Published in final edited form as:

Psychiatry Res. 2012 August 30; 199(1): 1–7. doi:10.1016/j.psychres.2012.03.009.

Predictors of antipsychotic dose changes in the CATIE schizophrenia trial

Eric Hermes^{a,*} and Robert Rosenheck

^aDepartment of Psychiatry, Yale School of Medicine, 300 George Street, Ste. 901, New Haven, CT 06511 USA, Eric.Hermes@yale.edu

^bVA New England Mental Illness, Research, Education and Clinical Center, VA Connecticut Health Care System; Department of Psychiatry, Epidemiology and Public Health, and the Child Study Center Yale Medical School, 950 Campbell Ave., West Haven, CT 06516 USA, Robert.Rosenheck@VA.gov

Abstract

Data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was used with the objective of evaluating factors associated with antipsychotic dose changes. CATIE was a randomized, comparative effectiveness trial for patients with schizophrenia in which a clinician prescribed a double-blind, flexible dose of 1 of 5 antipsychotic medications. The mean number of capsules prescribed monthly was evaluated to identify the period following up-titration with the least sample attrition in which dose changes were likely in response to clinical factors.

Demographic, efficacy and tolerability variables were evaluated in two regression models predicting a one capsule dose decrease or increase. The mean dose increased to 2.7 capsules over the first 3 months. The post-titration plateau was identified as between 3 and 6 months. Factors associated with dose increases included the Clinical Global Impression Scale at 6 months and change in the Positive and Negative Syndrome Scale between 3 and 6 months. Decreased dosing was associated only with *lower* patient rated 6-month global impression of health. Neither tolerability measures, nor body weight were significantly associated with dose changes. In conclusion, dose changes were weakly associated with measures of current or changing clinical status and not affected by measures of side effects.

Keywords

Antipsychotic Agents; Psychiatric Status Rating Scales; Decision Making; Choice Behavior

1. Introduction

Antipsychotic medications are the principal treatment of psychotic spectrum disorders and are increasingly used in the treatment of affective disorders. The Schizophrenia Patient Outcomes Research Team has developed the most extensive recommendations for the pharmacologic treatment of schizophrenia in the acute and maintenance phases. These

© 2012 Elsevier Ireland Ltd. All rights reserved.

*Address correspondence to: Eric D.A. Hermes, M.D., Department of Psychiatry, Yale School of Medicine, 300 George Street, Ste. 901, New Haven, CT 06511, Tel: (203) 974-7526, Fax: (203) 785-4207, eric.hermes@yale.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

guidelines recommend the prescription of antipsychotic doses within a specified chlorpromazine equivalence range and suggest that doses be decreased, after achieving symptom stabilization, to the lowest effective level in order to avoid side effects (Lehman and Steinwachs, 1998). However, the recommendations do not indicate specifically how antipsychotic doses should be modulated in relation to factors such as efficacy, tolerability and patient assessment of their global health status. The imprecision of these guidelines is understandable as little is known about how providers and patients determine the optimally effective dose or how they adjust dose in response to clinical phenomena. Recent enthusiasm about data-based prescribing (Trivedi and Daly, 2007) would suggest that measures of efficacy and tolerability should guide dose adjustments but such decisions may be influenced by unmeasured factors such as information from package inserts, research findings, personal rules of thumb and past clinical experience.

In clinical practice, the dosing of antipsychotics is likely to involve two phases. The first phase comprises basic up-titration to a potentially effective dose range as suggested by the FDA approved package insert, expert opinion, published guidelines and local practice conventions. The second phase involves dose modulation and is presumably based on levels of psychopathology and side-effects. However, prescribers may also take into account other factors such as age, gender, race, duration of illness and baseline symptoms, etc. Flexible dose trials and naturalistic studies where clinical status is periodically assessed with standard measures and in which providers are free to choose and change the dose in accordance with their clinical judgment provide the best opportunity study the relationship between measures of clinical status and real-world prescribing practices. A previous effort by Suarez et al. (2009) found that both current general clinical impression of illness severity and change in the clinical impression from previous assessments predicted antipsychotic dose increases while improvement in sexual and extrapyramidal side effects predicted dose decreases (Suarez et al., 2009). A second study found that the baseline severity of symptoms and symptom change predicted dose increase while side effect profiles but not symptom levels predicted dose decreases (Lipkovich et al., 2005).

