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A comparison of olanzapine and risperidone on the risk of psychiatric hospitalization in the naturalistic treatment of patients with schizophrenia

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Abstract

Background: Decreasing hospital admissions is important for improving outcomes for people with schizophrenia and for reducing cost of hospitalization, the largest expenditure in treating this persistent and severe mental illness. This prospective observational study compared olanzapine and risperidone on one-year psychiatric hospitalization rate, duration, and time to hospitalization in the treatment of patients with schizophrenia in usual care.

Methods: We examined data of patients newly initiated on olanzapine (N = 159) or risperidone (N = 112) who continued on the index antipsychotic for at least one year following initiation. Patients were participants in a 3-year prospective, observational study of schizophrenia patients in the US. Outcome measures were percent of hospitalized patients, total days hospitalized per patient, and time to first hospitalization during the one-year post initiation. Analyses employed a generalized linear model with adjustments for demographic and clinical variables. A two-part model was used to confirm the findings. Time to hospitalization was measured by the Kaplan-Meier survival formula.

Results: Compared to risperidone, olanzapine-treated patients had significantly lower hospitalization rates, (24.1% vs. 14.4%, respectively, p = 0.040) and significantly fewer hospitalization days (14.5 days vs. 9.9 days, respectively, p = 0.035). The mean difference of 4.6 days translated to $2,502 in annual psychiatric hospitalization cost savings per olanzapine-treated patient, on average.

Conclusions: Consistent with prior clinical trial research, treatment-adherent schizophrenia patients who were treated in usual care with olanzapine had a lower risk of psychiatric hospitalization than risperidone-treated patients. Lower hospitalization costs appear to more than offset the higher medication acquisition cost of olanzapine.

Introduction

Schizophrenia is a severe and persistent mental illness in which most patients alternate between acute psychotic episodes and stable periods [1]. This chronic and recurrent illness is associated with cognitive, behavioral, social, and occupational impairments that often require a variety of costly therapeutic options [2]. Psychiatric hospitalization is the most restrictive therapeutic alternative for these

patients and is often reserved for individuals who are gravely ill and/or are dangerous to themselves or others. Psychiatric hospitalization is a costly treatment alternative in terms of personal and familial anguish and in other societal terms [3]. Economically, hospitalization is known as the costliest treatment option for patients with schizophrenia, accounting for one-third to two-thirds of the total direct health care costs for the illness [3]. Expectedly, the long-term goals of treatment are to stabilize the patient's clinical and functional status, help maintain the patient in the community, and prevent relapse.

The term "relapse" is, however, a relative term that lacks a consensus definition [4] and is typically measured by symptom exacerbation, behavioral worsening, and psychiatric hospitalization either singly or in their combination [4,5]. Although far from perfect, parameters of psychiatric hospitalization are frequently used to measure relapse, particularly hospitalization rates, but also duration of hospitalization and time to hospitalization [3,6-8].

The most powerful predictor of relapse and hospitalization among patients with schizophrenia is non-adherence with the antipsychotic treatment regimens [8,9]. The risk of relapse is estimated to increase by at least 100% in patients who interrupt their drug treatment [3]. In addition to non-adherence, other factors modify the risk of relapse [8], including the type of antipsychotic drug regimen. A number of studies have demonstrated that the second-generation antipsychotics (SGAs), such as clozapine, olanzapine, and risperidone, confer a significantly lower risk of relapse than the first generation antipsychotics [5-8]. These benefits are thought to be attributable to the more favorable adverse event profile of SGAs, since adverse effects can undermine medication adherence, treatment response and relapse prevention [8].

The SGAs are known to differ in their pharmacological structure, tolerability, safety, and efficacy profiles [10] and may also differ in their ability to prevent relapse and hospitalization [11]. At present, findings from only two controlled randomized double blind studies have been published on the differences between SGAs on relapse prevention [12,13]. Both clinical trials defined relapse as a psychiatric hospitalization and demonstrated that olanzapine-treated patients had a lower risk of hospitalization. The first study, which was 6-months long, found that olanzapine-treated patients had fewer hospital days than patients treated with risperidone, and attributed this finding to a higher rate of psychiatric hospitalization among the risperidone patient group. The second efficacy study was one year in duration and demonstrated that the olanzapine-treated patients had a significantly lower rate of hospitalization than the risperidone-treated patients [13].

