The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 22, 2005 VOL. 353 NO. 12

Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia

Jeffrey A. Lieberman, M.D., T. Scott Stroup, M.D., M.P.H., Joseph P. McEvoy, M.D., Marvin S. Swartz, M.D., Robert A. Rosenheck, M.D., Diana O. Perkins, M.D., M.P.H., Richard S.E. Keefe, Ph.D., Sonia M. Davis, Dr.P.H., Clarence E. Davis, Ph.D., Barry D. Lebowitz, Ph.D., Joanne Severe, M.S., and John K. Hsiao, M.D., for the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators*

ABSTRACT

BACKGROUND

The relative effectiveness of second-generation (atypical) antipsychotic drugs as compared with that of older agents has been incompletely addressed, though newer agents are currently used far more commonly. We compared a first-generation antipsychotic, perphenazine, with several newer drugs in a double-blind study.

METHODS

A total of 1493 patients with schizophrenia were recruited at 57 U.S. sites and randomly assigned to receive olanzapine (7.5 to 30 mg per day), perphenazine (8 to 32 mg per day), quetiapine (200 to 800 mg per day), or risperidone (1.5 to 6.0 mg per day) for up to 18 months. Ziprasidone (40 to 160 mg per day) was included after its approval by the Food and Drug Administration. The primary aim was to delineate differences in the overall effectiveness of these five treatments.

RESULTS

Overall, 74 percent of patients discontinued the study medication before 18 months (1061 of the 1432 patients who received at least one dose): 64 percent of those assigned to olanzapine, 75 percent of those assigned to perphenazine, 82 percent of those assigned to quetiapine, 74 percent of those assigned to risperidone, and 79 percent of those assigned to ziprasidone. The time to the discontinuation of treatment for any cause was significantly longer in the olanzapine group than in the quetiapine ($P<0.001$) or risperidone ($P=0.002$) group, but not in the perphenazine ($P=0.021$) or ziprasidone ($P=0.028$) group. The times to discontinuation because of intolerable side effects were similar among the groups, but the rates differed ($P=0.04$); olanzapine was associated with more discontinuation for weight gain or metabolic effects, and perphenazine was associated with more discontinuation for extrapyramidal effects.

CONCLUSIONS

The majority of patients in each group discontinued their assigned treatment owing to inefficacy or intolerable side effects or for other reasons. Olanzapine was the most effective in terms of the rates of discontinuation, and the efficacy of the conventional antipsychotic agent perphenazine appeared similar to that of quetiapine, risperidone, and ziprasidone. Olanzapine was associated with greater weight gain and increases in measures of glucose and lipid metabolism.

From the Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York State Psychiatric Institute, New York (J.A.L.); the Department of Psychiatry, School of Medicine (T.S.S., D.O.P.), and the Department of Biostatistics, School of Public Health (S.M.D., C.E.D.), University of North Carolina at Chapel Hill, Chapel Hill; Quintiles, Research Triangle Park, N.C. (S.M.D.); the Department of Biological Psychiatry, John Umstead Hospital, Butner, N.C. (J.P.M.); the Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, N.C. (J.P.M., M.S.S., R.S.E.K.); the Department of Psychiatry, Yale University School of Medicine, New Haven, Conn. (R.A.R.); and the Division of Services and Intervention Research, National Institute of Mental Health, National Institutes of Health, Bethesda, Md. (B.D.L., J.S., J.K.H.). Address reprint requests to Dr. Lieberman at the Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York State Psychiatric Institute, 1051 Riverside Dr., New York, NY 10032, or at jlieberman@columbia.edu.

*The CATIE investigators are listed in the Appendix.

N Engl J Med 2005;353:1209-23.

Antipsychotic drugs have become the cornerstone of treatment for schizophrenia. The first-generation "conventional" antipsychotic drugs are high-affinity antagonists of dopamine D2 receptors that are most effective against psychotic symptoms but have high rates of neurologic side effects, such as extrapyramidal signs and tardive dyskinesia.[1] The introduction of second-generation, or "atypical," antipsychotic drugs promised enhanced efficacy and safety.[2] The atypical agents differ pharmacologically from previous antipsychotic agents in their lower affinity for dopamine D2 receptors and greater affinities for other neuroreceptors, including those for serotonin (5-hydroxytryptamine$_{1A, 2A, 2C, 3, 6,}$ and $_{7}$) and norepinephrine (α_1 and α_2).[1]

Although studies indicated that the atypical drugs are similar to the conventional drugs in reducing psychotic symptoms and produce few neurologic effects, the evidence of their superior efficacy has been neither consistent nor robust,[3-8] with the exception of clozapine, which repeatedly has been effective in patients whose condition is refractory to treatment with other types of agents but has severe side effects that limit its use.[9-11] The newer agents appear more efficacious than conventional drugs in reducing negative symptoms (e.g., lack of emotion, interest, and expression), possibly owing to the absence of extrapyramidal symptoms[12] or other secondary causes of negative symptoms (e.g., depression) rather than to direct therapeutic effects.[13] The results of studies of the effects of treatment on cognitive impairment and mood symptoms have been inconclusive.[14,15] The ability of atypical agents to prevent relapse and their effects on social and vocational functioning, quality of life, long-term outcome, and the caregivers' burden have been incompletely explored.[8,12,16]

The safety advantages of the atypical drugs have been questioned because of their propensity to induce weight gain[17] and alter glucose and lipid metabolism.[18,19] Nevertheless, these medications are widely used and have a 90 percent market share in the United States,[20,21] resulting in burgeoning costs. In the wake of this trend, questions have been raised about the clinical advantages and cost effectiveness of the atypical drugs. We report the primary outcomes of a double-blind, active-control clinical trial sponsored by the National Institute of Mental Health (NIMH) that was designed to compare the effectiveness of atypical and conventional antipsychotic drugs.[22,23]

METHODS

STUDY SETTING AND DESIGN

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study was initiated by the NIMH to compare the effectiveness of antipsychotic drugs. Its rationale, design, and methods have been described previously.[24-28] The protocol was made available to the public for comment, and a committee of scientific experts, health care administrators, and consumer advocates critiqued the study under the auspices of the NIMH. The study was conducted between January 2001 and December 2004 at 57 clinical sites in the United States (16 university clinics, 10 state mental health agencies, 7 Veterans Affairs medical centers, 6 private nonprofit agencies, 4 private-practice sites, and 14 mixed-system sites). Patients were initially randomly assigned to receive olanzapine, perphenazine, quetiapine, or risperidone under double-blind conditions and followed for up to 18 months or until treatment was discontinued for any reason (phase 1). (Ziprasidone was approved for use by the Food and Drug Administration [FDA] after the study began and was added to the study in January 2002 in the form of an identical-appearing capsule containing 40 mg.) Patients whose assigned treatment was discontinued could receive other treatments in phases 2 and 3.[24] The present report is limited to phase 1 results.

PARTICIPANTS

Eligible patients were 18 to 65 years of age; had received a diagnosis of schizophrenia, as determined on the basis of the Structured Clinical Interview of the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition; and were able to take oral antipsychotic medication, as determined by the study doctor. Patients were excluded if they had received a diagnosis of schizoaffective disorder, mental retardation, or other cognitive disorders; had a history of serious adverse reactions to the proposed treatments; had had only one schizophrenic episode; had a history of treatment resistance, defined by the persistence of severe symptoms despite adequate trials of one of the proposed treatments or prior treatment with clozapine; were pregnant or breast-feeding; or had a serious and unstable medical condition.

The study was approved by the institutional review board at each site, and written informed consent was obtained from the patients or their legal guardians.

INTERVENTIONS

Identical-appearing capsules contained olanzapine (Zyprexa, Eli Lilly) (7.5 mg), quetiapine (Seroquel, AstraZeneca) (200 mg), risperidone (Risperdal, Janssen Pharmaceutica) (1.5 mg), perphenazine (Trilafon, Schering-Plough, at the time of the study) (8 mg), or (after January 2002) ziprasidone (Geodon, Pfizer) (40 mg). The packaging was done by Quintiles. The dose of medications was flexible, ranging from one to four capsules daily, and was based on the study doctor's judgment. Overlap in the administration of the antipsychotic agents that patients received before study entry was permitted for the first four weeks after randomization to allow a gradual transition to study medication. Concomitant medications were permitted throughout the trial, except for additional antipsychotic agents. Patients had monthly visits with study doctors.

