Among the Severely Mentally Ill, Who Responds to Ziprasidone?

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Abstract

So far, demographic variables have not consistently been found to predict clinical response to antipsychotics. This study examines some differences in response to ziprasidone, which has been shown to be effective, with a better metabolic side effect profile, but was little used in New York State Hospitals. The aim was to study state hospital patients switched to ziprasidone. The results led to questions about different responses in different groups. Subjects from state hospitals who needed a change of antipsychotic participated in this open-label, 8-week trial of up to 240-mg ziprasidone. Analyses included comparisons of the very different results from two sites. Of the 36 study subjects, 12 terminated early. The 17 outpatients from Buffalo, who were older and on lower doses of antipsychotics pre-study, improved significantly. The 19 inpatients from the Bronx, overall younger and on higher pre-study doses, barely changed. Improvements in PANSS total score were significantly associated with older age, greater baseline severity, and lower doses of antipsychotics pre-study. The subjects improved on metabolic parameters. The results suggest that ziprasidone may be just as effective as previous antipsychotics taken by these severely mentally ill patients, and with fewer metabolic side effects. *Note: The study described here includes a dosage of ziprasidone that has not been approved by the U.S. Food and Drug Administration (FDA). The FDA has approved daily doses of ziprasidone no greater than 100 mg PO bid.*

Key Words: Ziprasidone, Antipsychotic, Schizophrenia, Metabolic Side Effects, Demographics, Age

Introduction

Many patients with schizophrenia are not having satisfactory results on their current medications, and they experience significant side effects. The choice of an appropriate agent often depends on side effects rather than an established advantage in efficacy.

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The "atypical" or second-generation antipsychotics (SGAs), as a whole, are generally thought to cause fewer extrapyramidal side effects (EPS) than the high-potency "typical" or first-generation antipsychotic (FGA) agents; a few (e.g., clozapine, olanzapine) have consistently been shown to cause less EPS than low-potency FGAs (1, 2). Yet many SGAs cause significantly more metabolic disturbance and weight gain than FGAs, but not ziprasidone (1-3).

A recent, open-label study of long-stay subjects with diabetes mellitus (DM) type II and a stable antipsychotic regime at another New York State Hospital examined the overall effects of a switch to ziprasidone on both symptom improvement and metabolic disturbances. Those who completed the study (n=16) showed significant improvement in glucose, weight, and body mass index (BMI), with no changes in serum lipids or Positive and Negative Syndrome Scale (PANSS) scores. But 38% of the subjects terminated early because of worsening psychiatric symptoms (4). It would be useful to know who does respond to ziprasidone.

Clinical Implications

Many people with chronic schizophrenia are not having satisfactory results with their current medications, especially those being treated in state, county, or city public services. With long-term use, they often have significant side effects, particularly with metabolic problems and movement disorders. This study demonstrates that these people may be helped by ziprasidone. We found that older patients, those with greater baseline severity, and those on lower doses of medication pre-study, were all more likely to improve psychiatrically, and that even if their psychopathology does not change, their metabolic measures may improve. Ziprasidone is worth trying in patients with chronic schizophrenia not adequately treated by another medication, or with significant metabolic side effects.

Carbon and Correll (2014) summarized the recent literature on clinical predictors of treatment response and remission in first-episode psychosis (5). Later age of onset predicted response in two of the studies cited (6, 7). Absence of recent cannabis use predicted response (8) and remission (9) in two separate studies, and one found that the absence of substance misuse more generally was predictive of remission (10). Urban residence predicted remission in one study (11), and another found that hospitalized patients were less likely to exhibit response (6). Higher total baseline symptom severity also predicted better response (6, 10, 12, 13) in four studies, but lower severity predicted greater likelihood for remission (14, 15).

Furukawa et al. (2015), in a large meta-analysis of chronic patients, quantified the effects of baseline severity on response, and found that mild baseline illness (PANSS total score of 58) was associated with a decrease of 9.5 points on the PANSS, moderate illness (PANSS total 75) with a 13.7 point decrease, and markedly severe illness (PANSS total 95) with an 18.8 point decrease (16).

While recent studies in first-episode psychosis have not found age to significantly predict treatment response (5), two analyses in chronic patients reported significant, but contradictory results. Teo et al. (2013) found patients resistant to treatment to have significantly younger age of onset (20 vs. 22 years; $p=.007$), longer duration of illness (21 vs. 15 years; $p<.001$), and older age at assessment (41 vs. 37 years; $p<.001$) (17). Rabinowitz et al. (2014), however, did not find age at onset, nor duration of illness, nor age alone, to be associated with differences in response to treatment versus placebo. Yet greater improvement was observed in adults 30 years old or younger with 4 or more years since onset of illness (15% vs. 9% improvement in PANSS total; $p\leq.002$), and patients with durations of illness in the middle half of the study population (9–24 years for females; 8–21 years for males) showed greater improvement than those at outer quartiles (18). Unfortunately, the participants in both of these studies consisted of a relatively narrow age range of younger patients, and these studies, like many of the studies on first-episode psychosis, are limited by the specific nature of their populations.