The National Institute of Mental Health (NIMH) [14] has emphasized the need to take findings generated by clinical research and translate them into treatment for patients who are seen in day-to-day non-research settings. This need stems primarily from the realization that randomized clinical trials often have strict inclusion and exclusion criteria for patient enrollment that may limit the ability to generalize the findings to the more varied and complex patient population that is treated in usual care [15]

The purpose of this study was to compare olanzapine and risperidone on the risk of hospitalization during the treatment of adherent patients with schizophrenia in usual care settings. Patients who were newly initiated on olanzapine or risperidone and continued treatment with the index antipsychotic drug for one year post initiation were compared on three parameters of psychiatric hospitalization – percent of patients hospitalized, total hospitalized duration, and time to first psychiatric hospitalization. The ability of an antipsychotic drug to prevent hospitalization is recognized as an indicator of the drug's cost-effectiveness [6,16], a property of substantial clinical and economic utility, particularly to the payer at this time of constrained health care resources.

Methods

Data source

This study used data from the U.S. Schizophrenia Care and Assessment Program (US SCAP), a non-randomized, naturalistic, prospective study in which patients with schizophrenia-spectrum disorders were periodically assessed with standardized measures and followed for 3 years. The ultimate goal of this large study (N = 2327) was to understand the treatments currently provided to schizophrenia patients in usual care settings. The six participating sites represented large systems of care in the U.S. including university health care systems, community mental health centers (CMHC), the Department of Veterans Affairs Health Services (VA), and community and state hospitals. Participants were recruited from a broad geographical area including the Northeast, Southwest, Mid-Atlantic, and West. Institutional Review Board (IRB) approval was received at each study site prior to initiation of the study and informed consent was received from all participants. All study sites offered multidisciplinary professional staffing, had open and unrestricted formulary access to all novel antipsychotics, and did not employ an algorithm for the treatment of schizophrenia. SCAP was launched in July 1997 and will be completed at the end of 2003. The current analysis is based on the interim data that included the first 2287 participants enrolled in the study. Most of these participants (2063/2287 or 90.2%) completed at least one year of follow-up.

Data were collected at baseline and at 6-month or 1-year intervals and included participant self-report (6 month), clinical assessments (1 year), and medical record abstraction of resources used in the prior interval (6 month). Patients were queried about use of psychiatric resources outside of their regular treatment site. When this occurred, systematic efforts were made to abstract out-of-site medical records. Data underwent rigorous quality checks to identify out-of-range values, inconsistent data, claim duplicates, and unexpected missing values.

The SCAP database is similar to other administrative and pharmacy claims database, as it provides detailed information about patients' resource utilization over a predetermined period of time. Unlike most claims databases, SCAP not only covers mental health resources but also includes information about psychiatric medications prescribed during psychiatric hospitalizations. SCAP also provides information on patients' clinical and functional status as measured at enrollment and at each of the 6 follow-up assessments. These periodic assessments were not designed to coincide with changes in patients' medication regimens and did not reflect patients' status at the time of initiation on the index drug. Resultantly, this information was not included in the current analysis.

Inclusion and exclusion criteria

SCAP enrolled patients who met DSM-IV criteria for schizophrenia, schizoaffective, or schizophreniform disorder; were at least 18 years of age; and understood and provided informed consent. Patients were excluded if they had participated in a controlled clinical drug trial in the month prior to enrollment. Unlike randomized clinical trials the criteria for inclusion of patients in the SCAP study were very broad in order to secure a representative sample of schizophrenia patients treated in usual care settings. Consequently, participation in SCAP was independent of patients' psychiatric and medical comorbidities, substance abuse behaviors, use of concomitant medications of any type, level of suicidality, display of aggressive behaviors, pregnancy, and lactating status. It is also noteworthy that in clinical trials participants' adherence with medication may be artificially induced, for example by enrolling only highly motivated participants, by scheduling frequent visits, by counting the number of unused pills returned by the participant at each visit, and by study termination of participants who discontinued the study drug. In contrast, level of adherence with medication by SCAP participants was not affected by any of these practices, thus patients' discontinuation of a prescribed medication would tend to reflect various decisions and preferences by the patients and/or their providers, as they naturally unfold in usual care.