Because of product labeling, quetiapine and ziprasidone are given twice daily and olanzapine, perphenazine, and risperidone once daily. To protect blinding, half the patients randomly assigned to perphenazine, olanzapine, and risperidone were assigned to twice-daily dosing and half to once-daily dosing. To minimize initial side effects, patients assigned to quetiapine began treatment by receiving one 100-mg capsule on days 1 and 2, one twice daily on day 3, and one for the first dose of day 4. All patients assigned to twice-daily dosing received five identical-appearing capsules to begin treatment. Patients with current tardive dyskinesia could enroll, but the randomization scheme prevented their assignment to treatment with perphenazine.

OBJECTIVES AND OUTCOMES

We hypothesized that there would be significant differences in the overall effectiveness of olanzapine, perphenazine, quetiapine, risperidone, and ziprasidone in treating schizophrenia that reflected variations in efficacy and tolerability. The primary outcome measure was the discontinuation of treatment for any cause, a discrete outcome selected because stopping or changing medication is a frequent occurrence and major problem in the treatment of schizophrenia. In addition, this measure integrates patients' and clinicians' judgments of efficacy, safety, and tolerability into a global measure of effectiveness that reflects their evaluation of therapeutic benefits in relation to undesirable effects. The key secondary outcomes were the specific reasons for the discontinuation of treatment (e.g., inefficacy or intolerability owing to side effects such as weight gain, extrapyramidal signs, or sedation as judged by the study doctor). Additional secondary efficacy outcomes included scores on the Positive and Negative Syndrome Scale (PANSS) and the Clinical Global Impressions (CGI) Scale. PANSS scores can range from 30 to 210, with higher scores indicating more severe psychopathology. Scores for the CGI Scale can range from 1 to 7, with higher scores indicating greater severity of illness. Secondary safety and tolerability outcomes, which were evaluated at months 1, 3, 6, 9, 12, 15, and 18, included the incidence of serious adverse events, the incidence of adverse events during treatment, the incidence of neurologic side effects, and changes in weight, electrocardiographic findings, and laboratory analytes.

STATISTICAL ANALYSIS

Randomized patients who received at least one dose of study medication made up the intention-to-treat population. Two hundred thirty-one patients with tardive dyskinesia were excluded from random assignment to perphenazine. Ziprasidone was added to the trial after approximately 40 percent of the patients had been enrolled. Consequently, comparisons involving the perphenazine group were limited to patients without tardive dyskinesia, and comparisons involving the ziprasidone group were limited to the cohort of patients who underwent randomization after ziprasidone was added (the ziprasidone cohort). In general, the trial had a statistical power of 85 percent to identify an absolute difference of 12 percent in the rates of discontinuation between two atypical agents; however, it had a statistical power of 76 percent for comparisons involving perphenazine and of 58 percent for comparisons involving ziprasidone.

We used Kaplan–Meier survival curves to estimate the time to the discontinuation of treatment. Treatment groups were compared with use of Cox proportional-hazards regression models[29] stratified according to site, with adjustment for whether the patient had had an exacerbation of schizophrenia in the preceding three months and tardive dyskinesia status (for models excluding perphenazine). Sites with 15 or fewer patients were grouped according to the sites' health care systems.

The overall difference among the olanzapine, quetiapine, risperidone, and perphenazine groups was evaluated with the use of a test with 3 degrees of freedom (df). If the difference was significant at a P value of less than 0.05, the three atypical-drug

groups were compared with each other by means of step-down or closed testing, with a P value of less than 0.05 considered to indicate statistical significance. Each group was then compared with the perphenazine group by means of a Hochberg adjustment for multiple comparisons.[30] The smallest resulting P value was compared with a value of 0.017 (0.05 ÷ 3). The ziprasidone group was directly compared with the other three atypical-drug groups and the perphenazine group within the ziprasidone cohort by means of a Hochberg adjustment for four pairwise comparisons. The smallest resulting P value was compared with a value of 0.013 (0.05 ÷ 4).

Successful treatment time was defined as the number of months of treatment during phase 1 in which patients had a CGI Scale score of at least 3 (mildly ill) or a score of 4 (moderately ill) with an improvement of at least two points from baseline. Treatment groups were compared with use of proportional-hazards regression.

A sensitivity analysis of the Cox model for the discontinuation of treatment for any cause evaluated the effects of potentially important baseline covariates and their interaction with the treatment group.

The PANSS total scores and CGI Scale scores over time were compared among the groups with the use of a mixed model including the same fixed covariates as for the time to discontinuation, plus baseline value, time, the interaction between treatment and time, and the interaction between baseline value and time. Time was classified into months (1, 3, 6, 9, 12, 15, and 18). The results of assessments made at the end of phase 1 were assigned to the next interval. The correlation of the repeated measures within each patient was modeled with the use of a random subject intercept and an unstructured covariance matrix.

The study was funded by the NIMH. The pharmaceutical companies whose drugs were included in the study donated drug supplies, and each provided advice on the dose of its own drug; they were otherwise not involved in the design of the study, analyses, or interpretation of results. The manuscript was written solely by the listed authors.

RESULTS

CHARACTERISTICS AND DISPOSITION OF PATIENTS

Table 1 shows the baseline demographic and clinical characteristics of the patients. Figure 1 depicts the enrollment, randomization, and follow-up of study patients; 1493 patients were enrolled in the study and randomly assigned to treatment. All data from one site (33 patients) were excluded before analysis, owing to concern about the integrity of data from that site before the end of the study and before unblinding. The mean modal doses were 20.1 mg per day for olanzapine, 20.8 mg per day for perphenazine, 543.4 mg per day for quetiapine, 3.9 mg per day for risperidone, and 112.8 mg per day for ziprasidone (Table 2). Seventy-four percent of patients in the intention-to-treat analysis (1061 of 1432) discontinued their assigned treatment in phase 1 before 18 months (median, 6).

DISCONTINUATION OF TREATMENT

The time to the discontinuation of treatment for any cause was longer in the olanzapine group than in the quetiapine group (hazard ratio, 0.63; P<0.001), the risperidone group (hazard ratio, 0.75; P=0.002), or the perphenazine group (hazard ratio, 0.78; P=0.021) (Table 2). However, the difference between the olanzapine group and the perphenazine group was not significant after adjustment for multiple comparisons (required P value, ≤0.017). Within the cohort of 889 patients who underwent randomization after ziprasidone was added to the trial, those receiving olanzapine had a longer interval before discontinuing treatment for any cause than did those in the ziprasidone group (hazard ratio, 0.76; P=0.028). However, this difference was not significant after adjustment for multiple comparisons (required P value, ≤0.013).

The time to the discontinuation of treatment for lack of efficacy was longer in the olanzapine group than in the perphenazine group (hazard ratio, 0.47; P<0.001), the quetiapine group (hazard ratio, 0.41; P<0.001), the risperidone group (hazard ratio, 0.45; P<0.001), or the ziprasidone group (hazard ratio, 0.59; P=0.026), but the difference between the olanzapine and ziprasidone groups was not significant after adjustment for multiple comparisons (required P value, ≤0.013) (Table 2). There were no significant differences between groups in time until discontinuation owing to intolerable side effects (P=0.054). The time until discontinuation owing to the patient's decision (i.e., the patient independently chose to stop treatment) was similar to that for discontinuation for any cause (Table 2).

The duration of successful treatment was significantly longer in the olanzapine group than in the quetiapine group (hazard ratio, 0.53; P<0.001), the risperidone group (hazard ratio, 0.69; P=0.002), or the perphenazine group (hazard ratio, 0.73;

Table 1. Baseline Demographic and Clinical Characteristics of Randomized Patients.*

