A Naturalistic Study of Risperidone Treatment Outcome Using Prognosis-Adjusted Discharge Rates in New York State Inpatients

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Background: Information concerning the effectiveness of newer atypical antipsychotics is derived largely from controlled clinical trials of relatively short duration. Limited information is available concerning naturalistic outcome of patients selected for clinical treatment with atypical antipsychotics. This study evaluates 1-year discharge rates among all patients treated with risperidone within the New York State inpatient psychiatric hospital system during the calendar years 1994 and 1995 ("period of interest") relative to patients treated with all other antipsychotic medications.

Method: Data from the Integrated Research Database at Nathan Kline Institute (Orangeburg, N.Y.) were used. This database maintains complete treatment records for all inpatients within the New York State psychiatric inpatient system along with demographic, diagnostic, admission, and discharge information. Patients were identified at admission or first change in antipsychotic during the period of interest, and 1-year outcome was determined.

Results: 2198 risperidone-treated patients were identified versus 3259 treated with other antipsychotics. Length of hospitalization prior to treatment initiation was the primary predictor of discharge rate for both risperidone and control groups. When adjustment was made for between-group difference in prognosis (dischargeability), patients treated with risperidone within 30 days of admission were less likely to be discharged than those treated with all other agents (including clozapine), whereas risperidone was more effective in patients who had been hospitalized for 90 days or more prior to switch from another antipsychotic to risperidone.

Conclusion: When database information is utilized to evaluate treatment effectiveness, adjustment must be made for a priori differences in prognosis or dischargeability. With appropriate methodology, database studies may indicate which patient groups are most likely to benefit from newer atypical antipsychotic agents.

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Schizophrenia is an important psychiatric illness with major morbidity among affected individuals. Over the past decade, significant new medications have been developed for schizophrenia, including atypical antipsychotics such as risperidone, olanzapine, and quetiapine. These medications have been shown to be effective in double-blind, placebo-controlled efficacy trials, to be moderately more effective in the treatment of negative symptoms than typical antipsychotics, and to have an improved side effect profile compared with that of the typical antipsychotics.[1,2] An important consideration, however, is the degree to which these medications reduce disability and, particularly, the need for long-term hospitalization among patients with chronic schizophrenia. This information can be difficult to obtain from prospective randomized trials because of the artificial treatment conditions imposed and the relatively small number of subjects that can be studied. Further, demographic and clinical characteristics of subjects enrolled in prospective trials often differ considerably from those of patients who eventually receive treatment with newer medications once they are approved.[3,4] Thus, alternative sources of information concerning treatment outcome must be developed from real-world, naturalistic settings.

The present study utilizes the New York State Integrated Research Database (NYS-IRDB) to evaluate treatment outcome for newer atypical antipsychotics relative to traditional agents. The first of the newer atypical agents, risperidone, became available within the New York State inpatient system in April 1994. An initial naturalistic outcome

study of risperidone performed using chart review during this period demonstrated that extremely chronic inpatients benefited significantly from risperidone as reflected by increases in ward privilege levels even though no significant increase in discharge rates was observed.[3] This finding was subsequently confirmed in an independent state hospital cohort.[4]

Several more recent studies have also addressed naturalistic consequences of risperidone treatment, with generally favorable results.[5–9] The largest of these studies,[7] however, involved only slightly over 1000 patients and did not incorporate a control population.

For the present study, data were obtained by reviewing computerized records for all patients within the New York State inpatient psychiatric system treated with risperidone for the period April 1994 through December 1995 and capturing specified information to 1 year following medication initiation relative to a comparison population. The primary outcome measure consisted of discharge within 1 year of medication initiation. Demographic and clinical information were captured as control variables. This is the first study of which we are aware to utilize a computerized inpatient database to evaluate predictors of discharge within a naturalistic treatment setting and the first to evaluate outcome within an entire state hospital network.

