Treatment Discontinuation Following Randomization to Open-Label Olanzapine, Risperidone or Typical Antipsychotics During a One-Year Treatment for Schizophrenia

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Abstract

Objective: To compare olanzapine, risperidone and typical antipsychotics on medication discontinuation for any cause during one-year, open-label treatment for schizophrenia. **Methods:** This post hoc analysis used data from a one-year, randomized, open-label, multi-site, cost-effectiveness study of schizophrenia conducted between May 1998 and September 2002. If clinically warranted, patients could switch antipsychotics. Patients randomized to olanzapine (n=222), risperidone (n=217) or typical antipsychotic of physician's choice (n=209) were compared on average time to all-cause medication discontinuation and survival rates over the one-year study. **Results:** The average time to all-cause discontinuation was longer for olanzapine than for risperidone (p<.001), typical antipsychotics (p<.001), and versus perphenazine, a medium potency typical antipsychotic (p=.002). Treatment with risperidone was longer than with typicals (p<.01), but not significantly different from perphenazine. One-year survival rate was higher for olanzapine therapy (55%) compared to risperidone (47%, p=.006), typical antipsychotics (32%, p≤.001) and perphenazine (31%, p<.001). Survival rate for risperidone-treated patients was higher than on typicals (p<.001), but not significantly different from perphenazine. Patients randomly assigned to continue their baseline medication ("stayers") had significantly longer times until discontinuation than did those assigned to switch antipsychotics, but treatment group differences were essentially unchanged when analyses excluded the "stayers." **Conclusions:** In the long-term, open-label treatment of patients with schizophrenia, antipsychotics appear to significantly differ on time to all-cause medication discontinuation, a measure considered a proxy index of a medication's effectiveness. Findings were essentially unchanged when treatment group comparisons took into account whether the medications being compared were newly initiated.

Key Words: Schizophrenia, Olanzapine, Risperidone, Perphenazine, Treatment Discontinuation

Introduction

In the treatment of schizophrenia, time to medication discontinuation for any cause has been recognized as an important global proxy measure of a medication's effectiveness and is assumed to capture the medication's efficacy, safety and tolerability from both patients' and clinicians' perspectives (1, 2). Longer treatment duration has been shown to be associated with better clinical and functional outcomes (3-9) and reduced risk of relapse and hospitalization (1, 6, 8-13).

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The National Institute of Mental Health (NIMH)-funded Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial (1) is the first to use time to all-cause medication discontinuation as a primary effectiveness measure. This large, eighteen-month, randomized, double-blind study compared a medium-potency conventional antipsychotic (perphenazine) and four atypical antipsychotics (olanzapine, risperidone, quetiapine and ziprasidone) in the treatment of schizophrenia in the United States. The primary phase of the CATIE, Phase 1, found significant differences on time to all-cause medication discontinuation between the studied atypical antipsychotics (longer on olanzapine than on risperidone and quetiapine, numerically but not statistically longer than ziprasidone), but did not find significant differences when comparing perphenazine with each of the atypical drugs, as significant differences favoring olanzapine turned nonsignificant following adjustment for multiple comparisons.

The CATIE findings have been criticized on a number of grounds (14-16), including the dosing range of the atypical drugs, the randomization of some patients to continue on the medication they had been receiving at study baseline, and the double-blind nature of the study. Concerns about dosing included the use of olanzapine in high "off-label" doses, up to 30 mg/day (doses within label are up to 20 mg/day), with a mean modal dose of 20.1 mg/day, which was claimed by some to have biased the findings in favor of olanzapine. In addition, a sizable proportion of patients who were randomized to olanzapine or risperidone were treated at baseline with the same drug (23% and 18%, respectively), thus did not have to undergo the potentially disruptive process of medication switching. Further concerns were noted about the double-blind design of CATIE, suggesting that the blinding method may have impaired clinicians' ability to decide which specific doses are most appropriate for the patients, thus reducing the ability to generalize the CATIE findings to open-label treatment in usual care setting.