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was one of the largest and longest flexible dose schizophrenia medication trials conducted to date. CATIE compared the effectiveness of multiple antipsychotic treatments in a variety of treatment settings using broad inclusion criteria using multiple symptom and side effect measures. The use of blinded medications, the lack of significant outcome differences between treatments in CATIE (Lieberman et al., 2005; Rosenheck and Sernyak, 2009) and the relative dose equivalence across treatments (Rosenheck et al., 2009) allow pooling of data across antipsychotic type. The objective of this effort is to investigate dosing patterns and the factors associated with dose changes in order to draw conclusions about provider decision making.

2. Methods

2.1 Sample

CATIE was designed to compare the effectiveness and cost-effectiveness of available second generation antipsychotics in a large, National Institute of Mental Health funded, randomized double-blind trial at 57 US sites, including both academic and community providers. 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. Participants were 18 to 65 years of age with a diagnosis of Schizophrenia. Those diagnosed with schizoaffective disorder, a cognitive disorder or who had only one schizophrenic episode were excluded. Details of the study design have been presented elsewhere (Stroup et al., 2003; Lieberman et al., 2005). The current analysis uses data from 1432 individuals who

took at least one dose of randomized study medication (olanzapine 7.5 mg per capsule, quetiapine 200 mg per capsule, risperidone 1.5 mg per capsule, perphenazine 8 mg per capsule, ziprasidone 40 mg per capsule) in phase 1 of the trial. A study physician who evaluated subjects monthly could recommend a flexible dose of study medication in the form of one to four blinded capsules as described in Lieberman et al. (2005). Since instructions to study physicians did not include specific guidelines for dosing, dosing was at the discretion of physicians and patients entirely.

2.2 Measures

The number of capsules prescribed in a daily regimen was documented for each month. Outcome measures in CATIE evaluated efficacy, tolerability and safety constructs at baseline and months 1, 3, 6, 9, 12, 15, and 18. The Positive and Negative Syndrome Scale (PANSS) measures psychopathology in schizophrenia based on 30 items rated from one to seven (range=30–210) with higher scores indicating more severe symptoms (Kay et al., 1987). The Clinical Global Impressions Scale (CGI-S) is a widely used measure of global illness severity scored on a seven-item scale by clinicians with higher scores indicating more severe symptoms (Guy, 1976). CATIE also included a patient-rated, visual analog scale (VAS) of global impression of health scored from 0 to 100 where higher scores indicate superior rating of global health. The Calgary Depression Rating Scale (CDRS) is a nine-item scale which assesses the severity of depressive symptoms in patients with schizophrenia with higher scores indicating more depressive symptomatology (Addington et al., 1990). The Barnes Akathisia Rating Scale (BAS) is a widely used measure of drug-induced akathisia that uses a 4-item scale with higher scores indicating more akathisia (Barnes, 1989). The Abnormal Involuntary Movement Scale (AIMS) is a twelve item scale that rates severity of dyskinetic movements with increasing scores indicating more severe movements (Guy, 1976). The Simpson-Angus Extrapyramidal Side Effect Scale (SAEPS) contains 10 items rated on a scale of 0 to 4 and was used as an additional rating of extrapyramidal symptoms where higher scores indicate more symptoms (Simpson, 1970). Body weight was also analysed. Measures were completed by trained raters and patients prior to contact with the study provider who recommended the study medication dose after a clinical interview and without reviewing empirical measures collected for research purposes.

2.3 Analysis of Treatment Dose

In order to investigate general changes in dosing patterns over time, the mean dose for all participants was calculated for every month after initial randomization in phase 1. Our hypothesis was that the mean dose would increase during the first several months in the study as subjects were titrated up on their study medication. The time period from 3–6 months was chosen for the analysis of factors associated with dose changes as doses were relatively stable and sample attrition was minimal.

2.4 Statistical Analysis

Subjects remaining in Phase 1 of CATIE who received a one capsule dose increase, one capsule dose decrease, or no change in dose between 3 and 6 months formed the base sample for statistical analysis (N=542) (Figure 1). The change in dose and outcome measures over the selected time period was calculated by subtracting values at the end of the time period from those at the beginning. Dose changes greater than one capsule, 36 and 16 for dose increase or decrease, respectively, were not evaluated due to low frequencies and the desire to limit the analysis to a single capsule dose change. Using data from this time period, two dependent, dichotomous variables were created: one representing a one capsule dose increase between 3 and 6 months (excluding those already at 4 capsules, who could have no increase) vs. no change in dose (n=362) and the other representing a one capsule dose decrease (excluding those already at 1 capsule, who could have no decrease) vs. no

change in dose (n=442). Individuals with no change in dose were included for reference in both analyses while those who had no room for an increase (n=140) or for a decrease (n=23) were excluded from the respective analyses. This analytic strategy can be contrasted to one with a single, categorical dependent variable incorporating individuals with a single dose increase, no change in dose or a dose decrease. This strategy, although maintaining parsimony, was not selected as it would have decreased sample size and not lead to an improved interpretability of results.