A current limitation of naturalistic treatment studies is that it is difficult to differentiate medication effects from a priori consequences of differential severity of illness among patients receiving atypical versus typical antipsychotics, especially since patients whose symptoms are most refractory to conventional treatment may be preferentially selected for treatment with newer medications. Absent formal clinical assessment, the best current method is to utilize demographic and diagnostic measures as surrogate markers for illness severity and consequent prognosis. An alternative method evaluated for the first time in this study is the use of prognosis-adjusted discharge rates (PADRs). In this approach, the discharge rate for patients on a particular index medication is compared with the discharge rate for patients discontinued from that medication and switched to an alternative therapy. The PADR approach makes the argument that if a high percentage of patients are discharged on treatment with a particular index medication and if few patients are discharged following discontinuation of that medication, then this indicates relative medication effectiveness. In contrast, if few patients are discharged while on treatment with a particular medication and many are discharged following discontinuation and switch to an alternative medication, then this indicates relative ineffectiveness.

To evaluate the PADR approach, 2 sets of analyses were performed. The first utilized potential outcome predictors (e.g., age, diagnosis, length of hospitalization) as covariates in a logistic regression analysis with discharge within 1 year (yes/no) as the outcome variable. The second utilized PADRs, with or without covariates. The goal was first to evaluate whether similar results were obtained from the 2 sets of analyses and second to evaluate the degree to which calculation of PADRs eliminates the contribution of a priori differences in clinical characteristics of patients to observed outcome. Although parameters such as prior length of stay are available in our database, such measures are not available in all computerized systems. Thus, development of a technique for minimizing the contribution of clinical characteristics of particular samples of patients to observed outcome would greatly extend the degree to which database information could be used for outcome evaluation. This system has been used previously to evaluate cross-sectional characteristics of patients receiving depot neuroleptics.[10]

METHOD

Sample and Data Collection

Data were obtained from the NYS-IRDB at Nathan Kline Institute (Orangeburg, N.Y.). Records were followed until December 30, 1996, permitting 1-year follow-up of all patients. Patients participating in randomized trials of risperidone were excluded. The risperidone group was divided into 2 cohorts. The admission cohort consisted of patients who received risperidone as their first medication following admission. The switch cohort consisted of patients who received risperidone following a switch from another antipsychotic medication. Risperidone-treated patients were compared with a group of patients treated with all antipsychotics other than risperidone, including both typical antipsychotics and clozapine. For both risperidone and comparison groups, outcome was defined relative to the day the new medication was initiated (index date).

After identification of index date, records were scanned for the year following medication initiation, and all discharges were flagged. Discharges were then subdivided into 2 categories on the basis of medication status at time of discharge. Category A consisted of patients who were discharged while receiving index medication. Category B consisted of patients who were discontinued from index medication, switched to a subsequent medication, and then discharged within the 1-year follow-up period. PADRs were calculated by dividing the number of patients discharged on treatment with a particular index medication (category A) by the number of patients discharged from that index group during the entire 1-year follow-up period, whether or not they were still receiving index medication at the time of discharge (categories A + B). Days to discharge or medication discontinuation was also captured and compared between treatment groups.

Statistical Methods

Between-group differences in discharge rate were analyzed using z-transformed Mann-Whitney U test scores. Logistic regression was used to evaluate potential predic-

Table 1. Demographics of Admission and Switch Cohorts for Risperidone-Treated and Comparison Subjects[a]

	Admission Cohort		Switch Cohort	
Variable	Risperidone (N = 569)	Comparison (N = 569)	Risperidone (N = 1629)	Comparison (N = 2690)
Age, y	39.8 ± 11.4	38.5 ± 10.1	41.0 ± 10.3*	38.7 ± 11.0
Sex, M/F, N	345/224	342/227	1000/629	1711/979
Length of stay at index, d	N/A	N/A	1267.6 ± 2093.1*	622.3 ± 1507.8
Total days in hospital in previous 3 years	113.0 ± 225.3	116.7 ± 21.8	602.4 ± 426.6*	370.0 ± 419.0

[a]Values shown as mean ± SEM unless otherwise noted. Abbreviation: N/A = not applicable.
*p < .001 vs. comparison group.

