	77.3 (8.7)	77.3 (7.0)
Male, No. (%)	186 (44.2)	45 (45)	36 (42.4)	44 (46.81)	61 (43.0)
Race/ethnicity, No. (%)					
White	331 (78.6)	80 (80)	68 (80.0)	76 (80.85)	107 (75.4)
Black	75 (17.8)	14 (14)	15 (17.6)	15 (15.96)	31 (21.8)
Hispanic	22 (5.2)	9 (9)	1 (1.2)	8 (8.51)	4 (2.8)
Other/missing	15 (3.6)	6 (6)	2 (2.4)	3 (3.19)	4 (2.8)
Marital status, No. (%)					
Married	249 (59.1)	63 (63)	49 (57.6)	56 (59.57)	81 (57.0)
Separated/divorced	25 (5.9)	3 (3)	4 (4.7)	10 (10.64)	8 (5.6)
Never married	13 (3.1)	2 (2)	1 (1.2)	3 (3.19)	7 (4.9)
Widowed	134 (31.8)	32 (32)	31 (36.5)	25 (26.60)	46 (32.4)
MMSE ²⁶ score	15 (5.8)	14.99 (5.43)	15.66 (6.06)	14.91 (6.05)	14.67 (5.76)
BPRS ²⁷ score	27.8 (12.3)	27.0 (11.8)	27.7 (13.6)	28.0 (12.3)	28.2 (12.0)
NPI ²⁸ score	36.9 (18.3)	31.8 (16.4)	38.3 (20.2)	37.6 (18.4)	39.1 (17.8)
Caregiver distress score	16.5 (8.6)	14.6 (8.0)	16.4 (8.9)	16.6 (8.7)	17.8 (8.5)
ADRQL ^{41,42} score	67.3 (14.7)	69.2 (14.6)	68.1 (16.3)	66.9 (13.2)	68.7 (14.6)
ADCS-ADL ⁴³ score	39.4 (17.1)	39.9 (17.5)	40.3 (18.1)	39.5 (17.5)	38.6 (16.1)
AD Dependence Scale ^{44,45} score	3.3 (1.0)	3.4 (1.0)	3.2 (1.0)	3.3 (1.0)	3.3 (0.9)
CAS ⁵³ score	16.3 (11.9)	16.2 (12.3)	14.6 (12.7)	16.6 (11.2)	17.3 (11.6)
EPS score	0.38 (0.47)	0.41 (0.52)	0.36 (0.46)	0.38 (0.44)	0.38 (0.47)

Abbreviations: AD, Alzheimer disease; ADCS-ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living Scale; ADRQL, Alzheimer's Disease-Related Quality of Life Scale; BPRS, Brief Psychiatric Rating Scale; CAS, Caregiver Activity Survey; EPS, extrapyramidal symptoms; MMSE, Mini-Mental State Examination; NPI, Neuropsychiatric Inventory.

RESULTS

Altogether, 421 participants entered the study: 100 were randomized to olanzapine, 85 to risperidone, 94 to quetiapine, and 142 to placebo. Data on screening, enrollment, completion of phase 1, and continuation into phase 2 were presented in Figure 1 of the primary report of this study.¹⁶ Altogether, 231 patients (54.9%) participated in phase 2; 99 (23.5%), in phase 3; and 174 (41.3%), in phase 4.

A total of 280 participants (66.8%) had at least 1 follow-up visit while receiving the initially randomized treatment (ie, during phase 1): 72 (72.0%) who had been randomized to olanzapine; 60 (57.4%), to risperidone; 54 (71.4%), to quetiapine; and 94 (66.7%), to placebo. There were no differences between groups in these proportions ($\chi^2_3 = 5.74$; $P = .20$).

There were no significant differences on baseline characteristics (**Table 1**) or in the proportion of monthly follow-up assessments that were completed between groups (80% overall: olanzapine, 80%; risperidone, 80%; quetiapine, 78%; placebo, 81%; $\chi^2_3 = 6.7$; $P = .10$). However, the proportion of monthly assessments that were completed during phase 1 treatment (31% overall) was significantly higher for those assigned to risperidone (34.9%) and olanzapine (33%) as compared with those assigned to quetiapine (30%) and placebo (27.9%) ($\chi^2_3 = 13.7$; $P < .01$). A total of 8 patients died during phase 1 (1.9%) and 30, during the entire trial (7.1%), with no statistically significant differences between groups.