Factors potentially associated with these measures of dose change were first analyzed using t-tests and Chi Square then by logistic regression. A variable representing the number of capsules the subject was taking at the beginning of the time period was included in both logistic regression models to adjust for the possibility that the number of capsules a patient was prescribed affect the decision to increase or decrease dose. This variable was limited to individuals on 1, 2, and 3 capsules with one capsule as the reference level in the dose increase model, and 4, 3, and 2 capsules with 4 capsules as the reference condition in the dose decrease model to assure that the possibility of change existed for all subjects.

Potential factors associated with dose changes included variables representing demographics, cross sectional health status scores, and body weight at 6 months assumed to represent clinical status at the time of dose change. Independent variables also included the change in these clinical variables between 3 and 6 months. The specific variables tested are listed in Tables 1 and 2. In addition, medication type was not used as an independent variable as analysis showed no significant inter-drug differences in dose change rates between individual medications in phase 1 of CATIE. Our hypothesis was that cross sectional variables would display stronger associations compared to change variables. Cross sectional and change variables were first tested in a series of bivariate analyses. Cross sectional and change variables were then tested in two logistic regression models, one for increased dose and another for decreased dose. Variables in these models were selected from the group listed in Tables 1 and 2 on the basis of forward stepwise selection at $p < 0.05$ using the PROC STEPWISE function in SAS® Version 9.2 (SAS Institute, Cary NC). Because of the large number of variables tested and their hypothesized greater importance, cross sectional variables were tested using PROC STEPWISE first. Statistically significant cross sectional variables and 3-month dosage levels were then forced into the model and change variables were added using the PROC STEPWISE function in the second model.

3. Results

3.1 Change in mean dose

The mean antipsychotic dose increased to an average of 2.74 capsules at the end of the first three months and then increased by only 8% to 2.97 capsules by month 18, averaging between 2.74 at month 3 and 2.84 capsules at month 6, a 4% increase (Figure 2). For reference, the mean number of capsules over this period of time, 2.79, corresponded to 20.9mg of olanzapine, 558mg of quetiapine, 4.2mg of risperidone, 22.3mg of perphenazine, and 111.6mg of ziprazidone. This period was selected for analysis as it represented a period of relative dose stability while maximizing sample size. Over this period, 77 of 362 individuals (21.3%) who could experience an increase in dose did so while only 40 of 442 (9.1%) who could have experienced a decrease did so.

3.2 Bivariate analysis

Demographic variables such as age, sex, race/ethnicity and duration of treatment were not significantly associated with either dose increase or decrease (Table 1). The mean cross sectional PANSS and CGI-S scores at 6 months were significantly higher (6 points [$t = -2.68$,

DF=354, $p=0.008$] and 0.6 points [$t=-4.80$, DF=351, $p<0.001$] respectively) for individuals with an increase in dose compared to those with no change indicating that those deemed more ill and who had more psychopathology received a dose increase. Those with an increased dose also had a 6.3 point lower self-rated global health score ($t=2.26$, DF=351, $p=0.025$). Among those with a dose increase, mean PANSS scores increased by 3.8 points while the mean CGI-S decreased by 0.3 points ($t=-2.32$, DF=350, $p=0.021$ and $t=-3.02$, DF=347, $p=0.003$ respectively) compared to those with no change in dose indicating that increasing psychopathology and worsening of global impression of illness were both associated with dose increases.

Individuals with a decreased dose displayed a statistically significant mean VAS score 13.3 points lower than those with no change ($t=3.55$, DF=430, $p<0.001$), indicating that those whose dosing declined rated their own health as worse than those who had no change in dose (Table 2).

