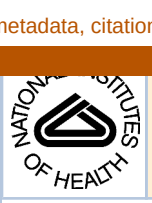

Published in final edited form as:

Schizophr Res. 2009 January ; 107(1): 1–12. doi:10.1016/j.schres.2008.10.011.

Results of Phase 3 of the CATIE Schizophrenia Trial

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Abstract

Objective—The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study examined the comparative effectiveness of antipsychotic treatments for individuals with chronic schizophrenia. Patients who had discontinued antipsychotic treatment in phases 1 and 2 were eligible for phase 3, in which they selected one of nine antipsychotic regimens with the help of their study doctor. We describe the characteristics of the patients who selected each treatment option and their outcomes.

Method—Two hundred and seventy patients entered phase 3. The open-label treatment options were monotherapy with oral aripiprazole, clozapine, olanzapine, perphenazine, quetiapine, risperidone, ziprasidone, long-acting injectable fluphenazine decanoate, or a combination of any two of these treatments.

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Disclosures: Dr. Stroup reports having received consulting fees from Janssen Pharmaceutica Products, Eli Lilly and Co., Lundbeck, and Solvay. Dr. Lieberman reports having received research funding from AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb, GlaxoSmithKline, Janssen Pharmaceutica Products, and Pfizer Inc.; and consulting and educational fees from AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb, Eli Lilly and Co., Forest Pharmaceutical Company, GlaxoSmithKline, Janssen Pharmaceutica Products, Novartis, Pfizer Inc., and Solvay. Dr. McEvoy reports having received research funding from AstraZeneca, Forest Research Institute, Eli Lilly and Co., Janssen Pharmaeutica, and Pfizer Inc.; consulting or advisory board fees from Pfizer Inc. and Bristol-Myers Squibb; and lecture fees from Janssen Pharmaceutica, and Bristol-Myers Squibb. Dr. Sonia M. Davis is an employee of Quintiles Inc.; she reports no additional funding. Dr. Swartz reports having received research funding from Eli Lilly and Co., and consulting and educational fees from AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb, Eli Lilly and Co., and Pfizer Inc. Dr. Keefe reports having received research funding from AstraZeneca, Eli Lilly and Co., and Janssen Pharmaeutica; consulting fees or advisory board payments from Forest Labs, Eli Lilly and Co., Janssen Pharmaceutica, Pfizer Inc., and Bristol-Myers Squibb; and lecture fees from Eli Lilly and Co. and Janssen Pharmaceutica. Dr. Miller reports having received research funding and consulting and speaking fees from Alexza, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Pfizer, and Solvay. Dr. Rosenheck reports having received research funding from AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb, and Eli Lilly and Co.; and consulting fees from Bristol-Myers Squibb, Eli Lilly and Co., and Janssen Pharmaceutica Products. Dr. Hsiao and Dr. Davis report no competing interests.

Contributors

All of the authors were involved in the design and conduct of the study. The analyses were planned by Drs. Stroup and Davis. Dr. Davis conducted the analyses. Drs. Stroup and Davis drafted the manuscript. All other authors reviewed and edited the manuscript.

Results—Few patients selected fluphenazine decanoate (n=9) or perphenazine (n=4). Similar numbers selected each of the other options (range 33–41). Of the seven common choices, those who selected clozapine and combination antipsychotic treatment were the most symptomatic, and those who selected aripiprazole and ziprasidone had the highest body mass index. Symptoms improved for all groups, although the improvements were modest for the groups starting with relatively mild levels of symptoms. Side effect profiles of the medications varied considerably but medication discontinuations due to intolerability were rare (7% overall).

Conclusions—Patients and their doctors made treatment selections based on clinical factors, including severity of symptoms, response to prior treatments, and physical health status. Fluphenazine decanoate was rarely used among those with evidence of treatment non-adherence and clozapine was underutilized for those with poor previous response. Combination antipsychotic treatment warrants further study.

Keywords

Schizophrenia; clinical trial; antipsychotic; effectiveness

1.0 Introduction

Several recent studies, including the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia project, the Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS), and the European First-Episode Schizophrenia Trial (EuFEST) sought to provide objective evidence regarding the comparative effectiveness of antipsychotic drugs in real-world settings (Jones et al. 2006; Kahn et al. 2008; Lewis et al. 2006; Lieberman et al. 2005). The National Institute of Mental Health (NIMH) initiated the CATIE schizophrenia project to determine the comparative effectiveness of antipsychotic drugs for individuals with chronic schizophrenia in typical clinical settings and situations in the United States (Stroup et al. 2003). Intended to mirror typical clinical practice, in which individuals with schizophrenia may require multiple medication trials before finding one that is adequately efficacious and tolerable, the CATIE study design allowed for patients who discontinued one study antipsychotic drug to enter subsequent phases of the study to receive additional antipsychotics.

The main results of all randomized phases of the CATIE study, including the initial random assignment (to olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone—phases 1 and 1A), phase 1B (involving patients who discontinued perphenazine in phase 1), and the efficacy and tolerability arms of the second phase (phases 2E and 2T) have been reported. (Lieberman et al. 2005; McEvoy et al. 2006; Stroup et al. 2007; Stroup et al. 2006) In this article we present results of phase 3, in which participants who discontinued either arm of phase 2 could select, with the assistance of their study doctor, from nine antipsychotic treatment regimens. The purpose of phase 3 was to allow participants to stay in the study for the entire scheduled 18 months and to gather systematic data on the efficacy, safety, and tolerability of these treatment regimens when selected and used openly.

2.0 Experimental Methods

2.1 Study Setting and Design

The goal of the CATIE schizophrenia study was to examine the comparative effectiveness of antipsychotic drugs. Its rationale, design, and methods were previously described in detail. (Davis et al. 2003; Keefe et al. 2003; Stroup et al. 2003; Swartz et al. 2003) The study was conducted between January 2001 and December 2004 at 57 U.S. clinical sites. Figure 1 details the enrollment, treatments, and follow-up of patients in the study. Patients were initially

randomly assigned to receive olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone under double-blind conditions and followed for up to 18 months or until treatment was discontinued for any reason. In phase 2, patients discontinuing from phase 1, 1A or 1B and their study doctors could choose between two randomization pathways.(Stroup et al. 2003)

Patients who discontinued treatment in phase 2 before study completion were eligible for phase 3. In phase 3, participants selected openly from the following nine possible treatment regimens: antipsychotic monotherapy with oral aripiprazole, clozapine, olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone; long-acting injectable fluphenazine decanoate; or a combination of any two of these treatments.(Stroup et al. 2003) If the selected treatment was not discontinued because of inadequate efficacy, intolerability, or any other reason, patients could continue taking this regimen until the completion of 18 months of study treatment. The ziprasidone and aripiprazole options were added after approximately 20% and 65% of patients had enrolled in phase 3, respectively, after the FDA approved these treatments.

2.2 Participants

The initial inclusion criteria required an age of 18 to 65 years, a diagnosis of schizophrenia (determined by the Structured Clinical Interview for DSM-IV), and appropriateness for oral antipsychotic medication.(Stroup et al. 2003) The exclusion criteria were a diagnosis of schizoaffective disorder; diagnosis of mental retardation or other cognitive disorder; past serious adverse reaction to any of the proposed treatments; first episode of schizophrenia; history of treatment resistance, defined by persistence of severe symptoms despite an adequate trial of one of the proposed treatments or prior treatment with clozapine for treatment resistance; current pregnancy or breast-feeding; or serious and unstable medical condition. If patients discontinued perphenazine in phase 1, then they entered phase 1B and then either phase 2E or 2T before enrolling in phase 3.