The proportion of patients at study entry who were taking first-generation antipsychotics (5%) or SGAs (10%)

did not differ significantly between groups and the proportion of patients who took such medications outside the study protocol (1% and 3%, respectively) was also quite small (Table 1 and Table 3 in the original report from this study).¹⁵

Table 2 reports average monthly costs by treatment group. As expected, the group initially assigned to placebo (ie, watchful waiting) had significantly lower experimental drug costs of about \$55 per month (**Figure 1**), which led to significantly lower total drug costs despite there being no statistically significant differences in the cost of concomitant medications across the treatment groups. Mean health service costs (log transformed) were also not significantly different across the treatment groups. Although unadjusted mean total costs were higher for the group initially assigned to placebo than for the group assigned to risperidone, this result was driven by outlier observations. The group assigned to placebo had the lowest median costs, and when the top and bottom 3% of the distribution were set to the third and 97th percentile values, respectively (creating a "winsored" mean), total average monthly costs fell to \$1023 for the group initially assigned to placebo as compared with the other groups: \$1118 for olanzapine, \$1215 for quetiapine, and \$1092 for risperidone (**Figure 2**). Retransformed log data using the smearing estimator showed even greater mean cost differences favoring the group assigned to placebo, totaling \$400 to \$500 per month in total drug plus health service costs (data available on request).

Table 3 reports mixed model-adjusted means of the effectiveness measures by treatment group across months

Table 2. Average Monthly Costs by Treatment Group Over 9 Months^a

	Olanzapine, \$		Risperidone, \$		Quetiapine, \$		Placebo, \$		F Test	Overall P Value	Paired Comparisons ^b
	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median	Mean (SD)	Median			
Intent to Treat^c											
Type of cost											
Monthly drug costs	302 (177)	264	311 (216)	269	311 (196)	283	264 (180)	254	6.83	<.001	P<O, R, Q
Experimental medications	106 (70)	97	92 (75)	91	102 (74)	94	45 (65)	25	15.10	<.001	P<O, R, Q
Concomitant medications	196 (188)	151	219 (215)	165	209 (202)	157	219 (176)	207	0.56	.64	NS
Monthly health service costs	1194 (2235)	326	1004 (1566)	168	1354 (3543)	486	1222 (2691)	221	1.15	.33	NS
Monthly total costs ^d	1495 (2241)	645	1315 (1593)	577	1665 (3565)	810	1487 (2704)	572	3.40	.02	P<O, R, Q
Phase 1 Only											
Type of cost ^e											
Monthly drug costs	327 (151)	300	308 (204)	278	342 (217)	300	165 (146)	150	36.16	<.001	P<O, R, Q
Experimental medications	176 (47)	168	103 (29)	94	173 (61)	178	0 (0)	0	317.10	<.001	P<O, R, Q; R<O, Q
Concomitant medications	151 (153)	134	205 (203)	159	169 (189)	139	165 (146)	150	0.74	.53	NS
Monthly health service costs	393 (732)	76	827 (1912)	90	530 (702)	230	382 (1000)	66	1.46	.22	NS
Monthly total costs	720 (741)	463	1135 (1961)	483	871 (722)	625	547 (1009)	282	15.39	<.001	P<O, R, Q

Abbreviations: NS, not significant; O, olanzapine; P, placebo; Q, quetiapine fumarate; quetiapine, quetiapine fumarate; R, risperidone.

^aRaw (unadjusted) mean costs are presented. Statistical tests were based on the results of a mixed model using log-transformed costs.

^bBased on Hochberg adjustment for multiple comparisons.

^cTotal follow-up observations for olanzapine=717, risperidone=628, quetiapine=661, and placebo=1028. The number of monthly follow-up interviews completed was 380 at 1 month, 369 at 2 months, and 364 at 3 months followed by 338, 333, 331, 299, 306, and 314 at 9 months. χ^2 Analysis of the number of observations at each point showed no differences across groups ($\chi^2_{27}=2.4$; $P>.99$).