3.3 Multivariate analysis of dose change

In the multivariate logistic regression model predicting increased dose, cross sectional variables listed in Tables 1 and 2 were first evaluated alone in forward stepwise selection and only CGI-S was statistically significant. (Table 3) After all change variables listed in Tables 1 and 2 were tested in forward stepwise selection, there were significant predictions of dose increase for both the CGI-S and the change in PANSS (Odds Ratio [OR] = 1.82, Confidence Interval [CI] = 1.35, 2.43 and OR = 1.03, CI = 1.00, 1.05 respectively), indicating that higher clinician rated global illness severity and increasing psychopathology was associated with an increased dose. In the two models predicting decreased dose, only the cross sectional VAS was statistically significant (OR = 0.98, CI = 0.97, 0.99) while no 3–6 month change measures were significant, indicating that lower subject assessed perception of health was related to decreasing dose (Table 4). In both models predicting dose changes, the variable representing the number of capsules the subject was taking was not statistically significant.

4. Discussion

The role of measurable clinical factors influencing patient and provider decisions to change antipsychotic dose in the treatment of schizophrenia has not been well studied. This analysis of data from the CATIE Schizophrenia Trial evaluated the change in blinded antipsychotic dose over time and the predictors of dose change after initial up titration. The mean antipsychotic dose in CATIE increased to a plateau after 3 months indicating that clinicians initially dose antipsychotics to a standardized level suggested by clinical guidelines and recommendations. After the initial titration, global illness severity at the time of dosing was the main driver of dose increase while the change in psychopathology over the previous three months played a smaller albeit statistically significant role. Patient assessed global perception of health was inversely associated with decreasing antipsychotic dose and neither the current number of blinded capsules nor the level of depression, side effects or body weight were associated with dose changes.

Our finding that global illness severity as measured by the CGI-S was the factor most strongly related to antipsychotic dose increase is similar to that found by Suarez et al. (2009) and Lipkovich et al. (2008) where increasing dose was associated with baseline CGI and PANSS respectively (Lipkovich et al., 2005; Suarez et al., 2009) In addition, both previous studies also demonstrated that a *change* in illness severity was related to dose increase, a result replicated here. Global illness severity at the time of dosing displayed a stronger association with dose increase compared with change in symptomatology in this study, again similar to the findings of Lipkovich et al. (2008) but contrasting with those of Suarez et al.

(2009) where the relationship with both variables had a similar magnitude. Taken together, these results indicate that the level of symptoms and function during the current evaluation is the most important predictor of dose increase, and has stronger effects than changes in the severity of symptoms from previous visits.

The only significant driver of dose decrease in our study was the patient's global impression of health as measured by their VAS rating. Perhaps paradoxically, VAS scores indicating better self-perceived health decreased the odds of a dose decrease. A likely explanation for this finding is that patient distress reflected in lower ratings of general health may be attributed to the medications themselves, which may trigger a request for a lower dose even though no increase in standardized side effect measures was observed. Side effects not identified by conventional measures have been purported to go unrecognized or become confounded with core psychiatric symptoms of schizophrenia (Chouinard and Chouinard, 2008; Demily et al., 2010). It may be that patients and providers in the CATIE study correctly identified these symptoms as side-effects and appropriately lowered the dose of antipsychotics. However, it must be noted that the VAS does not contain specific enough information to determine exactly what aspects of health status were rated by patients. This fact makes it difficult to fully interpret the somewhat weak association between lower perception of health and decreased dose.

Perhaps the most striking finding of the current analysis is the relative weakness of standardized measures at predicting dose changes and especially dose decreases. Dose decrease was a less frequent occurrence, perhaps reflecting the severity and chronic course of schizophrenia and may represent a trend of providers to avoid dose decreases in an effort to prevent relapse. It is also possible that measures using in CATIE did not address the variables important in predicting dose changes.

Counter to our hypothesis, antipsychotic dose decrease was not significantly related to side effect measures in this study. This is in contrast to the findings from Lipkovich et al. (2008) where the SAEPS, BAS and an additional measure of EPS were all related to antipsychotic dose decrease. One reason may be that clinicians in the CATIE trial were allowed to use additional medications to treat akathisia and EPS related side effects, which may have resulted in the relatively low scores on these measures (Chouinard and Chouinard, 2008). If these symptoms could be effectively addressed by the use of concomitant medications, a decrease in antipsychotic dose may not have been needed. In addition and as pointed out by Lipkovich et al. (2008), the lack of association between side effect measures and dose decreases may reflect an uncertainty by the clinician of the interpretation of these symptoms and how they relate to antipsychotic dose.