So far, demographic predictors of response to ziprasidone have not been consistently demonstrated. An analysis of Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) data found that Hispanics were more likely to discontinue ziprasidone for lack of efficacy (71% for Hispanics vs. 40% for non-Hispanic whites and 24% for African Americans) (19). But generally, studies on ziprasidone (20) and other antipsychotics have not found significant differences in response on the basis of race.

Ziprasidone, despite being shown to be generally effective, with superior effects on weight and other metabolic indices compared to previous agents of its class (1, 2), is not widely used in New York State Hospitals. Among inpatients at non-forensic New York State psychiatric hospitals in 2005, ziprasidone was prescribed to 5.8% of those receiving any antipsychotic medication (21). Ziprasidone is widely available, however, and the reasons for its relatively low use are unclear. The current study originally sought to evaluate ziprasidone as a safe and effective alternative for certain patients who remain symptomatic on their current medications, and to corroborate previous findings of a relative benefit for ziprasidone on metabolic parameters. In contrast to the open-label study of DM type II patients described above, the present study did not select for patients with metabolic abnormalities, but rather for those who needed a change of antipsychotic because of poor response. The very different results between sites led to an examination of possible response predictors. The ultimate purpose of the analysis of this study is to establish demographic conditions of the population that responds to ziprasidone.

Methods

The study was approved by the Institutional Review Boards (IRBs) of three hospitals and the Research Foundation for Mental Hygiene, which oversees research at hospitals in New York State. It was conducted at Bronx Psychiatric Center, Buffalo Psychiatric Center, and Rochester Psychiatric Center, on subjects diagnosed with schizophrenia or schizoaffective disorder, according to the criteria in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)* (22). While individuals

with schizoaffective disorder have been found to be more responsive to treatment in some studies (23), their combination with schizophrenia patients here is appropriate, as these patients are clinically very similar to those with a diagnosis of schizophrenia in the populations of the current study. The instability of the schizoaffective disorder diagnosis and overlap with schizophrenia in *DSM-IV-TR* (23-25) provided additional justification. And the combination of patients with both disorders is typical in prominent studies on efficacy and response predictors (1, 26).

For reasons unrelated to this research, the study at Rochester was canceled and its two valid subjects dropped from this report. The participants at Buffalo were all outpatients, while those in the Bronx were only inpatients and with very different demographics and characteristics. As well, patients are admitted to Bronx Psychiatric Center only after they have been unsuccessfully managed at other hospitals. The Bronx patients included in this study had an average length of stay of 15.8 weeks (SD 13.6), slightly less than that for the typical patient at Bronx Psychiatric Center, where the median length of stay was 20.1 weeks.

Subjects who needed a change of antipsychotic, had not previously had an adequate trial of ziprasidone, and had no uncontrolled medical illness, were invited to participate. They were informed of the trial in detail, its procedures, and possible side effects, and signed a written consent form. All subjects had a screening evaluation. If a subject was receiving two antipsychotics, one was stopped before starting ziprasidone. Ziprasidone was 40 mg bid the first day and 80 mg bid the next day, given within a half hour of meals. Their one antipsychotic was continued unchanged for 3 days, then halved, and stopped 4 days later. Ziprasidone could be increased to 120 mg bid after 3 weeks if there was inadequate clinical response.

Evaluations occurred at weeks 1 and 2 and then every 2 weeks till week 8. Raters at both sites underwent training and reliability assessment on the PANSS and other clinical measures at the Bronx site before the study began. The PANSS, CGI (Clinical Global Impression: -I improvement, -S severity), movement ratings, vital signs, and weight were done at each evaluation. Lipid profile, glucose, and electrocardiogram (ECG) were done at baseline, week 4, and end. The Brief Assessment of Cognition in Schizophrenia (BACS), Medical Outcomes Study Cognitive Functioning Scale (MOS-COG), and the Calgary Depression Scale for Schizophrenia (CDSS), as well as insulin and prolactin levels, were performed at beginning and end.

All antipsychotic medications, including depot, were converted into chlorpromazine (CPZ) equivalents using data from Woods (2003) to provide a daily dose (27). Separate analyses were performed for Lindenmayer's PANSS five factor components (28). In the BACS, the total score was analyzed using z-scores based on normal controls in Keefe et al. (2008) (29).