Subjects were included in the current analysis if they (a) were newly initiated on olanzapine or risperidone, defined as being free of both olanzapine and risperidone in the 60 days prior to initiation date, (b) were continuously treated with the index antipsychotic drug for at least one-year following initiation without any larger than 14-day gap between prescriptions for the index drug, and (c) were not initiated on olanzapine and risperidone on the same day. Importantly, the inclusion of patients who were continuously treated with the index drug during the year following initiation was aimed at avoiding the potential pitfalls associated with an intent-to-treat methodology in which all health resources used subsequent to initiation of the drug therapy are assigned to that therapy, even if therapy is discontinued [17]. In contrast, the inclusion of patients who were continuously treated with the index drug during the study period permitted a more optimal and equitable comparison of the two treatment groups, because both groups were assumed to have a similar level of adherence with the index antipsychotic regimen, and medication adherence was previously shown to be a potent predictor of relapse and hospitalization in the treatment of schizophrenia patients [8,9].

Measurement

Following screening for eligibility and meeting inclusion and exclusion criteria, study enrollees responded to the Baseline Data Collection Form (BDCF), a semi-structured interview that collected information about psychiatric history and background characteristics. Medical history data were extracted from the participant's medical record and entered by study staff into the Medical Record Abstraction Form (MRAF), summarizing mental health resource utilization during the preceding 6 months.

Outcome measures

Three outcome measures were used to assess risk of psychiatric hospitalization: (a) hospitalization rate, defined as the percent of patients newly hospitalized at least once for psychiatric purposes during the year following initiation on the index drug, (b) duration of hospitalization, measured as the total number of days hospitalized per patient in the year following initiation, and (c) time to hospitalization, defined as the number of days from initiation to the first hospitalization during the year post initiation. Individuals who were inpatients at initiation and were not discharged from their index hospitalization by the end of the year post initiation were considered hospitalized on measures of hospitalization and had zero days to re-hospitalization. The MRAF provided admission and discharge dates for each psychiatric hospital admission.

Hospitalization cost measure

SCAP did not collect data on the cost of resource utilization. In order to estimate the cost of psychiatric

hospitalization, we used the U.S. National mean reimbursed rate for 2001, as reported by the National Association of Psychiatric Health Systems (NAPHS) [18]. The NAPHS' most recent annual survey reported a flat mean rate of $556 per patient per day based on information provided by 136 psychiatric facilities owned and operated by NAPHS system members. These facilities often provide hospital care for patients in the public sector, especially for Medicaid and/or Medicare populations, who account for nearly half of all admissions in NAPHS member hospitals.

Measures of patient characteristics

The BDCF and MRAF provided information on patients' demographic and clinical characteristics. The current analysis compared the olanzapine (OLZ) and risperidone (RIS) treatment groups on patient characteristics that were previously found to be associated with relapse and hospitalization, such as younger age [9], male gender [9], younger age at illness onset [20], greater prior use of psychiatric medications [7], and a higher likelihood of having a prior psychiatric hospitalization [7]. The treatment groups were also compared on their distribution across treatment sites, type of insurance coverage, DSM-IV diagnostic subtypes, and lifetime episodes of schizophrenia, defined as a period of time in which the patient had worsening of symptoms that changed the patient's daily routines and pattern of care seeking. Further, in order to address the potential impact of changes in the U.S. health care environment on the rate and/or duration of psychiatric hospitalizations during the conduct of the study, we assessed potential period bias by comparing the treatment groups on the length of time between initiation on the index drug and a reference point, arbitrarily chosen as July 1, 2000.

Antipsychotic medication

The MRAF provided information for each psychiatric medication prescribed during the previous 6-month interval. Details included the drug name, start and stop dates, dose, frequency, route of administration, and whether or not it was prescribed as needed (PRN). Antipsychotic medications were routinely prescribed for up to 30 days at a time.