On average, neither weight nor weight change influenced dose changes in this study, although they may have influenced clinical decisions for individual patients. Lipkovich et al. (2008) reported an inverse association between BMI increase and dose increase in acutely ill individuals treated with olanzapine. Since CATIE was a trial of treatment effectiveness in chronic schizophrenia where the average duration of antipsychotic treatment at baseline was 14.4 years (Lieberman et al., 2005) and the average BMI was 29.9 (Daumit et al., 2008), clinicians may not have viewed weight or weight change as an effect of study medication dosage.

It was also noteworthy that the current antipsychotic dose as specified by the number of capsules the subject was taking did not influence the decision to change the antipsychotic dose. The finding that the mean dosed increased to a plateau of just under 3 capsules as well as the finding that clinician and patient view of illness severity are the major drivers of dose increase indicates that clinicians did not seem to use dosing heuristics based on the current

number of capsules or maximizing the number of capsules independent of efficacy or tolerability measures.

Several limitations of this descriptive study require comment. The main limitation of this study is that the documentation of dose changes occurred monthly while major efficacy and tolerability assessments were conducted every 3 months, limiting the precision of the observed temporal relationship between dose changes and clinical changes. In some cases the dose change may have preceded the documented clinical changes. We were able to determine that dose increases were distributed relatively equally across the 3-month period, indicating that at approximately one third of the dose increases took place directly after the assessments were completed. Other research efforts of this type have experienced the same ambiguity of timing (Lipkovich et al., 2005; Suarez et al., 2009). As a result, we cannot know for certain that dose decreases represented the clinician's response to the patient's clinical status at the precise time of dosing decisions. This is less likely to affect the analysis of dose increases, since it is unlikely that increasing medication doses would increase symptoms, but it is possible that decreasing dosage would lead to increased symptoms rather than the reverse. In addition, the CATIE study was not designed to test correlates of dose changes and used blinded treatments that assumed dose equivalence between agents, thus caution is advised when interpreting results. However, a previous study suggested that potential nonequivalence did not seem to affect study results (Rosenheck et al., 2009).

In conclusion, this analysis investigated antipsychotic dosing changes and the clinical factors that were associated with these changes in a relatively representative sample of patients with schizophrenia in a large trial of double blind treatment. Clinician global impression of illness and change in symptoms were associated with the decision to increase antipsychotic doses while the patient report of poorer global health status was associated with the decision to decrease dose. Given the partial effectiveness of the pharmacologic treatment of schizophrenia, a greater understanding of patient and provider preferences and decision making may eventually lead to more refined management of psychotic disorders.

Acknowledgments

We wish to acknowledge the contributions of all investigators, study personnel and subjects from all of the CATIE Schizophrenia Trial sites. This analysis was supported by the New England Mental Illness Research and Education Center. The funding source had no role in the design, analysis or interpretation of data or in the preparation of the report or decision to publish.

References

- Addington D, Addington J, Schissel B. A depression rating scale for schizophrenics. *Schizophrenia Research*. 1990; 3:247–251. [PubMed: 2278986]
- Barnes TR. A rating scale for drug-induced akathisia. *British Journal of Psychiatry*. 1989; 154:672–676. [PubMed: 2574607]
- Chouinard G, Chouinard VA. Atypical antipsychotics: CATIE study, drug-induced movement disorder and resulting iatrogenic psychiatric-like symptoms, supersensitivity rebound psychosis and withdrawal discontinuation syndromes. *Psychotherapy and Psychosomatics*. 2008; 77:69–77. [PubMed: 18230939]
- Demily C, Chouinard VA, Chouinard G. Iatrogenic psychiatric-like symptom recognition. *L'Encéphale*. 2010; 36:417–421.
- Daumit GL, Goff DC, Meyer JM, Davis VG, Nasrallah HA, McEvoy JP, Rosenheck RA, Davis SM, Hsiao JK, Stroup TS, Lieberman JA. Antipsychotic effects on estimated 10-year coronary heart disease risk in the CATIE schizophrenia study. *Schizophrenia Research*. 2008; 105:175–187. [PubMed: 18775645]