Table 2. Diagnostic Composition of Admission and Switch Cohorts for Risperidone-Treated and Comparison Subjects[a]

	Admission Cohort				Switch Cohort			
	Risperidone (N = 569)		Comparison (N = 569)		Risperidone (N = 1629)		Comparison (N = 2690)	
Diagnosis	N	%	N	%	N	%	N	%
Schizophrenia	309	54.3	309	54.3	977	60.0	1205	44.8
Schizoaffective disorder	156	27.4	156	27.4	350	21.5	545	20.3
Bipolar disorder	47	8.3	47	8.3	131	8.0	381	14.2
Other psychosis	24	4.2	24	4.2	56	3.4	242	9.0
Major depression	27	4.7	27	4.7	31	1.9	96	3.6
OMS/dementia	3	0.5	3	0.5	26	1.6	46	1.7
Substance abuse	3	0.5	3	0.5	24	1.5	65	2.4
Other/unknown	0	0	0	0	34	2.1	110	4.1

[a]Abbreviation: OMS = organic mental syndrome.

tors of discharge, including days in hospital during the 3 years preceding index hospitalization (for the new admission group), length of stay at index switch (for the switch group), and diagnosis. Diagnosis and medication group membership (risperidone/comparison) were treated as categorical variables. Differences in days to discharge or discontinuation were analyzed by between-group Student t tests. Two-tailed statistics were used throughout. Data in text represent mean ± SD.

The logistic equation correlation (R) was used as a measure of effect size. For interpretation, an R value of 0.1, corresponding to a 10% increase in success rate of treatment,[11] was considered a small effect. An R value of 0.2, corresponding to a 20% increase in treatment success,[11] was considered moderate.

RESULTS

Demographics of the admission and switch cohorts are provided in Table 1. Within the admission cohort, it was possible to perform a 1:1 match stratified by age, sex, and diagnosis within the database. The admission cohort consisted of 569 risperidone-treated patients and 569 comparison patients selected from a total of over 3000 admissions over the period of interest. Because of the stratified match, groups within the admission cohort were similar demographically.

In contrast, in the switch cohort 1:1 matching was not possible due to the much larger number of patients (N = 1629) and the wide range of demographic values within the risperidone group. All patients who switched from one antipsychotic to a second antipsychotic other than risperidone within the period of interest were therefore included as a comparison group (N = 2690). Within this cohort, patients chosen for switch to risperidone were significantly older (t = 6.7, df = 4317, p < .001) and had been hospitalized longer prior to medication switch than patients chosen for switch to other agents (t = 11.7, df = 4317, p < .001).

Dose Effects

An initial analysis evaluated effect of medication dose. Risperidone dose was typically titrated upward over a period from 3 days to 2 weeks following medication initiation. Patients reached a mean dose of 7.2 ± 4.4 mg/day by day 14 of treatment. The dose remained stable during treatment, with no significant difference between admission and switch cohorts. Risperidone dose did not differ between patients discharged on risperidone treatment (7.2 ± 3.8 mg/day) and those discontinued or not discharged (7.6 ± 4.9 mg/day; t = 1.80, df = 2238, p = .07). Dose, therefore, was not included as a covariate in any subsequent analysis.

Effects of Demographic and Clinical Variables

Demographic and clinical variables utilized as potential predictors of discharge for both cohorts (admission and switch) included age, gender, and number of days in hospital in the 3 years prior to admission or switch. In the switch cohort, length of index hospitalization prior to switch was also used as a potential predictor variable. Neither age nor gender was a significant predictor of discharge. In both the admission (R = –0.11, p = .02) and switch (R = –0.09, p < .001) cohorts, the mean number of days in hospital during the preceding 3-year period proved a significant, but weak, predictor of discharge. In the switch group, the length of hospitalization prior to switch was a significant independent predictor of discharge (R = –0.20, p < .001).

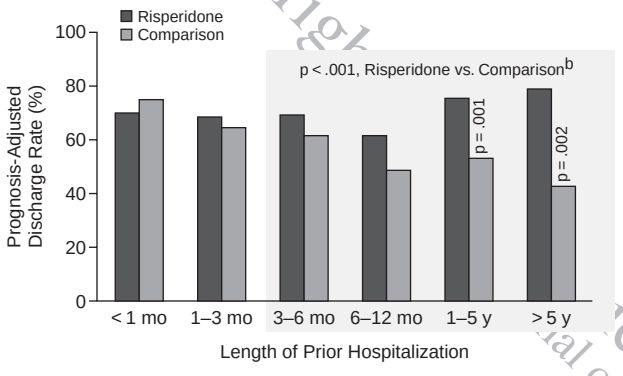
The majority of patients in all groups were diagnosed with either schizophrenia or schizoaffective disorder, based on chart diagnosis (Table 2). Diagnosis was not significantly correlated to discharge rate within the admission cohort (R = 0.00, NS). Within the switch cohort, a significant, but weak, correlation was observed, with schizophrenia patients showing worse outcome than other groups (R = 0.06, p < .001). Within the switch cohort,

