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Can a Nonequivalent Choice of Dosing Regimen Bias the Results of Flexible Dose Double Blind Trials? The CATIE Schizophrenia Trial

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Abstract

Background: One of the major challenges in the design of double-blind flexible-dosing clinical trials comparing active drugs is the selection of dosing regimens that are equivalent across drugs. This study uses data from the CATIE schizophrenia trial to evaluate the hypothesis that drugs that were dosed somewhat higher in the trial than in typical practice would show greater efficacy and more side effects, especially at high capsule levels, than drugs that were dosed at lower relative strengths.

Methods: CATIE was a large (N=1460) randomized trial comparing 5 antipsychotics in patients with chronic schizophrenia. The blind was maintained in CATIE by prescribing identical-looking capsules of each medication. Dosing was flexible, such that PIs could prescribe from one to four capsules per day, and could modify the dose based on a patient's symptoms and side effects. Capsule strengths for olanzapine (7.5 mg) and quetiapine (200mg) were relatively higher than for risperidone (1.5 mg), perphenazine (8 mg) or ziprasidone (40 mg). Proportional hazards models of time to all cause discontinuation and mixed regression models for continuous measures of symptoms, quality of life and side effects were used to test for interactions between randomly assigned drug and number of capsules prescribed per visit. We hypothesized that if a dosing bias was present, the flex-dosing design would result in a significant interaction such that drugs with higher relative dosing per capsule would be more effective and have more side effects than drugs

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with lower relative dosing and that this effect would be greatest at the largest prescribed dosing regimen (4 capsules).

Results.—There were no significant interactions between drug assignment and number of capsules in the proportional hazards analyses of time to all cause discontinuation ($p=.77$, excluding ziprasidone and .74 in the ziprasidone cohort) or in the mixed model analysis of PANSS symptoms ($p=.49$), quality of life ($p=.45$); or measures of tardive dyskinesia (AIMS, $p=.47$). However a significant interaction was observed on the Barnes akathisia scale ($p=.0005$), on the Simpson Angus EPS scale ($p=.10$) and on the analysis of weight($p=0.014$). Paired comparisons did not show the hypothesized pattern of relationships for akathisia or EPS, but such a pattern was suggested for olanzapine in the analysis of weight although it emerged at 2,3 and 4 capsules indicating a general drug effect rather than a relative dosing difference.

Conclusion: Dosing biases do not seem to have affected the results of the CATIE trial.

Keywords

Antipsychotic medications; schizophrenia; clinical trials

It has been increasingly recognized that short-term, fixed-dose randomized medication trials may have limited relevance to real-world clinical practice because they involve carefully selected patients treated under highly controlled circumstances (Tunis et al., 2003). Practical clinical trials, in contrast, are larger scale studies designed to evaluate the effectiveness of treatments under conditions that more closely approximate those of community practice. Such trials are characterized by: a) large sample sizes, b) flexible clinically driven dosing, c) extended duration of follow-up, d) inclusion of diverse and representative patient samples and clinic settings, and e) collection of data on a broad range of health and economic outcomes. Two common features of these studies that do deviate from typical clinical practice but that are necessary to guarantee unbiased results are: a) random assignment to assure equivalence of treatment groups, and b) maintenance of double blind conditions so that neither prescribers nor patients know the treatment assignments.

One of the major challenges in the design of practical drug trials is the selection of dosing regimens that are “equivalent” across drugs. Head-to-head comparison studies carried out under double blind conditions with flexible dosing require that prescribers choose between identical capsules representing doses of each medication that should be clinically equivalent. If one medication in a trial is offered at a higher dose than the comparison treatment, it is generally assumed that prescribing physician will adjust medication doses according to the presenting level of symptoms and side effects, and thus as long as a wide enough range of doses is offered, no bias will be introduced favoring one drug over another. However, it is possible that if one drug is offered at a higher dose level not offered at all for other drugs, it may falsely appear to be more efficacious and/or associated with a higher frequency of adverse drug effects, assuming that efficacy and tolerability are dose dependent. Conversely, medications that are offered at a lower relative ceiling dose may falsely appear to be less effective and have lower risk of some side effects. Unfortunately, short-term FDA registration trials are often the principal source of information available to guide dosing in practical trials. Such trials may rely on only two or three fixed doses (Marder and Meibach,