- Guy, W. ECDEU assessment manual for psychopharmacology. Rockville, MD: US Department of Health, Education, and Welfare, Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration, National Institute of Mental Health, Psychopharmacology Research Branch, Division of Extramural Research Programs; 1976.
- Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*. 1987; 13:261–276. [PubMed: 3616518]
- Lehman AF, Steinwachs DM. Translating research into practice: the schizophrenia patient outcomes research team (PORT) treatment recommendations. *Schizophrenia Research*. 1998; 24:1–10.
- Lieberman JA, Stroup TS, McEvoy JP, Swartz MS, Rosenheck RA, Perkins DO, Keefe RSE, Davis SM, Davis CE, Lebowitz BD, Severe J, Hsiao JK. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *New England Journal of Medicine*. 2005; 353:1209–1223. [PubMed: 16172203]
- Lipkovich I, Baron D, Houston J, Ahl J, Rotelli M. Flexible-dose clinical trials: predictors and outcomes of antipsychotic dose adjustments. *Journal of Clinical Psychopharmacology*. 2005; 25:381–386. [PubMed: 16012284]
- Rosenheck RA, Davis VG, Davis SM, Stroup S, McEvoy J, Swartz M, Lieberman J. Can a nonequivalent choice of dosing regimen bias the results of flexible dose double blind trials? *Schizophrenia Research*. 2009; 113:12–18. [PubMed: 19545976]
- Rosenheck RA, Sernyak MJ. Developing a policy for second-generation antipsychotic drugs. *Health Affairs*. 2009; 28:782–793.
- Simpson GM. A rating scale for extrapyramidal side effects. *Acta Psychiatrica Scandinavica*. 1970; 45:11–19. [PubMed: 4917967]
- Stroup TS, McEvoy JP, Swartz MS, Byerly MJ, Glick ID, Canive JM, McGee MF, Simpson GM, Stevens MC, Lieberman JA. The national institute of mental health clinical antipsychotic trials of intervention effectiveness (CATIE) project: schizophrenia trial design and protocol development. *Schizophrenia Bulletin*. 2003; 29:15–31. [PubMed: 12908658]
- Suarez D, Haro JM, Novick D, Perrin E, Ochoa S, Naber D. Reasons and Outcomes of Olanzapine Dose Adjustments in the Outpatient Treatment of Schizophrenia. *Pharmacopsychiatry*. 2009; 42:135–140. [PubMed: 19585391]
- Trivedi MH, Daly EJ. Measurement-based care for refractory depression: a clinical decision support model for clinical research and practice. *Drug and Alcohol Dependence*. 2007; 88:S61–S71. [PubMed: 17320312]

Figure 1.
Sample selection for evaluation of dose increase and dose decrease from Phase 1 of the CATIE Schizophrenia Trial

Figure 2.
The mean (standard deviation indicated by error bars) number of antipsychotic capsules by month in Phase 1 of the CATIE Schizophrenia Trial

Table 1

Bivariate analysis for cross-sectional and change variables by increasing dose vs. no change in dose between month 1 and 3 of Phase 1 in the CATIE Trial

	Increased Dose n=77 [†]		No Change in Dose n=285 [†]		Test [*]	df	P-Value
	n (%) [‡]	Mean (SD)	n (%) [‡]	Mean (SD)			
Demographic Variables							
Age	77 (100.0)	40.6 (10.9)	285 (100.0)	41.7 (10.0)	0.79	360	0.729
Sex					0.31	1	0.576
Male	54 (70.1)		209 (73.3)				
Female	23 (29.9)		76 (26.7)				
Race					0.43	2	0.806
Black	23 (29.9)		96 (33.7)				
White	49 (63.6)		172 (60.4)				
Other	5 (6.5)		17 (6.0)				
Ethnicity					0.54	1	0.462
Hispanic	11 (14.3)		32 (11.2)				
Other	66 (85.7)		253 (88.8)				
Trt Duration	74 (96.1)	15.5 (15.1)	276 (96.8)	14.5 (12.2)	-0.72	348	0.473
Cross-Sectional Variables (values at 6 months)							
PANSS Tot	75 (97.4)	67.3 (16.7)	281 (98.6)	61.5 (16.6)	-2.68	354	0.008
CGI-S	75 (97.4)	3.8 (1.0)	278 (97.5)	3.2 (0.9)	-4.80	351	<0.001
VAS	75 (97.4)	65.9 (21.4)	278 (97.5)	72.2 (21.7)	2.26	351	0.025
CDRS	75 (97.4)	1.5 (0.5)	281 (98.6)	1.4 (0.5)	-1.68	354	0.094
BAS	76 (98.7)	0.2 (0.4)	280 (98.2)	0.2 (0.4)	0.47	354	0.637
AIMS	76 (98.7)	0.2 (0.6)	280 (98.2)	0.2 (0.5)	-0.25	354	0.801
SAEPS	76 (98.7)	0.2 (0.2)	283 (99.3)	0.2 (0.3)	0.00	357	0.998
Weight (lbs)	76 (98.7)	206.2 (62.1)	279 (97.9)	197.8 (48.9)	-1.25	353	0.214
Change Variables (between 3 and 6 months)							
PANSS Tot	74 (96.1)	2.0 (12.7)	278 (97.5)	-1.8 (12.4)	-2.32	350	0.021
CGI-S	74 (96.1)	0.2 (0.9)	275 (96.5)	-0.1 (0.9)	-3.02	347	0.003
VAS	74 (96.1)	-0.2 (26.7)	274 (96.1)	0.4 (25.8)	0.17	346	0.863

