Published in final edited form as:

J Psychopharmacol. 2012 September ; 26(9): 1194–1200. doi:10.1177/0269881112443744.

Choice of randomization to clozapine versus other second generation antipsychotics in the CATIE schizophrenia trial

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Abstract

There is evidence to suggest that clozapine is underutilized in treatment-refractory schizophrenia. Data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE), a multi-phase, randomized comparative effectiveness trial for schizophrenia, were used to identify factors associated with choosing randomization to clozapine. Two pathways were available in phase 2 of CATIE: randomization to clozapine or an untried atypical antipsychotic (2E), or randomization to an untried atypical antipsychotic (2T). We examined the proportion of entrants who chose to enter phase 2E due to the lack of efficacy of the phase 1 treatment, along with their demographic and clinical characteristics. Only 31.2% who discontinued phase 1 for lack of efficacy entered phase 2E. In multivariable analysis, males showed significantly increased odds of choosing phase 2E (adjusted odds ratio (AOR) = 2.38; confidence interval (CI) = 1.20, 4.70) as did patients with higher Positive and Negative Syndrome Scale total scores (AOR = 1.01; CI = 1.00, 1.03), more inpatient days (AOR = 1.06; CI = 1.02, 1.10) and more outpatient visits, (AOR = 1.06; CI = 1.02, 1.11). More effort examining the decision-making process of patients and providers is needed in order to increase the utilization of this effective treatment.

Keywords

Psychiatric status rating scales; drug prescriptions; decision making; choice behavior; psychiatry

Introduction

Clozapine is widely considered both the first and most effective atypical antipsychotic medication. The drug's efficacy in patients with treatment-refractory schizophrenia and when compared with other typical and atypical antipsychotics is documented in several large trials (Kane et al., 1988; McEvoy et al., 2006). In addition, the medication carries a low risk of movement-related side effects, resulting in its use in populations with tardive dyskinesia (TD) and other movement disorders (Breier et al., 1999). However, clozapine is also associated with troublesome side effects such as sedation, excessive salivation, constipation,

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Conflict of interest

Dr Hermes has no conflict of interest to declare. Dr Rosenheck has received consultancy Fees from Otsuka Pharmaceutical, Janssen Pharmaceutical, and Wyeth Pharmaceutical. He is currently providing expert testimony to the Jones ex rel. the State of Texas v. Janssen Pharmaceutica Products.

weight gain and seizure, in addition to rare but significant risks of cardiomyopathy, neutropenia, and agranulocytosis (Young et al., 1998). This clinical profile has led to specific recommendations for clozapine use based on previous poor treatment response and side effects (American Psychiatric Association, 2004). For example, the Patient Outcome Research Team (PORT) recommendations advocate the use of clozapine in 'patients with schizophrenia who experience persistent and clinically significant positive symptoms... after at least two adequate trials...including at least one second generation agent.' (Lehman et al., 2004).

In spite of its superior efficacy and promotion in clinical guidelines, some feel clozapine is underutilized. Several research efforts have shown that the percentage of antipsychotic prescriptions for clozapine in some US populations has progressively decreased from 21% of all antipsychotic prescriptions in 1997 (Martin et al., 2001) to 7% in 2000 (Wang et al., 2000). Other atypical antipsychotics continue to display a much larger share of antipsychotic prescribing (Hermann et al., 2002; Weissman, 2002). These rates differ greatly from those of other countries, where greater proportions of patients diagnosed with schizophrenia receive clozapine (Conley et al., 2005; Downs and Zinkler, 2007; Xiang et al., 2007a). Explanations for the less frequent use of clozapine in the US are unknown, but likely involve its rare but life-threatening side effects, demanding requirements for blood count monitoring, and convoluted approval history through the Federal Drug Administration (Crilly, 2007; Weissman, 2002). Instead of transitioning pharmacotherapy to clozapine, providers may prefer to use higher than PORT-recommended doses of other antipsychotics or combination therapy to control symptoms or prevent decompensation (Sernyak and Rosenheck, 2007).