Characteristic	Olanzapine (N=336)	Quetiapine (N=337)	Risperidone (N=341)	Perphenazine (N=261)†	Ziprasidone (N=185)	Total (N=1460)
Demographic characteristics						
Age — yr	40.8±10.8	40.9±11.2	40.6±11.3	40.0±11.1	40.1±11.0	40.6±11.1
Sex — no. (%)						
Male	244 (73)	255 (76)	253 (74)	199 (76)	129 (70)	1080 (74)
Female	92 (27)	82 (24)	88 (26)	62 (24)	56 (30)	380 (26)
Race — no. (%)‡						
White	196 (58)	213 (63)	204 (60)	152 (58)	109 (60)	874 (60)
Black	119 (35)	114 (34)	122 (36)	93 (36)	65 (36)	513 (35)
Other	21 (6)	10 (3)	15 (4)	16 (6)	9 (5)	71 (5)
Spanish, Hispanic, or Latino ethnicity — no. (%)	42 (12)	48 (14)	38 (11)	24 (9)	18 (10)	170 (12)
Education — yr	12.2±2.2	12.1±2.4	12.0±2.2	12.1±2.1	12.0±2.5	12.1±2.3
Marital status — no. (%)						
Married	36 (11)	34 (10)	37 (11)	43 (16)	17 (9)	167 (11)
Previously married§	105 (31)	90 (27)	101 (30)	68 (26)	61 (33)	425 (29)
Never married	195 (58)	213 (63)	203 (60)	150 (57)	107 (58)	868 (59)
Unemployed — no. (%)¶	281 (85)	274 (84)	288 (86)	219 (85)	155 (85)	1217 (85)
Exacerbation in previous 3 mo — no. (%)	90 (27)	89 (26)	95 (28)	68 (26)	60 (32)	402 (28)
PANSS total score‖	76.1±18.2	75.7±16.9	76.4±16.6	74.3±18.1	75.4±18.6	75.7±17.6
Clinician-rated CGI severity score**	4.0±1.0	3.9±0.9	4.0±0.9	3.9±1.0	3.9±0.9	4.0±0.9
Psychiatric history						
Age at 1st treatment for any behavioral or emotional problem — yr	24.1±9.0	23.6±8.1	23.7±9.3	24.5±8.6	24.1±9.7	24.0±8.9
Years since 1st antipsychotic medication prescribed	14.5±11.0	14.6±10.3	14.8±10.7	13.8±11.0	14.0±10.5	14.4±10.7
SCID diagnosis in past 5 yr — no. (%)						
Depression	86 (26)	84 (25)	104 (30)	71 (27)	60 (32)	405 (28)
Alcohol dependence or alcohol abuse	74 (22)	81 (24)	92 (27)	74 (28)	37 (20)	358 (25)
Drug dependence or drug abuse	86 (26)	95 (28)	110 (32)	74 (28)	57 (31)	422 (29)
Obsessive–compulsive disorder	10 (3)	22 (7)	21 (6)	12 (5)	8 (4)	73 (5)
Other anxiety disorder	44 (13)	46 (14)	52 (15)	29 (11)	28 (15)	199 (14)
Baseline antipsychotic medications — no. (%)††						
Olanzapine alone	78 (23)	69 (20)	76 (22)	58 (22)	41 (22)	322 (22)
Quetiapine alone	24 (7)	17 (5)	22 (6)	15 (6)	17 (9)	95 (7)
Risperidone alone	57 (17)	59 (18)	63 (18)	64 (25)	32 (17)	275 (19)
Any combination including olanzapine, quetiapine, or risperidone	31 (9)	32 (10)	33 (10)	21 (8)	8 (4)	95 (7)
All others	52 (15)	58 (17)	60 (18)	30 (11)	29 (16)	229 (16)
None	94 (28)	102 (30)	87 (26)	73 (28)	58 (31)	414 (28)
Baseline medical diagnoses — no. (%)						
Diabetes (type 1 or 2)	36 (11)	40 (12)	32 (9)	29 (11)	17 (9)	154 (11)
Hyperlipidemia	56 (17)	44 (13)	42 (12)	36 (14)	26 (14)	204 (14)
Hypertension	68 (20)	67 (20)	63 (18)	60 (23)	31 (17)	289 (20)

* Plus–minus values are means ±SD. Because of rounding, percentages may not sum to 100. SCID denotes Structured Clinical Interview for DSM-IV.
† Patients with tardive dyskinesia were excluded from the perphenazine group.
‡ Race was self-reported. "Other" includes American Indian or Alaska Native (less than 1 percent of patients), Asian (2 percent), Native Hawaiian or other Pacific Islander (less than 1 percent), and two or more races (2 percent). Percentages are based on the number of patients with data available: 336 in the olanzapine group, 337 in the quetiapine group, 341 in the risperidone group, 261 in the perphenazine group, and 183 in the ziprasidone group.
§ This category includes patients who were widowed, divorced, or separated.
¶ Percentages are based on the number of patients with data available: 330 in the olanzapine group, 328 in the quetiapine group, 336 in the risperidone group, 259 in the perphenazine group, and 182 in the ziprasidone group.
‖ Scores on the Positive and Negative Syndrome Scale (PANSS) for schizophrenia can range from 30 to 210, with higher scores indicating more severe psychopathology.
** The CGI severity score can range from 1 to 7, with higher scores indicating greater severity of illness.
†† Percentages for baseline medications are based on the number of patients with data on concomitant medications: 333 in the olanzapine group, 333 in the quetiapine group, 340 in the risperidone group, 259 in the perphenazine group, and 184 in the ziprasidone group.

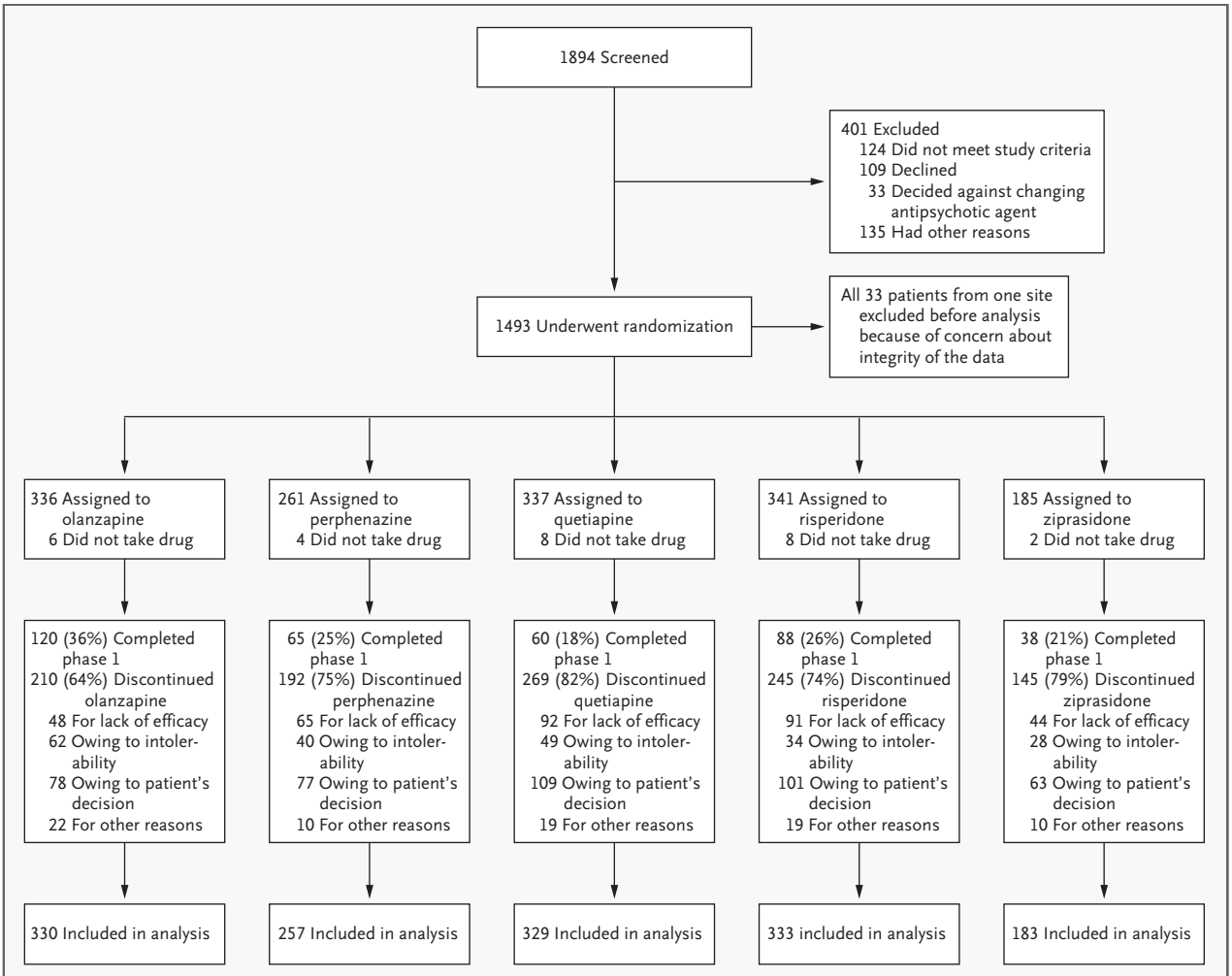

Figure 1. Enrollment and Outcomes.

Patients with tardive dyskinesia were not assigned to perphenazine. Ziprasidone was added to the study after approximately 40 percent of patients had been enrolled.

P=0.013) and was significantly longer in the risperidone group than in the quetiapine group (hazard ratio, 0.77; P=0.021).

