Comparison of Longer-Term Safety and Effectiveness of 4 Atypical Antipsychotics in Patients Over Age 40: A Trial Using Equipoise-Stratified Randomization

Hua Jin, MD; Pei-an Betty Shih, PhD; Shahrokh Golshan, PhD; Sunder Mudaliar, MD; Robert Henry, MD; Danielle K. Glorioso, MSW; Stephan Arndt, PhD; Helena C. Kraemer, PhD; and Dilip V. Jeste, MD

ABSTRACT

Objective: To compare longer-term safety and effectiveness of the 4 most commonly used atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone) in 332 patients, aged > 40 years, having psychosis associated with schizophrenia, mood disorders, posttraumatic stress disorder, or dementia, diagnosed using *DSM-IV-TR* criteria.

Method: We used equipoise-stratified randomization (a hybrid of complete randomization and clinician's choice methods) that allowed patients or their treating psychiatrists to exclude 1 or 2 of the study atypical antipsychotics due to past experience or anticipated risk. Patients were followed for up to 2 years, with assessments at baseline, 6 weeks, 12 weeks, and every 12 weeks thereafter. Medications were administered employing open-label design and flexible dosages, but with blind raters. The study was conducted from October 2005 to October 2010.

Outcome Measures: Primary metabolic markers (body mass index, blood pressure, fasting blood glucose, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides), percentage of patients who stay on the randomly assigned atypical antipsychotic for at least 6 months, psychopathology, percentage of patients who develop metabolic syndrome, and percentage of patients who develop serious and nonserious adverse events.

Results: Because of a high incidence of serious adverse events, quetiapine was discontinued midway through the trial. There were significant differences among patients willing to be randomized to different atypical antipsychotics ($P < .01$), suggesting that treating clinicians tended to exclude olanzapine and prefer aripiprazole as one of the possible choices in patients with metabolic problems. Yet, the atypical antipsychotic groups did not differ in longitudinal changes in metabolic parameters or on most other outcome measures. Overall results suggested a high discontinuation rate (median duration 26 weeks prior to discontinuation), lack of significant improvement in psychopathology, and high cumulative incidence of metabolic syndrome (36.5% in 1 year) and of serious (23.7%) and nonserious (50.8%) adverse events for all atypical antipsychotics in the study.

Conclusions: Employing a study design that closely mimicked clinical practice, we found a lack of effectiveness and a high incidence of side effects with 4 commonly prescribed atypical antipsychotics across diagnostic groups in patients over age 40, with relatively few differences among the drugs. Caution in the use of these drugs is warranted in middle-aged and older patients.

Trial Registration: ClinicalTrials.gov identifier: NCT00245206

J Clin Psychiatry

Submitted: *July 5, 2012; accepted October 3, 2012.*
Online ahead of print: *November 27, 2012 (doi:10.4088/JCP.12m08001).*
Corresponding author: *Dilip V. Jeste, MD, Clinical and Translational Research Institute, University of California, San Diego, 9500 Gilman Drive, #0664, La Jolla, CA 92093 (djeste@ucsd.edu).*

Psychotic disorders are serious mental illnesses that usually need to be treated vigorously with effective therapy. Most treatment research in psychosis has focused on schizophrenia, and much less is known about the management of psychotic disorders associated with other conditions such as posttraumatic stress disorder (PTSD) or dementia. Antipsychotic drugs have been approved by the US Food and Drug Administration (FDA) primarily for schizophrenia and bipolar disorder, yet they are commonly used off-label for other psychiatric disorders.[1–13] The risk of cardiovascular disease increases significantly over age 40.[14] Yet, 62% of all the prescriptions for antipsychotics in 2009–2010 were written for people aged > 40.[15] A majority of antipsychotic prescriptions in patients over 40 involve off-label use of atypical antipsychotics.[2,16] However, there are inadequate published data on longer-term safety and effectiveness of atypical antipsychotics in older patients with different diagnoses.

There has been a growing concern about cardiovascular and metabolic morbidity with certain atypical antipsychotics, such as olanzapine.[17–25] The FDA issued a warning regarding cerebrovascular adverse events and a boxed warning regarding increased mortality with atypical antipsychotic use for dementia-related psychosis, based on randomized controlled trials of 6–12 weeks' duration.[26] Large ground-breaking randomized trials of atypical antipsychotics such as CATIE[27] and EUFEST[28] did not have direct measures of cardiovascular or cerebrovascular pathology, as those studies were designed prior to the FDA warnings. Taken together, there is considerable public health interest in systematically assessing longer-term safety and effectiveness of atypical antipsychotics in middle-aged and older patients.

The present study was designed as a hybrid of explanatory and pragmatic clinical trials[29,30] for assessing the effects of the 4 most frequently used atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone) in patients > 40 years with psychotic symptoms associated with different primary psychiatric disorders. The patients were followed for up to 2 years. We employed a practical randomization technique—the equipoise-stratified method,[31] few exclusion criteria, clinically relevant assessment procedures, open-label treatments, and, as in the CATIE schizophrenia trial, no placebo group because of ethical considerations.

Clinical Points

- Caution is needed in long-term use of commonly prescribed atypical antipsychotics (aripiprazole, olanzapine, quetiapine, and risperidone) in middle-aged and older patients with psychotic disorders.
- When these medications are used, they should be given in low dosages, for short durations, and their side effects should be monitored closely.
- Shared decision making with patients and their caregivers is recommended, including discussions of risks and benefits of atypical antipsychotics and those of available treatment alternatives.

We hypothesized that there would be significant differences among the 4 atypical antipsychotics in their effects on (1) primary metabolic markers (body mass index [BMI], blood pressure, fasting blood glucose, low-density lipoprotein [LDL] cholesterol, high-density lipoprotein [HDL] cholesterol, and triglycerides), (2) percentage of patients who stay on the randomly assigned atypical antipsychotic treatment for at least 6 months, (3) psychopathology, (4) percentage of patients who develop metabolic syndrome, and (5) percentage of patients who develop serious and nonserious adverse events.