^dAlthough the raw monthly total costs were higher for placebo than for risperidone, this result is driven by outliers. When the top and bottom 3% of the distribution are omitted, average monthly total costs fall to \$1023 for placebo compared with \$1118 for olanzapine, \$1215 for quetiapine, and \$1092 for risperidone. This trimming was not used in the statistical analysis.

^eTotal follow-up observations in phase 1 for olanzapine=297, risperidone=264, quetiapine=250, and placebo=354. The number of monthly follow-up interviews completed was 280 at 1 month, 197 at 2 months, and 154 at 3 months followed by 114, 100, 92, 73, 78, and 77 at 9 months. χ^2 Analysis of the number of observations at each point showed no differences across groups ($\chi^2_{24}=6.9$; $P=.99$).

3, 6, and 9. There were no significant differences across the treatment groups in QALYs (Figure 3), Alzheimer's Disease–Related Quality of Life Scale scores, or Dependence Scale scores. However, participants assigned to olanzapine were actually more impaired on the ADCS-ADL Scale than those assigned to the placebo (ie, watchful waiting) group (mean score, 30.4 vs 34.4 [−4.0 points]; $P=.004$). These differences were greatest at the 3-month assessment (mean [SE], −5.5 [1.56] points; $df=1603$; $P<.001$), still significant at 6 months (mean [SE], −3.7 [1.61] points; $df=1603$; $P=.02$), and not significant at 9 months (mean [SE], −2.8 [1.64] points; $df=1603$; $P=.09$).

Results of the secondary analysis, limited to observations during phase 1, the period of treatment with the initially assigned drug, were similar to the ITT analysis, although since data loss was substantial, these results should be interpreted very cautiously. Phase 1 cost differences were generally larger, with the placebo group showing significantly lower total drug costs, experimental drug costs, and total costs of \$200 to \$600 per month (Table 2).

With respect to the effectiveness measures, participants in the placebo group showed significantly higher functioning on the ADCS-ADL Scale relative to each of the SGAs (mean [SE], 10.03 [1.96] points greater than olanzapine; $df=1148$; $P<.001$; 4.78 [2.1] points greater than quetiapine; $df=1148$; $P=.02$; and 5.47 [2.08] points greater than risperidone; $df=1148$; $P=.01$). The placebo (ie, watchful waiting) group had significantly lower scores on the Dependence Scale compared with the olanzapine group (mean [SE], −0.41 [0.146]; $df=1153$; $P=.005$)

(Table 3). In the analyses of both the ADCS-ADL and Dependence scale scores, the advantages for placebo increased from the 3-month to the 9-month follow-up assessment.

Analysis of net health benefits showed that when the value of health benefits was estimated at \$50 000 per QALY, placebo was superior to olanzapine, with a probability of 88% on ITT and 90% on phase 1-only analysis, and superior to quetiapine, with a probability of 89% on ITT and 90% on phase 1-only analysis. Risperidone was superior to placebo, with a probability of 51% on ITT, while placebo was superior to risperidone, with a probability of 77% on phase 1-only analysis.

When the value of a QALY was estimated at \$100 000 per QALY, placebo was superior to olanzapine, with a probability of 87% on both ITT and phase 1-only analysis, and superior to quetiapine, with a probability of 72% on ITT and 74% on phase 1-only analysis. Risperidone was superior to placebo, with a probability of 68% on ITT, while placebo was superior to risperidone, with a probability of 55% on phase 1-only analysis. Thus, as the estimated value of a QALY increases from \$50 000 to \$100 000, treatments with better QALY results are more likely to be superior or less likely to be inferior. Similarly, as one shifts from ITT to phase 1-only analysis, placebo appears to be superior because the cost differential becomes greater when excluding observations after patients switched from placebo to expensive active medications. These analyses were repeated on nonwinsored means, with no change in the pattern or magnitude of results.

Thus, while there were no significant differences between treatments with regard to net health benefits at the conventional 95% probability standard, placebo was most often superior to the SGAs on net health benefit analysis,¹⁶ with probabilities ranging from 50% to 90%.