ADJUSTMENT OF OUTCOMES FOR COVARIATES

An exploratory analysis identified the following predictors of an earlier time to discontinuation: higher baseline PANSS score (P=0.001), younger age (P<0.001), longer duration since the first use of antipsychotic medication (P=0.057), and the antipsychotic drug taken before study entry (P=0.001). Baseline antipsychotic agents were grouped into six categories (Table 1). Patients receiving olanzapine or risperidone before enrollment stayed in phase 1 of the trial longer than those taking no antipsychotic agents, those taking combination treatments, or those receiving a single antipsychotic agent excluding olanzapine, quetiapine, or risperidone; pairwise hazard ratios ranged from 0.68 (P<0.001) to 0.80 (P<0.02). No interactions with treatment group were significant at a P value of less than 0.10. After adjustment for these predictors of discontinuation, the results of treatment-group comparisons were similar to the primary results.

EFFICACY MEASURES

Total PANSS scores improved over time in all groups (Fig. 2). The mixed model revealed significant vari-

ation in treatment effects over time (P=0.002). Improvement was initially greatest in the olanzapine group, but its advantage diminished over time. The pattern of change in the scores for the CGI Scale was similar to that for the PANSS scores (P=0.004 for the interaction between treatment and time).

ADVERSE EVENTS

The rates of adverse events and side effects are listed in Table 3. Fewer patients in the olanzapine group than in the other four groups were hospitalized for an exacerbation of schizophrenia (11 percent vs. 15 to 20 percent, P<0.001). After adjustment for the different durations of treatment, the olanzapine group had a risk ratio for hospitalization of 0.29 per person-year of treatment, as compared with risk ratios of 0.45 to 0.66 in the other groups.

The rates of treatment discontinuation due to intolerable side effects differed between treatments (P=0.04). Risperidone had the lowest rate (10 percent), and olanzapine had the highest rate (18 percent). Moreover, more patients discontinued olanzapine owing to weight gain or metabolic effects (9 percent vs. 1 percent to 4 percent with the other four drugs, P<0.001) and more patients discontinued perphenazine owing to extrapyramidal effects (8 percent vs. 2 percent to 4 percent, P=0.002).

Patients in the olanzapine and quetiapine groups had lower rates of insomnia (16 and 18 percent, respectively) than did patients in the other groups (24 percent in the risperidone group, 25 percent in the perphenazine group, and 30 percent in the ziprasidone group). Quetiapine was associated with a higher rate of anticholinergic effects than were the other drugs (31 percent vs. 20 to 25 percent, P<0.001).

Neurologic Side Effects

There were no significant differences among the groups in the incidence of extrapyramidal side effects, akathisia, or movement disorders as reflected by rating-scale measures of severity.

Weight Gain and Metabolic Changes

Patients in the olanzapine group gained more weight than patients in any other group, with an average weight gain of 2 lb (0.9 kg) per month. A larger proportion of patients in the olanzapine group than in the other groups gained 7 percent or more of their baseline body weight (30 percent vs. 7 to 16 percent, P<0.001).

Olanzapine had effects consistent with the potential development of the metabolic syndrome and was associated with greater increases in glycosylated hemoglobin, total cholesterol, and triglycerides after randomization than the other study drugs, even after adjustment for the duration of treatment. Ziprasidone was the only study drug associated with improvement in each of these metabolic variables. Only risperidone was associated with a substantial increase in prolactin levels.

Other Potential Adverse Events

There were no substantially different effects of the medications on the corrected QT interval on electrocardiography, and torsades de pointes did not develop in any patients. There were no significant differences among the groups in the incidence of new cataracts. There were no significant differences among the groups in the rates of suicide attempts or suicidal ideation reported as serious adverse events.

CONCOMITANT MEDICATIONS

There were few substantial differences among the groups in the rates or types of medications added during the study. Patients in the olanzapine and risperidone groups were the least likely to have anxiolytic agents added (9 and 10 percent, respectively, vs. 14 to 15 percent). Fewer patients receiving quetiapine were prescribed anticholinergic drugs (3 percent vs. 8 to 10 percent).

DISCUSSION

All second-generation antipsychotic drugs were included in phase 1 of this study except aripiprazole (which was approved by the FDA in November 2002) and clozapine, which was included in phase 2 for patients who discontinued phase 1 of treatment owing to lack of efficacy of the assigned drug. Although haloperidol is the first-generation agent most commonly used for comparison, we chose to use perphenazine because of its lower potency and moderate side-effect profile.[31]

Only a minority of patients in each group took their assigned drug for the duration of phase 1 (rates of discontinuation ranged from 64 to 82 percent). This outcome indicates that antipsychotic drugs, though effective, have substantial limitations in their effectiveness in patients with chronic schizophrenia. Although the rates of discontinuation may have been increased by the fact that patients were participating in a blinded, controlled trial, the rates are generally consistent with those previously ob-

Table 2. Outcome Measures of Effectiveness in the Intention-to-Treat Population.*

Outcome	Olanzapine (N=330)	Quetiapine (N=329)	Risperidone (N=333)	Perphenazine (N=257)†	P Value‡	Ziprasidone (N=183)§
Dose¶						
Mean modal dose — mg per day/total no. of patients	20.1/312	543.4/309	3.9/305	20.8/245		112.8/165
Maximal dose received — no. of patients (%)	124/312 (40)	137/309 (44)	122/305 (40)	98/245 (40)	<0.001	80/165 (48)
Discontinuation of treatment for any cause						
Discontinuation — no. of patients (%)	210 (64)	269 (82)	245 (74)	192 (75)		145 (79)
Kaplan–Meier time to discontinuation — mo						
Median (95% CI)	9.2 (6.9–12.1)	4.6 (3.9–5.5)	4.8 (4.0–6.1)	5.6 (4.5–6.3)		3.5 (3.1–5.4)
Cox-model treatment comparisons‖						
Olanzapine						
Hazard ratio (95% CI)		0.63 (0.52–0.76)	0.75 (0.62–0.90)	0.78 (0.63–0.96)	0.004**	0.76 (0.60–0.97)
P value		<0.001**	0.002**	0.021		0.028
Quetiapine						
Hazard ratio (95% CI)			1.19 (0.99–1.42)	1.14 (0.93–1.39)		1.01 (0.81–1.27)
P value			0.06	0.21		0.94
Risperidone						
Hazard ratio (95% CI)				1.00 (0.82–1.23)		0.89 (0.71–1.14)
P value				0.99		0.36
Perphenazine						
Hazard ratio (95% CI)						0.90 (0.70–1.16)
P value						0.43
Discontinuation of treatment for lack of efficacy						
Discontinuation — no. of patients (%)	48 (15)	92 (28)	91 (27)	65 (25)		44 (24)
Kaplan–Meier time to discontinuation — mo						
25th percentile (95% CI)	—††	6.0 (4.5–8.0)	6.0 (4.4–9.0)	6.1 (4.5–9.1)		6.9 (3.2–12.1)
Cox-model treatment comparisons‖						
Olanzapine						
Hazard ratio (95% CI)		0.41 (0.29–0.57)	0.45 (0.32–0.64)	0.47 (0.31–0.70)	<0.001**	0.59 (0.37–0.93)
P value		<0.001**	<0.001**	<0.001**		0.026
Quetiapine						
P value			0.49	0.47		0.69
Risperidone						
P value				0.59		0.93
Perphenazine						
P value						0.44
Discontinuation of treatment owing to intolerability‡‡						
Discontinuation — no. (%)	62 (19)	49 (15)	34 (10)	40 (16)		28 (15)
Cox-model treatment comparisons‖						
Risperidone						
Hazard ratio (95% CI)	0.62 (0.41–0.95)	0.65 (0.42–1.00)		0.60 (0.36–0.98)	0.054	0.79 (0.46–1.37)
P value	0.027	0.051		0.043		0.41
Olanzapine						
P value		0.84		0.49		0.28
Quetiapine						
P value				0.97		0.87
Perphenazine						
P value						0.19

Patient's decision to discontinue treatment§§						
Discontinuation — no. (%)	78 (24)	109 (33)	101 (30)	77 (30)		63 (34)
Kaplan–Meier time to discontinuation — mo						
25th percentile (95% CI)	12.3 (8.0–17.8)	4.9 (3.1–7.0)	4.5 (3.1–8.8)	6.2 (4.7–8.1)		3.4 (3.0–6.1)
Cox-model treatment comparisons‖						
Olanzapine						
Hazard ratio (95% CI)		0.56 (0.42–0.75)	0.67 (0.50–0.90)	0.70 (0.50–0.98)	0.034**	0.63 (0.43–0.93)
P value		<0.001**	0.008**	0.036		0.018
Quetiapine						
P value			0.21	0.46		0.63
Risperidone						
P value				0.95		0.21
Perphenazine						
P value						0.27
Duration of successful treatment¶¶						
Kaplan–Meier time to discontinuation — mo						
Median (95% CI)	3 (2–5)	1 (0–1)	1 (0–1)	1 (1–2)		1 (0–1)
Cox-model treatment comparisons‖						
Olanzapine						
Hazard ratio (95% CI)		0.53 (0.43–0.67)	0.69 (0.55–0.87)	0.73 (0.57–0.93)	<0.001**	0.75 (0.58–0.94)
P value		<0.001**	0.002**	0.013**		0.017
Quetiapine						
Hazard ratio (95% CI)			1.30 (1.04–4.63)	1.28 (1.00–1.64)		1.06 (0.85–1.33)
P value			0.02**	0.05		0.61
Risperidone						
P value				0.72		0.74
Perphenazine						
P value						0.25