The study was approved by an institutional review board at each site, and written informed consent was obtained from each patient or the patient's legal guardian.

2.3 Interventions

Patients and study physicians selected medication regimens in phase 3 based on the clinical situation of each individual. To help inform the choice, patients entering phase 3 and their clinicians were informed about which medications had been assigned to that patient in previous phases of the study. In order to protect the blind in earlier phases of the study, this unblinding at the outset of phase 3 occurred after all assessments for the previous phase had been completed and entered into the data system. In addition, the previous drug names were provided alphabetically rather than chronologically in order to protect the study blind. Medications taken by a patient in previous phases of the trial were allowed both as a lone antipsychotic and as one drug in combination treatment during phase 3.

All of the study medicines in phase 3 were flexibly dosed on the basis of the study doctor's judgment. Overlap in the administration of the antipsychotic that the patient received in the prior phase was permitted for the first 4 weeks to allow for gradual transition to the new medication regimen. Concomitant medications were permitted throughout the trial, except additional antipsychotics. The patients had monthly visits with study doctors, until their total CATIE study participation across all phases reached 18 months, or they discontinued the phase 3 treatment for any reason. Because patients entered phase 3 after different durations of study participation, there was a wide range of possible treatment durations in Phase 3.

2.4 Objectives and Outcomes

Our objective was to gather systematic data on the overall effectiveness of common antipsychotic treatments. We had no *a priori* hypotheses to test, but instead examined the overall effectiveness of the drugs, including measures of efficacy and safety. As in other phases of the CATIE schizophrenia trial, the primary outcome measure of interest was treatment discontinuation for any cause; this discrete outcome measure reflects the enduring acceptability of a medication and integrates patient and clinician judgments of efficacy, safety, and tolerability into a global measure of effectiveness. We also examined the reason for treatment discontinuation as judged by the study doctor. Additional secondary efficacy outcomes included scores on the Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impression scale (CGI), which were collected at study baseline and after 1, 3, 6, 9, 12, 15, and 18 months of study participation, as well as any visit in which there was a transition from one phase to another (e.g., beginning and end of Phase 3). Secondary safety and tolerability outcomes included incidence of serious adverse events, incidence of treatment-emergent adverse events, and changes in weight, measures of neurologic side effects, and laboratory analytes.

2.5 Statistical Methods

Since there were no a priori hypotheses, and treatment regimens were openly selected, all statistical testing is intended for descriptive purposes only. No adjustment was made for multiple comparisons due to the number of treatment groups nor the number of parameters evaluated.

The nine treatment regimens were compared at baseline for continuous parameters with an 8 degree of freedom analysis of variance (ANOVA) test, with the exception of laboratory parameters which were compared with a Kruskal-Wallis rank test. Groups were compared for baseline categorical outcomes with a chi-squared test, or Fisher's exact test.

Groups were compared for Phase 3 discontinuation rates using a chi-squared or Fisher's exact test. Time to discontinuation was estimated via Kaplan-Meier survival curves, and evaluated with a logrank test. Duration in phase 3 was evaluated with an ANOVA. Compliance and duration as a percent of available study months were evaluated with a Kruskal-Wallis rank test.

Treatment regimens were compared for change from phase 3 baseline for PANSS and CGI-severity scores at 3 months and 6 months of Phase 3 participation using an analysis of covariance (ANCOVA) with adjustment for the baseline value. A within-sample t-test evaluated whether the PANSS change was different from zero. Since assessments were collected at various points relative to baseline, for each patient, data is from the latest post-baseline measurement collected within the windows of 0–3 and 4–6 months.

Groups were compared for categorical safety and tolerability outcomes with Poisson regression accounting for each patient's duration of Phase 3 participation, or Fisher's exact test in the case of small counts. Change in laboratory parameters from baseline to the average of the two largest reported values in Phase 3 are presented with baseline- and exposure-adjusted ANCOVA least squares means, but due to skewed distributions, p-values comparing groups are from a ranked ANCOVA adjusting for baseline and duration of Phase 3 study participation. Weight and QTc changes were evaluated with ANCOVA adjusting for baseline value (for weight) and duration of participation in phase 3.

3.0 Results

3.1 Patient Characteristics and Disposition

Figure 1 shows the flow of patients in the study. Of the 410 who were eligible for phase 3, 270 (66%) enrolled. The baseline demographic and diagnostic characteristics of subjects who entered phase 3 were generally representative of the original study participants. The mean age of subjects was 40.5 years (SD 11.0); 70% were men, 67% were white, 30% black, and 3% were from other races. (See supplemental table.) There were no substantial demographic or diagnostic differences between the groups of patients who selected the various treatments. Table 1 reveals that there were substantial differences in the clinical characteristics of patients who selected, with the guidance of study physicians, the nine treatment strategies offered.

Similar numbers of subjects selected 7 of the 9 antipsychotic medication strategies (33 to 41 participants for each). Single first-generation antipsychotics were used much less often--only nine individuals selected fluphenazine decanoate and four selected perphenazine. Because of these small numbers we will limit further discussion of treatment with these two first-generation antipsychotic drugs. Among the 40 patients who selected combination treatment, no specific pair of antipsychotics was selected by more than five patients; because of these small numbers all patients selecting combination treatment have been pooled together. The frequency of the various combinations can be seen in Table 2. Individual antipsychotics were selected to be one of the pair combinations by the following number of patients: aripiprazole 8, clozapine 11, fluphenazine decanoate 6, olanzapine 11, perphenazine 10, quetiapine 14, risperidone 15, and ziprasidone 8.

Patients who selected clozapine were earlier in the course of illness than those who selected all the other drug treatments (mean 8.3 years since first antipsychotic treatment for clozapine compared to 11.8–16.1 years for all others). Patients who selected clozapine and combination antipsychotic treatment were more symptomatic, as indicated by total PANSS scores (mean 85.3–88.6), and patients selecting ziprasidone were less symptomatic (71.4) than patients who selected the other oral second-generation antipsychotics (75.2–77.6). The small number of patients selecting a first generation antipsychotic had high PANSS scores, which had worsened since the beginning of the study.

Patients with the highest BMI selected aripiprazole and ziprasidone (mean BMI 34.3 for both) compared to all the other treatment options (mean BMI 26.7–31.7). In general, these same patients had gained more weight since study baseline than patients in the other groups, and also had the highest blood glucose and glycosolated hemoglobin levels. There were no remarkable differences in total cholesterol or triglyceride levels between the treatment groups at the beginning of phase 3.

Patients who selected clozapine, ziprasidone, and aripiprazole had been in the study longer (mean 8.6, 9.4, and 9.5 months, respectively) than those who selected all the other drugs (4.0 to 7.6 months). Because ziprasidone became available after 20% of patients had enrolled in phase 1/1A, and aripiprazole after approximately 65%% of patients had enrolled, the time to selecting these newest two drugs likely reflects the logistics of the study.