In order to complement the CATIE findings and help address the potential impact of these methodological limitations on time to all-cause medication discontinuation, we performed a post hoc analysis using data from a Lilly-funded, randomized, open-label (doses within package insert recommendations), one-year, cost-effectiveness study of antipsychotics in the treatment of schizophrenia in the United States. Using time to all-cause medication discontinuation as the primary outcome measure, we hypothesized it will be: 1) significantly longer for patients randomized to olanzapine and to risperidone, compared to patients randomized to typical antipsychotics of physicians' choice; 2) significantly longer for patients randomized to olanzapine, but not risperidone, compared to perphenazine; 3) significantly longer for patients randomized to olanzapine compared to risperidone; and, 4) results will be essentially unchanged when "stayers"—those assigned to continue taking the medication being received at baseline—were excluded. These hypotheses were empirically driven, based on previous research consistently showing longer time to all-cause medication discontinuation and higher study completion rates for patients treated with olanzapine compared to typical antipsychotics (1, 17-24) and compared to oral risperidone (1, 9, 17, 20, 25-33). To our knowledge, there is no one study showing the opposite; namely, a significantly longer time to all-cause medication discontinuation on risperidone or typical antipsychotics compared to olanzapine in the treatment of patients with schizophrenia. Our "stayers"-related hypothesis was also based on a CATIE study demonstrating that, when "stayers" were excluded, differences seen in the original CATIE Phase 1 analyses on time to all-cause discontinuation were attenuated, but that the original pattern of results has remained (34).

Methods

Data Source

This post hoc analysis was performed using data from a one-year, randomized, open-label, Lilly-supported study of the cost effectiveness of olanzapine, risperidone and typical antipsychotics in the treatment of patients with schizophrenia (HGGD). Data were collected at twenty-one U.S. sites between May 1998 and September 2002. The protocol and consent procedures were approved by institutional review boards, and signed consent forms were obtained from patients prior to participation in the study. A brief summary of the study design is provided in this section. Additional details are available in the primary publication of the parent study (35). In that paper, we reported rate of medication switching but not the time to all-cause medication discontinuation, the primary topic of the current study.

Individuals were eligible to participate in the study if they were at least eighteen years of age; met *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)* criteria for schizophrenia, schizoaffective or schizophreniform disorders based on the Structured Clinical Interview (SCID) for DSM-IV (36); and, had a minimum score of 18 on the Brief Psychiatric Rating Scale (BPRS) (37) extracted from the Positive and Negative Syndrome Scale (PANSS) (38) and scored on a 0–6 scale. Excluded were individuals with serious or unstable physical illnesses, those at high risk of suicide, women currently lactating or pregnant, and individuals with medical conditions contraindicating use of any study medication. Individuals with tardive dyskinesia or substance use disorders were not excluded from entry into this study to help enhance generalizability of the findings to schizophrenia patients typically treated in usual care settings in the United States.

Table 1 Key Baseline Characteristics of Patients Randomized to Olanzapine, Risperidone and Typical Antipsychotics

Variable*	TYP†‡ (n=209)	OLZ‡ (n=222)	RIS‡ (n=217)	PER (n=48)
Age, mean (SD)	43.7 (12.1)	42.7 (12.2)	42 (11.8)	44.2 (11.9)
Gender, n (%)				
Male	141 (67)	138 (62)	130 (60)	28 (58)
Female	68 (33)	84 (38)	87 (40)	20 (42)
Race, n (%)				
Caucasian	110 (53)	124 (56)	118 (54)	27 (56)
African-American	75 (36)	68 (31)	75 (35)	16 (33)
Other	24 (11)	30 (14)	24 (11)	5 (10)
Primary health insurance, n (%)				
Medicaid	73 (37)	76 (36)	81 (40)	19 (41)
Medicare	55 (28)	62 (30)	51 (25)	11 (24)
Private	29 (15)	23 (11)	27 (13)	9 (20)
Other options	4 (2)	7 (3)	8 (4)	0 (0)
No insurance	38 (19)	42 (20)	38 (19)	7 (15)
Age at first psychiatric hospitalization, mean (SD)	26.0 (9.2)	27.0 (10.0)	25.6 (9.3)	25.8 (8.8)
Number of previous schizophrenia episodes, mean (SD)	6.9 (10.5)	7.4 (10.0)	6.2 (8.6)	6.2 (8.2)
Comorbid substance use disorder, n (%)	92 (44)	103 (47)	91 (42)	12 (25)
Past year psychiatric hospital duration, n (%)				
None	143 (70)	147 (68)	149 (70)	37 (79)
<1 month	39 (19)	44 (20)	38 (18)	7 (15)
1 month plus	23 (11)	25 (12)	26 (12)	3 (6)
Tardive dyskinesia, n (%)	30 (14)	42 (19)	32 (15)	7 (15)
PANSS, mean (SD)	85.9 (19.6)	87.1 (19.6)	87.4 (20.7)	81.0 (18.9)
BPRS, mean (SD)	31.2 (11.2)	31.9 (11.3)	32.4 (12.2)	28.9 (10.4)
Inpatient at enrollment, n (%)	7 (3)	11 (5)	12 (6)	1 (2)