A new prescription for clozapine represents a decision or shared decision between patient and provider. Factors related to the shared decision-making process in medicine involve knowledge of the choice, efficacy and side effects of treatments, preferences and values of both parties, and the level of communication between the two (Mistler and Drake, 2008). The relationship of these factors to the decision to prescribe a specific antipsychotic such as clozapine are not well understood. However, the characteristics of patients who receive clozapine have been evaluated in only a few studies, which found that those who receive clozapine are more likely to be men, to be younger, and to have had a longer treatment course prior to initiation, in addition to more hospitalizations and less Axis I comorbidity (Rothbard et al., 2003; Wheeler, 2008; Xiang et al., 2007a).

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was one of the largest and longest comparative effectiveness trials of treatment for schizophrenia. The trial used several phases and broad inclusion criteria as well as multiple outcome measures of symptoms and side effects (Lieberman et al., 2005). In phase 2 of the trial, participants who had discontinued phase 1 treatment but agreed to be randomly assigned to additional treatments were given a choice of two alternatives: one that included either clozapine or another atypical antipsychotic, and the other which consisted of a non-clozapine atypical antipsychotic other than the one they took in phase 1 (McEvoy et al., 2006). The randomization that included clozapine was to be offered to all patients whose unsatisfactory response to the phase 1 treatment was judged by the treating clinician to reflect a lack of efficacy. The second phase of CATIE offers a unique opportunity to examine patient and/or provider decisions concerning clozapine, since this medication represented the only difference between the two phase 2 alternatives. This analysis of CATIE data investigates the proportions and characteristics of the sample that entered the randomization that included clozapine and compares it with the sample that was randomized to a different atypical antipsychotic other than clozapine.

Methods

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 doubleblind trial. Treatment comparisons in CATIE were divided into phases. In phase 1, subjects were randomized to double-blind treatment with one of four atypical antipsychotics or one conventional antipsychotic (perphenazine). Subjects who discontinued phase 1 could directly enter phase 2 unless their phase 1 treatment was perphenazine, in which case they were invited to enter phase 1B in which they were randomly assigned to double-blind treatment with olanzapine, quetiapine, or risperidone. If these patients discontinued treatment in phase 1B, they then entered phase 2. Further details of the study design have been presented elsewhere (Lieberman et al., 2005; Stroup et al., 2003).

In phase 2, subjects and their providers were invited to choose one of two study pathways primarily based on the provider's assessment of their reason for discontinuation of phase 1: lack of efficacy, lack of tolerability, or patient choice. Phase 2E was recommended to subjects who discontinued phase 1 or 1B due to lack of efficacy, and compared open label treatment with clozapine to blinded treatment with olanzapine, quetiapine, or risperidone. Phase 2T was recommended to subjects who discontinued phase 1 or 1B due to tolerability issues or patient choice, and compared treatment with olanzapine, quetiapine, risperidone, or ziprasidone. In both phase 2 pathways, treatment lasted up to 6 months and was blinded except for open label treatment with clozapine (McEvoy et al., 2006). Although the recommendation to enter a given pathway was made on the basis of discontinuation of phase 1 due to tolerability or efficacy, the final choice between pathways was left to the subject and provider. The sample in the current study consisted of all individuals entering phase 2 (either phase 2E or 2T) and who had discontinued phase 1 for lack of efficacy (see Figure 1).

Measures

Factors potentially associated with choosing phase 2E, randomization to clozapine or another atypical, were selected from demographic characteristics, clinical measures, treatment variables in addition to healthcare usage and other study-specific variables as assessed at the time of initiation of phase 2 treatment (Table 1). Psychopathology was measured by the Positive and Negative Syndrome Scale (PANSS) which is based on 30 items rated from 1–7 (range = 30–210) and can be divided into its sub-scores of positive, negative and general psychopathology 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 0–100, 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).

Side effects were assessed with the Barnes Akathisia Rating Scale (BAS), a widely used measure of drug-induced akathisia based on a four-item scale, with higher scores indicating more akathisia (Barnes, 1989). In addition, the Abnormal Involuntary Movement Scale (AIMS) is a 12-item scale that was used to rate the severity of dyskinetic movements, with increasing scores indicating more severe movements (Guy, 1976), while the Simpson-Angus Extrapyramidal Side Effect Scale (SAEPS), which contains 10 items rated on a scale

of 0–4, was used as an additional rating of extrapyramidal symptoms, where higher scores indicate more symptoms (Simpson, 1970).