Most patients who selected clozapine (78%) or combination antipsychotic treatment (65%) in phase 3 had discontinued the previous treatment due to inadequate efficacy on the previous drug. Only 33% who selected quetiapine had stopped the previous drug due to inadequate efficacy, while for all the other study treatment options the range was 42–50%. Only 3% of patients who selected clozapine had discontinued the previous treatment due to unacceptable side effects. On the other end of the spectrum, unacceptable side effects were cited as the cause for discontinuation in phase 2 by a substantial portion of patients who selected quetiapine

(46%), aripiprazole (39%), and ziprasidone (35%). Weight or metabolic problems were the reason the phase 2 antipsychotic was discontinued for 27% and 19% of patients who selected aripiprazole and ziprasidone in phase 3, while none of these patients selected clozapine or olanzapine.

The mean modal doses of each treatment are in Table 3. The proportion of phase 3 study visits at which patients were judged, using pill counts and any other clinical information available to study clinicians, to have taken prescribed medication always or almost always was lowest for risperidone (61%) compared to all the other treatments (77–86%).

3.2 Treatment Discontinuation

In phase 3, 106 of the 270 patients (39%) discontinued treatment before completion of the study. The mean treatment duration was 7.7 months, which corresponds to an average of 75% of the maximum possible participation time. Discontinuation outcomes are presented in Table 3. There were no substantial differences between treatments in the proportion of patients who discontinued the commonly selected medication regimens (range 33–46%) or in the proportion of possible treatment time that patients stayed on treatment (range 67–80%). The rates of discontinuation for lack of efficacy were lower for clozapine, risperidone, quetiapine, and ziprasidone (0–5%) compared to aripiprazole, olanzapine, combination antipsychotic treatment, and olanzapine (13–18%).

3.3 Efficacy Measures

The results of the PANSS and CGI analyses are presented in Table 4. There were no differences in the PANSS total or subscale score changes among the treatment groups at 3 months or 6 months. Using a within-sample t-test for change on the PANSS total score from baseline with $p=0.05$ as an indicator of substantial change, all of the commonly used treatments were associated with substantial symptom improvement at 3 months and 6 months, with the exception of aripiprazole at 3 months and both quetiapine and ziprasidone at 6 months.

3.4 Adverse Events and Safety Outcomes

Adverse events, side effects, and laboratory results are listed in Table 5. When we accounted for multiple hospitalizations and for the differential time in treatment we found the rates ranged from 0.21 hospitalizations per person-year of exposure for risperidone to 0.45 for aripiprazole and ziprasidone, and 0.49 for combination antipsychotic treatment. The rates of spontaneous adverse events rated as moderate or severe were lowest for olanzapine and risperidone (17% for each) and highest for quetiapine (45%), clozapine (35%), and combination antipsychotic treatment (30%).

Anticholinergic side effects were common with quetiapine (36%) and not reported at all for risperidone, with all the other drugs intermediate (11–25%). Incontinence or nocturia were most common with clozapine (19%) and olanzapine (12%) and 5% or lower for the other treatments. Sialorrhea and orthostatic faintness were reported much more commonly with clozapine (38% and 24% respectively) than with all other treatment groups (0–12%).

Among the commonly selected treatments, clinically significant weight gain of at least 7% was most common for clozapine (32%), combination antipsychotic treatment (39%) and olanzapine (23%); the rates were lowest for aripiprazole and ziprasidone (both 7%). Mean weight gain per month of treatment was highest for clozapine (1.3 pounds) and olanzapine (1 pound). All the other second-generation antipsychotics were associated with weight loss, with the most monthly weight loss associated with aripiprazole (1.4 pounds) and ziprasidone (1.3 pounds).

Exposure-adjusted blood glucose increased the most for patients taking aripiprazole and increased for those taking clozapine and quetiapine but declined for patients taking all the other treatment regimens. Only risperidone among the second-generation antipsychotics was associated with substantial increases in prolactin levels.

Anxiolytics were added for a higher proportion of patients on combination antipsychotic regimens (23%) as compared to quetiapine (15%), olanzapine (12%), and the other second-generation antipsychotics (0–6%).

4.0 Discussion

The results presented here provide additional information on the use and effectiveness of antipsychotic medications commonly used by patients with chronic schizophrenia. The differences in the clinical status of patients at the time of entry into Phase 3 can be interpreted to reflect the views of study clinicians and participating patients regarding the selection of antipsychotics during the years the study was conducted (2001–2004). The study provides new information from CATIE about aripiprazole and combination antipsychotic treatment.

Very few patients and clinicians selected antipsychotic monotherapy with a first-generation antipsychotic, reflecting the dominance of second-generation drugs among antipsychotic prescriptions in the United States. Long-acting fluphenazine decanoate was used by only 3% of patients in phase 3 although only 77% of patients in phase 2 were judged by clinicians to be always or almost always compliant with their antipsychotic medication regimen.

Clozapine and combination antipsychotic treatment regimens were frequently selected by patients with relatively severe psychopathology and by those who stopped the previous medication due to inadequate therapeutic effect. Although clozapine is the only treatment consistently shown to be effective when others are not (Chakos et al. 2001), it was used by only 11% (37 of 270) of patients in phase 3 although 51% (138 of 270) had discontinued the previous medication due to inadequate therapeutic effect. When used, clozapine was selected by patients who reached phase 3 more quickly than patients who selected the other medicines, suggesting that it was used for individuals who were repeatedly not getting adequate symptom reduction and quickly failing trials on other medications.

This is the first report from CATIE regarding aripiprazole, which was not available when the study began and was not included in other study phases. Aripiprazole and ziprasidone were selected by patients with the highest body mass indexes and most weight gain during the trial, and for those with the highest blood glucose and glycosolated hemoglobin levels. Aripiprazole was similar to all the other treatments in the proportion of patients who discontinued treatment for any reason. Aripiprazole was almost identical to ziprasidone both in the small proportion of patients with clinically significant weight gain and in average weight loss per month. However, aripiprazole was associated with greater increases in blood glucose than all of the other treatment regimens. This is not what would be expected from a recent systematic review that found no clear trends among antipsychotic drugs and blood sugar changes (Bushe and Leonard 2007). Given the lack of concordance of this finding with larger studies that used random assignment to treatments, the most likely explanation for the finding is chance. Another possible explanation for this finding, given that those who chose aripiprazole treatment had among the highest blood glucose levels at baseline and high rates of previous medication discontinuations due to intolerability, is that pre-existing problems with glucose metabolism at baseline deteriorated further in phase 3. However, those treated with ziprasidone in phase 3 had the highest mean levels of blood glucose at baseline and blood glucose for this group declined in phase 3. Because treatment with aripiprazole is a common medication choice for

individuals with metabolic problems, this finding of increased blood glucose may deserve additional investigation.

Weight change in the study prior to entry in phase 3 was greatest for those who selected aripiprazole and ziprasidone, and the mean BMI was higher for these patients than for those selecting other drugs. The weight loss associated with these drugs may therefore be due to the removal of previous weight-gain inducing drugs or simply regression to the mean. However, the findings may still be relevant to practitioners because these medicines are commonly chosen preferentially for patients in clinical situations who are overweight just as they were in phase 3. It is also notable that clozapine, combination treatment, and olanzapine were associated with weight gain even though patients selecting these options had also gained weight during earlier phases of the study.