* Due to missing values, sample size differed among baseline variables.
† For TYP group, any typical antipsychotic was considered "study drug."
‡ There were no significant differences among the therapy groups on key baseline characteristics.
Abbreviations: TYP=typicals; OLZ=olanzapine; RIS=risperidone; PER=perphenazine; SD=standard deviation; PANSS=Positive and Negative Syndrome Scale; BPRS=Brief Psychiatric Rating Scale

Table 2 Mean Daily Antipsychotic Dose, by Medication

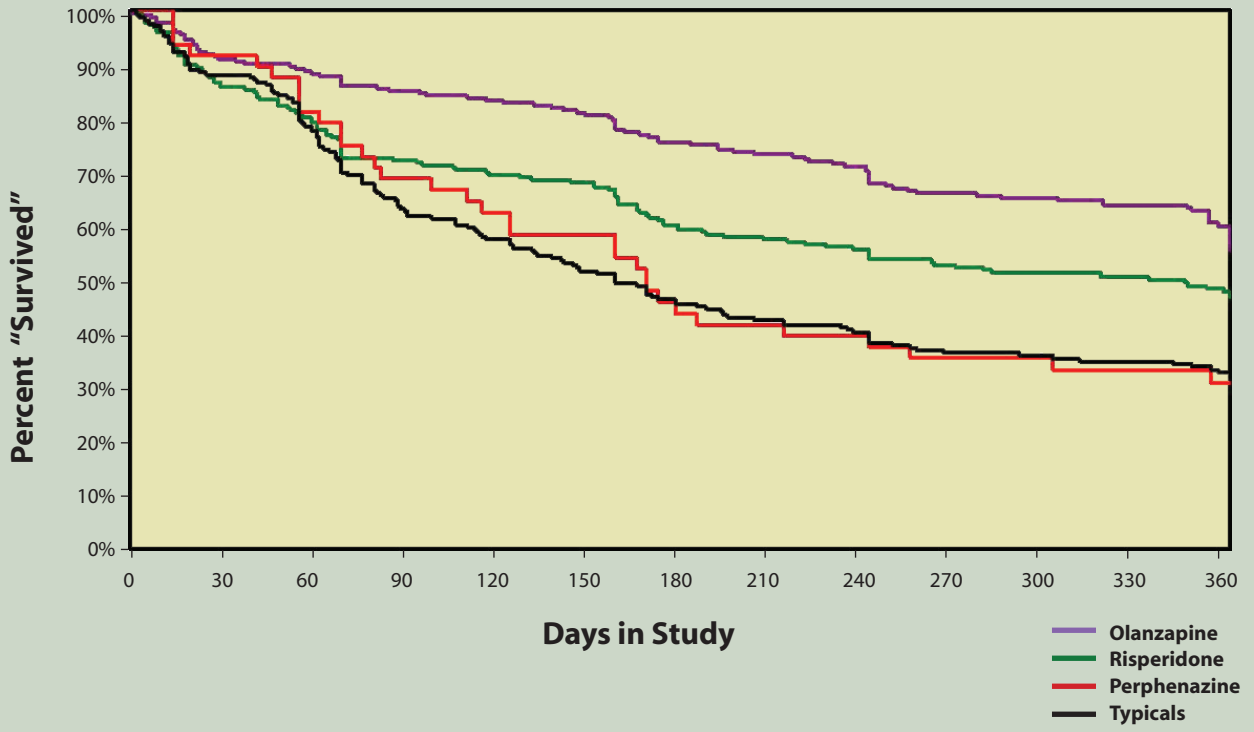
Antipsychotic	N	Mean Modal Dose (SD)
Olanzapine	222	13.31±7.86
Risperidone	217	4.85±2.61
Perphenazine	48	13.48±10.60
Haloperidol	34	8.56±5.34
Loxapine	34	44.38±31.80
Thiothixene	32	16.28±13.62
Fluphenazine	23	12.59±9.70
Trifluoperazine	10	12.15±12.45
Mesoridazine	8	67.50±40.18
Thioridazine	6	163.33±121.72
Chlorpromazine	6	216.67±68.31
Molindone	6	61.67±52.60