COMMENT

This study reports on the cost-benefit analysis of a relatively large clinical trial of 3 SGA medications and placebo in the treatment of outpatients with AD with psychosis, aggression, or agitation. We found that SGA treatment groups had significantly higher costs than the group that initially received placebo, representing a watchful waiting treatment approach, but there were no statistically significant differences on QALYs, the main measure of effectiveness. These results are consistent with

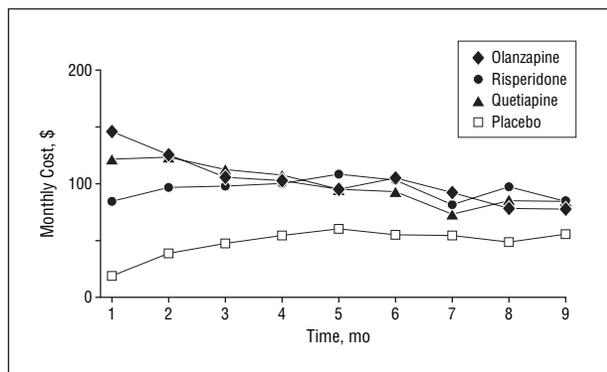


Figure 1. Comparison of treatments on average monthly medication costs (experimental drugs and concomitant medications). Quetiapine was given as quetiapine fumarate.

the primary CATIE-AD phase 1 outcomes,¹⁵ in which there were no differences across treatment groups in time to all-cause discontinuation of phase 1 medication, although participants originally assigned to olanzapine and risperidone were less likely to discontinue taking the assigned medication because of lack of efficacy than the other drugs and participants initially assigned to treatment with placebo were less likely to discontinue use for intolerability.

Consistent with these findings, the present study found that initial assignment to each active medication was more costly than placebo (ie, than watchful waiting before active treatment), predominantly because of greater drug costs. While there were no differences between the groups in QALYs, the placebo group was superior to the olanzapine group on the activities of daily living measure of ef-

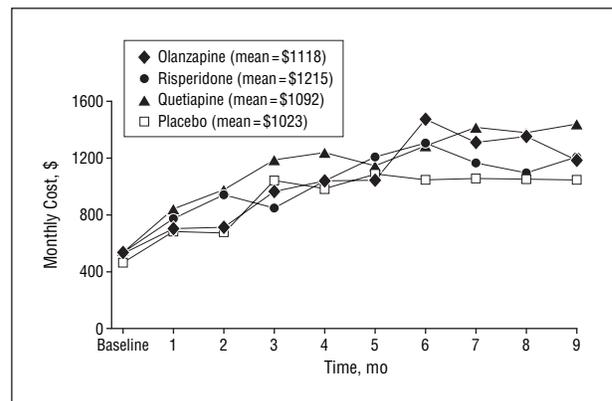


Figure 2. Comparison of treatments on total average monthly health care costs including medications. Values are given as winsored means, in which the top and bottom 3% of observations are set to the value of the third and 97th percentiles, respectively. Quetiapine was given as quetiapine fumarate.

Table 3. Comparison of Effectiveness by Treatment Group (Adjusted Means Across All Points Based on Mixed Models)

Effectiveness measure	Mean (SE)				F Test	Overall P Value	Paired Comparisons ^a
	Olanzapine	Risperidone	Quetiapine	Placebo			
Intent to Treat^b							
QALYs ^c	0.12 (0.02)	0.16 (0.02)	0.15 (0.02)	0.14 (0.02)	0.95	.42	NS
ADRQOL ^{41,42C}	72.44 (1.23)	71.08 (1.31)	72.19 (1.27)	72.12 (1.02)	0.22	.88	NS
ADCS-ADL ^{43C}	30.4 (1.07)	33.27 (1.15)	33.79 (1.12)	34.4 (0.9)	3.00	.03	O < P
AD Dependence Scale ^{44,45C}	3.73 (0.07)	3.69 (0.08)	3.7 (0.07)	3.62 (0.06)	0.53	.66	NS
Phase 1 Only^d							
QALYs ^c	0.15 (0.03)	0.22 (0.03)	0.21 (0.04)	0.20 (0.03)	0.92	.43	NS
ADRQOL ^c	76.2 (1.9)	71.9 (2.0)	75.2 (2.1)	77.4 (1.8)	1.49	.22	NS
ADCS-ADL ^c	31.9 (1.4)	36.4 (1.6)	37.1 (1.7)	41.9 (1.3)	8.80	<.001	O, Q, R < P
AD Dependence Scale ^c	3.69 (0.11)	3.59 (0.12)	3.48 (0.12)	3.28 (0.10)	2.87	.04	P < O