Table 1 Demographic and Other Subject Information

	All (n=36)	Bronx (n=19)	Buffalo (n=17)
Age, mean (yrs)	42	**32**	**52**
Age, range (yrs)	22–66	22–49	34–66
Male (%)	45	53	41
African American (%)	25	**37**	**12**
Hispanic (%)	28	**53**	**0**
White (%)	44	**5.3**	**88**
Asian (%)	2.8	5.3	0
Education (yrs)	12	11	12
Schizophrenia (%)	47	53	37
Schizoaffective (%)	53	47	63
Age of onset	24	20	28
Duration of illness (yrs)	18	12	23
Substance abuse history (%)	45	**68**	**24**
Inpatients (%)	55	**100**	**0**
Outpatients (%)	45	**0**	**100**
Pre-study antipsychotic, in CPZ	893	**1,269**	**578**
Pre-study FGA, in CPZ	272	**430**	**127**
Pre-study SGA, in CPZ	621	**836**	**451**
Pre-study clozapine, olanzapine, quetiapine, in CPZ	571	**768**	**369**
On depot antipsychotic (%)	5.6	5.3	5.9
Completed study (%)	67	63	71

CPZ: chlorpromazine mg equivalents; FGA: first-generation antipsychotic; SGA: second-generation antipsychotic

Analyses of changes during the study and comparisons between the Bronx and Buffalo groups were performed with t-tests. The significant differences in results between Bronx and Buffalo sites, coupled with their very different demographics, led the authors to pursue additional analyses to determine whether certain demographics might explain the different responses. The variables were chosen for inclusion in the study based primarily on the literature and also on prominent preliminary findings in the current study. Multiple linear regression with backward elimination was used with 9 candidate predictors in spite of the small sample size because the analysis was exploratory in nature and intended primarily to guide additional research. The categories of substance abuse, Bronx/Buffalo status, and race were coded to facilitate the analysis (negative history of substance abuse=0, positive=1; Bronx=0, Buffalo=1; white=1, black=2, Hispanic=3).

Table 2 Mean Clinical Rating Scores at Baseline and End (8 Weeks or Last Observation Carried Forward) for All, Bronx, Buffalo Patients

	All baseline Mean (SD)	All end Mean (SD)	p	Bronx baseline Mean (SD)	Bronx end Mean (SD)	p	Buffalo baseline Mean (SD)	Buffalo end Mean (SD)	p	p (between groups)
PANSS total	83 (21)	80 (29)	.5	95 (16)	99 (25)	.5	72 (22)	62 (19)	**.008**	**.01**
PANSS Positive	21 (8.1)	21 (9.7)	.9	25 (5.2)	27 (8.0)	.2	16 (7.7)	14 (5.8)	**.009**	.3
PANSS Negative	21 (6.1)	19 (7.1)	.3	23 (6.0)	23 (7.4)	.9	19 (5.9)	16 (4.7)	.09	.4
PANSS General	41 (11)	40 (14)	.5	47 (8.0)	49 (13)	.5	36 (11)	31 (7.9)	**.008**	**.02**
Positive factor	16 (6.6)	15 (7.1)	.5	19 (5.4)	20 (5.7)	.5	12 (6.1)	10 (4.4)	**.003**	**.01**
Negative factor	14 (4.6)	15 (6.2)	.7	15 (4.8)	17 (6.9)	.08	14 (4.6)	12 (3.7)	.1	**.01**
Cognitive factor	15 (4.9)	14 (6.7)	.08	17 (4.3)	16 (4.2)	.7	13 (4.9)	11 (3.4)	**.03**	.1
Excitement factor	8.4 (3.4)	9.8 (5.8)	.1	10 (2.8)	13 (6.2)	.07	6.5 (2.9)	6.2 (1.9)	.6	.1
Depression factor	9.8 (3.1)	9.4 (3.8)	.4	11 (2.5)	11 (4.0)	.5	8.9 (3.4)	7.3 (2.4)	**.007**	**.03**
CGI-S	4.1 (1.1)	4.1 (1.2)	.7	4.7 (0.8)	4.8 (1.0)	.8	3.3 (0.7)	3.2 (0.8)	.2	.3
CGI-I	4 (0)	3.5 (1.5)	.08	4.0 (0)	4.3 (1.5)	.4	4.0 (0)	2.8 (1)	**.0001**	**.002**
CDSS	4.3 (4.1)	3.1 (3.5)	.2	5.4 (4.4)	5.3 (3.8)	1.0	3.4 (3.7)	1.3 (2.0)	.05	.3
BACS total	-13 (6.0)	-12 (5.9)	.08	-14 (6.0)	-13 (5.3)	.2	-12 (5.9)	-11 (6.5)	.3	.8
AIMS	1.5 (2.6)	0.9 (1.2)	.1	0.3 (0.8)	0.3 (0.7)	1.0	2.9 (3.1)	1.6 (1.4)	.1	.1
SAS (1-7, 9)	2.0 (3.1)	1.5 (2.2)	.09	0.3 (0.6)	0.2 (0.5)	.7	3.6 (3.6)	2.6 (2.5)	.1	.1
BARNES	1.0 (1.6)	0.9 (1.7)	.9	0.6 (1.7)	0.8 (1.7)	.7	1.4 (1.5)	1.1 (1.7)	.6	.2
PETiT	44 (10)	46 (12)	.3	43 (9.7)	45 (11)	.4	46 (11)	48 (13)	.6	.8
MOS-COG	18 (5.5)	18 (5.2)	1.0	17 (5.8)	16 (6.3)	.6	18 (5.4)	19 (3.9)	.5	.4