Table 3. Outcome Rates Among Admission and Switch Groups

	Admission Group				Switch Group			
	Risperidone (N = 569)		Comparison (N = 569)		Risperidone (N = 1629)		Comparison (N = 2690)	
Outcome Variable	%	N/Total N	%	N/Total N	%	N/Total N	%	N/Total N
A. Discharged on index medication	53.3**	303/569	71.7	408/569	27.9**	454/1629	44.2	1188/2690
B. Discontinued	41.3**	235/569	24.3	138/569	44.4*	724/1629	49.3	1327/2690
Discharged following discontinuation	69.8	164/235	69.6	96/138	27.1**	196/724	41.3	548/1327
C. Total discharges from index group	82.1	467/569*	88.6	504/569	39.9**	650/1629	64.5	1736/2690
D. Prognosis-adjusted discharge rate (A/C)	64.9**	303/467	81.0	408/504	69.8	454/650	68.4	1188/1736

*p < .01 vs. comparison group. **p < .001 vs. comparison group.

Figure 1. Prognosis-Adjusted Discharge Rate by Length of Prior Hospitalization at Time of Switch to Index Medication for Risperidone-Treated and Comparison Patients[a]



[a]Data are based on analysis of a total of 1642 discharges across all groups. Individual bars reflect analysis of 33 to 1044 discharges each.
[b]Comparison after data were collapsed across stratifications.

therefore, diagnosis was maintained as a categorical covariate for logistic regression analyses.

Admission Cohort

The primary outcome analysis compared 1-year discharge rate on drug treatment between the risperidone and comparison groups (Table 3). In the admission cohort, significantly fewer patients were discharged on index medication from the risperidone group than from the comparison group (53.3% vs. 71.7%; z = 6.3, p < .001). More patients were discontinued from index medication prior to 1 year in the risperidone group than from the comparison group (41.3% vs. 24.3%; z = 6.1, p < .001). Because the 2 groups were closely matched for prior days in hospital, the between-group difference in discharge rates remained significant even following covariation for demographic variables (R = 0.16, p < .001).

In the admission cohort, conclusions from the PADR approach were similar to those from the logistic regression analysis. Total discharge rates were lower for the risperidone group than for the comparison group (82.1% vs. 88.6%; z = 3.02, p < .01). Therefore, even when discharge rates on index medication were adjusted for total discharge rate, prognosis-adjusted rates remained lower for the risperidone group than for the comparison group (64.9% vs. 81.0%; z = 5.58, p < .001).

Switch Cohort

In the switch cohort, a significantly lower percentage of patients were also discharged from the risperidone group than from the comparison group (27.9% vs. 44.2%; z = 10.7, p < .001). However, review of the computerized records revealed that patients chosen to receive risperidone on medication switch were significantly older and had significantly longer length of stay than those switched to other medications. Therefore, when rates of discharge on index medication were covaried for demographic and clinical characteristics in the switch cohort, no significant difference was observed between groups (R = 0.00, p > .6), indicating that the difference was driven primarily by between-group differences in prior length of stay and diagnosis.

A prognosis-adjusted discharge rate analysis yielded a similar conclusion. Significantly fewer patients in the risperidone group were discharged following medication discontinuation and switch to alternative medication than in the comparison group (27.1% vs. 41.3%; z = 6.3, p < .001), leading to markedly lower total discharge rates in the risperidone group than in the comparison group (39.9% vs. 64.5%; z = 15.7, p < .001). Therefore, the PADR for the risperidone group, 69.8% (454/650), was highly similar to that for the comparison group, 68.4% (1188/1736), despite the between-group difference in raw discharge rates. PADRs were substantially less correlated with length of stay prior to switch (R = 0.04, p = .01) than were nonadjusted rates (R = 0.18, p < .001).