The mean modal doses of olanzapine and risperidone used in this open label phase of CATIE are quite similar to those used in previous phases that involved patients not selected because of persistent symptoms (i.e., phases 1/1A, 1B and 2T) (Lieberman et al. 2005; Stroup et al. 2007; Stroup et al. 2006). On the other hand, ziprasidone was used at a somewhat higher dose in phase 3 (132.1 mg/day) compared to both blinded phases in which it was used (112.8 mg/day in phase 1/1A and 115.9 mg/day in phase 2T) while quetiapine was used at a lower dose in phase 3 (500 mg/day) compared to the doses in blinded phases (543.4–586.1 mg/day). It is possible that the doses of quetiapine and ziprasidone used in this open-label phase more closely resemble usual practice than the doses used in blinded phases of the study.

Patients with chronic schizophrenia who entered phase 3 of the CATIE schizophrenia trial had discontinued two consecutive second-generation antipsychotics before choosing a phase 3 treatment regimen. Levels of psychopathology, the reason for previous treatment discontinuation, and indicators of metabolic functioning seemed to guide treatment selection. Clinicians and patients did not, however, closely follow evidence-based clinical recommendations that suggest using clozapine for individuals with poor treatment response and the use of long-acting injectable medications when treatment adherence is a problem (Lehman et al. 2004). Clozapine was underutilized for people with poor therapeutic response, and fluphenazine decanoate was rarely used in spite of the high prevalence of medication non-adherence in individuals with schizophrenia. We again found variation in the adverse effects associated with antipsychotic medications that may help guide patients and clinicians in making treatment choices. Combination antipsychotic treatment was a common strategy that warrants further systematic study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This article was based on results from the Clinical Antipsychotic Trials of Intervention Effectiveness project, supported by the National Institute of Mental Health (NO1 MH90001). The aim of this project is to examine the comparative effectiveness of antipsychotic drugs in conditions for which their use is clinically indicated, including schizophrenia and Alzheimer's disease. The project was carried out by principal investigators from the University of North Carolina, Duke University, the University of Southern California, the University of Rochester, and Yale University in association with Quintiles, Inc.; the program staff of the Division of Interventions and Services Research of the NIMH; and investigators from 56 sites in the United States (CATIE Study Investigators Group). AstraZeneca Pharmaceuticals LP, Bristol-Myers Squibb Company, Forest Pharmaceuticals, Inc., Janssen Pharmaceutica Products, L.P., Eli Lilly and Company, Otsuka Pharmaceutical Co., Ltd., Pfizer Inc., and Zenith Goldline Pharmaceuticals, Inc., provided medications for the studies.

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Funding for this study was provided by NIMH contract N01 MH 90001; the NIMH was involved in all phases of the study. Study drugs were donated by the manufacturers; the companies were not involved in designing or conducting the study, analyzing or interpreting the data, or deciding to submit the paper for publication.

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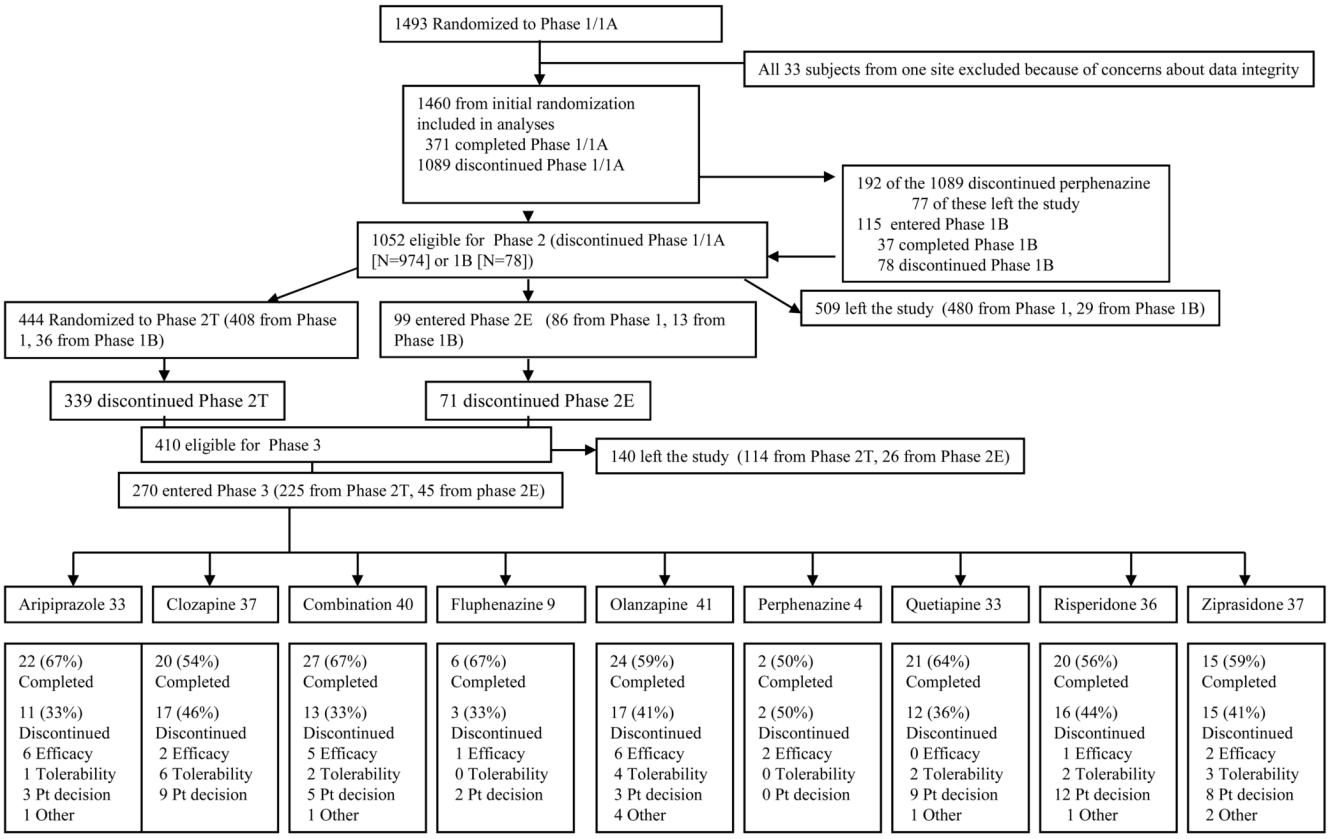