1994) and often fail to clearly establish either the minimum effective dose or the maximum dose that limits the risk of side effects. To our knowledge, whether the selection of non-equivalent dosing regimens can bias the results of practical clinical trials has yet to be empirically investigated.

In 1999, the National Institute of Mental Health (NIMH) initiated the Clinical Antipsychotic Trial of Intervention Effectiveness (CATIE), a practical clinical trial of pharmacotherapy for chronic schizophrenia that compared the effectiveness of one first generation antipsychotic (FGA), perphenazine, and all four second generation antipsychotics (SGAs), other than clozapine, that were available in the U.S. in January, 2002, olanzapine, risperidone, quetiapine, and ziprasidone (Lieberman et al., 2005). A series of papers from this 18-month trial has shown that while patients stayed on olanzapine longer than risperidone and quetiapine (Lieberman et al., 2005), none of the four SGAs showed a statistically significant advantage over the FGA perphenazine in either time to all cause discontinuation or on measures of symptoms, neurologic side effects, quality of life, neuropsychological functioning, violent behavior or employment, although olanzapine did show a significantly greater time to discontinuation specifically for lack of efficacy (Lieberman et al., 2005; Miller, 2008; Rosenheck et al., 2006; Swartz et al., 2006; Keefe et al., 2006; Swanson et al., 2008; Resnick et al., 2008). The blind was maintained in CATIE by prescribing from one to four identical capsules of each medication. While the intention was for each capsule to represent a roughly equivalent dose and that unexpected inequalities would be balanced in clinical practice, critics have suggested that the unexpected findings of CATIE may be explained in part by the fact that the dosing regimens for these drugs were not equivalent in that the effectiveness of olanzapine may have been boosted by higher dosing of that drug while the extrapyramidal side effects of perphenazine may have been minimized by lower dosing (Kane, 2006; Meltzer, 2007 allow). The The highest available dose of olanzapine, for example, was 30mg/day, 10 mg (50%) higher than the maximum FDA recommended dosage (20mg) while the highest dose of quetiapine at 800mg/day was also higher than typically prescribed in the treatment of schizophrenia (Rosenheck, Doyle et al., 2003). In contrast, the maximal allowed doses of risperidone (6mg) and perphenazine (32mg) were lower than the highest FDA recommended doses for these agents (8mg and 64mg, respectively) -- although the recommended FDA perphenazine dosage specifically for outpatients (the population treated in CATIE) is only 24 mg. The maximal dose of ziprasidone (160 mg) in CATIE was equal to the highest recommended FDA dose, although it is lower than the doses recommended in two recent reviews of antipsychotic dose recommendations (Kane, Leucht, Carpenter et al. 2003; Woods, 2003). Unfortunately no documentation exists of the rationale for these dosing decisions although all were made by the investigators.

Clinically meaningful non-equivalence of dosing across medications, at least for ziprasidone may also be suggested by statistically significant differences in the proportion of patients who reached the highest allowable dose (4 capsules) on their initially prescribed medication -- 48% for ziprasidone, 44% for quetiapine and 40% for the other three medications (Lieberman et al., 2005). If the relative dosing of ziprasidone, for example, was lower than that of other drugs, patients might have had poorer clinical responses at lower capsule levels and that their physicians could have responded by prescribing greater numbers of capsules.