Quality of life was also measured in several ways. The SF-12 is a 12-item measure of functional health and well being which can be scored as both a mental and physical health component (Ware et al., 1996). The Heinrichs–Carpenter Quality of Life Scale is a 21-item scale assesses deficit symptoms in schizophrenia (Heinrichs et al., 1984). The Lehman Quality of Life Interview is a structured interview with nine domains for patients with chronic mental illness (Lehman, 1988).

In addition, alcohol and drug use were assessed by the clinician-rated Alcohol or Drug Use Scale (ADUS), a five-point rating scale developed as a research instrument for clinical case managers to assess the extent of substance-related problems among severely ill psychiatric patients in the community (Drake and Wallach, 1989; Drake et al., 1990). Other measures addressed total years of treatment for schizophrenia prior to entrance into the CATIE study in addition to the antipsychotic used in phase 1/1A of CATIE as well as the number of capsules prescribed at the end of phase 1 (1–4 dose-equivalent capsules.)

Healthcare utilization variables based on patient self-report addressed the number of mental health inpatient days and outpatient visits as well as the total non-drug healthcare costs during the last month of phase 1. The number of days employed and the amount of public support dollars received in the last month of phase 1 were also measured. Finally, treatment site type was classified as: academic, state, private or Veterans Health Administration. All symptom and utilization measures were recorded at the beginning of phase 2, while demographic and historical variables were measured at baseline prior to phase 1.

Analysis

The analytic sample consisted of all individuals who discontinued phase 1A or 1B due to lack of efficacy and were thus recommended by protocol to enter phase 2E, the randomization that included clozapine. Within this sample, those who entered phase 2E as recommended were compared with those who entered phase 2T in spite of discontinuing phase 1 due to lack of efficacy. Factors potentially associated with the decision to enter phase 2E or not were first analyzed using bivariate tests including *t*-tests and Chi Square. Variables significant at < 0.05 were then tested in a multivariable logistic regression model predicting entry in to phase 2E on the basis of forward stepwise selection, using $p < 0.05$ as a cutoff with the PROC STEPWISE function in SAS® Version 9.2 (SAS Institute, Cary NC, USA). Total healthcare costs were not evaluated in the multivariate model because they were presumed a priori to be highly correlated with inpatient days and out patient visits, which we believe are the clinically more pertinent factors in clinical decision-making. This analysis identified factors independently related to participation in the randomization that included clozapine.

Results

Sample

Of the 274 individuals who discontinued phase 1 due to the clinician's judgment of lack of efficacy and agreed to enter phase 2, only 86 (31.4%) participated in phase 2E, the randomization that included clozapine.

Bivariate results

In bivariate analysis (Table 1), there were significantly more males who entered the clozapine randomization (82.6%) compared with randomization to another atypical

antipsychotic (69.7%). Those who went into phase 2E also had significantly higher PANSS total scores (by 5.4 points or 2.5%) and, more specifically, 3.2% higher scores on the PANSS positive symptom subscale. On side effect measures, those who entered the clozapine randomization had significantly higher AIMS scores, a mean of 2.4 compared with 1.5. They also displayed higher healthcare utilization in the form of more inpatient days and outpatient visits in the month prior to re-randomization, resulting in higher mean non-drug healthcare costs (US\$4387 compared with US\$1982).

Multivariate results

In the multivariate analysis of factors associated with entering the clozapine arm (Table 2), the subscale of positive symptoms on the PANSS and the total healthcare costs were excluded from the model due to multi-coliniarity with other variables. Male gender was associated with significantly greater odds of entering the clozapine phase (adjusted odds ratio (AOR) = 2.38; confidence interval (CI) = 1.20, 4.70). In addition, patients with higher PANSS total score (AOR = 1.01; CI = 1.00, 1.03), more inpatient days (AOR = 1.06; CI = 1.02, 1.10) and more outpatient visits, (AOR = 1.06; CI = 1.02, 1.11) were also more likely to enter phase 2E. To put these findings in a clinical context, patients with a 15.3 point higher PANSS (equal to the minimal clinically important difference in the PANSS) (Hermes et al., 2012) have a 1.2 times greater odds of entering phase 2E compared with 2T. Patients with five more inpatient days or five more outpatient visits in the last month have a 1.3 and 1.4 time greater odds, respectively, of entering phase 2E compared with 2T.