MATERIALS AND METHODS

The study was approved by the University of California, San Diego (UCSD) institutional review board, and all participants provided written informed consent. The study was conducted from October 2005 to October 2010 at the UCSD General Clinical Research Center, the VA Medical Center, and various board and care facilities in San Diego, California. The study is registered at ClinicalTrials.gov (identifier: NCT00245206).

Patients

Inclusion criteria were age > 40 years; schizophrenia/schizoaffective disorder; psychosis associated with mood disorder, PTSD, or dementia; and either receiving atypical antipsychotics at baseline or having a treating psychiatrist propose prescription of an atypical antipsychotic. Diagnoses were based on the *DSM-IV-TR*.[32]

Exclusion criteria were active substance abuse in the past 30 days, unstable medical conditions, and being treated with multiple antipsychotics at baseline. A total of 568 patients were screened (Figure 1), 406 signed consent, and 332 patients completed a baseline visit. The data reported in this article reflect follow-up for up to 2 years on randomized medication (as proposed a priori).

Equipoise-Stratified Randomization

Our study design was a simplified version of that used in the National Institute of Mental Health–funded STAR*D trial.[31] This approach represents a balancing of advantages and disadvantages of a completely randomized design (advantage = randomization; disadvantage = exclusion of patients for whom *any one* of the study treatments is unacceptable) and clinician's choice method (advantage = greater treatment flexibility for treating clinician; disadvantage = loss of ability to compare specific treatment options). The patient and his or her treating psychiatrist could exclude 1 or even 2 of the 4 study medications for randomization. (The patients who excluded 3 atypical antipsychotics could not be randomized, and consequently those subjects were excluded from the trial). Thus each patient made a list of the medications to which she or he could be randomized. Depending on the number of atypical antipsychotics excluded, this list included 2, 3, or 4 drugs that were acceptable for randomization and of rough parity to the patient—ie, for him or her, the selected atypical antipsychotics were approximately equal in terms of likelihood of success. This list was called "equipoise stratum." The numbers of patients in each equipoise stratum are listed in Figure 1. Only 16.6% of the patients agreed to be randomized to all 4 medications—ie, 83.4% of the patients would not have participated in a traditional randomized trial. All the consenting patients were randomly assigned with equal probability to one of the options within their respective lists. This procedure allowed pairwise contrasts of treatments, optimized the available recruitment resources, and enabled the greatest number of patients among different medication options.[31] Every pairwise comparison of atypical antipsychotics was evaluated on all patients for whom that choice was acceptable (see Statistical Analysis, below). Randomized atypical antipsychotic was supplied to the patients at no cost, in an open-label manner.

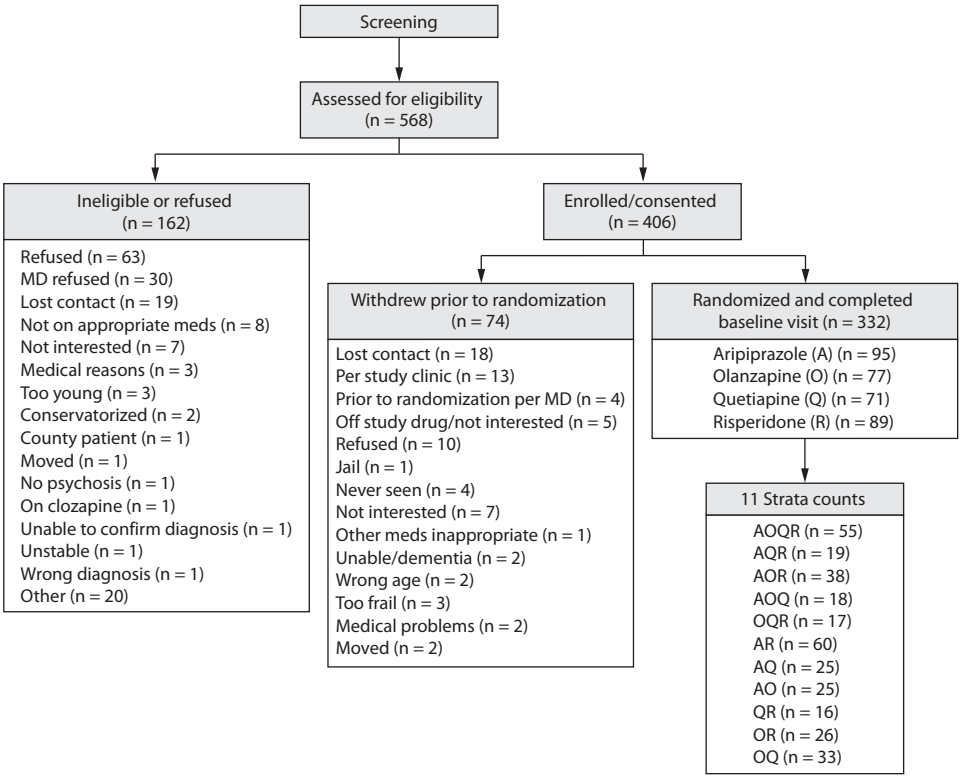
Reasons for Refusing Specific Atypical Antipsychotics for Randomization

The most common reason given for refusing specific atypical antipsychotics was possible side effects, which ranged from 43% for aripiprazole to 78% for olanzapine. The percentages of patients citing lack of effectiveness as the reason for refusal ranged from 8% for olanzapine to 23% for quetiapine.

Clinical Assessment

Study raters were masked to the atypical antipsychotic assignment. For interrater reliability, an intraclass correlation coefficient of ≥ 0.80 for psychopathology measures was established. A summary of our baseline assessments has been published previously.[33] Briefly, the baseline evaluation included medical and medication history, physical examination (by trained physician assistants), anthropomorphic measurements including BMI and waist circumference, psychopathology ratings (primarily, the Brief Psychiatric Rating Scale [BPRS]),[34] medication side effects,[35] and fasting plasma glucose and lipids. A clinical diagnosis of metabolic syndrome was made using standard American Heart Association–modified National Cholesterol Education Program guidelines.[36]

Figure 1. CONSORT Diagram for Patient Recruitment



Follow-Up

The assessments were repeated at 6 weeks, 12 weeks, and then every 12 weeks. Patients were followed for up to 2 years.