Medication adherence

The MRAF provided information about the prescription of the index antipsychotic drug and did not guarantee that the patient filled the prescription or ingested the medication. In order to demonstrate that (a) the continuous receipt of prescriptions was a valid proxy for SCAP patients' self-reported adherence with medication, and (b) that the treatment groups were comparable on self-reported adherence, we performed an additional analysis. To that end, we used the SCAP Health Questionnaire (SCAP-HQ), which was administered to SCAP participants every 6 months. This is a validated self-report measure assessing outcome domains that are integral to schizophrenia care [19]. One of its items measured how regularly the patients reported taking their medications based on their choice of one of five response alternatives: "(1) I never missed taking my medicine; (2) I missed only a couple of times, but basically took all the medicine; (3) I missed the medicine several times, but took at least half of it; (4) I took less than half of what was prescribed; and (5) I stopped taking the medicine altogether." Based on this self-report measure of medication adherence, almost all the patients in each treatment group chose alternative 1 or 2, indicating they were highly adherent with ingestion of their prescribed antipsychotic medications (OLZ 92.8% vs. RIS 90.7%). Findings lend support for the use of continuous prescription of the medication as a valid proxy measure of these patients' self reported medication adherence.

Statistical methods

Comparisons of baseline characteristics between the two treatment groups included chi-square tests for categorical variables and t-test for continuous variables. A Logistic Model compared the treatment groups on psychiatric hospitalization rate during the year following initiation, and a Generalized Linear Model (GLM) compared the groups on the total number of days hospitalized. The GLM employed log transformation because the distribution of hospitalization days was skewed. In order to enable log transformation for patients with zero hospitalization days, one hospitalization day was added to each study patient. This statistical approach is consistent with the literature [21]. As this was a non-randomized study, it was necessary to address selection bias by controlling for a number of potential confounding variables. Analyses were adjusted for variables that were previously found to be associated with hospitalization and included age, race, gender, age at illness onset, prior use of psychiatric hospitalization, oral antipsychotics, antipsychotics in depot formulation, and of mood stabilizers in the 60 days prior to initiation (yes/no). The length of the prior-to-initiation period is similar to that used in a recent study of hospitalization rates in patients with schizophrenia [22]. Analyses did not adjust for adherence with medication because the analytical sample included participants who were deemed to be comparable on this variable.

A two-part model [23] was used to confirm the findings of the Generalized Linear Model. This model is considered appropriate for handling the skewed number of hospitalization days and the high proportion of patients with zero days hospitalized. The two-part model involved (a) calculating for each patient the probability of being hospitalized vs. not being hospitalized in the year following

Table 1: Patient characteristics

Characteristic		Olanzapine n = 169	Risperidone n = 115
Age at enrollment, mean (SD)†		43.5 (11.2)	39.3 (12.8)
Age at illness onset, mean (SD)		19.5 (9.0)	19.6 (10.1)
Male, %		62.9%	54.5%
Race, %			
	White	52.8%	49.1%
	Black	41.5%	39.1%
	Other	5.7%	11.8%
Diagnosis, %			
	Schizoaffective	34.0%	32.1%
	Schizophrenia, paranoid	37.1%	31.2%
	Schizophrenia, undifferentiated	18.2%	19.6%
	Other	10.7%	17.1%
Number of prior episodes of schizophrenia, mean (SD)‡		25.6 (37.1)	28.9 (39.7)
Prior use of antipsychotic, %§		66.0%	66.1%
Prior use of depot formulation, %§		23.9%	18.7%
Prior use of mood stabilizer, %§		33.3%	24.1%
Prior psychiatric hospitalization, %§		16.0%	14.8%
Days with concomitant antipsychotic, mean (SD)		162 (12.6)	158.3 (15.3)

† Significant group differences at $p < 0.05$ ‡ At enrollment, response to, "How many previous episodes of schizophrenia have you had? §Binary variable (yes / no); Prior period: 60 days prior to initiation of the index drug

initiation, (b) for patients who were hospitalized in the year post initiation, using linear regression on log transformed number of days hospitalized, (c) usinge the model from b to calculate the predicted hospitalization value for all patients, hospitalized and not hospitalized, and (d) multiplying the patient's predicted value from c by the probability of being hospitalized in the year post initiation from a to get an estimated value of the number of days hospitalized for each patient and for each treatment group.