This study sought to further examine data from the CATIE trial to evaluate these potential dosing biases. We hypothesized that if olanzapine had an efficacy advantage over other medications in the treatment of symptoms because of its higher dosing per capsule such differences would be most likely to emerge at the higher dosing levels (i.e. at 4 capsules) than at lower levels because at the highest dosing levels, other treatments might have faced a dose ceiling that could have impaired their efficacy. At lower capsule levels, incompletely responsive patients could simply be prescribed a greater number of capsules. We further hypothesized that if there were significant dosing biases in CATIE, the advantage of olanzapine at higher dosing levels would be greatest in comparison to medications that were given at relatively lower doses, for example, risperidone or ziprasidone. These biases could be identified analytically if there was a statistically significant interaction between randomly assigned drug and the number of capsules prescribed, for example if the advantages of olanzapine over other drugs on symptoms was greatest when higher numbers of capsules were prescribed. The question we seek to address is thus quite different from that of a fixed dosing study in which patients are randomly assigned to various doses of medications. Fixed dosing studies seek to evaluate whether, on average, patients respond better to higher or lower doses of a given medication. In a double blind, variable dosing study, such as CATIE, the question is whether non-equivalence of dosing regimens can pose a dose ceiling for drugs provided at lower dose equivalents per capsule and thus may bias the overall results of the trial in favor of drugs provided at higher relative dosing levels. Since patients in variable dosing studies are assigned to different dosage levels on the basis of their clinical status, patients on different dosage levels are likely to be systematically different from one another. Our approach to adjusting for these differences, is to identify baseline differences between patients who received greater numbers of capsules and to use multivariate analysis to control for these differences in the analysis of the interaction of medication and dose.

Methods

Study Design

The CATIE trial was designed to compare the effectiveness and cost-effectiveness of currently available SGA and one FGA medications through a randomized clinical trial involving a large sample of patients treated for schizophrenia at multiple sites, including both academic and more representative community providers. Participants gave written informed consent to participate in protocols approved by local Institutional Review Boards. Details of the study design and entry criteria have been presented elsewhere (Lieberman et al., 2005; Stroup et al., 2003). The diagnosis of schizophrenia was confirmed by the SCID (First, 1996). CATIE was conducted between January 2001 and December 2004 at 57 U.S. sites and included an algorithmically determined series of treatment phases. Patients were initially assigned to olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone under double-blind conditions. However, patients with TD (15% of the sample) were excluded from the randomization that included perphenazine and ziprasidone was only included after 40% of the sample had been assigned. Patients who discontinued their first treatment were invited to receive other second generation antipsychotics, but the current study only includes data from phase 1, during which patients were treated with their initially assigned medication.

Interventions

Identical capsules contained olanzapine (7.5 mg), quetiapine (200 mg), risperidone (1.5 mg), perphenazine (8 mg) or ziprasidone (40 mg). Maximum doses were thus 30mg, 800mg, 6 mg, 32 mg and 160 mg respectively. Medications were flexibly dosed with one to four capsules daily, as judged by the study doctor. Concomitant medications were permitted, except for additional antipsychotic agents. Further details about blinding, later phases of treatment, and modal dosing have been presented elsewhere (Stroup et al., 2003. Lieberman et al., 2005)

Measures

Basic sociodemographic data documented age, race, hispanic ethnicity, gender, education, and marital status. The primary outcome measure in CATIE assessed time to discontinuation of the randomly assigned drug for any reason on the assumption that this outcome would reflect symptoms side effects, and patients choices.

Symptoms of schizophrenia were assessed with the Positive and Negative Syndrome Scale (PANSS)(Kay et al., 1987), which yields a total average symptom score, based on 30 items rated from 1–7 (with higher scores indicating more severe symptoms), as well as subscales reflecting positive symptoms, negative symptoms and symptoms of general psychiatric distress. Overall quality of life was assessed with the Heinrichs-Carpenter Quality of Life Scale (QOLS)(Heinrichs et al., 1984), a rater-administered scale that assesses overall quality of life and functioning on 21 items rated from 0–6 (with higher scores reflecting better quality of life).