Abbreviations: AD, Alzheimer disease; ADCS-ADL, Alzheimer's Disease Cooperative Study Activities of Daily Living Scale; ADRQOL, Alzheimer's Disease-Related Quality of Life Scale; NS, not significant; O, olanzapine; P, placebo; Q, quetiapine fumarate; QALY, quality-adjusted life-year; quetiapine, quetiapine fumarate; R, risperidone.

^aBased on Hochberg adjustment for multiple comparisons.

^bTotal follow-up observations for olanzapine=345, risperidone=299, quetiapine=319, and placebo=489. The number of monthly follow-up interviews completed was 373 at 3 months, 339 at 6 months, and 319 at 9 months. χ^2 Analysis of the number of observations at each point showed no differences across groups ($\chi^2_9=0.4$; $P>.99$).

^cRange for QALYs=0 to 1, higher is better; ADRQOL range=0 to 100, higher is better; ADCS-ADL range=0 to 78, higher is better; and AD Dependence Scale range=0 to 5, lower score is better.

^dTotal follow-up observations in phase 1 for olanzapine=85, risperidone=78, quetiapine=72, and placebo=95. The number of monthly follow-up interviews completed was 158 at 3 months, 197 at 6 months, and 154 at 9 months. χ^2 Analysis of the number of observations at each point showed no differences across groups ($\chi^2_6=1.69$; $P=.96$).

fectiveness in the ITT analysis and superior to all medication groups on this measure in the phase 1-only analysis, as well as to the olanzapine group on the Dependence Scale. One conclusion of this analysis would thus be that the watchful waiting strategy, entailing general medical management, nonspecific support, and delayed initiation of antipsychotic pharmacotherapy, is slightly less costly and no less effective than immediate treatment with SGA medications. Cost-benefit analysis using the net health benefit approach^{16,51} and applying estimates of \$50 000 per QALY and \$100 000 per QALY in a sensitivity analysis suggested that placebo/watchful waiting was superior to SGAs, with probabilities ranging from 50% to 90%, not reaching the conventional standard of 95% confidence. The secondary finding that patients taking olanzapine scored worse on the activities of daily living measure than patients treated with watchful waiting most likely represents the greater level or combination of sedation, gait disturbances, and behaviorally inhibiting adverse effects with this drug.

Strengths of the study included its large sample size, high follow-up rate on primary analysis, and moderate duration. However, several limitations of the study require comment. First, the study was conducted under highly controlled conditions. Although medications could be discontinued or switched after 2 weeks, results may not be generalizable to real-world clinical settings in which placebo, for example, is not offered as a treatment, although we feel it can be usefully understood to represent a conservative strategy of watchful waiting, a strategy that was sufficient during the entire 9 months for 15% of patients assigned to placebo.

It could, furthermore, be argued that continuing to assign participants to their original treatment condition following a medication switch is misleading since the treatment has actually changed. However, this study sought specifically to test different treatment initiation strategies through a true ITT analysis. There has been growing interest in stepped treatment strategies in which patients are initially expected to try a first-line drug, sometimes an older generic drug or sometimes watchful waiting, and are only offered additional medications if they do not respond to the initial treatment. In the secondary analyses in which observations following the first medication switch were excluded (ie, the phase 1-only analysis), the pattern of results found in the ITT analysis was strengthened. Cost differences favoring placebo were greater in the phase 1-only analysis, with similar results for QALYs and some evidence of lower functioning among participants assigned to SGAs as their first treatment.

Statistical power was limited, especially in the phase 1-only results. Although there was an 80% chance of detecting moderate effect sizes (ie, from 0.31-0.49), power was inadequate to detect small differences of effect size (0.20 to 0.30 or 0.04-0.08 QALYs) that could be of clinical importance. It has been demonstrated that panels of judges cannot differentiate between health states that differ by 0.03 QALYs or less.^{52,54} Since the maximal average superiority of any drug over placebo was 0.02 QALYs in this study (on both the ITT analysis and the phase 1-only analysis), it is somewhat less likely that important clinical benefits were missed.