	Increased Dose n=77 [†]		No Change in Dose n=285 [†]		Test [*]	df	P-Value
	n (%) [‡]	Mean (SD)	n (%) [‡]	Mean (SD)			
CDRS	74 (96.1)	0.02 (0.5)	278 (97.5)	-0.02 (0.5)	-0.60	350	0.549
BAS	75 (97.4)	-0.05 (0.5)	277 (97.2)	-0.03 (0.5)	0.37	350	0.711
AIMS	75 (97.4)	0.00 (0.5)	276 (96.8)	0.05 (0.6)	0.86	350	0.390
SAEPS	75 (97.4)	0.01 (0.3)	277 (97.2)	0.00 (0.3)	-0.20	350	0.849
Weight (lbs)	75 (97.4)	-1.2 (10.4)	274 (96.1)	0.1 (9.7)	1.09	347	0.275

Abbreviations: df, Degrees of Freedom; SD, Standard Deviation; PANSS, Positive and Negative Syndrome Scale; CGI-S, Clinical Global Impression Scale of Severity; VAS, Visual Analogue Scale of Patient Reported Symptom Severity; CDRS, Calgary Depression Rating Scale; BAS, Barnes Akathisia Rating Scale; AIMS, Abnormal Involuntary Movement Scale; SAEPS, The Simpson-Angus Extrapyramidal Side Effect Scale

^{*} Two-tailed T Test, testing mean differences in continuous variables and chi square, testing proportional differences in categorical variables

[†] Categories may not sum to the total due to missing values

[‡] Percentages may not sum to 100% due to rounding

Table 2

Bivariate analysis for cross-sectional and change variables by decreasing dose vs. no change between month 1 and 3 of Phase 1 in the CATIE Trial

	Decreased Dose n=40 [†]		No Change in Dose n=402 [‡]		Test [*]	df	P-Value
	n (%) [§]	Mean (SD)	n (%) [§]	Mean (SD)			
Demographic Variables							
Age	40 (100.0)	39.8 (11.1)	402 (100.0)	41.5 (11.1)	0.90	440	0.370
Sex					2.93	1	0.087
Male	26 (65.0)		310 (77.1)				
Female	14 (35.0)		92 (22.9)				
Race					2.19	2	0.335
Black	10 (25.0)		136 (33.8)				
White	29 (72.5)		245 (61.0)				
Other	1 (2.5)		21 (5.2)				
Ethnicity					3.54	1	0.060
Hispanic	8 (20.0)		41 (10.2)				
Other	32 (80.0)		361 (89.8)				
Tt Duration	39 (97.5)	12.6 (11.0)	388 (96.5)	14.4 (10.9)	0.96	425	0.335
Cross-Sectional Variables (values at 6 months)							
PANSS Tot	40 (100.0)	67.9 (17.9)	397 (98.8)	63.4 (16.8)	-0.70	435	0.484
CGI-S	39 (97.5)	3.6 (1.0)	392 (97.5)	3.4 (1.0)	-1.22	429	0.222
VAS	40 (100.0)	57.4 (26.8)	392 (97.5)	70.7 (22.2)	3.55	430	<0.001
CDRS	40 (100.0)	1.5 (0.5)	397 (98.8)	1.4 (0.5)	-1.37	435	0.171
BAS	40 (100.0)	0.3 (0.4)	395 (98.3)	0.2 (0.5)	-0.84	433	0.399
AIMS	40 (100.0)	0.1 (0.3)	394 (98.0)	0.2 (0.5)	1.13	432	0.260
SAEPS	40 (100.0)	0.3 (0.3)	401 (99.8)	0.2 (0.3)	-1.59	439	0.112
Weight (lbs)	39 (97.5)	195.4 (62.1)	390 (97.0)	197.2 (48.3)	0.23	427	0.820
Change Variables (between 3 and 6 months)							
PANSS Tot	40 (100.0)	-3.0 (15.0)	394 (98.0)	-1.4 (12.5)	0.75	432	0.451
CGI-S	39 (97.5)	0.0 (1.0)	389 (96.8)	-0.1 (0.9)	-0.60	426	0.549
VAS	40 (100.0)	-8.3 (32.6)	386 (96.0)	0.1 (25.7)	1.91	424	0.057