Study participants were randomly assigned to open-label treatment with olanzapine (n=229), risperidone (n=221) or typical antipsychotics (n=214) in standard oral formulation. Choice of a particular typical agent was made by the treating physician and was based upon an individual's clinical and treatment history. All decisions regarding initial dosing and ongoing medication management were made by the treating physician with instructions to consider current product labeling and package insert recommendations (39). Switching antipsychotic agents was allowed in this study and was at the discretion of treating physicians. Barring any clinically significant adverse events, all patients were to remain on their randomized treatment regimen for at least eight weeks, but could continue on their initial regimen for as long as clinically indicated during the one-year trial period. Patients' medical records were systematically extracted to obtain data on prescribed antipsychotic and other medications. The current study included all randomized patients with post-baseline medication data.

Primary Outcome Measure

Time to all-cause medication discontinuation during the one-year following randomization was the primary outcome

Figure 1 One-Year Survival Rates for Patients Randomized to Olanzapine, Risperidone, Typicals and Perphenazine



OLZ=olanzapine; RIS=risperidone; TYP=typicals; PER=perphenazine
Significant group differences: OLZ vs. RIS: p=.007; OLZ vs. TYP: p<.001; RIS vs. TYP: p=.002; OLZ vs. PER: p<.001; RIS vs. PER: p=.060

measure in the current post hoc analysis. This was calculated as the number of days from treatment randomization up to either a switch to another medication or study discontinuation for any cause. This measure was examined for treatment with olanzapine, risperidone or typical antipsychotics. Per protocol, a one-time change from one typical agent to another was not considered a switch, thus providing a conservative definition of switching for patients randomized to typicals. Patients randomized to treatment with a typical antipsychotic who were initiated on perphenazine were also studied, as perphenazine was the typical antipsychotic used most often in HGGD and is the typical antipsychotic studied in CATIE.

Statistical Analyses

Survival analysis was used to assess time to all-cause discontinuation of the randomized medication (olanzapine, risperidone, all typicals and perphenazine). Comparisons of treatment groups on overall one-year survival distributions were made using Kaplan-Meier estimates and logrank tests. Analyses were repeated excluding "stayers"—patients randomized to continue their baseline medication. Furthermore, "stayers" and "non-stayers" were compared on time to all-cause discontinuation using survival analyses. The average number of days to all-cause discontinuation of the randomized medication was calculated and compared between the treatment groups using unpaired t-tests. Two-tailed α=0.05 significance level tests were conducted, with adjustment for multiple pair-wise comparisons, by means of a Hochberg adjustment for multiple comparisons (40), which was used in the CATIE trial. While the primary analysis of CATIE adjusted for three comparisons, we adjusted for six pair-wise comparisons between four treatment groups (olanzapine, risperidone, typicals and perphenazine). The smallest resulting p value was compared with a value of 0.008 (0.05÷6). Statistical Analysis Software® (SAS®) (41) was used for all analyses.