PANSS: Positive and Negative Syndrome Scale; CGI-S: Clinical Global Impression-Severity of Illness scale; CGI-I: Clinical Global Impression-Global Improvement scale; CDSS: Calgary Depression Scale for Schizophrenia; BACS: Brief Assessment of Cognition in Schizophrenia; AIMS: Abnormal Involuntary Movement Scale; SAS: Simpson-Angus Scale; BARNES: Barnes Akathisia Scale; PETiT: Personal Evaluation of Transitions in Treatment Scale; MOS-COG: Medical Outcomes Study Cognitive Functioning

Results

The study consisted of 36 subjects. The 17 outpatients from Buffalo were mainly white, older, on a lower pre-study dose of antipsychotics, and with less severe symptoms. The 19 inpatients in the Bronx were younger, all but two black or Hispanic, on a higher pre-study dose, and with more severe symptoms (see Table 1). All the Bronx subjects had their ziprasidone increased to 240 mg per day; none of the Buffalo subjects went above 160 mg per day.

Overall, there was no significant change in any psychiatric, cognition, or movement ratings from baseline to end (with last observation carried forward) (see Table 2). But there were overall significant decreases in pulse, weight, prolactin, cholesterol, and low-density lipoprotein (LDL), and significant increases in QTc and systolic blood pressure (see Table 3; Figure 1).

On separate analysis of the groups, the Buffalo outpatients showed significant improvements in PANSS

Table 3 Mean Blood Pressure, Pulse, Weight, Glucose, HbA1c, Insulin, Prolactin, Lipids, QTc, and QT at Baseline and End (8 Weeks or Last Observation Carried Forward) for All, Bronx, Buffalo Patient

	All baseline Mean (SD)	All end Mean (SD)	p	Bronx baseline Mean (SD)	Bronx end Mean (SD)	p	Buffalo baseline Mean (SD)	Buffalo end Mean (SD)	p	p (between groups)
BP systolic (mm Hg)	117 (14)	121 (17)	**.04**	112 (11)	114 (12)	.6	123 (16)	130 (18)	**.02**	.2
BP diastolic (mm Hg)	72 (8.2)	74 (11)	.4	70 (8.4)	70 (6.0)	.7	75 (7.3)	78 (13)	.4	.8
Pulse (bpm)	82 (10)	78 (13)	**.01**	80 (3.9)	76 (12)	.2	85 (12)	80 (13)	**.03**	.8
Weight (lbs)	202 (51)	198 (49)	**.0006**	193 (44)	188 (44)	**.005**	213 (57)	208 (54)	**.03**	.7
Glucose (mg/dL)	92 (23)	84 (26)	.3	93 (28)	76 (29)	.2	92 (16)	93 (19)	.7	.4
HbA1c (%)	5.7 (0.9)	5.6 (0.7)	.4	5.3 (0.6)	5.4 (0.7)	.5	6.0 (0.9)	5.7 (0.8)	.07	.07
Insulin (µIU/mL)	11 (8.4)	16 (14)	.09	10 (7.2)	13 (14)	.5	12 (9.2)	17 (14)	.1	.4
Prolactin (ng/mL)	47 (45)	20 (29)	**.005**	71 (53)	30 (40)	**.04**	28 (27)	11 (7.7)	.05	.3
Cholesterol (mg/dL)	182 (46)	165 (37)	**.007**	180 (48)	154 (34)	**.005**	183 (45)	176 (38)	.4	.05
Triglycerides (mg/dL)	164 (83)	143 (90)	.2	142 (76)	113 (74)	.2	185 (85)	176 (96)	.6	.6
HDL (mg/dL)	45 (13)	44 (14)	.6	46 (13)	46 (11)	.8	44 (13)	43 (17)	.7	.7
LDL (mg/dL)	105 (40)	94 (34)	**.02**	109 (38)	94 (31)	**.05**	101 (43)	95 (39)	.2	.3
QTc (msec)	403 (19)	418 (20)	**.0005**	396 (16)	411 (16)	**.006**	412 (20)	427 (22)	**.04**	.9
QT (msec)	372 (35)	398 (31)	**.00004**	359 (38)	386 (34)	**.004**	388 (23)	412 (21)	**.004**	.6

HbA1c: glycosylated hemoglobin; QTc: corrected QT interval; QT: QT interval; BP: blood pressure; HDL: high-density lipoprotein; LDL: low-density lipoprotein

Figure 1 Mean Weight, Prolactin, Cholesterol, and Low-Density Lipoprotein (LDL)at Baseline and End (8 Weeks or Last Observation Carried Forward) for All Patients, All ps <.05