Medication Management

After a patient was randomized to a study atypical antipsychotic, starting dosage was determined by the treating psychiatrist, who could alter the dose (or stop medication) anytime to meet the patient's needs.

Statistical Analysis

We analyzed data on all randomized patients for whom there was a baseline assessment and at least 1 postbaseline evaluation. These patients were stratified into subgroups (strata) defined by the treatments they had chosen to be randomized among. With a total of 4 treatments, there were 11 possible strata (aripiprazole-olanzapine-quetiapine-risperidone [AOQR], aripiprazole-quetiapine-risperidone [AQR], aripiprazole-olanzapine-risperidone [AOR], aripiprazole-olanzapine-quetiapine [AOQ], olanzapine-quetiapine-risperidone [OQR], aripiprazole-risperidone [AR], aripiprazole-quetiapine [AQ], aripiprazole-olanzapine [AO], quetiapine-risperidone [QR], olanzapine-risperidone [OR], and olanzapine-quetiapine [OQ]) (Figure 1). Initially, all baseline characteristics were compared among these 11 strata groups with analyses of variance or χ^2 analyses, adjusting for multiple comparisons using the Tukey method. Next, data from different strata were pooled using all appropriate strata for each particular contrast for hypothesis testing. Four strata were involved for each pairwise comparison—eg, to compare aripiprazole and risperidone, we pooled data from all the strata that accepted both aripiprazole and risperidone (AOQR, AQR, AOR, and AR). Next, for each pair, the risk difference (difference between the 2 proportions having a particular outcome with those drugs) was calculated. For longitudinal data on metabolic markers (BMI, blood pressure, glucose, LDL, HDL, and triglycerides) as well as BPRS, an individual's slope across the first 6 months of study treatment was calculated. Group means were adjusted according to different randomization probabilities in different strata. Each pair of medications was compared using *Z*-test, and a 95% 2-tailed confidence interval was computed. Finally, we used survival analysis technique (Kaplan-Meier survival curves) to determine the cumulative probability of discontinuation for each of the randomized atypical antipsychotics. Kaplan-Meier estimator is nonparametric and requires no parametric assumptions. This survival analysis, which combines data on each atypical antipsychotic from diverse strata, is a simplified version of the more appropriate survival analysis with pairwise comparison, although the conclusions were similar.

RESULTS

The 332 patients who completed baseline visit and the 74 patients who dropped out after signing the consent were

demographically and clinically similar, except that the study sample was older than the dropouts: mean (SD) age = 67 (13) years versus 62 (16) years, respectively ($f_{1,404} = 7.4$, $P < .007$). The mean (SD) doses of the randomized medications prescribed during the study, in mg/d, were aripiprazole (A) = 10.8 (7), olanzapine (O) = 8.8 (7), quetiapine (Q) = 212 (211), and risperidone (R) = 1.8 (2). The mean daily doses were highest in schizophrenia and lowest in dementia.

Comparison of Baseline Demographic and Clinical Characteristics Among the 11 Strata

The 11 strata groups (AOQR, AQR, AOR, AOQ, OQR, AR, AQ, AO, QR, OR, OQ) differed from one another in gender, education, body weight, waist circumference, and fasting glucose (Tables 1 and 2). Pairwise strata analyses revealed that patients in stratum AOQR had significantly lower waist circumference than those in AQR, AOQ, and AR, while stratum AQ patients had significantly higher fasting glucose levels that those in AOQR, AQR, AO, OQ, and OR, suggesting that the clinicians tended to exclude olanzapine but include aripiprazole in the list of acceptable medications for randomization among patients at risk for metabolic syndrome. The overall prevalence of metabolic syndrome was 50% at the baseline visit. There was a significant difference in the proportions of people with different diagnoses in terms of those who had versus did not have metabolic syndrome at baseline ($\chi^2_3 = 14.56$, $P < .002$). Patients with dementia had a significantly lower proportion of those who had metabolic syndrome at baseline compared to those with schizophrenia/schizoaffective disorders ($\chi^2_1 = 8.83$, $P < .003$), mood disorders ($\chi^2_1 = 10.59$, $P < .001$), and PTSD ($\chi^2_1 = 8.54$, $P < .003$). This possibly could be attributed to differences in duration and daily doses of atypical antipsychotics at baseline; however, retrospective information on atypical antipsychotic use prior to baseline assessment was of uncertain reliability.

Time to Discontinuation of Randomized Drug

The proportion of patients who discontinued their randomized medication before the end of the 2-year follow-up period ranged from 78.6% taking quetiapine to 81.5% taking aripiprazole. The median number of weeks to discontinuation of randomized medication was 26.0 weeks (25th percentile = 6.0; 75th percentile = 75.9). It is possible that the early discontinuation reflected significant clinical improvement or at least adherence to the treatment guidelines for using atypical antipsychotics for as short a period as possible, especially in patients with dementia.[37] However, there was no relationship between diagnosis and duration of atypical antipsychotic treatment. A majority of the patients whose randomized atypical antipsychotic was discontinued were switched to another atypical antipsychotic by their own treating clinicians. Among the patients with known reasons for discontinuation, 51.6% did so due to side effects, 26.9% for lack of effectiveness, and 21.5% for other reasons. Figure 2 shows survival curves for the 4 atypical antipsychotics in terms of time to discontinuation of medication. There were no significant differences among the 4 drugs on this measure. However, using a cutoff point of 6 months' duration of atypical antipsychotic use (as included in our a priori hypothesis), the percentage of patients who stayed on the randomized medication for at least 6 months was significantly lower for aripiprazole than for olanzapine (Table 3). There was no significant association between the stratum group and reason for medication discontinuation.

Discontinuation of Quetiapine During the Trial

Approximately 3.5 years after the study began, our Data and Safety Monitoring Board (consisting of 4 individuals, including a statistician, from outside of UCSD) concluded that there was a significantly higher incidence of serious adverse events with quetiapine (38.5%) than with the other 3 atypical antipsychotics combined (19.0%, $\chi^2_1 = 9.56$, $P < .002$). These differences were not related to age, prior antipsychotic treatment, medical burden, or duration of treatment. Consequently, the quetiapine arm of the trial was discontinued. These interim data on serious adverse events were published previously as a letter to the editor.[38]

Psychopathology

We found no significant main effects of stratum, visit, or medication, or any 2-way or 3-way interactions for BPRS total and psychosis subscale scores, suggesting no significant change in psychopathology with any of the study atypical antipsychotics.