Results

Patient Characteristics

Of the 664 randomized participants, 648 (97.6%) were included in this post hoc analysis as they began treatment with their randomized medication and had post-baseline data. These participants were randomized to

Table 3 One-Year Survival Rates by Treatment Group and after Exclusion of Patients Randomized to Continue on Baseline Medication

Survival Rates by Treatment Group

Randomized Treatment	8-Week Survival	6-Month Survival	365-Day Survival	p-Value vs. OLZ	p-Value vs. RIS
Olanzapine (N=222)	89.2%±2.1%	75.7%±2.9%	55.3%±3.6%		0.007
Risperidone (N=217)	81.1%±2.7%	59.3%±3.3%	46.8%±3.5%	0.007	
Typicals (N=209)	79.4%±2.8%	45.5%±3.4%	31.7%±3.3%	<0.001	0.002
Perphenazine (N=48)	81.3%±5.6%	43.8%±7.2%	30.8%±6.8%	<0.001	0.060

Survival Rates for Treatment Groups after Excluding Patients Randomized to Continue Baseline Medication ("Stayers")

Randomized Treatment	8-Week Survival	6-Month Survival	365-Day Survival	p-Value vs. OLZ	p-Value vs. RIS
Olanzapine (N=220)	89.1%±2.1%	75.5%±2.9%	54.9%±3.6%		0.004
Risperidone (N=208)	80.3%±2.8%	58.5%±3.4%	45.4%±3.6%	0.004	
Typicals (N=89)	70.8%±4.8%	36.0%±5.1%	19.8%±4.3%	<0.001	<0.001
Perphenazine (N=47)	80.9%±5.7%	42.6%±7.2%	29.3%±6.7%	<0.001	0.062

Survival Rates for Patients Randomized to Typical Antipsychotics: Comparison of Patients Randomized to Continue ("Stayers") or Not Continue ("Non-Stayers") on Typicals

	8-Week Survival	6-Month Survival	365-Day Survival	p-Value	
"Stayers" (N=102)	87.3%±3.3%	50.0%±5.0%	36.6%±5.1%	0.002	
"Non-stayers" (N=89)	70.8%±4.8%	36.0%±5.1%	19.8%±4.3%		

olanzapine (n=222), risperidone (n=217) or typical antipsychotics (n=209 [including perphenazine, n=48]).

The three treatment groups did not significantly differ on any key baseline characteristic (see Table 1). At baseline, participants had moderately severe symptoms as demonstrated by an average total score of 86.8 on the PANSS. Tardive dyskinesia (TD), per Schooler and Kane criteria (42), was present in 16% of the participants, and substance abuse was the most prevalent comorbid condition with an overall rate of 44%. Almost all patients (95%) were outpatients at enrollment, and one-third had at least one psychiatric hospitalization in the previous year. During the one-year study, participants were treated with mean modal daily doses that were within package inserts of the respective antipsychotics (see Table 2).

Atypical versus Typical Antipsychotics

Olanzapine versus Typicals

Olanzapine-treated patients had significantly longer time to all-cause discontinuation (mean 277.2 days, standard deviation [SD]=123.9; median 358 days or 11.9 months) compared to typical antipsychotics (mean 193.5 days, SD=137.9; median 161 days or 5.4 months, p<.001) and a significantly higher one-year survival rate (55.3%) compared to patients treated with typical antipsychotics (31.7%, p<.001, see Table 3 and Figure 1). The findings were essentially unchanged when the analysis excluded "stayers."