Neurological side effects were assessed using 6 items of the Simpson-Angus EPS Scale (each scored 0–4) (Simpson and Angus, 1970); 4 items of the Barnes Akathisia Scale (Barnes, 1989), and the first 7 items from the AIMS measure of TD (addressing movements of specific body regions)(Guy, 1978).

The natural log of total health costs at baseline was measured using methods described in detail elsewhere (Rosenheck et al., 2006)

Analysis

Analysis proceeded in several steps. First, although patients were randomly assigned to treatment groups, this is an observational study as far as dosing is concerned, i.e. patients were not randomly assigned to various numbers of capsules, and there would be obvious potential biases determining which patients received higher doses. To identify these biases multinomial logistic regression was used to identify baseline characteristics that predicted use of higher doses. Significant variables in this analysis were included as co-variables in all subsequent analyses.

In the primary analysis each observation represented the experience of one patient at one post-baseline time point while they were receiving randomly assigned phase 1 study drug. For all models, the independent variables of principal interest were categorical measures of the number of capsules taken at that time point; the randomly assigned medication and an interaction term representing capsules by treatment group. The interaction term tested

whether there were different patterns in the differences between the medications across the capsule strengths for an outcome variable..

Time to all cause discontinuation..—Treatment-capsule groups were compared with use of Cox proportional hazards regression models (Cox, 1972) with effects for treatment group, time-dependent number of capsules, and their interaction term, stratified according to site, and with adjustment for the set of baseline measures that predicted the number of capsules prescribed, as well as TD status and exacerbation of schizophrenia in the preceding 3 months. Sites with 15 or fewer patients were grouped according to the sites' health care systems. Analyses were conducted using the counting process style of input in PROC PHREG of SAS ©, with a robust sandwich estimate (Lin and Wei, 1989) for the covariance matrix, allowing for correlation between observations over multiple time periods for the same patient. Olanzapine at 1 capsule was used as the reference condition to calculate hazard ratios for comparisons of treatments at each capsule strength.

Because ziprasidone was added after approximately 40% of the patients had been enrolled, a separate model was used to evaluate the dose by treatment interaction in this cohort of patients who underwent randomization after ziprasidone was added. A further analysis used the same model to examine time to discontinuation specifically for lack of efficacy.

Continuous outcomes.—In the analysis of continuous measures of symptoms and side effects, the unit of analysis was each follow-up assessment of each patient during phase 1, and mixed models were used to adjust for the fact that the several observations from a given patient are correlated with one another. A categorical measure of time was also included as a covariate in these models, as were variables representing site, exacerbation at the time of entry, TD at baseline and entry in the ziprasidone cohort; along with the set of baseline measures that predicted the number of capsules prescribed, and a baseline-by-time interaction. The baseline-by-time term adjusts for baseline differences on the dependent measure that characterize patients who dropped out early and thus are less well represented at later time points.

The interaction term representing dose (number of capsules) by treatment group was used to generate least-squares (i.e. adjusted) means representing the average value of the dependent measures for each treatment at each capsule strength. A random subject effect and a first-order autoregressive covariance structure (PROC MIXED of SAS ©) was used to adjust standard errors for the correlation of observations from the same individual. These analyses were repeated for subscales of the PANSS, measures of quality of life and neurological side effects

In all analyses, for descriptive purposes, we used a liberal alpha of $p=.10$ as the criterion for further evaluation of the interaction terms. If the interaction between capsules and drug assignment met this standard, paired comparisons were conducted between treatment groups, at each dose-level (capsules).

Results

Characteristics of the CATIE sample have been presented previously (Lieberman et al., 2005). Averaging about 40 years of age, the sample was about three-fourths male and two-thirds Caucasian with mean PANSS scores of 75.4 (sd=17.3) indicating moderately symptomatic illness.