Figure 1.
Enrollment, Allocation, Follow-up, and Analysis

Table 1

Baseline Clinical Characteristics by Phase 3 Treatment

Assessment	Statis-tic	ARIP (n=33)	CLOZ (n=37)	Comb. (n=40)	Flu-D (n=9)	OLAN (n=41)	PERP (n=4)	QUET (n=33)	RISP (n=36)	ZPR (n=37)	Total (n=270)	p-value [1]
Years Since First Antipsychotic Medication Prescribed	Mean (S.D.)	11.8 (9.6)	8.3 (8.5)	15.9 (11.0)	15.3 (10.4)	15.1 (10.2)	14.3 (8.1)	15.9 (10.5)	16.1 (11.4)	13.9 (11.1)	13.9 (10.5)	0.039
PANSS Total score (30–210):												
Phase 3 Baseline	Mean (S.D.)	76.4 (19.5)	85.3 (16.9)	88.6 (23.2)	91.2 (24.2)	77.6 (23.6)	91.0 (16.1)	75.2 (15.3)	75.6 (17.6)	71.4 (18.4)	79.4 (20.5)	0.002
Change in study before Phase 3	Mean (S.D.)	−0.2 (20.4)	1.7 (15.9)	6.2 (17.8)	18.1 (20.6)	4.5 (17.1)	10.5 (6.0)	−0.2 (16.0)	0.0 (18.9)	−8.5 (18.7)	1.4 (18.4)	0.003
Clinician Rated CGI Severity Score (1–7) Phase 3 Baseline	Mean (S.D.)	4.0 (0.9)	4.7 (0.9)	4.6 (0.8)	4.9 (1.1)	4.1 (1.1)	4.5 (1.0)	4.1 (0.9)	4.2 (1.0)	3.9 (0.8)	4.3 (1.0)	0.002
Neurologic Outcomes at Phase 3 Baseline:												
AIMS Total Score	Mean (S.D.)	2.3 (3.8)	2.1 (4.1)	1.2 (2.2)	2.4 (4.5)	2.1 (3.6)	0.3 (0.5)	2.1 (2.9)	1.1 (2.1)	1.3 (2.3)	1.7 (3.1)	0.507
Barnes Global Clinical Assessment of Akathisia	Mean (S.D.)	0.6 (1.0)	0.6 (1.0)	0.6 (1.0)	0.4 (0.9)	0.6 (1.0)	0.0 (0.0)	0.7 (1.0)	0.3 (0.8)	0.9 (1.1)	0.6 (1.0)	0.397
Simpson-Angus EPS Mean Scale Score	Mean (S.D.)	0.2 (0.2)	0.3 (0.3)	0.2 (0.3)	0.3 (0.4)	0.2 (0.3)	0.2 (0.2)	0.2 (0.3)	0.1 (0.2)	0.3 (0.5)	0.2 (0.3)	0.660
Weight (lbs):												
Phase 3 Baseline	Mean (S.D.)	220.4 (56.4)	208.2 (40.0)	205.8 (50.1)	190.3 (32.4)	197.9 (44.6)	187.8 (32.3)	201.2 (42.9)	200.2 (51.8)	223.7 (59.5)	207.2 (49.4)	0.239
Change in study before Phase 3	Mean (S.D.)	12.1 (28.6)	3.9 (16.6)	3.3 (24.6)	1.3 (20.4)	5.3 (12.7)	−8.3 (9.2)	2.5 (15.3)	0.6 (14.9)	13.1 (18.5)	5.5 (19.6)	0.064
BMI at Phase 3 Baseline	Mean (S.D.)	34.3 (9.5)	30.7 (5.6)	31.0 (7.6)	28.3 (5.5)	30.2 (5.9)	26.7 (5.3)	31.7 (7.9)	29.8 (8.3)	34.3 (7.5)	31.5 (7.6)	0.041
Blood Chemistry at Phase 3 Baseline:												
Blood glucose (mg/dL)	Mean (S.D.) Median	107.1 (30.9) 100.0	99.1 (33.5) 93.0	96.3 (33.3) 87.0	95.8 (14.5) 96.0	105.9 (43.6) 90.5	73.3 (5.1) 72.0	97.2 (33.7) 89.0	96.3 (38.1) 85.5	123.1 (66.9) 96.0	103 (41.5) 91.0	0.027
Hemoglobin A1C (%)	Mean (S.D.) Median	5.8 (1.2) 5.6	5.2 (0.5) 5.3	5.6 (1.3) 5.6	5.3 (0.4) 5.4	5.5 (0.8) 5.3	5.2 (0) 5.2	5.7 (0.4) 5.8	5.3 (0.6) 5.2	5.9 (1.2) 5.7	5.6 (1.0) 5.5	0.031
Cholesterol (mg/dL)	Mean (S.D.) Median	204.3 (46.7) 199.5	196.9 (44.9) 202.0	199.6 (41.3) 195.0	189.8 (35.6) 178.0	193.1 (27.6) 193.0	199.7 (53.2) 190.0	203.2 (61.3) 198.0	189.3 (51.8) 187.5	202.9 (45.3) 198.5	198.1 (45.2) 195.0	0.949
Triglycerides (mg/dL)	Mean (S.D.) Median	250.2 (242) 197.5	194.8 (122) 160.0	230.5 (149.2) 188.0	192.7 (104.9) 171.0	192.8 (108.5) 167.5	183.3 (56.2) 156.0	193 (173.3) 163.0	156 (96.3) 139.0	252.1 (239.9) 178.0	209.5 (167.6) 166.0	0.264
Total Time in Prior Phases (months):	Mean (S.D.)	9.5 (4.1)	8.6 (4.7)	7.4 (5.2)	9.2 (5.0)	5.8 (4.1)	4.0 (3.3)	7.6 (4.6)	7.1 (4.0)	9.4 (4.5)	7.8 (4.6)	0.003
Compliance in Prior Phases:												