Effects on Primary Metabolic Markers

There were no significant differences among the drug groups on primary metabolic markers (BMI, blood pressure, glucose, LDL cholesterol, HDL cholesterol, and triglycerides).

Incidence of Metabolic Syndrome

Cumulative 1-year incidence of metabolic syndrome (among those patients who did not meet the criteria for metabolic syndrome at baseline) was 36.5%. There were no significant differences among the strata-eligible patients in the proportion of subjects developing metabolic syndrome except for the aripiprazole–olanzapine pairwise comparison: 86% of patients taking aripiprazole developed metabolic syndrome compared to 55% taking olanzapine in 1 year (risk difference = 34%, $P < .02$).

Serious and Nonserious Adverse Events

Overall, 23.7% of the patients treated with different atypical antipsychotics developed serious adverse events including deaths, hospitalizations, and emergency room visits for life threatening conditions ($\chi^2_3 = 13.43$, $P < .005$), while 50.8% developed nonserious adverse events ($\chi^2_3 = 8.57$, $P < .04$) within 24 months of follow-up. Pairwise medication comparisons found no significant differences in proportion of subjects developing serious adverse events. However, in comparing nonserious adverse events, 49% of aripiprazole users versus 78% of quetiapine users developed nonserious adverse events ($P < .03$), and 46% of risperidone patients

Table 1. Baseline Demographic Data by Equipoise Stratum

Characteristic	AOQR (n = 55)	AQR (n = 19)	AOR (n = 38)	AOQ (n = 18)	OQR (n = 17)	AR (n = 60)	AQ (n = 25)	AO (n = 25)	QR (n = 16)	OR (n = 26)	OQ (n = 33)	Total (N = 332)
Age, mean (SD), y	64.1 (12.3)	60.3 (8.2)	69.4 (14.2)	63.9 (12.3)	68.7 (15.2)	66.6 (13.4)	64.7 (12.8)	64.4 (12.3)	67 (14)	70.7 (12.4)	70.6 (13.9)	66.6 (13.1)
Gender, male, n (%)[a]	33 (60)	14 (74)	24 (63)	12 (67)	16 (94)	51 (85)	13 (52)	13 (52)	12 (75)	17 (65)	20 (61)	225 (68)
Education												
n[b]	52	19	36	15	17	59	24	24	16	25	32	319
Mean (SD), y[c]	13.3 (2.6)	14.5 (2)	10.6 (5)	14.2 (2.3)	12.5 (2)	13.7 (2.4)	13.4 (3.2)	13.5 (2.4)	13.4 (2.9)	12.6 (2.2)	13.8 (3.1)	13.2 (3.1)
Diagnosis, n (%)												
Schizophrenia, schizoaffective disorders, or BPD	21 (38)	8 (42)	16 (42)	7 (39)	3 (18)	22 (37)	15 (60)	12 (48)	6 (38)	10 (38)	8 (24)	128 (39)
Other	34 (62)	11 (58)	22 (58)	11 (61)	14 (82)	38 (63)	10 (40)	13 (52)	10 (63)	16 (62)	25 (76)	204 (61)

[a]There were significant differences among the strata groups on this variable. Gender, group difference: $\chi^2_{10} = 22.68$, $P = .012$. Post hoc pairwise significant differences: There were higher proportions of male patients in the strata OQR and AR than in a majority of other strata.
[b]Differences in n amounts reflect missing data.
[c]There were significant differences among the strata groups on this variable. Education, group difference: $F_{10,308} = 3.996$, $P < .001$. Post hoc pairwise significant differences: AOR < AOQR, AQR, AOQ, AR, AQ, AO, and OQ.
Abbreviations: A = aripiprazole, BPD = bipolar disorder, O = olanzapine, Q = quetiapine, R = risperidone.

Table 2. Baseline Clinical Data by Equipoise Stratum[a]

Characteristic	AOQR (n = 55)	AQR (n = 19)	AOR (n = 38)	AOQ (n = 18)	OQR (n = 17)	AR (n = 60)	AQ (n = 25)	AO (n = 25)	QR (n = 16)	OR (n = 26)	OQ (n = 33)	Total (N = 332)
BPRS total score												
n	41	19	17	12	12	49	18	19	12	18	21	238
Mean (SD)	41.2 (11.3)	42.2 (8.3)	38.0 (7.8)	37.4 (7.4)	38.4 (9.5)	38.1 (10.6)	44.9 (10.1)	43.7 (12.2)	41.3 (13.0)	35.4 (6.9)	40.7 (10.0)	40.1 (10.3)
Waist circumference, in[b]												
n	54	19	37	14	15	59	23	24	15	25	31	316
Mean (SD)	38.0 (6.3)	43.6 (7.5)	39.2 (5.2)	43.8 (8.2)	40.0 (4.0)	41.9 (5.6)	38.8 (6.9)	38.9 (5.7)	39.4 (4.6)	38.4 (5.4)	39.0 (5.1)	39.9 (6.1)
Body weight, kg[c]												
n	54	19	38	16	16	60	24	25	15	26	32	325
Mean (SD)	79.0 (20.6)	96.9 (25.5)	80.8 (24.4)	97.4 (26.3)	84.4 (12.9)	89.7 (18.3)	83.8 (22.1)	81.3 (23.0)	84.7 (19.2)	76.7 (18.0)	80.4 (18.6)	84.1 (21.4)
Fasting glucose, mg/dL[d]												
n	45	16	32	13	16	49	17	20	9	24	24	265
Mean (SD)	101.0 (26.4)	101.3 (17.0)	120.7 (71.3)	106.4 (32.4)	104.3 (40.9)	117.1 (44.0)	159.4 (120.6)	102.8 (27.6)	110.1 (50.4)	104.4 (21.6)	98.5 (21.3)	111.1 (50.4)