A nonparametric survival analysis with Kaplan-Meier estimates was used to obtain the time to first hospitalization for the two treatment groups. For outpatients it was the first hospitalization following initiation on the index drug. For inpatients at time of initiation on the drug, it was the first re-hospitalization following discharge from the index hospitalization. Log rank test was used to compare the two treatment groups. All statistical tests were two-tailed at an alpha level of 0.05.

Results

Patient characteristics

Of 516 patients who were newly initiated on OLZ or RIS, a total of 271 patients met the above criteria comprising the OLZ (N = 159) and RIS (N = 112) treatment groups. A similar proportion of OLZ and RIS-treated patients were excluded due to discontinuation of the index drug prior to the end of the one-year period (OLZ N = 138/297 or 46.5% vs. RIS N = 107/219 or 48.9%, p = 0.47), with a numerically but not statistically longer time to drug discontinuation for the OLZ treatment group as compared to the RIS-treated patients (138.4 (SD 94.3) days vs. 122.6 (SD 97.2) days, p = 0.17). As illustrated in Table 1, the treatment groups differed on age at enrollment, as patients in the olanzapine treatment group were older by 4.2 years, on the average. The two groups were comparable on all other demographic and clinical characteristics including gender, race, age of onset, diagnostic subtype, number of lifetime episodes of schizophrenia, treatment with oral antipsychotics, depot formulation antipsychotics, and mood stabilizers in the 60 days prior to initiation on the index antipsychotic, and prior use of psychiatric hospitalization (yes/no), the mean number of hospital admission in the 60 days prior to initiation (0.176 for OLZ vs. 0.179 for RIS), and on the mean duration on concomitant antipsychotic drugs in the year post initiation of the index drug (162.16 (SD 12.61) days for OLZ vs.158.3 (SD 15.3) days for RIS, p = 0.846). The treatment groups were also found to be similar on their patient distribution across treatment sites, type of insurance coverage (96% of the patients were covered by a public payer, mostly Medicaid), on outpatient status at the time of initiation on the index drug (79.2% vs. 71.4%, p = 0.067 for olanzapine and risperidone treatment groups, respectively), and for the number of days between initiation of the index and discharge from the hospital for individuals who were inpatient at the time of initiation on the index drug (36.7 days vs. 37.5 days, p = 0.97 for olanzapine and risperidone groups, respectively).

Table 2: Results for the adherent group and for the combined adherent and non-adherent groups (intent-to treat analysis, ITT) *

	Adherent group (n = 271)			Adherent and non-adherent groups combined (n = 516)		
Hospitalization parameter	OLZ (n = 159)	RIS (n = 112)	P-value	OLZ (n = 297)	RIS (n = 219)	P-value
% Patients hospitalized						
Unadjusted	14.5%	24.1%	0.044†	23.6%	31.5%	0.045†
Adjusted	2.0%	9.8%	0.040‡	7.6%	20.7%	0.085‡
Days hospitalized						
Days, Average Unadjusted	9.9	14.5	0.425	19.1	17.6	0.755
Log Days, Unadjusted	0.59	0.94	0.070§	0.73	0.99	0.039§
Log Days, Adjusted	1.24	1.61	0.035||	1.30	1.48	0.139||
Days, 2-Part Estimate, Adj.	7.3	19.0	--	15.9	21.0	--
Time to first hospitalization						
Mean	176.1	111.0	0.107#	156.4	167.8	0.476#
Median	173	94	--	153	146	--

* Time to hospitalization: Number of days to first hospitalization for outpatients following initiation of the index drug; Number of days to first re-hospitalization post discharge from index hospitalization for participants who were inpatients at the time of initiation on index drug Adjusted: Controlling for gender, age at illness onset, race, age at baseline, prior use (60 days pre-initiation) of oral antipsychotics, mood stabilizers, antipsychotics in depot formulation (Y/N). † Mantel-Haenszel test ‡Logistic Regression test § t-test for the log transformation of hospital stay + 1 || GLM for log transformation test # Log Rank test of the Kaplan – Meier survival analysis