* CI denotes confidence interval.
† Patients with tardive dyskinesia were excluded from the perphenazine group.
‡ The overall P value is for the comparison of olanzapine, quetiapine, risperidone, and perphenazine with the use of a 3 df test from a Cox model for survival outcomes, excluding patients with tardive dyskinesia. If the difference among the groups was significant at a P value of less than 0.05, the three atypical agents were compared with each other by means of step-down or closed testing to identify significant differences (P<0.05) between groups. Each atypical agent was then compared with perphenazine by means of a Hochberg adjustment. The smallest P value for the perphenazine group was compared with a value of 0.017 (0.05÷3).
§ Statistical analyses involving the ziprasidone group were confined to the cohort of patients who underwent randomization after ziprasidone was added to the study, with the use of a Hochberg adjustment for four pairwise comparisons. The smallest P value was compared with a value of 0.013 (0.05÷4).
¶ The modal dose and percentages of patients taking the maximal dose are based on the number of patients with data on the dose. Information on dose was not available for some patients who dropped out early. The P values for the percentage of patients reaching the maximal dose were calculated with the use of a 4 df test comparing all treatment groups from a Poisson regression accounting for differential exposure times, and adjusting for whether the patient had had an exacerbation in the preceding three months.
‖ For pairwise comparisons of treatment groups, Cox-model hazard ratios of less than 1 indicate a greater time to the discontinuation of the first treatment listed.
** P value is statistically significant.
†† The Kaplan–Meier 25th percentile for discontinuation owing to lack of efficacy could not be estimated for olanzapine because of the low event rates.
‡‡ The Kaplan–Meier 25th percentile for discontinuation owing to intolerability could not be estimated because of the low event rates.
§§ This category includes decisions made by both patients and their advocates.
¶¶ Successful treatment was defined by a CGI severity score of at least 3 (mildly ill) or by a score of 4 (moderately ill) with an improvement of at least two points from baseline.

served.[5] Within this limited range of effectiveness, the olanzapine group had the lowest rate of discontinuation, which might lead one to consider olanzapine the most effective of the medications studied. Its apparent superior efficacy is also indicated by the greater reduction in psychopathology, longer duration of successful treatment, and lower rate of hospitalizations for an exacerbation of schizophrenia. The results for the other second-generation antipsychotic agents and the representative conventional drug, perphenazine, were similar in most respects. It is important to note that the differences between olanzapine and perphenazine were moderate. Although there were no significant differences in the time until discontinuation owing to intolerable side effects, there were differences in rates. Moreover, olanzapine was associated with greater increases in weight and indexes of glucose and lipid metabolism than the other treatments.

Dose could have been a factor in the performance of the various agents studied. The dose ranges approved by the FDA for quetiapine and ziprasidone may be below their optimal therapeutic doses, and the recommended doses of risperidone (6 mg per day or less), intended to limit extrapyramidal symptoms, may not encompass its full therapeutic range.[32,33] However, the dose ranges we used were based on information from the manufacturer of each medication plus knowledge of clinical practice patterns. Moreover, the average prescribed doses of these drugs in the United States for patients with schizophrenia during the period in which the study was conducted (14 mg of olanzapine per day, 3.8 mg of risperidone per day, 388 mg of quetiapine per day, and 125 mg of ziprasidone per day) were generally similar to the ones we used.[34] The fact that a higher proportion of patients assigned to quetiapine and ziprasidone received the maximal dose allowed in the study suggests that these agents are either less effective or require higher doses (Table 2). The dose range of perphenazine was chosen to minimize the potential for extrapyramidal symptoms that may have biased previous comparisons of first- and second-generation drugs.[4,7,31]

The use of low-dose perphenazine appears to have diminished the frequency of extrapyramidal side effects in patients who received the first-generation drug. In contrast to previous studies,[35] the proportion of patients with extrapyramidal symptoms did not differ significantly among those who received first-generation and second-generation drugs in our study. Despite this finding, more patients discontinued perphenazine than other medications owing to extrapyramidal effects.

Figure 2 (facing page). Outcome Measures of Effectiveness.

The number of patients included at each assessment time point declined over time. Estimates are from a mixed model, which assumed that data were missing at random. Scores for the PANSS and CGI Scale were determined at study entry and 1, 3, 6, 9, 12, 15, and 18 months after randomization. Scores for the PANSS can range from 30 to 210, with higher scores indicating more severe psychopathology. Scores for the CGI Scale can range from 1 to 7, with higher scores indicating a greater severity of illness. Analyses involving the ziprasidone group were limited to the cohort of patients who underwent randomization after the addition of ziprasidone to the study (the ziprasidone cohort). Thus, the P value for the overall interaction between time and treatment excludes the ziprasidone group and is given separately for the ziprasidone cohort.

As in other studies, we found that risperidone was associated with hyperprolactinemia and olanzapine was associated with substantial weight gain in addition to adverse changes in glucose and lipid metabolism — all features of the metabolic syndrome. Concerns about potential prolongation of the corrected QT interval with ziprasidone and of cataracts with quetiapine were not realized in this study.

We used broad inclusion and minimal exclusion criteria and allowed the enrollment of patients with coexisting conditions and those who were taking other medications. The study was conducted in a variety of clinical settings in which people with schizophrenia are treated. These "real-world" features of the study, which were intended to make the results widely applicable, may account for the differences in results between this and previous studies comparing first- and second-generation antipsychotic agents.

In summary, patients with chronic schizophrenia in this study discontinued their antipsychotic study medications at a high rate, indicating substantial limitations in the effectiveness of the drugs. Within this limited range of effectiveness, olanzapine appeared to be more effective than the other drugs studied, and there were no significant differences in effectiveness between the conventional drug perphenazine and the other second-generation drugs. There were no significant differences among the drugs in the time until discontinuation of treatment owing to intolerable side effects. However, olanzapine was associated with greater weight