Discussion

The question of how clinicians and patients make the decision to initiate clozapine treatment in those with refractory schizophrenia is an important one, as this medication is believed by many to be seriously underutilized (Martin et al., 2001; Wang et al., 2000). This supposition is partly supported by the current study, in that only 31.2% of individuals who discontinued phase 1 due to lack of efficacy – those who were expected to receive a recommendation to enter the randomization that included clozapine – actually entered that arm of the trial. This relatively low proportion suggests that providers and/or subjects were actively deciding which phase 2 randomization to enter and more often choosing the non-clozapine arm. Although this study was unable to evaluate the specific process providers and subjects used to make these decisions, the study is distinct in that it evaluated objectively measured factors associated with the decision at the time it was made. Those choosing potential randomization to clozapine tended to be males with more severe positive symptoms and higher rates of healthcare utilization.

Several other studies have observed an increased likelihood of clozapine use in males (Rothbard et al., 2003; Weissman, 2002; Wheeler, 2008; Xiang et al., 2007a). Unfortunately, this may indicate that clozapine is further underutilized in females, especially given there is little evidence of a higher side effect burden in females or an increased risk of congenital anomalies during pregnancy (Yaeger et al., 2006).

PANSS total scores and scores on the positive symptom subscale were significantly higher in individuals who chose the clozapine pathway. One study from China found no difference in the BPRS or quality of life and affective symptom scales between patients treated with clozapine and other antipsychotics, but this may reflect the relatively high rate overall of clozapine use and use as an initial therapy for schizophrenia in China (Xiang et al., 2007b). This finding was further supported by data from phase 3 of CATIE, in which individuals choosing open label treatment with clozapine from eight other options also displayed more psychopathology (Stroup et al., 2009). Together, these findings are heartening in that they

show that those who are more symptomatic after prior treatment are more likely to receive this potentially more effective treatment.

In addition, individuals who chose clozapine displayed greater healthcare utilization in the month immediately proceeding randomization to phase 2. This finding is not surprising, given that increased service use may reflect poor treatment response in concordance with several treatment guidelines which advocate using clozapine in individuals who have failed trials with other antipsychotics (Lehman et al., 2004). Similar findings that prior treatment for schizophrenia and longer duration of treatment are predictive of individuals who use clozapine have also been observed in previous studies (Wheeler, 2008; Xiang et al., 2007a). However, the findings of the current study are intriguing in that duration of treatment prior CATIE was not a significant factor in choosing the clozapine path. It may be that both patient and providers saw CATIE as 'starting over' in terms of treatment and disregarded treatment prior to the study.

Other important factors examined in this study were not found to be associated with entering the clozapine pathway. For example, other studies have found that clozapine is more often prescribed for younger individuals (Rothbard et al., 2003; Weissman, 2002; Wheeler, 2008; Xiang et al., 2007a). Individuals who entered the clozapine randomization were not significantly younger than those who entered the alternative randomization. Weight was also not a factor in the selection of phase 2 or phase 3 pathways (Stroup et al., 2009). A similar result was found in the prescription of olanzapine, risperidone, and quetiapine for affective disorders (Prabhakar et al., 2011). This is unexpected, as one would imagine that individuals with weight or metabolic problems would avoid medications with a higher weight gain liability such as clozapine.

Although the rigorous comparative framework and extensive clinical data available in this study represent an improvement over studies which simply list the characteristics of individuals treated with clozapine (Rothbard et al., 2003; Wheeler, 2008; Xiang et al., 2007b), it did not include information on the decision-making process between provider and patient. As others have pointed out, associations between a decision and objective measures associated with that decision offer only limited insight into how decisions are actually made (Hamann et al., 2005). If one assumes a shared decision-making model for treatment pathway selection in CATIE, the factors essential to decision making in the pharmacologic treatment of chronic illness such as provider and patient perceptions, knowledge, subjective preferences, communication capabilities, and even provider age (Mistler and Drake, 2008) were not measured in the CATIE trial. CATIE also did not measure patient and provider perception of the side effect and treatment burden associated with clozapine treatment. There are serious yet uncommon side effects associated with clozapine treatment, such as agranulocytosis, myocarditis, seizure and diabetes, in addition to more common, bothersome and potentially stigmatizing side effects such as weight gain, sedation, orthostatic hypotension, sialorrhea, and constipation (Clozaril Prescribing Information, 2011) that most likely decrease the appeal of this medication to both patients and providers. In addition, there are major treatment and administrative requirements associated with the use of clozapine that effectively put a travel burden or restriction on patients (Herlihy and Holloway, 2010) and require relatively more effort on the part of providers, which may also limit its use. We would encourage the measuring of these variables in future multi-phase, flexible dose trials.