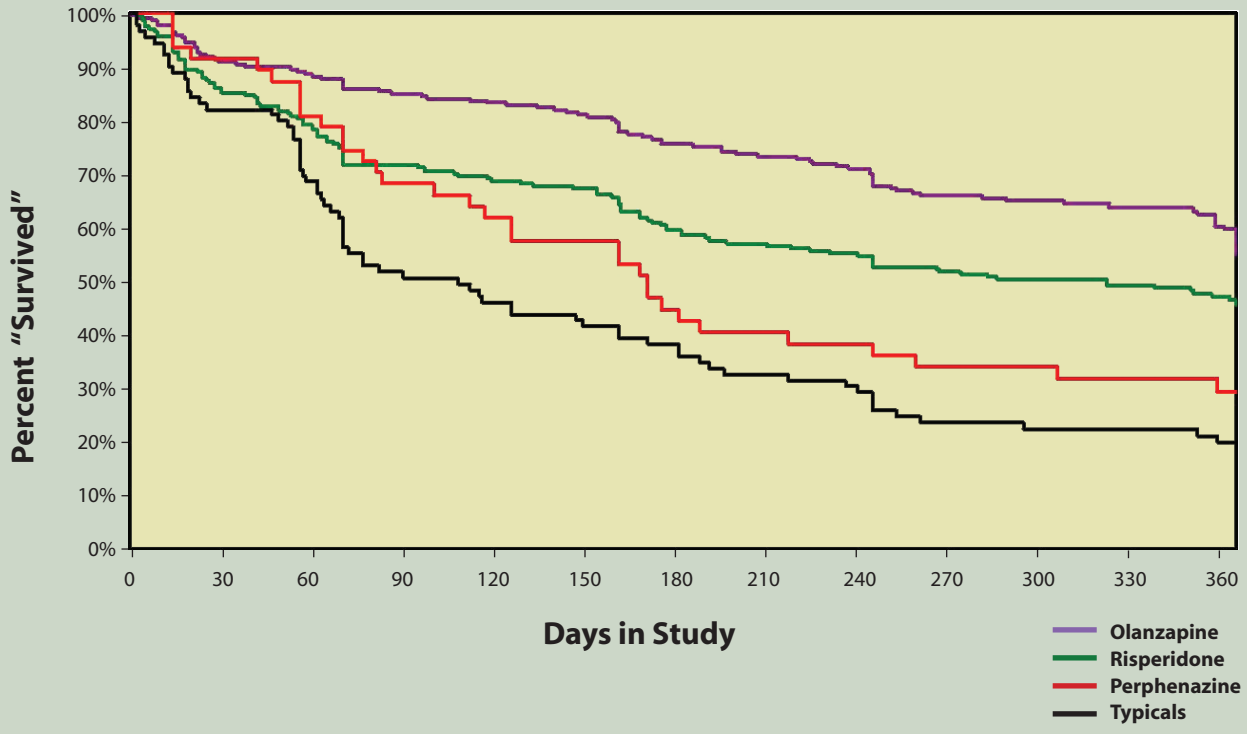
Risperidone versus Typicals

Risperidone-treated patients had significantly longer average time to all-cause medication discontinuation (mean 231.9 days, SD=142.2; median 322 days or 10.7 months) compared to typical antipsychotics (mean 193.5 days, SD=137.9; median 161 days or 5.4 months, p=.002) and a significantly higher one-year survival rate (46.8%) compared to patients treated with typical antipsychotics (31.7%, p=.002, see Table 3 and Figure 1). The findings were essentially unchanged when the analysis excluded "stayers."

Atypicals versus Perphenazine

The time to all-cause discontinuation of olanzapine (mean 277.2 days, SD=123.9; median 358 days) was significantly longer than perphenazine (mean 198.5 days, SD=132.0; median 171 days or 5.7 months, p<.001, see Table 3), and the survival rate on olanzapine (55.3%) was significantly higher than perphenazine (30.8%, p<.001, see Table 3 and Figure 1). There was no significant difference between risperidone and perphenazine on average time to all-cause medication

Figure 2 One-Year Survival Rates for Patients Randomized to Olanzapine, Risperidone, Typicals and Perphenazine, Excluding "Stayers," the Patients Randomized to Continue on Baseline Medication



OLZ=olanzapine; RIS=risperidone; TYP=typicals; PER=perphenazine
Significant group differences: OLZ vs. RIS: p=.004; OLZ vs. TYP: p<.001; RIS vs. TYP: p<.001; OLZ vs. PER: p<.001; RIS vs. PER: p=.062

discontinuation (231.9 days vs. 198.5 days, p=.23), or in one-year survival rates (46.8% vs. 30.8%, p=.06, see Table 3 and Figure 1). The findings were essentially unchanged when the analysis excluded "stayers" (see Figure 2).

Olanzapine versus Risperidone

The time to all-cause discontinuation for patients in the olanzapine-treatment group (mean 277.2 days; median 358 days) was significantly longer than for risperidone (mean 231.9 days; median 322 days, p<.001). One-year survival rate for olanzapine (55.3%) was significantly higher than for risperidone (46.8%, p=.007, see Table 3 and Figure 1). The findings were essentially unchanged when the analysis excluded "stayers" (see Figure 2).