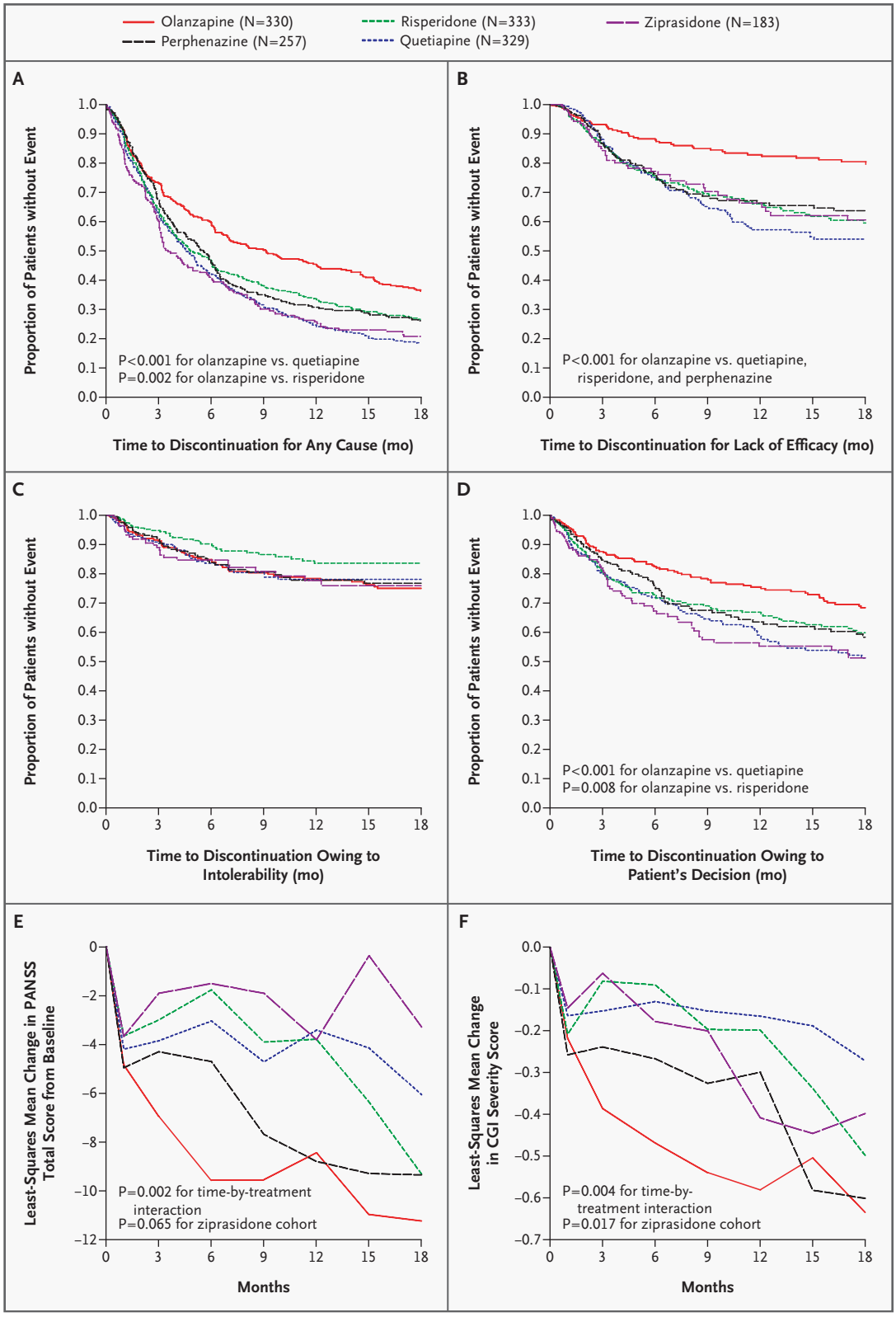

Table 3. Outcome Measures of Safety among Randomized Patients.

Outcome	Olanzapine (N=336)	Quetiapine (N=337)	Risperidone (N=341)	Perphenazine (N=261)*	Ziprasidone (N=185)	P Value†
Hospitalization for exacerbation of schizophrenia						
Hospitalized patients — no. (%)	38 (11)	68 (20)	51 (15)	41 (16)	33 (18)	<0.001
No. of hospitalizations/total person-yr of exposure	81/280	131/199	103/229	89/175	62/109	
Risk ratio	0.29	0.66	0.45	0.51	0.57	
Adverse events — no. (%)						
Any serious adverse event	32 (10)	32 (9)	33 (10)	29 (11)	19 (10)	0.47
Suicide attempt	2 (<1)	1 (<1)	2 (<1)	1 (<1)	1 (<1)	0.99
Suicidal ideation	1 (<1)	2 (<1)	4 (1)	3 (1)	2 (1)	0.49
Any moderate or severe adverse event identified by systematic inquiry	235 (70)	220 (65)	232 (68)	170 (65)	119 (64)	0.14
Insomnia	55 (16)	62 (18)	83 (24)	66 (25)	56 (30)	<0.001
Hypersomnia, sleepiness	104 (31)	103 (31)	96 (28)	74 (28)	45 (24)	0.18
Urinary hesitancy, dry mouth, constipation	79 (24)	105 (31)	84 (25)	57 (22)	37 (20)	<0.001
Decreased sex drive, arousal, ability to reach orgasm	91 (27)	69 (20)	91 (27)	64 (25)	35 (19)	0.59
Gynecomastia, galactorrhea	7 (2)	6 (2)	14 (4)	4 (2)	6 (3)	0.15
Menstrual irregularities‡	11 (12)	5 (6)	16 (18)	7 (11)	8 (14)	0.17
Incontinence, nocturia	18 (5)	15 (4)	25 (7)	6 (2)	10 (5)	0.04
Orthostatic faintness	31 (9)	38 (11)	37 (11)	29 (11)	24 (13)	0.08
Any moderate or severe spontaneously reported adverse event	122 (36)	113 (34)	123 (36)	79 (30)	65 (35)	0.10
Neurologic effects — no./total no. (%)§						
AIMS global severity score ≥2	32/236 (14)	30/236 (13)	38/238 (16)	41/237 (17)	18/126 (14)	0.23
Barnes Akathisia Rating Scale global score ≥3	15/290 (5)	16/305 (5)	20/292 (7)	16/241 (7)	14/158 (9)	0.24
Simpson–Angus Extrapyramidal Signs Scale mean score ≥1	23/296 (8)	12/298 (4)	23/292 (8)	15/243 (6)	6/152 (4)	0.47
Discontinuation of treatment owing to intolerability — no. %						
Discontinuation	62 (18)	49 (15)	34 (10)	40 (15)	28 (15)	0.04
Weight gain or metabolic effects	31 (9)	12 (4)	6 (2)	3 (1)	6 (3)	<0.001
Extrapyramidal effects	8 (2)	10 (3)	11 (3)	22 (8)	7 (4)	0.002
Sedation	7 (2)	9 (3)	3 (1)	7 (3)	0	0.10
Other effects	16 (5)	18 (5)	14 (4)	8 (3)	15 (8)	0.16
Weight change from baseline to last observation¶						
Weight gain >7% — no./total no. (%)	92/307 (30)	49/305 (16)	42/300 (14)	29/243 (12)	12/161 (7)	<0.001
Weight change — lb						
Mean ±SE	9.4±0.9	1.1±0.9	0.8±0.9	−2.0±1.1	−1.6±1.1	<0.001
Median	7	1	0	−1	−2	
Range	−14 to 42	−25 to 25	−24 to 24	−29 to 22	−24 to 18	
Weight change — lb/mo of treatment						
Mean ±SE	2.0±0.3	0.5±0.2	0.4±0.3	−0.2±0.2	−0.3±0.3	<0.001
Median	0.8	0.1	0.0	−0.1	−0.3	
Range	−1.4 to 9.5	−4.4 to 6.3	−4.6 to 5.7	−4.9 to 4.0	−5.3 to 5.9	
Change from baseline in laboratory values‖						
Blood glucose — mg/dl						
Mean ±SE	15.0±2.8	6.8±2.5	6.7±2.0	5.2±2.0	2.3±3.9	
Median	7.0	4.3	5.5	1.5	2.5	
Exposure-adjusted mean ±SE	13.7±2.5	7.5±2.5	6.6±2.5	5.4±2.8	2.9±3.4	0.59
Glycosylated hemoglobin — %						
Mean ±SE	0.41±0.09	0.05±0.05	0.08±0.04	0.10±0.06	−0.10±0.14	
Median	0.20	0.10	0.05	0.05	0.10	
Exposure-adjusted mean ±SE	0.40±0.07	0.04±0.08	0.07±0.08	0.09±0.09	0.11±0.09	0.01
Cholesterol — mg/dl						
Mean ±SE	9.7±2.1	5.3±2.1	−2.1±1.9	0.5±2.3	−9.2±5.2	
Median	8.5	3.5	−3.0	0.5	−1.0	
Exposure–adjusted mean ±SE	9.4±2.4	6.6±2.4	−1.3±2.4	1.5±2.7	−8.2±3.2	<0.001
Triglycerides — mg/dl						
Mean ±SE	42.9±8.4	19.2±10.6	−2.6±6.3	8.3±11.5	−18.1±9.4	
Median	33.5	17.5	3.0	2.0	−7.0	
Exposure-adjusted mean ±SE	40.5±8.9	21.2±9.2	−2.4±9.1	9.2±10.1	−16.5±12.2	<0.001

Table 3. (Continued.)

Outcome	Olanzapine (N=336)	Quetiapine (N=337)	Risperidone (N=341)	Perphenazine (N=261)*	Ziprasidone (N=185)	P Value†
Change from baseline in laboratory values‖ (cont.)						
Prolactin — ng/dl						
Mean ±SE	−6.1±1.2	−9.3±1.4	15.4±1.5	0.4±1.7	−4.5±1.6	
Median	−0.9	−2.7	9.2	1.4	−2.4	
Exposure-adjusted mean ±SE	−8.1±1.4	−10.6±1.4	13.8±1.4	−1.2±1.6	−5.6±1.9	<0.001
Electrocardiographic findings**						
Mean (±SE) change in corrected QT interval from baseline to last observation — msec	1.2±1.8	5.9±1.9	0.2±1.8	1.4±2.0	1.3±2.2	0.25
Prolonged corrected QT interval — no./total no. (%)	0/231	6/214 (3)	7/218 (3)	2/172 (1)	2/148 (1)	0.03
New cataracts — no./total no. (%)††	3/272 (1)	1/258 (<1)	2/260 (1)	1/210 (<1)	0/142	0.81
Medications added — no. (%)‡‡						
Lithium	1 (<1)	4 (1)	2 (<1)	3 (1)	1 (<1)	0.42
Anticonvulsants	10 (3)	11 (3)	13 (4)	9 (3)	8 (4)	0.63
Antidepressants§§	40 (12)	28 (8)	54 (16)	28 (11)	26 (14)	0.03
Hypnotics, sedatives¶¶	22 (7)	14 (4)	32 (9)	23 (9)	17 (9)	0.03
Anxiolytics	31 (9)	46 (14)	33 (10)	38 (15)	27 (15)	<0.001
Anticholinergic agents	25 (7)	11 (3)	32 (9)	26 (10)	14 (8)	0.01
Oral glucose-lowering drugs, insulin	12 (4)	7 (2)	8 (2)	5 (2)	4 (2)	0.95
Cholestatin drugs	15 (4)	14 (4)	11 (3)	7 (3)	2 (1)	0.28

* Patients with tardive dyskinesia were excluded from the perphenazine group.