[a]Differences in n amounts reflect missing data.
[b]There were significant differences among the strata groups on this variable. Waist circumference, group difference: $F_{10,315} = 3.089$, $P < .001$. Post hoc pairwise significant differences: AR stratum had higher waist circumference than all other strata.
[c]There were significant differences among the strata groups on this variable. Body weight, group difference: $F_{10,314} = 2.695$, $P < .004$. Post hoc pairwise significant differences: AR stratum had higher body weight than all other strata.
[d]There were significant differences among the strata groups on this variable. Fasting glucose, group difference: $F_{10,254} = 2.402$, $P < .01$. Post hoc pairwise significant differences: AQ > AOQR, AQR, AO, and OQ.
Abbreviations: A = aripiprazole, BPRS = Brief Psychiatric Rating Scale, O = olanzapine, Q = quetiapine, R = risperidone.

versus 73% of olanzapine patients developed nonserious adverse events ($P < .04$).

The 2 conditions for which there is an FDA warning (cerebrovascular adverse events) or boxed warning (mortality) for atypical antipsychotics in older dementia patients occurred in 6 patients. Two 75-year-old patients with mood disorders (but none with dementia) developed transient ischemic attack or stroke, one taking aripiprazole and one taking quetiapine. Four patients aged 74–89 years died, including 3 with dementia (one each taking aripiprazole, olanzapine, and quetiapine) and a 51-year-old patient with schizophrenia and late-stage cancer (taking quetiapine). There was no consistent underlying cause for cerebrovascular accident or death in these patients.

Relationship of Outcome Measures to Other Variables

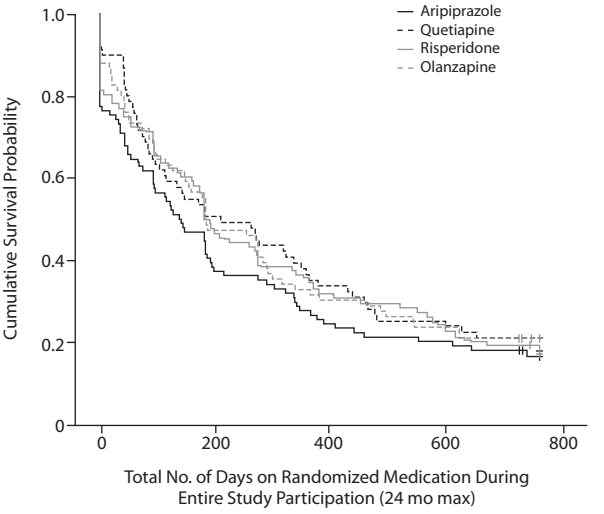
With 1 exception, there was no significant relationship of atypical antipsychotic daily dose with length of time patients stayed on their randomized medication or development of metabolic syndrome, serious adverse events, or nonserious adverse events. The only exception was that higher daily dose of aripiprazole was significantly associated with greater risk of developing serious adverse events and nonserious adverse events ($F_{1,86} = 6.6$, $P < .02$). Development of side effects (metabolic syndrome, serious adverse events, and nonserious adverse events) was not related to diagnosis or concurrent medications. However, older age was significantly associated with a greater incidence of serious adverse events ($F_{1,323} = 8.080$, $P < .005$).

DISCUSSION

Our results suggested a high discontinuation rate following a relatively short duration of drug treatment (median of 26 weeks), lack of significant improvement in psychopathology (on BPRS), and high incidence of metabolic syndrome (36.5% in 1 year) and serious (23.7%) and nonserious (50.8%) adverse events with atypical antipsychotics. These results are worrisome, since we had given a choice to the patients and their psychiatrists to exclude 1 or 2 of the 4 atypical antipsychotics for possible safety or effectiveness concerns. The clinicians could choose the daily dosage and change it as needed at any time. The daily dosages of the atypical antipsychotics prescribed were relatively low. Thus, we had sought to give all the study atypical antipsychotics the best chance of proving safe and effective, as is done in good clinical practice.

Designing a pragmatic clinical trial involves trade-offs between an ideal experimental design and practical considerations that would enhance its applicability to routine clinical management of patients. There is a certain amount of bias in almost every clinical trial. We believe that the equipoise-stratified randomization provided the least amount of bias for this "real world" type of investigation. Only 16.6% of the patients agreed to be randomized to all 4 medications. Thus, a traditional randomization design would have resulted in exclusion of 83.4% of the patients who participated in this study and thus, the study sample would not have been representative of the population to which clinical decisions are relevant. The conclusions of a traditional randomized trial apply only to those patients who are willing to accept randomization to any one of the drugs in that trial. Therefore, the success or failure rate of a drug when compared to placebo may not be the same as that when compared to an active comparator, not only because the comparator is different, but also because the population sampled is different—eg, patients who refuse a placebo trial are different from those who refuse a trial in which olanzapine is used.

Figure 2. Survival Curves for Time to Discontinuation of Randomized Medication[a]



[a]Survival analysis: $\chi^2_3 = 1.548$, $P = .663$ (Kaplan-Meier).

The flexibility that we offered to the patients and their treating psychiatrists in allowing them to exclude 1 or 2 atypical antipsychotics because of past experience or anticipated side effects led to expected differences in baseline characteristics of the medication groups. Thus, the patients who seemed to have a greater risk of developing metabolic syndrome (eg, high BMI) excluded olanzapine as a possible medication due to a fear of additional metabolic problems.[20,39] Similarly, there is a channeling or allocation bias,[40] when claimed advantages of a new drug channel it to patients with special preexisting morbidity—eg, the reportedly lower propensity of aripiprazole to cause adverse metabolic effects might have resulted in a greater likelihood of its being included in the list of medications acceptable for patients at risk of metabolic syndrome, such as those with abdominal obesity or elevated fasting blood glucose levels. Therefore, our findings of baseline differences among patient groups in different strata support the pragmatic value of the present study—in real life, clinicians prefer aripiprazole to olanzapine for patients at higher risk of metabolic syndrome. Yet, the reported metabolic advantages of aripiprazole compared to olanzapine were not borne out in this study. The higher incidence of metabolic syndrome with aripiprazole likely was related to the fact that the patients who included that drug in their list of acceptable medications were at a greater