In addition, this study used the selection of potential randomization to clozapine as a proxy for a clinical decision to select clozapine itself. Although these decisions are different, we feel that this was a valid assumption given that the other medications were the same in both of the available randomizations, i.e. the possibility of being prescribed clozapine was the

only difference between the two randomizations. The fact that only a relatively small proportion of patients eligible for the randomization that included clozapine accepted it suggests that the availability of clozapine was the factor that drove this choice.

Implications for clinical care

This study sought to answer a question of importance to current decision making about pharmacotherapy for schizophrenia: if clozapine is potentially more efficacious in individuals with treatment-resistant disease, why did only 31.2% of those entering phase 2 of the CATIE study chose a treatment pathway in which they could be treated with this medication, and what factors influenced this decision? After evaluating over 28 factors, only male gender in addition to psychopathology and healthcare utilization variables were associated with the decision to choose the randomization that included clozapine. Clinicians should be wary of over emphasizing the side effect and administrative burdens associated with clozapine and not under emphasize its efficacy.

Conclusion

The finding of a general paucity of significant factors underscores the importance of measuring both patient and provider views of treatment in addition to future exploration of the processes patients and providers use to make healthcare decisions in the treatment of chronic illness. Herbert Simon, Daniel Kahneman and Richard Thaler have proposed theories for human decision making in the field of behavioral economics which take into account cognitive processes, attitudes toward risk and heuristics (Kahneman et al., 1982; Simon, 1997; Thaler and Sunstein, 2008). These processes are most likely also at play in clinical decisions to start or change medications, especially ones that may both offer hope and that represent greater risk, such as clozapine with its significant side effect and administrative burden. With a greater understanding of these influences, providers, healthcare delivery organizations and policy makers may be better able to implement policies which will increase beneficial treatments that balance efficacy gains and side effect burdens.

Acknowledgments

We wish to acknowledge the contributions of all investigators, study personnel and subjects from all of the CATIE Schizophrenia Trial sites.

Funding

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.

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Figure 1.
Enrollment and assignment of patients to phase 2 of the CATIE trial.

Table 1

Bivariate analysis of variables potentially associated with the selection of phase 2 trials in the CATIE Schizophrenia study.

	Clozapine ^a (n=86)			Other atypical antipsychotics ^b (n=188)			p-value
	n	(%)	Mean (SD)	n	(%)	Mean (SD)	
Demographic variables							
Age			37.8 (10.4)			39.7 (11.5)	0.198
Sex							
Male	71	(82.6)		131	(69.7)		0.025
Female	15	(17.4)		57	(30.3)		
Race							0.182
Black	28	(32.6)		42	(22.3)		
White	56	(65.1)		139	(73.9)		
Other	2	(2.3)		7	(3.8)		
Ethnicity (Hispanic)	11	(12.8)		27	(14.4)		0.727
Marital status							0.060
Married	6	(7.0)		25	(13.3)		
Never married	67	(77.9)		113	(60.1)		
Other	13	(15.1)		50	(26.6)		
Years of education			12.6 (1.8)			12.2 (2.4)	0.158
Clinical measures							
CGI-S			4.6 (1.2)			4.5 (1.1)	0.181
PANSS			88.9 (20.1)			83.5 (18.3)	0.028
Positive			22.5 (6.1)			20.9 (5.7)	0.033
Negative			23.4 (7.2)			22.1 (6.9)	0.151
General psychiatric symptoms			43.0 (10.5)			40.5 (9.8)	0.056
VAS			58.5 (27.8)			55.7 (26.5)	0.430
SAEPS			0.24 (0.3)			0.24 (0.4)	0.972
AIMS			2.4 (3.8)			1.5 (2.7)	0.032
BAS			0.65 (0.9)			0.56 (0.9)	0.447
SF-12 (M)			37.3 (11.8)			37.4 (11.7)	0.944