† P values, presented for descriptive purposes, are from a test with 4 df comparing all treatment groups. P values for reasons of discontinuation are from a chi-square test. P values for percentages are from a Poisson regression accounting for differential exposure times and adjusting for whether the patient had had an exacerbation in the preceding three months. P values for a prolonged corrected QT interval and new cataracts are from Fisher's exact test. P values for laboratory values are based on a ranked analysis of covariance with adjustment for whether the patient had had an exacerbation in the preceding three months and the duration of exposure to the study drug during phase 1. P values for the change in weight and the corrected QT interval are based on an analysis of covariance with adjustment for whether the patient had had an exacerbation in the preceding three months and the duration of exposure to study drug during phase 1.

‡ Percentages are based on the number of female patients: 92 in the olanzapine group, 82 in the quetiapine group, 88 in the risperidone group, 62 in the perphenazine group, and 56 in the ziprasidone group.

§ Scores of 2 or more on the Abnormal Involuntary Movement Scale (AIMS) global severity score indicate at least mild severity of abnormal movements. Percentages are based on the number of patients without tardive dyskinesia who had an AIMS score of less than 2 at baseline and at least one post-baseline measurement. Scores of 3 or more for the global clinical assessment of the Barnes Akathisia Rating Scale indicate at least moderate severity of akathisia. Percentages are based on the number of patients who had a Barnes score of less than 3 at baseline and at least one post-baseline measurement. Average scores of 1 or more for the Simpson–Angus Extrapyramidal Signs Scale indicate at least mild severity of extrapyramidal signs. Percentages are based on the number of patients who had an average score for the Simpson–Angus Extrapyramidal Signs Scale of less than 1 at baseline and at least one post-baseline measurement.

¶ Percentages for weight gain are based on the number of patients with a baseline and at least one post-baseline measurement. To convert values for weight to kilograms, divide by 2.2. The range for weight change is the 5th to 95th percentile, which excludes extreme outliers.

‖ Patients were instructed to fast; nonfasting results were not excluded. Change was determined as the difference between the baseline value and the average of the two highest post-baseline values. The exposure-adjusted mean is the least-squares mean from an analysis of covariance adjusting for whether the patient had had an exacerbation in the preceding three months and for duration of exposure to study drug during phase 1. Since the measurement of glycosylated hemoglobin was added to the protocol as part of a protocol amendment, the numbers of patients are smaller for this test: 151 in the olanzapine group, 137 in the quetiapine group, 139 in the risperidone group, 107 in the perphenazine group, and 89 in the ziprasidone group. The analysis of all other laboratory variables included 286 patients in the olanzapine group, 268 in the quetiapine group, 262 in the risperidone group, 212 in the perphenazine group, and 143 in the ziprasidone group. 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.

** Percentages are based on the number of patients who had a normal corrected QT interval at baseline (450 msec or less for men and 470 msec or less for women) and at least one post-baseline measurement.

†† Percentages are based on the number of patients with a post-baseline assessment.

‡‡ Percentages are based on the number of patients with data available: 333 in the olanzapine group, 333 in the quetiapine group, 340 in the risperidone group, 259 in the perphenazine group, and 184 in the ziprasidone group.

§§ Trazodone was excluded.

¶¶ Trazodone was included.

gain and increases in glycosylated hemoglobin, cholesterol, and triglycerides, changes that may have serious implications with respect to medical comorbidity such as the development of the metabolic syndrome. How clinicians, patients, families, and policymakers evaluate the trade-offs between efficacy and side effects, as well as drug prices, will determine future patterns of use.

Supported by a grant (N01 MH90001) from the NIMH and by the Foundation of Hope of Raleigh, N.C. AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Forest Pharmaceuticals, Janssen Pharmaceutica, Eli Lilly, Otsuka Pharmaceutical, Pfizer, Zenith Goldline Pharmaceuticals, Schering-Plough, and Novartis provided medications for the studies.

Dr. Lieberman reports having received research funding from AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, GlaxoSmithKline, Janssen Pharmaceutica, and Pfizer and consulting and educational fees from AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly, Forest Pharmaceuticals, GlaxoSmithKline, Janssen Pharmaceutica, Novartis, Pfizer, and Solvay. Dr. Stroup reports having received research funding from Eli Lilly and consulting fees from Janssen Pharmaceutica, GlaxoSmithKline, and Bristol-Myers Squibb. Dr. McEvoy reports having received research funding from AstraZeneca, Forest Research Institute, Eli Lilly, Janssen Pharmaceutica, and Pfizer; consulting or advisory-board fees from Pfizer and Bristol-Myers Squibb; and lecture fees from Janssen Pharmaceutica and Bristol-Myers Squibb. Dr. Swartz reports having received research funding from Eli Lilly and consulting and educational fees from AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly, and Pfizer. Dr. Rosenheck reports having received research funding from AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, and Eli Lilly and consulting fees from Bristol-Myers Squibb, Eli Lilly, and Janssen Pharmaceutica. Dr. Perkins reports having received research funding from AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Otsuka Pharmaceutical, Eli Lilly, Janssen Pharmaceutica, and Pfizer and consulting and educational fees from AstraZeneca Pharmaceuticals, Bristol-Myers Squibb, Eli Lilly, Janssen Pharmaceuticals, and Pfizer. Dr. Keefe reports having received research funding from AstraZeneca, Eli Lilly, and Janssen Pharmaceutica; consulting or advisory-board fees from Forest Pharmaceuticals, Eli Lilly, Janssen Pharmaceutica, Pfizer, and Bristol-Myers Squibb; and lecture fees from Eli Lilly and Janssen Pharmaceutica. Dr. Sonia Davis is an employee of Quintiles. Dr. Clarence Davis reports having received consulting fees from Eli Lilly and Quintiles. Dr. Lebowitz is a former employee and Ms. Severe and Dr. Hsiao are current employees of the NIMH.

We are indebted to the 1493 participants in the CATIE study; to the late Mahmoud A. Parsa, M.D., of the Department of Psychiatry, Case Western Reserve University, Cleveland; to Grayson S. Norquist, M.D., M.S.P.H., previously director of the Division of Services and Intervention Research, NIMH, and currently chairman of the Department of Psychiatry and Human Behavior, University of Mississippi Medical Center, Jackson; to Ingrid Rojas-Eloi, B.S., project manager of the CATIE study, and Tiffany Harris, staff assistant, Department of Psychiatry, School of Medicine, University of North Carolina at Chapel Hill; to Allison Andors, Ph.D., director of Grants Development at the Research Foundation for Mental Hygiene, New York State Psychiatric Institute; and to the Quintiles CATIE project team.