	Decreased Dose n=40 [†]		No Change in Dose n=402 [†]		Test [*]	df	P-Value
	n (%) [‡]	Mean (SD)	n (%) [‡]	Mean (SD)			
CDRS	40 (100.0)	-0.05 (0.5)	394 (98.0)	0.0 (0.5)	0.68	432	0.495
BAS	40 (100.0)	0.00 (0.6)	392 (97.5)	0.0 (0.5)	0.03	430	0.976
AIMS	40 (100.0)	0.03 (0.3)	391 (97.3)	0.04 (0.5)	0.15	429	0.878
SAEPS	40 (100.0)	0.02 (0.4)	392 (97.5)	-0.01 (0.2)	-0.63	430	0.527
Weight (lbs)	39 (97.5)	1.1 (9.7)	384 (95.5)	0.1 (9.1)	-0.65	421	0.516

Abbreviations: df, Degrees of Freedom; SD, Standard Deviation; PANSS, Positive and Negative Syndrome Scale; CGI-S, Clinical Global Impression Scale of Severity; VAS, Visual Analogue Scale of Patient Reported Symptom Severity; CDRS, Calgary Depression Rating Scale; BAS, Barnes Akathisia Rating Scale; AIMS, Abnormal Involuntary Movement Scale; SAEPS, The Simpson-Angus Extrapyramidal Side Effect Scale

^{*} Two-tailed T Test testing mean differences in continuous variables and chi square testing proportional differences in categorical variables

[†] Categories may not sum to the total due to missing values

[‡] Percentages may not sum to 100% due to rounding

Table 3

Odds ratios for predictors of dose increase between month 1 and 3 of Phase 1 in the CATIE Schizophrenia Trial

Variable	OR	CI	P value
Model Incorporating Cross Sectional Variables Only (n=342) *			
Number of Capsules [†]			
2	0.75	0.32, 1.76	0.505
3	0.85	0.35, 2.09	0.728
CGI-S (6 months)	1.90	1.42, 2.54	<0.001
Model Incorporating Both Cross Sectional and Change Variables (n=337) [‡]			
Number of Capsules [†]			
2	0.72	0.30, 1.70	0.449
3	0.81	0.33, 2.01	0.654
CGI-S (6 months)	1.82	1.35, 2.43	<0.001
Change in PANSS [§]	1.03	1.00, 1.05	0.031

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; CGI-S, Clinical Global Impressions Scale – Severity; PANSS, Positive and Negative Syndrome Scale

* Logistic regression modeling dose increase vs. no change with cross sectional variables selected from the group listed in Tables 1 and 2 on the basis of forward stepwise selection. Variables significant at p<0.05 appear in the model along with the number of capsules prescribed, included to adjust for the possibility that this would affect the decision to increase or decrease dose

[†] 1 Capsule used as the referent group

[‡] Logistic regression modeling dose increase Vs. No change with change variables selected from the group listed in Tables 1 and 2 on the basis of forward stepwise selection at p<0.05 along with cross sectional CGI-S and the number of capsules prescribed

[§] Change in PANSS between 3 and 6 months

Table 4

Odds ratios for predictors of dose decrease between month 1 and 3 of phase 1 in the CATIE Schizophrenia Trial

Model Incorporating Both Cross Sectional and Change Variables (n=412)*			
Variable	OR	CI	P value
Number of Capsules [†]			
2	0.51	0.20, 1.32	0.166
3	1.97	0.91, 4.27	0.084
VAS (6 months)	0.98	0.97, 0.99	0.001

Abbreviations: OR, Odds Ratio; CI, Confidence Interval; CGI-S, VAS, Visual Analog Scale of Patient Rated Global Illness Severity

* Logistic regression modeling dose increase vs. no change with cross sectional variables selected from the group listed in Tables 1 and 2 on the basis of forward stepwise selection. Variables significant at $p < 0.05$ appear in the model along with the number of capsules prescribed, included to adjust for the possibility that this would affect the decision to increase or decrease dose

[†] 4 Capsules used as the referent group.