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Assessment	Statis-tic	ARIP (n=33)	CLOZ (n=37)	Comb. (n=40)	Flu-D (n=9)	OLAN (n=41)	PERP (n=4)	QUET (n=33)	RISP (n=36)	ZPR (n=37)	Total (n=270)	p-value [1]
Phase 1	Mean (S.D.)	88.4 (22.6)	90.5 (12.9)	90.5 (20.1)	72.0 (21.1)	77.6 (33.0)	71.0 (44.9)	90.1 (14.0)	77.9 (25.1)	87.9 (19.1)	85.3 (23.1)	0.012
Phase 2	Mean (S.D.)	85.1 (25.7)	80.0 (32.9)	85.1 (22.3)	64.3 (32.5)	64.7 (39.2)	75.3 (23.4)	71.0 (38.0)	69.9 (37.4)	88.3 (19.6)	77.2 (32.3)	0.010
Treatment Received in Phase 1:												N/A
Olanzapine	n (%)	6 (18%)	8 (22%)	13 (33%)	1 (11%)	3 (7%)	0 (0%)	10 (30%)	14 (39%)	9 (24%)	64 (24%)	
Perphenazine	n (%)	2 (6%)	2 (5%)	5 (13%)	0 (0%)	5 (12%)	0 (0%)	4 (12%)	1 (3%)	4 (11%)	23 (9%)	
Quetiapine	n (%)	7 (21%)	12 (32%)	8 (20%)	4 (44%)	13 (32%)	1 (25%)	4 (12%)	13 (36%)	13 (35%)	75 (28%)	
Risperidone	n (%)	8 (24%)	11 (30%)	9 (23%)	3 (33%)	17 (42%)	3 (75%)	10 (30%)	2 (6%)	11 (30%)	74 (24%)	
Ziprasidone	n (%)	10 (30%)	4 (11%)	5 (13%)	1 (11%)	3 (7%)	0 (0%)	5 (15%)	6 (17%)	0 (0%)	34 (13%)	
Treatment Received in Phase 2 :[N from clozapine arm of phase 2 in brackets]												N/A
Clozapine	n (%) [N]	1 (3%) [1]	0 (0%) [0]	2 (5%) [2]	0 (0%) [0]	0 (0%) [0]	0 (0%) [0]	5 (15%) [5]	4 (11%) [4]	2 (5%) [2]	14 (5%) [14]	
Olanzapine	n (%) [N]	4 (12%) [0]	7 (19%) [4]	10 (25%) [3]	2 (22%) [0]	5 (12%) [0]	2 (50%) [1]	12 (36%) [1]	7 (19%) [1]	11 (30%) [0]	60 (22%) [10]	
Quetiapine	n (%) [N]	13 (39%) [2]	10 (27%) [5]	10 (25%) [1]	2 (22%) [0]	14 (34%) [1]	1 (25%) [1]	0 (0%) [0]	10 (28%) [1]	12 (32%) [0]	72 (27%) [11]	
Risperidone	n (%) [N]	6 (18%) [0]	9 (24%) [6]	7 (18%) [1]	1 (11%) [0]	10 (24%) [2]	0 (0%) [0]	9 (27%) [0]	4 (11%) [1]	11 (30%) [0]	57 (21%) [10]	
Ziprasidone	n (%)	9 (27%)	11 (30%)	11 (28%)	4 (44%)	12 (29%)	1 (25%)	7 (21%)	11 (31%)	1 (3%)	67 (25%)	
Reason for Discontinuation from Phase 1 (2).												
Inadequate Therapeutic Effect	n (%)	11 (33%)	28 (76%)	18 (45%)	4 (44%)	20 (49%)	2 (50%)	16 (48%)	17 (3%)	16 (43%)	132 (49%)	0.052 F
Unacceptable Side Effects	n (%)	20 (61%)	6 (16%)	17 (43%)	2 (22%)	9 (22%)	-	14 (42%)	11 (31%)	15 (41%)	94 (35%)	0.002 F
Patient Decision	n (%)	2 (6%)	3 (8%)	4 (10%)	3 (33%)	11 (27%)	2 (50%)	3 (9%)	7 (19%)	5 (14%)	40 (15%)	0.038 F
Reason for Discontinuation from Phase 2 (3).												
Inadequate Therapeutic Effect	n (%)	16 (49%)	29 (78%)	26 (65%)	4 (44%)	17 (42%)	2 (50%)	11 (33%)	16 (44%)	17 (46%)	138 (51%)	0.005 F
Unacceptable Side Effects	n (%)	13 (39%)	1 (3%)	9 (23%)	0 (0%)	10 (24%)	0 (0%)	15 (46%)	10 (28%)	13 (35%)	71 (26%)	0.001
Patient Decision	n (%)	4 (12%)	6 (16%)	5 (13%)	5 (56%)	12 (29%)	2 (50%)	6 (18%)	9 (25%)	5 (14%)	54 (20%)	0.040
Side Effect Reason for Discontinuation from Phase 2:												
Extrapyramidal	n (%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	5 (12%)	0 (0%)	4 (12%)	1 (3%)	0 (0%)	11 (4%)	0.029 F
Sedation	n (%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	0 (0%)	2 (5%)	4 (2%)	0.474 F
Weight/metabolic	n (%)	9 (27%)	0 (0%)	4 (10%)	0 (0%)	0 (0%)	0 (0%)	1 (3%)	2 (6%)	7 (19%)	23 (9%)	< 0.001 F
Other	n (%)	4 (12%)	0 (0%)	4 (10%)	0 (0%)	5 (12%)	0 (0%)	9 (27%)	7 (19%)	4 (11%)	33 (12%)	

[1]P-values, presented for descriptive purposes, are based on an 8 df test of the main effect of treatment in an ANOVA for the continuous outcomes, from a Kruskal-Wallis rank test for all laboratory parameters, and from a Chi-Squared test for categorical outcomes, or Fisher's exact test in the case of small counts. P-value for reason for discontinuation excludes administrative category.

Note: sample sizes vary due to sporadic missing data.

2: 4 patients (1%) discontinued phase 1 for administrative reasons.

3: 7 patients (3%) discontinued phase 2 for administrative reasons

Note: Treatments received in phase 1b overall are Olanzapine:8 patients, Quetiapine, 7 patients Risperidone 8 patients.:

Note: Comb = combination of any two of the treatments.

Table 2

Frequency of antipsychotic combinations used in phase 3 of the CATIE schizophrenia trial (Total = 40)

	Clozapine	Fluphenazine decanoate	Olanzapine	Perphenazine	Quetiapine	Risperidone	Ziprasidone
Aripiprazole	2	0	1	2	2	1	0
Clozapine		1	1	0	0	1	4
Fluphenazine decanoate			1	1	2	1	0
Olanzapine				2	0	4	1
Perphenazine					2	3	0
Quetiapine						5	3
Risperidone							0

Table 3

Phase 3 Dosing, Compliance, and Duration

Statistic	ARIP (n=33)	CLOZ (n=37)	Comb. (n=40)	Flu-D (n=9)	OLAN (n=41)	PERP (n=4)	QUET (n=33)	RISP (n=36)	ZPR (n=37)	p- value [1]
Mean (S.D.) N	16.1 (5.3) 30	317.2 (212.6) 32	N/A	41.1 (20.0) 7	21.8 (15.4) 39	30.0 (16.5) 4	500.0 (225.0) 33	3.9 (1.9) 32	132.1 (76.8) 33	N/A
Mean (S.D.) N	0.78 (0.35) 33	0.81 (0.36) 37	0.77 (0.34) 40	0.86 (0.28) 9	0.85 (0.30) 41	0.79 (0.25) 4	0.79 (0.29) 33	0.61 (0.38) 36	0.77 (0.39) 37	0.011
Mean (S.D.) N	6.5 4.7 33	6.6 4.5 37	8.5 5.5 40	7.3 4.2 9	9.9 4.5 40	11.2 7.0 4	7.9 4.7 33	8.1 5.4 36	5.8 4.1 37	0.006
Mean (S.D.) N	0.75 0.38 33	0.67 0.38 37	0.80 0.34 40	0.86 0.26 9	0.80 0.31 40	0.71 0.35 4	0.78 0.33 33	0.70 0.39 36	0.71 0.38 37	0.785
N (%)	11 (33%)	17 (46%)	13 (33%)	3 (33%)	17 (41%)	2 (50%)	12 (36%)	16 (44%)	15 (41%)	0.940
N (%)	6 (18%)	2 (5%)	5 (13%)	1 (11%)	6 (15%)	2 (50%)	0	1 (3%)	2 (5%)	0.013
N (%)	1 (3%)	6 (16%)	2 (5%)	0	4 (10%)	0	2 (6%)	2 (6%)	3 (8%)	0.687
N (%)	3 (9%)	9 (24%)	5 (13%)	2 (22%)	3 (7%)	0	9 (27%)	12 (33%)	8 (22%)	0.059
25th %ile [95% CI]	2.8 [1.1, -] 0.32	3.0 [2.3, 6.0] 0.43	7.6 [2.3, -] 0.21	6.9 [3.5, -] 0.14	8.0 [4.9, 12.5] 0.21	5.3 [3.6, -] 0.25	5.2 [4.8, -] 0.26	3.8 [1.0, 10.5] 0.34	2.7 [1.9, 6.1] 0.39	0.806

oses, are based on an 8 df test of the main effect of treatment in an ANOVA for duration in phase 3, from a Kruskal-Wallis rank test for compliance and duration om a Chi-Squared test for categorical outcomes, or Fisher's exact test in the case of small counts (discontinuation for lack of efficacy, tolerability), and from a

s who discontinued very early. Duration of phase 3 is missing for one patient on olanzapine. There were 10 administrative discontinuations: ARIP: 1, Combination:

Table 4

PANSS and CGI

	Statistic	ARIP (n=33)	CLOZ (n=37)	Comb. (n=40)	Flu-D (n=9)	OLAN (n=41)	PERP (n=4)	QUET (n=33)	RISP (n=36)	ZPR (n=37)	p-value[1]
SS Change from Phase 3 Baseline											
seline	Mean (S.D.) n	76.4 (19.5) 32	85.3 (16.9) 36	88.6 (23.2) 40	91.2 (24.2) 9	77.6 (23.6) 40	91.0 (16.1) 4	75.2 (15.3) 31	75.6 (17.6) 34	71.4 (18.4) 36	0.002
	Mean (S.D.) n change from baseline p value	−2.2 (16.6) 26 0.506	−11.5 (18.4) 31 0.002	−10.4 (17.0) 32 0.002	−15.7 (12.5) 9 0.005	−9.3 (17.2) 38 0.002	−11.8 (9.2) 4 0.084	−7.0 (14.3) 30 0.013	−6.1 (15.5) 29 0.044	−5.3 (14.2) 32 0.045	0.832
	Mean (S.D.) n change from baseline p value	−13.7 (14.0) 18 <0.001	−13.3 (21.3) 24 0.006	−15.6 (19.2) 25 <0.001	−12.9 (13.3) 7 0.043	−9.7 (16.3) 30 0.003	−8.0 (3.4) 4 0.018	−7.0 (19.6) 23 0.100	−8.1 (13.9) 24 0.009	−3.1 (15.7) 21 0.371	0.515
ity Change from Phase 3 Baseline											
seline	Mean (S.D.) n	4.0 (0.9) 32	4.7 (0.9) 34	4.6 (0.8) 39	4.9 (1.1) 9	4.1 (1.1) 40	4.5 (1.0) 4	4.1 (0.9) 31	4.2 (1.0) 34	3.9 (0.8) 35	0.002
	Mean (S.D.) n	−0.2 (0.7) 26	−0.8 (1.1) 29	−0.3 (0.7) 31	−0.8 (1.1) 9	−0.4 (0.9) 38	−0.5 (0.6) 4	−0.3 (0.8) 30	−0.3 (1.3) 28	−0.5 (0.7) 29	0.249
	Mean (S.D.) n	−0.3 (0.8) 18	−1.0 (1.0) 24	−0.6 (0.8) 25	−0.1 (1.5) 7	−0.6 (1.1) 30	−0.3 (0.5) 4	−0.7 (1.0) 23	−0.5 (1.4) 24	−0.5 (0.6) 19	0.695

resented for descriptive purposes, are from an 8 df test of treatment based on an ANOVA for baseline and ANCOVA for change from baseline, adjusting for baseline value. P-value for last
mpleters also adjusts for duration of Phase 3 treatment.

3 baseline is the last measurement in Phase 2. Months 3 and 6 are based on the last measurement collected within windows of 0–3 and 4–6 months post-baseline.

Table 5

Outcome Measures of Safety by Phase 3 Treatment

	Statistic	ARIP (n=33)	CLOZ (n=37)	Comb. (n=40)	Flu-D (n=9)	OLAN (n=41)	PERP (n=4)	QUET (n=33)	RISP (n=36)	ZPR (n=37)	p- value[1]
e to											
	n (%)	7 (21%)	6 (16%)	10 (25%)	1 (11%)	9 (22%)	0	7 (21%)	4 (11%)	7 (19%)	0.581
rs of	Risk Ratio	0.45 (8/18)	0.30 (6/20)	0.49 (14/28)	0.18 (1/5)	0.33 (11/33)	0 (0/4)	0.41 (9/22)	0.21 (5/24)	0.45 (8/18)	NT
	n (%)	3 (9%)	7 (19%)	6 (15%)	0	1 (2%)	2 (50%)	2 (6%)	3 (8%)	3 (8%)	0.079 f
	n (%)	14 (43%)	29 (78%)	26 (65%)	6 (67%)	28 (68%)	3 (75%)	25 (76%)	17 (47%)	19 (51%)	0.075
	n (%)	6 (18%)	1 (3%)	10 (25%)	2 (22%)	7 (17%)	0	8 (24%)	4 (11%)	8 (22%)	0.133 f
	n (%)	8 (24%)	12 (32%)	8 (20%)	2 (22%)	8 (20%)	1 (25%)	11 (33%)	5 (14%)	9 (24%)	0.632 f
ation	n (%)	7 (21%)	7 (19%)	9 (23%)	1 (11%)	7 (17%)	1 (25%)	12 (36%)	0	6 (16%)	0.010 f
asm	n (%)	3 (9%)	10 (27%)	12 (30%)	1 (11%)	4 (10%)	1 (25%)	10 (30%)	6 (17%)	5 (14%)	0.100 f
	n (%)	1 (3%)	7 (19%)	2 (5%)	0	5 (12%)	1 (25%)	0	1 (3%)	2 (5%)	0.037 f
	n (%)	2 (6%)	14 (38%)	4 (10%)	1 (11%)	0	0	2 (6%)	3 (8%)	0	<0.001 f
	n (%)	2 (6%)	9 (24%)	4 (10%)	0	4 (10%)	0	4 (12%)	0	3 (8%)	0.077 f
usly	n (%)	9 (27%)	13 (35%)	12 (30%)	1 (11%)	7 (17%)	1 (25%)	15 (45%)	6 (17%)	9 (24%)	0.040
	n/N (%)[3]	2/22 (9%)	2/25 (8%)	5/29 (17%)	1/7 (14%)	0/31	1/4 (25%)	2/20 (10%)	5/27 (19%)	3/26 (12%)	0.231 f
3	n/N (%)[4]	0/26	1/30 (3%)	2/31 (6%)	2/9 (22%)	1/35 (3%)	0/4	2/29 (7%)	1/30 (3%)	4/27 (15%)	0.201 f
re ≥ 1	n/N (%)[5]	1/29 (3%)	2/29 (7%)	3/31 (10%)	1/8 (13%)	1/36 (3%)	1/4 (25%)	3/30 (10%)	1/30 (3%)	1/28 (4%)	0.493 f
e to											
	n/N (%)[6]	2/29 (7%)	10/31 (32%)	12/31 (39%)	1/8 (13%)	8/35 (23%)	2/4 (50%)	5/31 (16%)	4/29 (14%)	2/30 (7%)	0.031
	Mean (SD) Median Range[7]	−4.0 (16.0) −2 −40, 21	8.8 (24.2) 3 −19, 53	8.4 (14.8) 11 −16, 29	−6.1 (10.6) −7.5 −19, 15	8.0 (8.8) 6 −4, 28	10.5 (19.7) 6.5 −6, 35	0.7 (19.0) −2 −25, 39	−1.8 (19.5) 1 −56, 14	−4.6 (13.5) −5 −34, 17	0.007
bs/	Mean (SD) Median Range[7]	−1.4 (5.0) −0.3 −7.3, 4.1	1.3 (3.5) 0.9 −4.0, 8.5	0.5 (2.8) 1.0 −5.9, 3.7	0.5 (2.6) −1.7 −2.5, 5.7	1.0 (1.3) 0.8 −0.4, 4.1	0.7 (2.0) 0.9 −1.7, 2.6	−0.4 (2.5) −0.2 −6.2, 4.5	−0.1 (2.2) 0.2 −4.8, 2.6	−1.3 (2.6) −0.8 −7.0, 1.9	0.013
e 3 s[8]											