Table 3. Pairwise Strata Analysis for Categorical Outcome Measures[a]

Randomized Drug A, n	Randomized Drug B, n	Drug A, %[b]	Drug B, %[b]	Risk Difference %	Risk Difference 95% CI	Z	P
		Stayed on randomized medication for at least 6 mo					
Aripiprazole, 66	Risperidone, 66	32	48	−16	−0.37 to 0.049	−1.5	.13
Aripiprazole, 42	Quetiapine, 39	39	58	−19	−0.47 to 0.085	−1.36	.17
Aripiprazole, 44	Olanzapine, 40	26	58	−31	−0.57 to −0.05	−2.37	**.02***
Risperidone, 30	Quetiapine, 35	67	49	17	−0.12 to 0.47	1.15	.25
Risperidone, 50	Olanzapine, 41	67	58	9	−0.16 to 0.34	0.68	.50
Quetiapine, 41	Olanzapine, 40	56	58	−2	−0.33 to 0.28	−0.17	.87
		Developed metabolic syndrome within 1 y					
Aripiprazole, 66	Risperidone, 65	85	87	−2	−0.21 to 0.17	−0.22	.83
Aripiprazole, 39	Quetiapine, 38	82	88	−5	−0.29 to 0.19	−0.43	.67
Aripiprazole, 41	Olanzapine, 38	86	55	34	0.07 to 0.60	2.47	**.01***
Risperidone, 29	Quetiapine, 34	93	67	26	−0.01 to 0.52	1.89	.06
Risperidone, 48	Olanzapine, 39	71	65	6	−0.21 to 0.33	0.46	.65
Quetiapine, 39	Olanzapine, 37	77	65	12	−0.14 to 0.39	0.93	.35
		Developed serious adverse events					
Aripiprazole, 63	Risperidone, 64	23	12	11	−0.06 to 0.28	1.27	.10
Aripiprazole, 40	Quetiapine, 38	27	33	−5	−0.30 to 0.19	−0.43	.67
Aripiprazole, 42	Olanzapine, 39	23	28	−5	−0.28 to 0.18	−0.46	.65
Risperidone, 29	Quetiapine, 35	17	35	−18	−0.433 to 0.07	−1.41	.16
Risperidone, 49	Olanzapine, 40	20	27	−7	−0.28 to 0.14	−0.64	.52
Quetiapine, 41	Olanzapine, 39	34	30	4	−0.22 to 0.305	0.3	.76
		Developed nonserious adverse events					
Aripiprazole, 63	Risperidone, 64	52	52	0	−0.25 to 0.25	−0.006	1.00
Aripiprazole, 40	Quetiapine, 38	64	59	5	−0.022 to 0.33	0.037	.97
Aripiprazole, 42	Olanzapine, 39	49	78	−29	−0.55 to −0.026	−2.16	**.03***
Risperidone, 29	Quetiapine, 35	57	51	6	−0.25 to 0.37	0.37	.71
Risperidone, 49	Olanzapine, 40	46	73	−27	−0.53 to −0.006	−2.01	**.04***
Quetiapine, 41	Olanzapine, 39	69	79	−10	−0.38 to 0.18	−0.69	.95

[a]This table is a pairwise comparison of subjects randomized to a specific drug (randomized drug A) versus subjects randomized to another specific drug (randomized drug B). All potential randomized drug pairs are identified in the table.
[b]Drug A percentage is the percentage of patients taking drug A and meeting the outcome criteria. Drug B percentage is the percentage of patients taking drug B and meeting the outcome criteria.
*Statistically significant at $P < .05$.

risk of developing the metabolic syndrome at baseline than those who opted for olanzapine. The main point here is that aripiprazole did not prove to be safe in high-risk patients.

Metabolic syndrome is reported to be associated with increased risk of diabetes, obesity, hypertension, and heart disease.[41,42] The prevalence of metabolic syndrome in the older adults of the general population is reported to be 24%–44%.[43–46] The high baseline prevalence as well as elevated 1-year incidence rates of metabolic syndrome observed in our patients raise concerns about psychiatric patients' cardiometabolic and cerebrovascular health.

Quetiapine was removed from the trial before the study was completed because of the observed high incidence of serious adverse events.[38] This finding is consistent with a report by Tiihonen et al,[47] who found that the standardized mortality rate with quetiapine in patients with schizophrenia was twice that with clozapine. Similarly, quetiapine was recently removed by the US Central Command from its approved formulary list due to medication-associated mortality.[48]

Our study has several limitations. This was a sample of patients aged > 40 years; hence, our results may not generalize to younger patients. Some patients had been treated previously with different antipsychotics for varying duration, and those drugs might have contributed to metabolic changes seen early in our trial. Our sample included patients with different psychiatric disorders. The sample sizes in individual diagnostic groups were inadequate for testing small to medium size differences. Our study findings may not be applicable to newer antipsychotics such as lurasidone or iloperidone. Although we sought to make our study design mimic clinical practice, the two are not the same, and therefore, our results may not apply fully to everyday care. For example, in the real world, patients are not randomized. Lastly, it is usually not possible to conclude that a serious adverse event observed during the treatment is causally related to that drug.

Notwithstanding the limitations, the results of our study are sobering. One-half of the patients remained on the assigned drug for less than 6 months. Furthermore, there was no significant improvement in BPRS total or psychosis subscale scores over a 6-month period, and there was a high incidence of metabolic syndrome, serious adverse events, and nonserious adverse events. While there were a few significant differences among the 4 atypical antipsychotics included in this study, the overall risk-benefit ratio for the atypical antipsychotics in patients over age 40 was not favorable, irrespective of diagnosis and drug.

The use of atypical antipsychotics in older psychotic patients presents a major clinical dilemma. Psychotic

disorders, including those associated with conditions other than schizophrenia, have severe adverse consequences for the medical health, career, family, and quality of life of sufferers. Atypical antipsychotics, although not approved for these conditions, are commonly used off-label in these patients, and there are few, if any, evidence-based treatment alternatives in older patients with psychotic disorders. Indeed, Tiihonen et al[47] reported that no treatment with an antipsychotic was associated with higher mortality than treatment with an atypical antipsychotic. Thus there are risks associated with either no treatment or treatment with other medications including typical antipsychotics and mood stabilizers.[37] At the same time, the low safety and effectiveness of atypical antipsychotics found in our study, along with the high costs of these medications, make their use problematic.