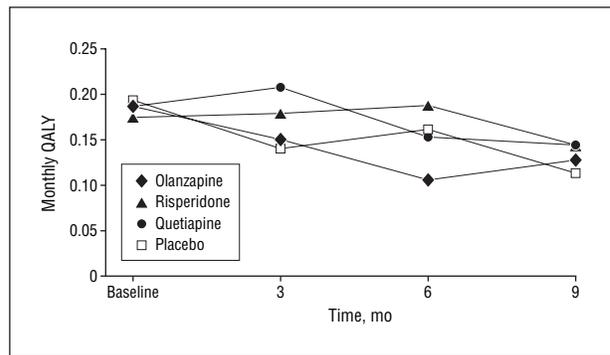


Figure 3. Comparison of treatments on quality-adjusted life-years (QALYs) measured by the Health Utilities Index Mark 3.³⁸ Quetiapine was given as quetiapine fumarate.

While data loss from attrition was modest in the primary ITT analysis, there was 80% power to detect small to moderate differences and there were only modest differences between groups in follow-up rates. Although data loss was more substantial in the phase 1-only analysis, significant differences were observed on cost measures and some outcome measures in both the ITT analysis and the phase 1-only analysis, suggesting that the study had sufficient statistical power to detect differences on these measures. While no analysis showed significant advantage for any SGA over either placebo/watchful waiting or over other SGAs, the group originally assigned to placebo had significantly lower costs and higher activities of daily living scores than some SGA groups on both the ITT analysis and the phase 1-only analysis, suggesting sufficient power to detect some group differences.

Costs were based on proxy self-reported use data from the patients' caregivers. Surveys of service use were conducted monthly to improve the accuracy of the service use data, but these data have not been validated. However, there is no reason to suspect any bias between the treatment conditions in the measures of service use and costs.

Participants in the trial were followed up for only 9 months, so any benefits or adverse effects that developed after 9 months of treatment are not captured in the study. In addition, since the study focused on outpatients, its generalizability to nursing home residents is unknown. Although dosing was flexible according to clinical need, it has been suggested that quetiapine was dosed lower than in other studies,⁵⁵ perhaps limiting its effectiveness.

To our knowledge, this study is the first cost-benefit analysis of SGA medication in the treatment of noncognitive symptoms of AD in outpatients, an off-label use of SGAs that is both common and costly. Annual sales of antipsychotic medications in the United States reached \$10.5 billion in 2005.⁵⁶ A study of antipsychotic use and costs among outpatients in the Department of Veterans Affairs found that 42.8% of outpatients who received antipsychotic medications in 1999 were prescribed the drug for an off-label use, and 5% were treated exclusively for dementia.³⁶ A more recent study of Medicare beneficiaries in nursing homes found that 27%, more than 600 000 patients, received a prescription for antipsychotic medi-

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cation in 2000 and 2001 and that antipsychotic use is increasing in nursing homes.⁵⁷ Together, these findings imply that at least \$500 million, and probably substantially more, is spent each year on SGA medications for the treatment of dementia, a condition for which they have not received Food and Drug Administration (FDA) approval.

FDA approval requires only that the manufacturer demonstrate that the drug is safe and effective in adequate and well-controlled studies as compared with placebo in a specified condition. However, once the drug is approved by the FDA, physicians are free to prescribe it

for other indications, including treating conditions for which the drug was not approved, although manufacturers are prohibited from marketing the drug for such uses. Off-label use is less often studied in randomized controlled trials than use for the indicated condition. As this study and others^{9,58,59} have shown, these drugs may offer little clinical efficacy overall when prescribed to patients for agitation and psychosis associated with AD and showed no overall health economic or effectiveness benefits compared with a strategy that begins with watchful waiting. Future research should examine the pharmacoeconomics of these drugs in dementia to identify cir-

cumstances under which they might be cost-effective. Further support is needed to encourage cost-benefit and cost-effectiveness evaluations of widely used and costly off-label prescription regimens.

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