"Stayers" versus "Non-Stayers"

At baseline, most patients (77%) were treated with typical antipsychotics. About half of the patients randomized to typicals (48.8%, 102/209) were previously treated with typicals, whereas 42.6% of those randomized to typicals were not (89/209). For a small proportion of those randomized to typicals (8.6%, 18/209), no information was available on the antipsychotic used at baseline, if any. Only a small number of the patients randomized to olanzapine (2) or risperidone (9) was treated with the same drug prior to randomization. Due to these small numbers, the comparison of "stayers" and "non-stayers" was confined to patients randomized to typical antipsychotics (see Table 3). As presented in Table 3 and Figure 2, the one-year survival rates for "stayers" was significantly higher than for "non-stayers" (36.6% vs. 19.8%, p=.002), with a significantly longer time to medication discontinuation (mean 216.2 days, SD=134.5 [median 186 days] versus mean 155.4 days, SD=130.1 [median 108 days], p=.002).

Results of comparisons for olanzapine versus typicals, risperidone versus typicals, atypicals versus perphenazine, olanzapine versus perphenazine and olanzapine versus risperidone maintained statistical significance following Hochberg adjustment for multiple comparisons. Adjustments for multiple comparisons were not conducted for "stayers"-related analyses.

Discussion

In this post hoc analysis of data from a one-year, open-label study, schizophrenia patients randomized to olanzapine had significantly higher survival rates and longer time to all-cause medication discontinuation compared to patients treated with either risperidone, typical antipsychotics, or specifically with perphenazine, the typical antipsychotic used in the CATIE schizophrenia trial. This study also found, like in CATIE (34), that the exclusion of "stayers"— patients who continue their baseline medication—did not alter the original pattern of results, although being randomized to stay on antipsychotics used prior to randomization ("stayers") is associated with a significantly longer treatment duration compared to patients who were not ("non-stayers"). This finding suggests that switching of antipsychotic medication is not a risk-free decision for the patient, and as was previously stated (34): "Unless the clinical situation requires a medication change, prescribers may want to take steps to optimize current medication regimens (e.g., dosage adjustments, behavioral or psychosocial interventions) before switching medications."

This study's CATIE-like comparison of antipsychotic treatment groups on time to all-cause medication discontinuation addressed some of the methodological limitations for which CATIE was criticized. Findings of the present study are generally consistent with those of CATIE Phase 1, in which patients randomized to olanzapine had a significantly longer time to all-cause discontinuation (median 9.2 months) compared to risperidone (median 4.8 months, p=.002), and perphenazine (median 5.6 months, p=.02, nonstatistically significant after adjustment for multiple comparisons, which required p≤.017) and the lowest all-cause medication discontinuation rate (based on the CATIE Kaplan-Meier 18-month survival figure, the one-year, all-cause discontinuation rates were 54% for olanzapine, 63% for risperidone and 69% for perphenazine).

Unlike CATIE, the current findings are observed in an open-label, naturalistic study (versus double blind) in which olanzapine was prescribed in doses within label (versus "off-label" doses), and risperidone was used in slightly higher doses (4.7 mg/day vs. 3.9 mg/day in CATIE). The CATIE and the present study also differed in overall study duration and patient population. The eighteen-month CATIE included outpatients diagnosed with schizophrenia, whereas our one-year study included predominately outpatients (only about 5% were inpatients at enrollment) diagnosed with schizophrenia, schizoaffective or schizophreniform disorder. Another study difference is the dosing of perphenazine. In CATIE, the mean dose of perphenazine was 20.8 mg/day, whereas in our study the mean dose was lower, 13.5 mg/day. It is possible that the lower dosing in our study was associated with poorer effectiveness of the drug and, consequently, with a shorter time to all-cause medication discontinuation. It is, however, unclear whether there is a dose-response for perphenazine considering previous research showing that higher perphenazine levels appear no more effective than moderate levels, but that higher levels may be associated with increased extrapyramidal symptoms (43). Yet another difference between our study and CATIE needs mentioning: the difference between olanzapine and risperidone in the median time to all-cause discontinuation was smaller in our open-label study (1.2 months) compared to CATIE (4.4 months). Although the reasons for the difference are unclear, this phenomenon could be an effect of unblinded clinicians in the current study.