Multinomial logistic regression showed that higher doses of medication were associated with the following baseline assessments: greater severity of symptoms on the PANSS; more severe neurological side effects on measures of tardive dyskinesia and akathisia; greater body mass index and greater service use as reflected by the log of health care costs (Table 1). Conversely lower doses were associated with female gender, younger age, and with greater baseline quality of life on both the Heinrichs Carpenter QOLS and the Lehman QOLI.

Table 2 shows the number of observations at each dose strength of each drug. Utilizing survival analysis, controlling for baseline measures noted above and excluding those assigned to ziprasidone, we found no significant interaction of treatment (olanzapine, perphenazine, risperidone or quetiapine) by dose (1–4 capsules) in the analysis of time to all cause discontinuation ($p=0.77$) (Table 3) or in the more specific analysis of time to discontinuation for lack of efficacy ($p=0.45$).

Comparing patients assigned to ziprasidone with those on olanzapine who entered the study after ziprasidone became available, no significant interaction of treatment by dose was observed in the analysis of time to all cause discontinuation ($p=0.74$) (Table 2) but a significant interaction was observed in the analysis of time to discontinuation for lack of efficacy ($p=0.001$). However the pattern of paired differences between hazard ratios for olanzapine and ziprasidone at each capsule strength showed no significant differences and trends showed ziprasidone to have a greater likelihood of discontinuing for lack of efficacy at 1, 2 and 4 capsules and olanzapine at 3 capsules (data available on request), a pattern that is not consistent with the pattern hypothesized to represent systematic dosing bias.

In the analysis of continuous measures of symptoms and quality of life there was no significant interaction of treatment and capsule number on the measure of symptom severity (PANSS, $p=.49$) (Figure 1) or quality of life as measured by the Heinrichs Carpenter QOLS ($p=.45$); nor was there a significant interaction on measures of tardive dyskinesia (AIMS, $p=.47$). However a strong interaction was observed on the Barnes akathisia scale ($p=.0005$), and interactions were also identified on the Simpson angus EPS scale ($p=.10$) and on weight ($p=0.014$).

Paired comparisons using t-tests to better understand these interactions show that greater akathisia scores for perphenazine as compared to both olanzapine and risperidone ($p<.05$) were only observed at a dose of one capsule (Figure 2). There were no noteworthy paired comparisons on the Simpson-Angus at any dose level (Figure 3) in spite of the $p=0.10$ overall interaction between drug and dose. The figures graphically show the mean value of each outcome with each drug at each strength and present the results of statistical tests of paired comparisons of all drugs at each dose.

The only set of paired comparisons that tended to fit our hypothesized pattern for dosing bias emerged in the analysis of weight (Figure 4). Patients assigned to olanzapine showed greater weight than those assigned to perphenazine and ziprasidone at 2, 3 and 4 capsules and greater weight than patients assigned to risperidone at 3 and 4 capsules. Patients assigned to quetiapine showed greater weight than perphenazine patients and ziprasidone patients at 4 capsules only (Figure 4). Thus both olanzapine and quetiapine, which were dosed at higher than usual capsule strengths showed higher mean weight at greater numbers of capsules than the drugs that were dosed at lower strength. However, since differences from olanzapine occurred at both 3 and 4 capsule doses this is likely to reflect a general dose-sensitive effect of these drugs on weight, not just a specific effect of higher capsule strength.

Discussion

When double blind flex-dose practical medication trials generate unexpected results it is natural to wonder whether inequalities in relative dosing of treatments led to a biased study design. The present study is the first of which we are aware to empirically evaluate whether such dosing biases may actually have distorted study findings. Although the capsule strengths used in CATIE were thought to be equivalent when the study was designed, in retrospect it appears that dosing of olanzapine (7.5 mg/capsule) and quetiapine (200mg/capsule) were relatively higher than dosing for risperidone (1.5 mg/capsule), perphenazine (8 mg/capsule) or ziprasidone (40 mg.capsule). We hypothesized that drugs that were dosed somewhat higher in a trial than in typical practice would potentially show greater efficacy and more side effects than drugs that were dosed at lesser strengths specifically when the highest level of capsules was prescribed, resulting in statistical interactions between drug and the number of capsules prescribed after adjusting for baseline predictors of future dosing. As in previous studies patients with more severe symptoms at baseline and poorer quality of life received higher doses of medications subsequently (Kunz et al., 1993).