Our findings do not suggest that atypical antipsychotics should be banned in older patients with psychotic disorders. There are currently no safe and effective treatment alternatives in these patients. Short-term use of atypical antipsychotics is often necessary for controlling severe psychotic symptoms. Also, specific atypical antipsychotics in low dosages may be useful for longer treatment of certain patients. However, our results and other reports[49] do indicate that considerable caution is warranted in off-label long-term use of atypical antipsychotics in older persons. Psychosocial treatments should be used whenever appropriate. Pharmacotherapeutic guidelines for "start low and go slow" should be followed along with close monitoring and medical management for metabolic side effects. Shared decision making, involving detailed discussions with the patients and their family members or legal guardians about the risks and benefits of atypical antipsychotics and of possible treatment alternatives, as well as of no pharmacologic treatment, is warranted.[1,37] Clearly, there is a critical need to develop and test new interventions that are safe and effective in older people with psychotic disorders.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), iloperidone (Fanapt), lurasidone (Latuda), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others).

Author affiliations: Department of Psychiatry (Drs Jin, Shih, Golshan, and Jeste and Ms Glorioso), Department of Neurosciences (Dr Jeste), and Department of Medicine (Drs Mudaliar and Henry), University of California, San Diego; Division of Medicine, VA San Diego Healthcare System, California (Drs Jin, Mudaliar, and Henry); Department of Psychiatry, University of Iowa, Iowa City (Dr Arndt); and Department of Psychiatry and Behavioral Sciences, Stanford University, California and Department of Psychiatry, University of Pittsburgh, Pennsylvania (Dr Kraemer).

Potential conflicts of interest: **Dr Mudaliar** is a consultant to, received grant/research support and honoraria from, and has participated in the speakers bureaus for AstraZeneca and Bristol Myers Squibb, which manufacture the drugs used in this study. **Drs Jin, Shih, Golshan, Henry, Arndt, Kraemer,** and **Jeste** and **Ms Glorioso** and their spouses have had no relevant financial interests or personal affiliations during at least the past 12 months.

Funding/support: This study was supported, in part, by the National Institutes of Health grants (MH071536, P30 MH080002-01, 1K01DK087813-01, NCRS UL1RR031980) and by the department of Veterans Affairs. It was carried out, in part, in the General Clinical Research Center, University of California, San Diego with funding provided by the National Center for Research Resources, M01RR 000827, United States Public Health Service. AstraZeneca, Bristol-Myers Squibb, Eli Lilly, and Janssen Scientific Affairs, LLC donated quetiapine, aripiprazole, olanzapine, and risperidone, respectively, for this National Institute of Mental Health–funded study.

Acknowledgment: We wish to thank Rebecca Daly (Department of Psychiatry, University of California, San Diego), who managed the complex longitudinal dataset. She has had no relevant financial interests or personal affiliations during at least the past 12 months.

REFERENCES

1. Salzman C, Jeste DV, Meyer RE, et al. Elderly patients with dementia-related symptoms of severe agitation and aggression: consensus statement on treatment options, clinical trials methodology, and policy. *J Clin Psychiatry*. 2008;69(6):889–898.
2. Jeste DV, Dolder CR. Treatment of non-schizophrenic disorders: focus on atypical antipsychotics. *J Psychiatr Res*. 2004;38(1):73–103.
3. Jeste DV, Alexopoulos GS, Bartels SJ, et al. Consensus statement on the upcoming crisis in geriatric mental health: research agenda for the next 2 decades. *Arch Gen Psychiatry*. 1999;56(9):848–853.
4. Alexopoulos GS, Streim JE, Carpenter D, et al; Expert Consensus Panel for Using Antipsychotic Drugs in Older Patients. Using antipsychotic agents in older patients. *J Clin Psychiatry*. 2004;65(suppl 2):5–99, discussion 100–102, quiz 103–104.
5. McDonald WM, Wermager J. Pharmacologic treatment of geriatric mania. *Curr Psychiatry Rep*. 2002;4(1):43–50.
6. Leslie DL, Mohamed S, Rosenheck RA. Off-label use of antipsychotic medications in the department of Veterans Affairs health care system. *Psychiatr Serv*. 2009;60(9):1175–1181.
7. Kamble P, Sherer J, Chen H, et al. Off-label use of second-generation antipsychotic agents among elderly nursing home residents. *Psychiatr Serv*. 2010;61(2):130–136.
8. Maher AR, Maglione M, Bagley S, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. *JAMA*. 2011;306(12): 1359–1369.
9. Waterreus A, Morgan VA, Castle D, et al. Medication for psychosis—consumption and consequences: the second Australian national survey of psychosis. *Aust N Z J Psychiatry*. 2012;46(8):762–773.
10. Kozarić-Kovacić D, Pivac N, Mück-Seler D, et al. Risperidone in psychotic combat-related posttraumatic stress disorder: an open trial. *J Clin Psychiatry*. 2005;66(7):922–927.
11. Kozarić-Kovacić D, Pivac N. Quetiapine treatment in an open trial in combat-related post-traumatic stress disorder with psychotic features. *Int J Neuropsychopharmacol*. 2007;10(2):253–261.
12. Mohamed S, Rosenheck RA. Pharmacotherapy of PTSD in the US Department of Veterans Affairs: diagnostic- and symptom-guided drug selection. *J Clin Psychiatry*. 2008;69(6):959–965.
13. Viana BM, Prais HA, Nicolato R, et al. Posttraumatic brain injury psychosis successfully treated with olanzapine. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010;34(1):233–235.
14. D'Agostino B Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation*. 2008;117:753.
15. IMS Health Incorporated. National Disease and Therapeutic Index. September 2009– September 2011. All Rights Reserved. https://web01.imshealth.com/ndti/ndtilogin.aspx. Accessed November 8, 2012.
16. Glick ID, Murray SR, Vasudevan P, et al. Treatment with atypical antipsychotics: new indications and new populations. *J Psychiatr Res*. 2001;35(3):187–191.
17. Casey DE. Metabolic issues and cardiovascular disease in patients with psychiatric disorders. *Am J Med*. 2005;118(suppl 2):15S–22S.
18. Goff DC, Sullivan LM, McEvoy JP, et al. A comparison of ten-year cardiac risk estimates in schizophrenia patients from the CATIE study and matched controls. *Schizophr Res*. 2005;80(1):45–53.
19. Daumit GL, Goff DC, Meyer JM, et al. Antipsychotic effects on estimated 10-year coronary heart disease risk in the CATIE schizophrenia study. *Schizophr Res*. 2008;105(1–3):175–187.
20. Wirshing DA, Boyd JA, Meng LR, et al. The effects of novel antipsychotics on glucose and lipid levels. *J Clin Psychiatry*. 2002;63(10):856–865.
21. Jin H, Meyer JM, Jeste DV. Atypical antipsychotics and glucose dysregulation: a systematic review. *Schizophr Res*. 2004;71(2–3):195–212.
22. Parsons B, Allison DB, Loebel A, et al. Weight effects associated with antipsychotics: a comprehensive database analysis. *Schizophr Res*. 2009;110(1–3):103–110.