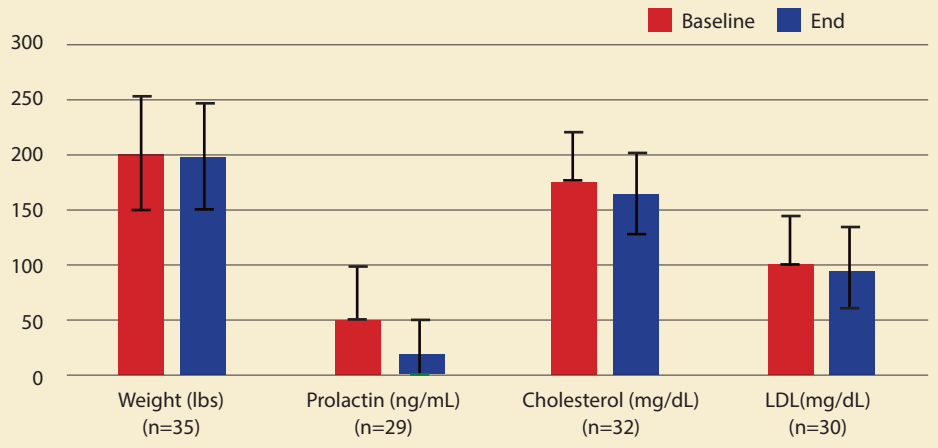
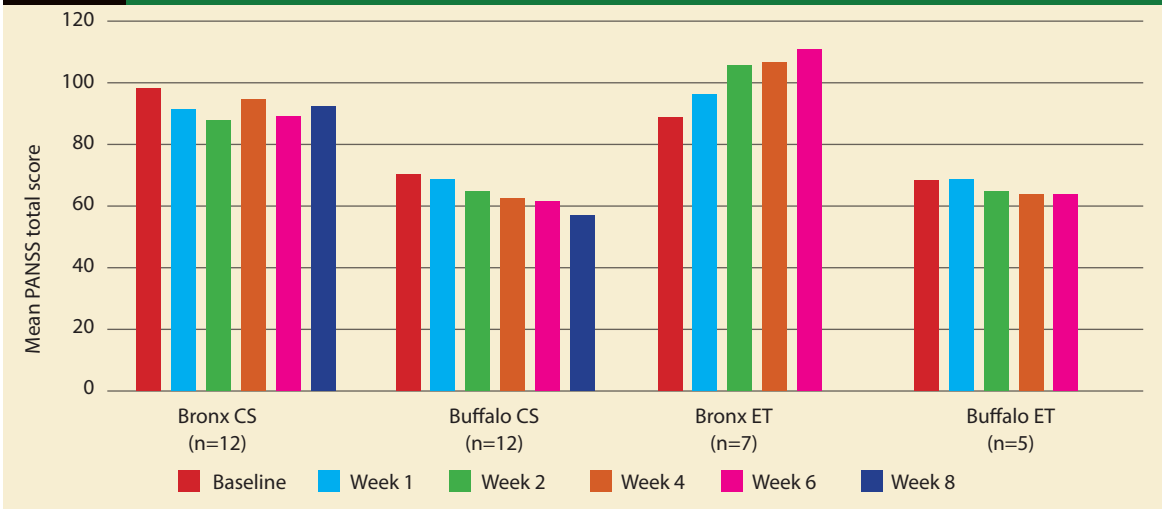


Figure 2 Mean Positive and Negative Syndrome Scale (PANSS) Total Score at Baseline and Weeks 1, 2, 4, 6 and 8 for All Patients at Bronx and Buffalo who Completed the Study (CS) and Terminated Early (ET)



total (15% improvement), and Positive and General scales; Positive, Cognitive, and Depression factors; and CGI-I. In contrast, the Bronx inpatients got slightly worse. The differences between groups were significant for PANSS total and General scale; Positive, Negative, and Depression factors; and for CGI-I (see Table 2). Comparisons between groups on improvement in laboratory values showed no significant differences (see Table 3).

In the Bronx, 7 subjects terminated early because of increased psychosis, their PANSS total score going from 89 to 111. This accounts for the overall worsening. Those who completed the study did not worsen, showing reduction in scores from 98 to 91. At Buffalo, 5 terminated early, but their PANSS total dropped from 68 to 64. The completers' scores went from 70 to 57 (19% reduction) (see Figure 2).

Three significant predictors of clinical response emerged from the final regression model: older age (β=-0.50) and greater baseline severity (β=-0.42) were associated with improvement, while greater pre-study antipsychotic dose was predictive of clinical worsening (β=0.35) (see Table 4). These 3 variables accounted for 35% of the variance in clinical response (R^2=.35; p=.006). Of note, severity was a significant predictor in all of the 7 sequential analysis models, whereas age and pre-study total antipsychotic dose became significant only in the last. There were no other significant predictors in any of the other models, though Bronx/Buffalo status came close (p=.08).

Collinearity diagnostics revealed a number of interrelations between the candidate predictors. Correlations between variables were highest for Bronx/Buffalo status and race (r=.818), followed by age and Bronx/Buffalo status (r=.794), age and race (r=-.793), pre-study total antipsychotic dose and pre-study dose of clozapine, olanzapine, and quetiapine combined (r=.767), age and duration of illness (r=.753), and age and age of onset (r=.750). The 3 variables mentioned above in the final regression model (i.e., age, baseline severity, and pre-study total baseline dose of antipsychotics), however, were not collinear.