In our analyses, we found no significant interactions between drug assignment and number of capsules in the proportional hazards analyses of time to all-cause discontinuation or in the mixed model analyses of symptoms, quality of life or measures of tardive dyskinesia. However, interactions were observed on measures of akathisia, EPS and weight. Paired comparisons found trends towards the hypothesized pattern reflecting dosing bias to be present only in the analysis of weight with greater weight for patients on olanzapine and quetiapine than among less highly dosed drugs, only when greater numbers of capsules were prescribed. – However, since these differences were present at multiple capsule strengths, not just the highest capsule strength, they most likely reflect a general dose sensitive effect of these drugs on weight, not a specific effect of increased capsule strength.

Considering these findings together we conclude that there is little evidence of dosing biases in CATIE, with suggestive evidence on only one measure (weight) and that more likely to reflect general dose-sensitive effects rather than differences in relative capsule strength.

It should be reiterated that this study did not test the effectiveness of different doses of drugs in highly symptomatic or treatment resistant patients. One recent study that randomized

partially respondent patients with schizophrenia to 10mg, 20mg, or 40 mg of olanzapine found no significant differences in response between these groups and no dose response relationship (Kinon et al., 2008). This study was methodological in nature and merely evaluated whether the use of presumably different capsule strengths in the CATIE trial may have biased the results. No evidence of such bias was found.

Several limitations of these analyses require comment. First, data on precise dose equivalence is generally not available for antipsychotics as for many other medications. Changing views of dose equivalence between drugs is rarely based on randomized trials pitting various dosages of various medications against one another. Rather changing impressions are most often based on clinical experience, which may be the main reason that the consensus on dose appropriateness and equivalence can change over the course of just a few years.

Second since dosing in a flexible-dosed double blind trial is based on clinical presentation and physician judgment it is not surprising that patients who receive higher numbers of capsules are systematically different from those who do not. To adjust for this bias we tested a multi-variable model of capsule number and used baseline correlates of higher dosing as covariates in our analyses of the interaction of drug and capsule number. As expected indicators of more severe symptoms and side effects at baseline were associated with subsequent prescribing of greater numbers of capsules. Nevertheless, as in any non-experimental study there may have been unmeasured factors that shape dosing, for which we did not make an adjustment in our analyses.

Finally, our analysis was based on the assumption that the risk of dosing bias is greatest at highest numbers of capsules. While this assumption seems plausible at face value, we do have empirical evidence of its validity as one might obtain in an experiment in which doses were deliberately prescribed at non-equivalent levels.

This study sought evidence of bias due to unequal relative dosing in the CATIE schizophrenia trial. Such evidence did not emerge on measures of effectiveness or quality of life and only emerged weakly in the analysis of weight. Dosing biases evidently can emerge in double blind clinical trials, especially for outcomes that appear to be dose sensitive and for which there are different outcomes across treatments. The major findings of CATIE do not seem to have been affected by dosing biases.

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Figure 1.
PANSS total score by drug and number of capsules (mixed model adjusting for correlations of higher dosing).

Figure 2.
Akathisia score by drug and number of capsules (mixed model adjusting for correlations of higher dosing).

Figure 3.
Simpson-Angus score by drug and number of capsules (mixed model adjusting for correlations with higher dosing).

Figure 4. Weight by drug and number of capsules (mixed model adjusting for correlations with higher dosing).

Table 1.

Significant predictors of higher numbers of capsule doses by multinomial logistic regression.