The prognosis-adjusted outcome analysis also permitted analyses to be stratified according to prior length of stay. When this analysis was performed (Figure 1), somewhat lower PADRs were found for risperidone-treated patients who had been hospitalized less than 30 days prior to initial medication switch relative to comparison patients (z = 1.62, p = .1), supporting findings from the new admission cohort. In contrast, higher PADRs were found among risperidone-treated patients who had been treated for 1 to 5 years (z = 3.34, p = .001) or more than 5 years

Table 4. Time to Discharge or Drug Discontinuation in the Risperidone and Comparison Groups[a]

	Admission Group		Switch Group	
Outcome Variable	Risperidone (N = 569)	Comparison (N = 569)	Risperidone (N = 1629)	Comparison (N = 2690)
Time to discharge on index medication, d	72.0 ± 72.7** (N = 303)	53.0 ± 63.3 (N = 408)	91.7 ± 88.5** (N = 454)	58.8 ± 68.6 (N = 1188)
Time to discontinuation, d	51.1 ± 64.5 (N = 235)	51.8 ± 63.4 (N = 138)	98.5 ± 91.9** (N = 721)	77.5 ± 86.8 (N = 1327)
No discharge following discontinuation	89.3 ± 92.0 (N = 71)	86.6 ± 80.9 (N = 42)	117.4 ± 95.5* (N = 525)	102.4 ± 96.2 (N = 779)
Discharge following discontinuation	34.5 ± 37.8 (N = 164)	36.6 ± 46.9 (N = 96)	47.8 ± 55.6 (N = 196)	42.0 ± 54.3 (N = 548)
Time to discharge following discontinuation, d	106.4 ± 80.6 (N = 164)	117.7 ± 77.0 (N = 96)	133.5 ± 87.9 (N = 196)	130.3 ± 79.2 (N = 548)

[a]Time values shown as mean ± SEM. N = number of subjects.
*p < .01 vs. comparison group.
**p < .001 vs. comparison group.

(z = 3.11, p = .002) prior to switch. When data were collapsed across stratifications, it was similarly observed that patients who had been hospitalized for more than 90 days before switch showed higher PADRs on risperidone treatment, 70.6% (204/289), than on treatment with a comparison agent, 53.4% (182/341; z = 4.42, p < .001).

Clozapine subgroup analysis. The alternative treatment group contained 147 subjects who received clozapine as their index medication. Within this group, the discharge rate on index medication, 18.4% (27/147), was significantly lower than for the remainder of the comparison group (z = 6.38, p < .001) and was also marginally smaller than the discharge rate among risperidone-treated patients (z = 2.39, p < .02). However, as with risperidone, the percentage of clozapine-treated subjects discharged following discontinuation of index medication (clozapine), 10.2% (15/147), was also significantly lower than for patients treated with conventional antipsychotics (z = 9.16, p < .001), so that the PADR for clozapine, 64.3% (27/42), was similar to the PADR for risperidone or comparison agents. Because of the small number of discharges within the clozapine group, it was not possible to stratify by length of stay. Nevertheless, these findings support the use of the PADR measure over measures of pure discharge rate.

Analysis of Time to Discharge

A secondary analysis focused on time to discharge within the risperidone and comparison groups (Table 4). Patients in the risperidone group required a significantly greater duration of treatment on index medication prior to discharge than did patients in the comparison group. The difference was significant for both the admission (t = 3.72, df = 709, p < .001) and switch (t = 8.00, df = 1640, p < .001) cohorts. However, when lengths of prior and current hospitalization were treated as covariates, between-group differences in duration of treatment prior to discharge were no longer significant for either the admission (F = 1.6, df = 1,250; p = .2) or switch (F = 0.7, df = 1,1631; p > .4) cohorts. In all groups, the time to discharge on treatment with index medication was longer than the time to discontinuation in patients who went on to ultimate discharge (Table 4, row 1 vs. row 4). However, the degree of difference was particularly pronounced in the risperidone group for both the admission (72.0 vs. 34.5 days; t = 6.17, df = 465, p < .001) and switch (91.7 vs. 47.8 days; t = 6.42, df = 648, p < .001) cohorts.

In the switch cohort, mean time to discontinuation was significantly longer for risperidone than comparison patients (t = 5.13, df = 2046, p < .001), especially within the subgroup that was not discharged following discontinuation (t = 2.78, df = 1302, p = .006). Other treatment durations, including time to discharge following index medication discontinuation, did not differ between groups.