Discussion

This study is consistent with previous research in finding an overall better metabolic profile for the patients who switched to ziprasidone from other medications (30-32). That the patients, overall, did not get worse clinically is consistent with most studies conducted since the time that ziprasidone was introduced, finding ziprasidone to have comparable efficacy to haloperidol (1, 33) and the FGAs generally (2, 3). Overall, the patients did not improve, though ziprasidone has been shown to cause significant improvement in patients not responding to other medications in some switch studies (30, 34), and for non-responders with treatment-resistant schizophrenia (35, 36).

There were significant limitations to the study and design. The numbers in this study are small. It was neither controlled nor randomized. As a result, a number of variables of interest (e.g., race and treatment setting, etc.) could not be completely isolated. For example, the evaluators were not the same in the Bronx and at Buffalo. This may have led to scoring differences as a result of different evaluators (even though they had joint training), and not different populations, although Bronx/Buffalo site status was included in the multiple regression to control for some of these differences. In general, the regression results should be interpreted cautiously as evidence in support of the variables' effects, but

Table 4 Multiple Regression Analysis of Possible Predictors of PANSS Total Score Change (%)

	Model 1 (R^2=.44; p=.080)				Model 6 (R^2=.37; p=.0090)				Model 7 (R^2=.35; p=.0058)			
	B	SE	β	p	B	SE	β	p	B	SE	β	p
Age (yrs)	-0.24	0.18	-13.07	.19	-0.0053	0.0048	-0.28	.28	-0.0093	0.0031	-0.50	**.0062**
Baseline PANSS total score	-0.0068	0.0024	-0.56	**.00094**	-0.0060	0.0022	-0.49	**.012**	-0.0051	0.0021	-0.42	**.020**
Pre-study total antipsychotic dose (CPZ)	0.000052	0.000085	0.16	.55	0.000084	0.000056	0.26	.14	0.00011	0.000050	0.35	**.036**
Bronx/Buffalo (Buffalo given)	-0.32	0.22	-0.66	.16	-0.16	0.15	-0.33	.28				
Age of onset (yrs)	0.24	0.18	8.69	.19								
Duration of illness (yrs)	0.24	0.18	8.66	.20								
Pre-study clozapine, olanzapine, quetiapine dose (CPZ)	0.000076	0.00012	0.16	.54								
History of substance abuse	0.0072	0.11	0.015	.95								
Race (white, black, Hispanic)	-0.0064	0.091	-0.022	.94								

PANSS: Positive and Negative Syndrome Scale; B: unstandardized coefficient; β: standardized coefficient; CPZ: chlorpromazine equivalents

they will require additional studies with larger numbers of subjects to be validated.

The rapid cross-taper may have affected the results. Quick discontinuation of clozapine, olanzapine, and quetiapine can cause cholinergic, histaminic, and α1-adrenergic rebound, with exacerbation of psychosis. It is for these reasons that it is often recommended that these be slowly tapered off over a period of 3–4 weeks. Compared to the Buffalo patients, subjects in the Bronx were prescribed pre-study more than double the doses of these drugs. Nevertheless, it is doubtful that their poorer response was just a withdrawal effect. The subjects' pre-study doses of clozapine, olanzapine, and quetiapine did not significantly predict clinical outcome in the regression models. Subjects' total pre-study dose of all antipsychotics, on the other hand, had significantly larger effects.

Overall, it is likely that high doses of medications, of whatever kind, are prescribed more often to patients who are relatively treatment refractory. Since Bronx Psychiatric Center patients are referred from other hospitals, they could be more likely to be refractory and be prescribed higher doses of medications. This could partially explain the different results between sites. But it would not explain the significant findings that resulted when the sites were combined for analysis.

It is unlikely that the differences in response between sites can be explained by greater adherence on the part of the Buffalo patients to taking the medication with food. Rise in QTc is a well-known side effect of ziprasidone. The rise was exactly the same in both groups under study: 15 msec in Buffalo (412 to 427 msec) and 15 msec in the Bronx (396 to 411 msec), suggesting equal absorption. And the changes in QTc were not associated with response to treatment in either simple or multiple regression analyses (data not shown).

It is unlikely that the better response in Buffalo outpatients results from cognitive or mood effects of ziprasidone that would be of particular benefit to outpatients. The Buffalo patients significantly improved in Cognitive and Depression factors of PANSS, with significantly greater improvement than the Bronx patients in the Depression factor of PANSS. However, the PANSS factors measure symptoms of schizophrenia and there was no improvement for either group on measures of cognition, the MOS-COG, or BACS, consistent with the literature on cognition and the SGAs generally. As

well, the reduction in depressive symptoms for Buffalo was only approaching significance on the CDSS.