	Odds ratio	(95% confidence interval)
Age (5 year intervals)	0.91	(.89-.93) ****
Female	0.62	(.50-.78) ****
PANSS total score	1.01	(1.0-1.02) **
Heinrichs Carpenter QOLI	0.80	(.72-.88) ****
Lehman QOLS	0.92	(.86-.98) *
BMI	1.02	(1.01-1.04) ***
Tardive Dyskinesia (AIMS)	1.40	(1.01-1.68) *
Akithesia (Barnes)	1.30	(1.02-1.5) *

Key:

* = 0<.05

** = 0<.01

*** = 0<.001

**** = 0<.0001

Table 2.

Number of person-visits recorded at each capsule strength *

Capsules	Olanzapine (n=330)	Perphenazine (n=257)	Quetiapine (n=329)	Risperidone (n=333)	Ziprasidone (n=183)
1	346 N=74 [†]	163 N=61	111 N=39	208 N=61	53 N=19
2	1003 N=208	739 N=185	840 N=238	965 N=236	423 N=126
3	821 N=148	454 N=108	443 N=128	661 N=141	289 N=81
4	914 N=124	557 N=96	749 N=137	693 N=122	423 N=79

* Patients came for monthly visits until they discontinued treatment.

[†] Of the 330 patients randomized to olanzapine, 74 patients took 1 capsule a day for a total of 346 person-visits.

Table 3.

Hazard Ratios and Pairwise Contrasts for Treatment within Capsule strength (as a time-dependent covariate) for All Cause Discontinuation in Phase 1 *

Capsules	Treatment	Hazard Ratio [‡]	S.E.	95% Confidence Interval for Hazard	
1	Olanzapine	1.00	---	---	---
	Perphenazine	1.32	0.43	0.70	2.49
	Quetiapine	1.96	0.62	1.06	3.63
	Risperidone	1.15	0.37	0.60	2.17
	Olanzapine	1.00	---	---	---
	Ziprasidone [†]	1.51	0.75	0.57	4.02
2	Olanzapine	0.79	0.20	0.49	1.29
	Perphenazine	1.32	0.32	0.83	2.13
	Quetiapine	1.16	0.27	0.73	1.84
	Risperidone	1.07	0.25	0.67	1.70
	Olanzapine	0.81	0.28	0.41	1.59
	Ziprasidone [†]	1.11	0.37	0.58	2.13
3	Olanzapine	0.79	0.21	0.47	1.33
	Perphenazine	0.89	0.25	0.51	1.56
	Quetiapine	1.22	0.33	0.72	2.06
	Risperidone	1.04	0.27	0.62	1.74
	Olanzapine	0.84	0.30	0.41	1.69
	Ziprasidone [†]	0.83	0.31	0.40	1.72
4	Olanzapine	1.18	0.30	0.72	1.95
	Perphenazine	1.50	0.38	0.91	2.47
	Quetiapine	1.94	0.47	1.21	3.12
	Risperidone	1.58	0.39	0.97	2.57
	Olanzapine	1.11	0.38	0.57	2.17
	Ziprasidone [†]	1.53	0.51	0.79	2.94

* In addition to treatment group, time-dependent number of prescribed capsules, and their interaction, the Cox proportional hazards model stratified on site and adjusted for the following baseline covariates: age, gender, BMI, exacerbation status, Phase 1A, PANSS total score, health costs, Barnes Score, AIMS severity index, and quality of life index.

[‡]Hazard is for each treatment-capsule strength relative to 1 capsule of olanzapine. Hazard ratios > 1 indicate a greater probability of discontinuing relative to 1 capsule olanzapine.

The overall p-value for the treatment by capsule interaction was nonsignificant for the model excluding ziprasidone patients (p=0.77) as well as the model for the ziprasidone cohort (p=0.74).

[‡]Due to a strong ziprasidone cohort effect (p<0.001), comparisons involving ziprasidone were run in a separate analysis which was limited to the cohort of patients who underwent randomization after this treatment was added.

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