	Clozapine ^a (n=86)			Other atypical antipsychotics ^b (n=188)			p-value
	n	(%)	Mean (SD)	n	(%)	Mean (SD)	
SF-12 (P)			48.1 (9.8)			48.6 (9.9)	0.696
CDRS			1.7 (0.6)			1.7 (0.7)	0.376
HCS			2.3 (1.1)			2.5 (1.1)	0.154
LQI			4.0 (1.6)			4.0 (1.4)	0.897
ADUS (Drugs)			1.2 (0.5)			1.2 (0.6)	0.582
ADUS (Alcohol)			1.3 (0.6)			1.3 (0.7)	0.593
Weight (lbs)			202.9 (40.0)			197.3 (48.4)	0.361

	Clozapine ^a			Other atypical antipsychotics ^b			p-value
	n	(%)	Mean (SD)	n	(%)	Mean (SD)	
Treatment variables							
Years of treatment			14.9 (14.9)			15.8 (14.9)	0.510
Phase 1 treatment							0.692
Olanzapine	14	(16.3)		32	(16.8)		
Perphenazine	12	(14.0)		17	(9.0)		
Quetiapine	28	(32.6)		57	(30.0)		
Risperidone	22	(25.5)		58	(30.5)		
Ziprazidone	10	(11.6)		26	(13.7)		
Capsules ^c			3.6 (0.8)			3.4 (0.8)	0.134
Inpatient Days ^d			3.9 (8.9)			1.8 (5.3)	0.017
Outpatient Visits ^e			6.1 (8.8)			3.6 (5.9)	0.005
Other variables							
Total healthcare costs ^f			4386.6 (7328.3)			1981.5 (2442.4)	<0.001
Months in phase 1			5.6 (4.0)			5.6 (4.1)	0.902
Days worked ^g			2.6 (5.7)			2.1 (5.7)	0.529
Public support ^h			595.0 (669.0)			631.3 (603.5)	0.654
Treatment site							0.159
Private	13	(15.1)		45	(23.7)		

	Clozapine ^a			Other atypical antipsychotics ^b			<i>p</i> -value
	<i>n</i>	(%)	Mean (SD)	<i>n</i>	(%)	Mean (SD)	
State	25	(29.1)		65	(34.2)		
University	40	(46.5)		64	(33.7)		
VHA	8	(9.3)		16	(8.4)		

SD, Standard Deviation; PANSS, Positive and Negative Syndrome Scale; CGI-S, Clinical Global Impression Scale of Severity; VAS, Visual Analog Scale of Patient Reported Symptom Severity; SF-12 (M), SF-12 Mental Health Component Score; SF-12 (P), SF-12 Physical Component Score; CDRS, Calgary Depression Rating Scale; SAEPS, The Simpson-Angus Extrapyramidal Side Effect Scale; AIMS, Abnormal Involuntary Movement Scale; BAS, Barnes Akathisia Rating Scale; HCS, Heinrichs-Carpenter Quality of Life Scale; LQLI, Lehman Quality of Life Interview; ADUS, Alcohol and Drug Use Scale.

^aIndividuals Selecting Phase 2E, randomization to clozapine vs. another atypical antipsychotic.

^bIndividuals Selecting Phase 2T, randomization to another atypical antipsychotic VHA, Veterans Health Administration

^cNumber of capsules prescribed at the end of phase 1.

^dNumber of inpatient days in the preceding month.

^eNumber of outpatient visits in the preceding month.

^fCost, in US dollars, reflects inpatient or outpatient days.

^gNumber of days worked in the last month.

^hAmount of public support in dollars received in last month.

Table 2

Odds ratios for predictors of choosing the clozapine arm for phase 2 of the CATIE schizophrenia trial.

variable	OR	CI	<i>p</i> -value
Sex (Male)	2.38	1.20, 4.70	0.013
PANSS total score	1.01	1.00, 1.03	0.055
Inpatient days ^a	1.06	1.02, 1.10	0.006
Outpatient visits ^b	1.06	1.02, 1.11	0.002

OR, Odds Ratio; CI, Confidence Interval; PANSS, Positive and Negative Syndrome Scale

^aNumber of outpatient visits in the preceding month.

^bNumber of outpatient visits in the preceding month.