DISCUSSION

The greatest challenge in the use of database information for assessment of drug efficacy is controlling for the different clinical characteristics of patients that were selected for treatment with specific agents. Unlike prospective, randomized clinical trials, it cannot be assumed a priori that patients being treated with different agents are similar in terms of clinical characteristics or likelihood of discharge. Two separate approaches were used in this study to equate patient and comparison groups for a priori prognosis. For patients newly admitted to New York State inpatient facilities, it was possible to select a group of comparison patients that were matched for key clinical characteristics, including age, sex, and diagnosis. However, for longer-stay patients (switch cohort), it was not possible to perform a 1:1 match, and statistical approaches to control for between-group differences had to be employed. These included (1) covariation for clinical factors likely to be associated with probability of discharge and (2) computation of a PADR by comparing the likelihood of discharge on treatment with index medication to the likelihood of discharge following discontinuation from index medication.

The primary findings of the present study are that (1) patients treated with risperidone within 30 days of

admission were less likely to be discharged on treatment with that medication than were patients started on treatment with other medications, but (2) patients who had been hospitalized for more than 90 days at the time of switch to risperidone were significantly more likely to be discharged than patients switched to an alternative antipsychotic agent.

The relatively poorer outcome among newly admitted patients, at initial appearance, contradicts results of double-blind, parallel-group studies that have, in general, shown superior efficacy of risperidone in the treatment of positive and negative symptoms. One explanation may be the dose of risperidone used (approximately 7 mg), which exceeded doses that are currently recommended (≤ 6 mg/day).[7] However, no correlation between dose and outcome was observed in either the admission or switch group in this study. An alternative explanation may be found in the time-to-discharge analysis. Patients successfully discharged on risperidone treatment required, on average, significantly longer treatment duration that those discharged on treatment with other antipsychotic medications (see Table 3), suggesting that risperidone trials may have to last at least 3 months before treatment success can be evaluated.

In contrast to recently admitted patients, those who had been hospitalized for more than 90 days prior to a medication switch had greater likelihood of discharge when switched to risperidone than when switched to a comparison agent. Patients treated with risperidone as index medication and not discharged on index medication were unlikely to be discharged on any subsequent medication. The most parsimonious explanation of this finding is that patients initially selected for risperidone treatment had greater severity of illness than those chosen for switch from one conventional antipsychotic to another. The differences in patient characteristics were captured in part by differences in diagnostic makeup and duration of hospitalization of the group. It is unlikely, however, that these variables fully captured the a priori likelihood of discharge for the different patient groups. The practical implication is that when discharge rates on a given medication are controlled for discharge rates following medication discontinuation, differential prognostic effects emerge that are not apparent from inspection of raw discharge rates alone. Because this is the first study to utilize the PADR measure, replication in additional samples is required.

Use of the PADR calculation substantially reduced the contribution of demographic variables in the prediction of discharge. This finding suggests that the measure can be applied even in systems where length-of-stay information is difficult to obtain. In the simplest implementation of a PADR analysis, the only items of data that are required are (1) date of medication initiation, (2) date of discharge (if any), and (3) discharge medication. Such information may be available even in systems that do not have computerized pharmacy records. The fact that prognosis-adjusted rates were less affected than nonadjusted rates by between-group differences in demographic characteristics potentially makes them more sensitive to between-drug differences than traditional prognostic measures. Because the present study uses data only from calendar years 1994 and 1995, it includes only patients on risperidone versus conventional antipsychotics + clozapine. Additional studies are needed to evaluate the relative effectiveness of newer atypical antipsychotics.

Naturalistic studies involving database information, even with matched samples, cannot be viewed as a replacement for controlled clinical trials. Nevertheless, the major finding of this study is that patients who have been hospitalized more than 90 days may benefit most from treatment with risperidone. At present, no prospective, double-blind studies have sought to evaluate outcome within this long-stay inpatient population. Further, the difficulty of obtaining access to such a population makes it unlikely that prospective, random-assignment studies will be conducted with sufficient follow-up interval and power to detect between-group differences in discharge rate. The present study suggests that such studies require treatment periods of at least 3 months and involve sample sizes of several hundred patients because of the low a priori rate of discharge (< 20% for patients hospitalized > 90 days). Absent such information, analysis of naturalistic database information provides a method for gaining insight into treatment outcome within such treatment-refractory populations.

Drug names: clozapine (Clozaril and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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