	Statistic	ARIP (n=33)	CLOZ (n=37)	Comb. (n=40)	Flu-D (n=9)	OLAN (n=41)	PERP (n=4)	QUET (n=33)	RISP (n=36)	ZPR (n=37)	p- value[1]
	Mean (SD) Median N Exposure-adjusted Mean (SE)	13.4 (62.1) −1.0 29 17.4 (6.9)	9.0 (34.0) 10.0 32 10.0 (6.6)	−2.3 (30.5) 0.5 31 −7.6 (6.8)	−9.3 (21.2) −6.0 7 −12.9 (14.1)	−1.4 (27.9) −1.0 32 −3.9 (6.7)	8.2 (15.5) 7.5 3 −5.8 (21.5)	9.9 (51.4) 4.0 26 6.4 (7.3)	−0.8 (32.8) 5.8 26 −4.3 (7.3)	−23.4 (50.1) −5.0 29 −11.5 (7.1)	0.030
	Mean (SD) Median N Exposure-adjusted Mean (SE)	−0.2 (1.5) 0.3 9 0.05 (0.2)	0.5 (1.0) 0.1 8 0.4 (0.2)	−0.1 (0.3) −0.1 12 −0.1 (0.2)	0.1 (0.2) 0.1 2 −0.1 (0.4)	0.1 (0.3) 0.2 4 0.0 (0.3)	-	0.3 (0.5) 0.3 8 0.3 (0.2)	−0.0 (0.4) 0.0 11 −0.2 (0.2)	−0.2 (0.4) −0.2 13 −0.1 (0.2)	0.121
	Mean (SD) Median N Exposure-adjusted Mean (SE)	−0.6 (34.3) −7.0 29 3.4 (5.4)	−0.0 (41.5) −2.8 32 1.4 (5.2)	2.1 (30.6) 6.0 31 −0.9 (5.3)	8.3 (16.4) 5.5 7 5.0 (10.9)	15.9 (27.7) 10.0 32 11.8 (5.2)	13.3 (43.8) 1.0 3 13.1 (16.7)	4.0 (35.4) 10.5 26 6.3 (5.7)	6.6 (29.1) 10.5 26 3.1 (5.7)	−16.1 (34.3) −11.5 29 −12.0 (5.4)	0.143
	Mean (SD) Median N Exposure-adjusted Mean (SE)	−6.9 (106.3) −5.5 29 9.2 (20.5)	55.6 (116.2) 34.0 32 54.1 (19.5)	2.8 (151.5) 6.0 31 5.4 (19.9)	−23.9 (87.6) −3.0 7 −30.7 (41.4)	27.5 (83.4) 39.5 32 15.0 (19.7)	28.2 (39.6) 25.5 3 17.8 (63.3)	13.9 (81.2) 7.0 26 9.6 (21.5)	24.6 (91.6) −3.5 26 3.1 (21.7)	−24.8 (194.9) −0.5 29 −2.3 (20.8)	0.309
	Mean (SD) Median N Exposure-adjusted Mean (SE)	−6.6 (11.1) −2.5 28 −9.8 (3.5)	−9.8 (15.0) −2.9 31 −8.2 (3.3)	−1.6 (20.7) −2.0 31 −1.9 (3.3)	6.8 (10.6) 9.9 7 7.4 (6.9)	−4.7 (12.0) −3.9 31 −5.0 (3.3)	9.2 (9.9) 14.1 3 1.9 (10.6)	−1.3 (25.7) −2.4 26 −2.1 (3.6)	24.2 (44.5) 13.4 24 26.7 (3.8)	−5.6 (19.6) −0.6 28 −4.1 (3.5)	< 0.001
ation	Mean (SD) Median N[9] a	−5.6 (27.6) −3.0 27	−3.4 (29.4) −3.5 24	0.6 (20.1) 6.0 25	5.0 (−) 5.0 1	−9.9 (32.0) −7.0 15	−12.7 (11.2) −17.0 3	3.2 (18.8) 1.0 18	−5.8 (25.2) −9.0 18	3.4 (23.9) −0.5 26	0.776
	n/N (%)[10]	0/27	1/24 (4%)	0/24	0/1	0/14	0/3	0/18	0/18	1/26 (4%)	0.833 f
	n (%)	0	1 (3%)	1 (3%)	0	0	0	1 (3%)	0	0	0.733 f
	n/N (%)[10]	2 (6%)	3 (8%)	4 (10%)	1 (11%)	5 (12%)	1 (25%)	2 (6%)	2 (6%)	4 (11%)	0.837 f
	n (%)	1 (3%)	5 (14%)	11 (28%)	2 (22%)	5 (12%)	0	5 (15%)	7 (19%)	6 (16%)	0.222 f
	n (%)	4 (12%)	1 (3%)	4 (10%)	1 (11%)	1 (2%)	1 (25%)	2 (6%)	1 (3%)	4 (11%)	0.279 f
	n (%)	2 (6%)	0	9 (23%)	1 (11%)	5 (12%)	1 (25%)	5 (15%)	0	2 (5%)	0.003 f
	n (%)	0	2 (5%)	5 (13%)	3 (33%)	1 (2%)	0	2 (6%)	3 (8%)	2 (5%)	0.069 f
ulin	n (%)	0	1 (3%)	0	0	0	0	0	0	0	NT

Schizophr Res. Author manuscript; available in PMC 2010 January 1.

	Statistic	ARIP (n=33)	CLOZ (n=37)	Comb. (n=40)	Flu-D (n=9)	OLAN (n=41)	PERP (n=4)	QUET (n=33)	RISP (n=36)	ZPR (n=37)	p- value[1]
	n (%)	1 (3%)	2 (5%)	1 (3%)	0	1 (2%)	0	1 (3%)	0	2 (5%)	0.927 f

poses, are from an 8 df test comparing all treatment groups. P-values for percentages are from a Poisson regression accounting for differential duration of exposure laboratory parameters are based on a ranked analysis of covariance (ANCOVA) adjusting for duration of exposure to Phase 3 study drug and baseline value. The from an ANCOVA adjusting for baseline weight. The p-values for change in weight and QTc are based on an ANCOVA adjusting for duration of exposure to for weight change. P-values for categorical outcomes are based on an 8 d.f. chi square test, or Fisher's exact text in the case of small sample sizes (noted with an

≥ 2 are based on the number of patients without TD and with an AIMS Severity Index < 2 at baseline and at least one post-baseline measure.

ased on the number of patients with Barnes GCA < 3 at baseline and at least one post-baseline measure.

Scale Score ≥ 1 are based on the number of patients with Simpson-Angus EPS Scale Score < 1 at baseline and at least one post-baseline measure.

on the number of patients with a baseline body weight value and at least one post-baseline measure.

rcentile to 95th percentile, which excludes extreme outliers.

sting results were not excluded. The exposure-adjusted mean is the ANCOVA least squares mean adjusting for duration of exposure to Phase 3 study drug and was added to the protocol as part of a protocol amendment, the number of patients with a baseline and post-baseline assessment are smaller for this test. Conversion lows: blood glucose: mg/dL* 0.05551 = mmol/L, Hemoglobin A1c: %*0.01=value, cholesterol: mg/dL*0.02586=mmol/L, triglycerides: mg/dL*0.01129=mmol/

ients with a baseline value and at least one post-baseline measure.

rolongated QTc are based on the number of patients with a normal baseline QTc value (≤450 for males or ≤470 for females) and at least one post-baseline measure.