APPENDIX

The CATIE Study Investigators Group includes the following: L. Adler, Clinical Insights, Glen Burnie, Md.; M. Bari, Synergy Clinical Research, Chula Vista, Calif.; I. Belz, Tri-County/Mental Health and Mental Retardation Services, Conroe, Tex.; R. Bland, Southern Illinois University School of Medicine, Springfield; T. Blocher, Mental Health and Mental Retardation Authority of Harris County, Houston; B. Bolyard, Cox North Hospital, Springfield, Mo.; A. Buffenstein, Queen's Medical Center, Honolulu; J. Burruss, Baylor College of Medicine, Houston; M. Byerly, University of Texas Southwestern Medical Center at Dallas, Dallas; J. Canive, Albuquerque Veterans Affairs Medical Center, Albuquerque, N.M.; S. Caroff, Behavioral Health Service, Philadelphia; C. Casat, Behavioral Health Center, Charlotte, N.C.; E. Chavez-Rice, El Paso Community Mental Health and Mental Retardation Center, El Paso, Tex.; J. Csernansky, Washington University School of Medicine, St. Louis; P. Delgado, University Hospitals of Cleveland, Cleveland; R. Douyon, Veterans Affairs Medical Center, Miami; C. D'Souza, Connecticut Mental Health Center, New Haven; I. Glick, Stanford University School of Medicine, Stanford, Calif.; D. Goff, Massachusetts General Hospital, Boston; S. Gratz, Eastern Pennsylvania Psychiatric Institute, Philadelphia; G.T. Grossberg, Saint Louis University School of Medicine–Wohl Institute, St. Louis; M. Hale, New Britain General Hospital, New Britain, Conn.; M. Hamner, Medical University of South Carolina and Veterans Affairs Medical Center, Charleston; R. Jaffe, Belmont Center for Comprehensive Treatment, Philadelphia; D. Jeste, University of California, San Diego, Veterans Affairs Medical Center, San Diego; A. Kablinger, Louisiana State University Health Sciences Center, Shreveport; A. Khan, Psychiatric Research Institute, Wichita, Kans.; S. Lamberti, University of Rochester Medical Center, Rochester, N.Y.; M.T. Levy, Staten Island University Hospital, Staten Island, N.Y.; J.A. Lieberman, University of North Carolina School of Medicine, Chapel Hill; G. Maguire, University of California Irvine, Orange; T. Manschreck, Corrigan Mental Health Center, Fall River, Mass.; J. McEvoy, Duke University Medical Center, Durham, N.C.; M. McGee, Appalachian Psychiatric Healthcare System, Athens, Ohio; H. Meltzer, Vanderbilt University Medical Center, Nashville; A. Miller, University of Texas Health Science Center at San Antonio, San Antonio; D.D. Miller, University of Iowa, Iowa City; H. Nasrallah, University of Cincinnati Medical Center, Cincinnati; C. Nemeroff, Emory University School of Medicine, Atlanta; S. Olson, University of Minnesota Medical School, Minneapolis; G.F. Oxenkrug, St. Elizabeth's Medical Center, Boston; J. Patel, University of Massachusetts Health Care, Worcester; F. Reimherr, University of Utah Medical Center, Salt Lake City; S. Riggio, Mount Sinai Medical Center–Bronx Veterans Affairs Medical Center, Bronx, N.Y.; S. Risch, University of California, San Francisco, San Francisco; B. Saltz, Mental Health Advocates, Boca Raton, Fla.; T. Simpatico, Northwestern University, Chicago; G. Simpson, University of Southern California Medical Center, Los Angeles; M. Smith, Harbor–UCLA Medical Center, Torrance, Calif.; R. Sommi, University of Missouri, Kansas City; R.M. Steinbook, University of Miami School of Medicine, Miami; M. Stevens, Valley Mental Health, Salt Lake City; A. Tapp, Veterans Affairs Puget Sound Health Care System, Tacoma, Wash.; R. Torres, University of Mississippi, Jackson; P. Weiden, SUNY Downstate Medical Center, Brooklyn, N.Y.; J. Wolberg, Mount Sinai Medical Center, New York.

REFERENCES

1. Miyamoto S, Duncan GE, Marx CE, Lieberman JA. Treatments for schizophrenia: a critical review of pharmacology and mechanisms of action of antipsychotic drugs. Mol Psychiatry 2005;10:79-104.
2. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45:789-96.
3. Leucht S, Pitschel-Walz G, Abraham D, Kissling W. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo: a meta-analysis of randomized controlled trials. Schizophr Res 1999;35:51-68.
4. Geddes J, Freemantle N, Harrison P, Bebbington P. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ 2000;321:1371-6.
5. Wahlbeck K, Tuunainen A, Ahokas A, Leucht S. Dropout rates in randomised antipsychotic drug trials. Psychopharmacology (Berl) 2001;155:230-3.
6. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry 2003; 60:553-64.
7. Leucht S, Wahlbeck K, Hamann J, Kissling W. New generation antipsychotics versus low-potency conventional antipsychotics: a systematic review and meta-analysis. Lancet 2003;361:1581-9.
8. Leucht S, Barnes TRE, Kissling W, Engel RR, Correll C, Kane JM. Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. Am J Psychiatry 2003;160: 1209-22.
9. Wahlbeck K, Cheine M, Essali A, Adams C. Evidence of clozapine's effectiveness in schizophrenia: a systematic review and meta-analysis of randomized trials. Am J Psychiatry 1999;156:990-9.
10. Chakos M, Lieberman J, Hoffman E, Bradford D, Sheitman B. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. Am J Psychiatry 2001;158:518-26.
11. Tuunainen A, Wahlbeck K, Gilbody S. Newer atypical antipsychotic medication in comparison to clozapine: a systematic review of randomized trials. Schizophr Res 2002;56:1-10.
12. Rosenheck R, Perlick D, Bingham S, et al. Effectiveness and cost of olanzapine and haloperidol in the treatment of schizophrenia: a randomized controlled trial. JAMA 2003;290:2693-702.
13. Tollefson GD, Sanger TM. Negative symptoms: a path analytic approach to a double-blind, placebo- and haloperidol-controlled clinical trial with olanzapine. Am J Psychiatry 1997;154:466-74.
14. Keefe RS, Silva SG, Perkins DO, Lieberman JA. The effects of atypical antipsychotic drugs on neurocognitive impairment in schizophrenia: a review and meta-analysis. Schizophr Bull 1999;25:201-22.
15. Tollefson GD, Sanger TM, Lu Y, Thieme ME. Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol. Arch Gen Psychiatry 1998;55:250-8. [Erratum, Arch Gen Psychiatry 1998;55:1052.]
16. Csernansky JG, Mahmoud R, Brenner R. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. N Engl J Med 2002;346:16-22. [Erratum, N Engl J Med 2002;346:1424.]
17. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156:1686-96.
18. Henderson DC, Cagliero E, Copeland PM, et al. Glucose metabolism in patients with schizophrenia treated with atypical antipsychotic agents: a frequently sampled intravenous glucose tolerance test and minimal model analysis. Arch Gen Psychiatry 2005;62:19-28.
19. Koro CE, Fedder DO, L'Italien GJ, et al. An assessment of the independent effects of olanzapine and risperidone exposure on the risk of hyperlipidemia in schizophrenic patients. Arch Gen Psychiatry 2002;59: 1021-6.
20. Atypical antipsychotics — generating evidence to inform policy and practice. London: IMS Health, 2002. (Accessed August 26, 2005, at http://research.imshealth.com/research/research_schizophrenia.htm.)
21. Harrington C, Gregorian R, Gemmen E, et al. Access and utilization of new antidepressant and antipsychotic medications. Falls Church, Va.: Lewin Group, 2000. (Accessed August 26, 2005, at http://aspe.hhs.gov/search/health/reports/Psychmedaccess/index.htm#TOC.)
22. 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: 1624-32.
23. Lebowitz BD, Vitiello B, Norquist GS. Approaches to multisite clinical trials: the National Institute of Mental Health perspective. Schizophr Bull 2003;29:7-13.
24. Stroup TS, McEvoy JP, Swartz MS, et al. The National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project: schizophrenia trial design and protocol development. Schizophr Bull 2003;29:15-31.
25. Swartz MS, Perkins DO, Stroup TS, McEvoy JP, Nieri JM, Haak DC. Assessing clinical and functional outcomes in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial. Schizophr Bull 2003;29:33-43.
26. Keefe RS, Mohs RC, Bilder RM, et al. Neurocognitive assessment in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) project schizophrenia trial: development, methodology, and rationale. Schizophr Bull 2003;29:45-55.
27. Rosenheck R, Doyle J, Leslie D, Fontana A. Changing environments and alternative perspectives in evaluating the cost-effectiveness of new antipsychotic drugs. Schizophr Bull 2003;29:81-93.
28. Davis SM, Koch GG, Davis CE, LaVange LM. Statistical approaches to effectiveness measurement and outcome-driven re-randomizations in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) studies. Schizophr Bull 2003;29:73-80.
29. Cox DR. Regression models and life-tables. J R Stat Soc [B] 1972;34:187-220.
30. Hochberg Y. A sharper Bonferroni procedure for multiple tests of significance. Biometrika 1988;75:800-2.
31. Rosenheck RA. Open forum: effectiveness versus efficacy of second-generation antipsychotics: haloperidol without anticholinergics as a comparator. Psychiatr Serv 2005;56:85-92.
32. Citrome L, Volavka J. Optimal dosing of atypical antipsychotics in adults: a review of the current evidence. Harv Rev Psychiatry 2002;10:280-91.
33. Davis JM, Chen N. Dose response and dose equivalence of antipsychotics. J Clin Psychopharmacol 2004;24:192-208.
34. Intercontinental Medical Systems National Disease and Therapeutic Index. Plymouth Meeting, Pa.: IMS Health, January 2001-December 2004.
35. Lehman AF, Lieberman JA, Dixon LB, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry 2004;161:Suppl:1-56.