In addition to the NIMH-funded CATIE, current findings are also consistent with meta-analyses of mostly industry-sponsored, randomized, double-blind, clinical trials (23, 33, 44, 45), with results from retrospective database studies (6, 9, 20, 46) and from prospective, nonrandomized, noninterventional, naturalistic studies (17, 46-49). Prior studies reporting differences in time to all-cause medication discontinuation between atypicals and typicals (primarily haloperidol) have been augmented with studies reporting olanzapine therapy to be associated with significantly longer time to all-cause discontinuation compared to typicals (17-23, 47) and compared to risperidone (9, 17, 20, 25, 27-32, 47).

The consistency of the current findings with those reported across diverse research methodologies, sample characteristics, study durations and geographic regions helps expand and strengthen the observation that atypical antipsychotics are not alike on time to medication discontinuation for any cause. This global index is considered a proxy measure of a drug's effectiveness, reflecting its perceived benefits and risk from both patient and clinician perspectives. Longer treatment duration has been associated with greater symptom improvement (3) and with greater functional long-term benefits in the treatment of schizophrenia (4), thus having important clinical and economic implications for patients, clinicians and other healthcare decision makers.

While olanzapine- and risperidone-treated patients demonstrated longer time to all-cause discontinuation than patients treated with typical antipsychotics, there were notable differences between the two atypicals. The olanzapine-treated patients, on both measures of survival rate and mean time to all-cause discontinuation, stayed on treatment significantly longer than patients treated with perphenazine, whereas risperidone-treated patients did not significantly differ from perphenazine on this measure. In addition to CATIE (1), the current findings are also consistent with another open-label, but nonrandomized, study in

the United States (17) in which olanzapine—but not risperidone—significantly differed from perphenazine on time to all-cause medication discontinuation and all-cause discontinuation rates in the one year following medication initiation.

Current findings must be evaluated in the context of their limitations. First is the post hoc nature of the analysis. Second is the open-label use of the antipsychotics, which we view as a strength but can also be considered a study limitation, since it introduces potential clinicians' bias which cannot be eliminated from this industry-sponsored study. Another limitation is the small sample size of the perphenazine group (n=49), which may limit generalization of the perphenazine-related findings. It is notable, however, that perphenazine was the typical antipsychotic used most often in this study, followed by haloperidol, despite the fact that our study was completed several years before CATIE's publication stimulated interest in using perphenazine in the United States. Another limitation is the focus on time to medication discontinuation for any cause without further delineation of reasons for the discontinuation (e.g., poor efficacy, medication intolerability or patient preference). Reasons for medication discontinuation were not assessed in this post hoc analysis due to the complexity of examining multiple comparisons across four treatment groups with a sample size much smaller than CATIE. While the chosen focus on "all-cause" discontinuation may yield less information, it is an important primary outcome measure. It is notable, however, that, as in the CATIE study, the most prevalent reason for medication discontinuation was patient decision (in the current study 38.6% discontinued due to patient preference/noncompliance), with a lower discontinuation rate due to poor medication efficacy (21.3%) and a lower discontinuation rate due to medication intolerability (14.4%). Furthermore, patients randomized to olanzapine in the current study did not differ from comparators on discontinuation due to medication intolerability (olanzapine 3.2%, risperidone 5.5%, and typicals 5.8%).

The strengths of this study include its randomized yet naturalistic, real-world, long-term perspective; the ability to provide comparative data on commonly used antipsychotics; the ability to follow patients after they discontinued the initial randomized drug; the use of multiple sites across the United States; and, the broad inclusion criteria, all of which may enable generalization of the current findings to schizophrenia patients treated in usual care settings in the United States.

In summary, this open-label, one-year, randomized study of antipsychotic treatments for patients with schizophrenia appears to complement and expand on prior independent and industry-sponsored research. Results show that antipsychotic treatment regimens significantly differ on time to medication discontinuation for any cause, an outcome measure that appears to capture medication effectiveness. Further research is needed to clarify the long-term psychiatric, medical and economic benefits of longer time on therapy for patients with schizophrenia treated in usual care settings.

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