For whatever reasons, ziprasidone continues to be used more often in outpatients (37). Overall, clinicians perceive ziprasidone to be less effective than other antipsychotics in the treatment of acute psychotic symptoms, which may be observed more often among inpatients. Further, because ziprasidone must be taken with food, some prescribers may be reticent to prescribe the medication for inpatients, who may be less compliant with the medication regimen at discharge. The better response to ziprasidone among outpatients in this study should be interpreted cautiously, as research has suggested that outpatients with schizophrenia achieve good outcomes from switching antipsychotics in general, and not just with ziprasidone (38). Outpatients who seek a change in medication (due to side effects or lack of efficacy) might show increased adherence with a switch (38), which could explain their greater response. This might help explain the better response among outpatients in this study, but it would not necessarily be a specific effect of ziprasidone.

In contrast to the results from Teo et al. (2013) and Rabinowitz et al. (2014), *older* age was a significant predictor of clinical improvement. Regression analyses showed that this was not simply due to Bronx/Buffalo patient status. It is difficult to explain these findings. The older patients at Buffalo had higher baseline scores on the Abnormal Involuntary Movement Scale (AIMS), a measure of tardive dyskinesia. Yet improvements among both groups on the AIMS were not significant.

This study suggests that it is appropriate in severely ill, chronic patients who do not sufficiently respond to medication, in New York State Hospitals and everywhere else, to consider a switch to ziprasidone. Even those who do not show a change in clinical symptoms may still improve in metabolic indices. The favorable metabolic effects that are seen with a switch to ziprasidone are not limited to those who improve psychiatrically, nor are they limited to those with diabetes, or another pre-existing metabolic disturbance. These findings suggest that greater baseline severity, older age, and lower baseline dose of antipsychotic medications are significant predictors of improvement with ziprasidone. But further research on these variables, as well as inpatient/outpatient status, are needed in light of the small numbers and the contradictory findings from other studies.

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References

1. Leucht S, Cipriani A, Spineli L, Mavridis D, Orey D, Richter F, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. Lancet 2013;382(9896):951-962.
2. Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009;373(9657):31-41.
3. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry 2003;60(6):553-564.
4. Lindenmayer JP, Tedeschi F, Yusim A, Khan A, Kaushik S, Smith RC, et al. Ziprasidone's effect on metabolic markers in patients with diabetes and chronic schizophrenia. Clin Schizophr Relat Psychoses 2012;5(4):185-192.
5. Carbon M, Correll CU. Clinical predictors of therapeutic response to antipsychotics in schizophrenia. Dialogues Clin Neurosci 2014;16(4):505-524.
6. Crespo-Facorro B, Pelayo-Teran JM, Perez-Iglesias R, Ramirez-Bonilla M, Martinez-Garcia O, Pardo-Garcia G, et al. Predictors of acute treatment response in patients with a first episode of non-affective psychosis: sociodemographics, premorbid and clinical variables. J Psychiatr Res 2007;41(8):659-666.
7. Levine SZ, Rabinowitz J. Trajectories and antecedents of treatment response over time in early-episode psychosis. Schizophr Bull 2010;36(3):624-632.
8. Pelayo-Teran JM, Diaz FJ, Perez-Iglesias R, Suarez-Pinilla P, Tabares-Seisdedos R, de Leon J, et al. Trajectories of symptoms dimensions in short-term response to antipsychotic treatment in patients with a first episode of non-affective psychosis. Psychol Med 2014;44(1):37-50.
9. Selten JP, Veen ND, Hoek HW, Laan W, Schols D, van der Tweel I, et al. Early course of schizophrenia in a representative Dutch incidence cohort. Schizophr Res 2007;97(1-3):79-87.
10. Boter H, Peuskens J, Libiger J, Fleischhacker WW, Davidson M, Galderisi S, et al. Effectiveness of antipsychotics in first-episode schizophrenia and schizophreniform disorder on response and remission: an open randomized clinical trial (EUFEST). Schizophr Res 2009;115(2-3):97-103.
11. Johnson S, Sathyaseelan M, Charles H, Jeyaseelan V, Jacob KS. Insight, psychopathology, explanatory models and outcome of schizophrenia in India: a prospective 5-year cohort study. BMC Psychiatry 2012;12:159.
12. Crespo-Facorro B, de la Fox VO, Ayesa-Arriola R, Perez-Iglesias R, Mata I, Suarez-Pinilla P, et al. Prediction of acute clinical response following a first episode of non affective psychosis: results of a cohort of 375 patients from the Spanish PAFIP study. Prog Neuropsychopharmacol Biol Psychiatry 2013;44:162-167.
13. Zhang HX, Shen XL, Zhou H, Yang XM, Wang HF, Jiang KD. Predictors of response to second generation antipsychotics in drug naïve patients with schizophrenia: a 1 year follow-up study in Shanghai. Psychiatry Res 2014;215(1):20-25.
14. Addington J, Addington D. Symptom remission in first episode patients. Schizophr Res 2008;106(2-3):281-285.
15. Schennach-Wolff R, Jager M, Mayr A, Meyer S, Kuhn KU, Klingberg S, et al. Predictors of response and remission in the acute treatment of first-episode schizophrenia patients--is it all about early response? Eur Neuropsychopharmacol 2011;21(5):370-378.
16. Furukawa TA, Levine SZ, Tanaka S, Goldberg Y, Samara M, Davis JM, et al. Initial severity of schizophrenia and efficacy of antipsychotics: participant-level meta-analysis of 6 placebo-controlled studies. JAMA Psychiatry 2015;72(1):14:21.
17. Teo C, Borlido C, Kennedy JL, De Luca V. The role of ethnicity in treatment refractory schizophrenia. Compr Psychiatry 2013;54(2):167-172.
18. Rabinowitz J, Werbeloff N, Caers I, Mandel FS, Stauffer V, Menard F, et al. Determinants of antipsychotic response in schizophrenia: implications for practice and future clinical trials. J Clin Psychiatry 2014;75(4):e308-316.