23. Hermes E, Nasrallah H, Davis V, et al. The association between weight change and symptom reduction in the CATIE schizophrenia trial. *Schizophr Res*. 2011;128(1–3):166–170.
24. Freedman R. The choice of antipsychotic drugs for schizophrenia. *N Engl J Med*. 2005;353(12):1286–1288.
25. Meyer JM, Davis VG, Goff DC, et al. Change in metabolic syndrome parameters with antipsychotic treatment in the CATIE Schizophrenia Trial: prospective data from phase 1. *Schizophr Res*. 2008;101(1–3): 273–286.
26. FDA Public Health Advisory. Deaths with Antipsychotics in Elderly Patients with Behavioral Disturbances. http://www.fda.gov/Drugs /DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ DrugSafetyInformationforHeathcareProfessionals/ PublicHealthAdvisories/ucm053171.htm. 2005. Updated March 2, 2010. Accessed October 9, 2012.
27. Schneider LS, Tariot PN, Dagerman KS, et al; CATIE-AD Study Group. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med*. 2006;355(15):1525–1538.
28. Kahn RS, Fleischhacker WW, Boter H, et al; EUFEST study group. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. *Lancet*. 2008;371(9618):1085–1097.
29. Tunis SR, Stryer DB, Clancy CM. Practical clinical trials: increasing the value of clinical research for decision making in clinical and health policy. *JAMA*. 2003;290(12):1624–1632.
30. Macpherson H. Pragmatic clinical trials. *Complement Ther Med*. 2004;12(2–3):136–140.
31. Lavori PW, Rush AJ, Wisniewski SR, et al. Strengthening clinical effectiveness trials: equipoise-stratified randomization. *Biol Psychiatry*. 2001;50(10):792–801.
32. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
33. Jin H, Lanouette NM, Mudaliar S, et al. Association of posttraumatic stress disorder with increased prevalence of metabolic syndrome. *J Clin Psychopharmacol*. 2009;29(3):210–215.
34. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale (BPRS): recent developments in ascertainment and scaling. *Psychopharmacol Bull*. 1988;24(1):97–99.
35. Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209–1223.
36. Grundy SM, Hansen B. Smith SC Jr, et al. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. *Arterioscler Thromb Vas Biol*. 2004;24(2):e19-e24.
37. Jeste DV, Blazer D, Casey DE, et al. ACNP White Paper: update on use of antipsychotic drugs in elderly persons with dementia. *Neuropsychopharmacology*. 2008;33(5):957–970.
38. Jeste DV, Jin H, Golshan S, et al. Discontinuation of quetiapine from an NIMH-funded trial due to serious adverse events. *Am J Psychiatry*. 2009;166(8):937–938.
39. American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004;27(2):596–601.
40. Petri H, Urquhart J. Channeling bias in the interpretation of drug effects. *Stat Med*. 1991;10(4):577–581.
41. Obunai K, Jani S, Dangas GD. Cardiovascular morbidity and mortality of the metabolic syndrome. *Med Clin North Am*. 2007; 91(6):1169–1184, x.
42. Lorenzo C, Williams K, Hunt KJ, et al. The National Cholesterol Education Program–Adult Treatment Panel III, International Diabetes Federation, and World Health Organization definitions of the metabolic syndrome as predictors of incident cardiovascular disease and diabetes. *Diabetes Care*. 2007;30(1):8–13.
43. Rathmann W, Haastert B, Icks A, et al. Prevalence of the metabolic syndrome in the elderly population according to IDF, WHO, and NCEP definitions and associations with C-reactive protein: the KORA Survey 2000. *Diabetes Care*. 2006;29(2):461.
44. Ravaglia G, Forti P, Maioli F, et al. Metabolic syndrome: prevalence and prediction of mortality in elderly individuals. *Diabetes Care*. 2006;29(11): 2471–2476.
45. Scuteri A, Najjar SS, Morrell CH, et al; Cardiovascular Health Study. The metabolic syndrome in older individuals: prevalence and prediction of cardiovascular events: the Cardiovascular Health Study. *Diabetes Care*. 2005;28(4):882–887.
46. Ford ES, Giles WH, Dietz WH. Prevalence of the metabolic syndrome among US adults: findings from the third National Health and Nutrition Examination Survey. *JAMA*. 2002;287(3): 356–359.
47. Tiihonen J, Lönnqvist J, Wahlbeck K, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet*. 2009;374(9690):620–627.
48. Kime P. DoD cracks down on off-label drug use. *Army Times*. http://www.armytimes.com/news/2012/06/military-dod-cracks-down -on-off-label-seroquel-use-061412w/. Updated June 14, 2012. Accessed October 11, 2012.
49. Ballard C, Hanney ML, Theodoulou M, et al; DART-AD investigators. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. *Lancet Neurol*. 2009;8(2):151–157.