19. Arnold JG, Miller AL, Canive JM, Rosenheck RA, Swartz MS, Mintz J. Comparison of outcomes for African Americans, Hispanics, and Non-Hispanic whites in the CATIE study. Psychiatr Serv 2013;64(6):570-578.

20. Lawson WB, Herman BK, Loebel A, Lazariciu I, Malik M. Ziprasidone in black patients with schizophrenia: analysis of four short-term, double-blind studies. CNS Spectr 2009;14(9):478-486.

21. Citrome L, Jaffe A, Levine J. How dosing of ziprasidone in a state hospital system differs from product labeling. J Clin Psychiatry 2009;70(7):975-982.

22. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, fourth edition, text revision. Arlington, VA: American Psychiatric Association; 2000. p. 943.

23. Cheniaux E, Landeira-Fernandez J, Lessa Telles L, Lessa JL, Dias A, Duncan T, et al. Does schizoaffective disorder really exist? A systematic review of the studies that compared schizoaffective disorder with schizophrenia or mood disorders. J Affect Disord 2008;106(3):209-217.

24. Malaspina D, Owen MJ, Heckers S, Tandon R, Bustillo J, Schultz S, et al. Schizoaffective disorder in the DSM-5. Schizophr Res 2013;150(1):21-25.

25. Heckers S. Diagnostic criteria for schizoaffective disorder. Expert Rev Neurother 2012;12(1):1-3.

26. Komossa K, Rummel-Kluge C, Hunger H, Schwarz S, Bhoopathi PS, Kissling W, et al. Ziprasidone versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev 2009;4:CD006627.

27. Woods SW. Chlorpromazine equivalent doses for the newer atypical antipsychotics. J Clin Psychiatry 2003;64(6):663-667.

28. Lindenmayer JP, Grochowski S, Hyman RB. Five factor model of schizophrenia: replication across samples. Schizophr Res 1995;14(3):229-234.

29. Keefe RS, Harvey PD, Goldberg TE, Gold JM, Walker TM, Kennel C, et al. Norms and standardization of the Brief Assessment of Cognition in Schizophrenia (BACS). Schizophr Res 2008;102(1-3):108-115.

30. Weiden PJ, Simpson GM, Potkin SG, O'Sullivan RL. Effectiveness of switching to ziprasidone for stable but symptomatic outpatients with schizophrenia. J Clin Psychiatry 2003;64(5):580-588.

31. Simpson GM, Glick ID, Weiden PJ, Romano SJ, Siu CO. Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. Am J Psychiatry 2004;161(10):1837-1847.

32. Stroup TS, Lieberman JA, McEvoy JP, Swartz MS, Davis SM, Rosenheck RA, et al. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. Am J Psychiatry 2006;163(4):611-622.

33. Goff DC, Posever T, Herz L, Simmons J, Kletti N, Lapierre K, et al. An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. J Clin Psychopharmacol 1998;18(4):296-304.

34. Arango C, Gomez-Beneyto M, Brenlla J, Gasto C, Sarramea-Crespo F, Chamorro L, et al. A 6-month prospective, observational, naturalistic, uncontrolled study to evaluate the effectiveness and tolerability of oral ziprasidone in patients with schizophrenia. Eur Neuropsychpharmacol 2007;17(6-7):456-463.

35. Sacchetti E, Galluzzo A, Valsecchi P, Romeo F, Gorini B, Warrington L, et al. Ziprasidone vs clozapine in schizophrenia patients refractory to multiple antipsychotic treatments: the MOZART study. Schizophr Res 2009;113(1):112-121.

36. Kane JM, Sumant K, Rajadhyaksha S, Giller E. Efficacy and tolerability of ziprasidone in patients with treatment-resistant schizophrenia. Int Clin Psychopharmacol 2006;21(1):21-28.

37. Montes JM. Use of ziprasidone in patients with schizophrenia in four European countries. Eur Psychiatry 2011;26(1 Suppl 1):29-37.

38. Roussidis A, Kalkavoura C, Dimelis D, Theodorou A, Ioannidou I, Mylonaki T, et al. Reasons and clinical outcomes of antipsychotic treatment switch in outpatients with schizophrenia in real-life clinical settings: the ETOS observational study. Ann Gen Psychiatry 2013;12(1):42.