Furthermore, the treatment groups were comparable for time between enrollment in the study and initiation on the index drug, and for time between initiation on the index drug and an arbitrary date (July 1, 2000). The latter was calculated to assess the potential of "period bias" and suggests that patients in the two medication groups were treated during a similar time span, thus changes in the pattern of mental health resource utilization in the U.S. during these patients' study period (July 1997 to January 2001) were likely to similarly impact the two treatment groups on the use of psychiatric resources. Of the patients who were hospitalized at the time of initiation (N = 65), all but one patient (a risperidone-initiated patient) were discharged from their index hospitalization by the end of the year post initiation on the index drug. Patients were prescribed OLZ or RIS at doses that are customarily dispensed to patients with schizophrenia in usual care settings [10], with daily mean and (median) doses of 14.5 mg (14.3 mg) and 4.5 mg (4.3 mg) for the OLZ and RIS treatment groups, respectively.

Outcome measures

Hospitalization rates

Results from the Generalized Linear Model on hospitalization rates (presented in Tables 2 and 3) demonstrate that compared to the RIS-treatment group, the OLZ treated patients had a significantly lower rate of hospitalization in the one year following initiation on the index drug (14.4% vs. 24.1% respectively; unadjusted p = 0.044; 2.03% vs. 9.8%, adjusted p = 0.040).

Total days hospitalized

The data on the total number of days hospitalized were found to be skewed and thus required log transformation. Tables 2 and 3 demonstrate that compared to patients receiving RIS, the OLZ-treated patients were hospitalized for significantly fewer days during the year following initiation (mean 14.5 days vs. 9.9 days, respectively, unadjusted p = 0.425; following log transformation with adjustment of covariates p = 0.035). This group difference was attributed to the higher rate of psychiatric hospitalizations among the RIS-treated patients. The Two-Part model confirmed the findings, also demonstrating a higher number of hospitalization days for the risperidone treatment group (19.0 days) than for the OLZ treatment group (7.3 days).

As figure 1 illustrates, treatment with OLZ was associated with significantly fewer hospitalization days starting with the first month post initiation and continuing through the end of the year. The mean cumulative days of hospitalization at the end of each of the 12 months post initiation indicated that the average number of hospitalization days for the RIS-treated patients was 1.4 to 2.1 times that of the olanzapine treatment group. By the end of the sixth month following initiation, the patients in the RIS-treatment group had a mean of 3.9 hospitalization days more than the OLZ treated patients (mean 9.7 days vs. 5.8 days per patient, respectively, p = 0.019). In terms of cost, the adjusted mean annual group difference of 4.6 days translated to $2,502 in cost savings per OLZ-treated patient, on the average when NAPHS rates were applied at $556 per day hospitalized in 2001 [18].

Table 3: Results of the regression models for comparing the treatment groups on days hospitalized and hospitalization rates

	GLM model Days hospitalized		Logistic regression model Patients hospitalized (%)	
	Coefficient	P-Value	Coefficient	P-Value
Gender (Male = 1)	-0.10364	0.5499	-0.2017	0.2666
Age at illness onset	-0.01344	0.1529	0.0325	0.1259
Age at baseline	0.00824	0.9302	0.00791	0.6474
White (=1)	-0.15644	0.6138	0.1781	0.4967
African-American (=1)	-0.33460	0.2819	0.3623	0.1789
Prior antipsychotic drug use (Y = 1)*	-0.08674	0.6244	-0.2275	0.2163
Prior mood stabilizer use (Y = 1)*	-0.05773	0.7545	0.1397	0.4617
Prior depot use (Y = 1)*	-0.24455	0.2276	-0.2159	0.3391
Prior psychiatric hospitalization (Y = 1)*	1.89301	<0.0001	0.7779	<0.0001
Adjusted R-square	0.2331		0.1891	

* Prior period: 60 days prior to initiation on the index drug

Time to hospitalization

The Kaplan-Meyer survival curve (Figure 2) demonstrated that in the year following initiation on the index drug, a larger percentage of OLZ-treated patients remained free of hospitalization and had a longer time to first psychiatric hospitalization compared with the RIS treatment group. As presented in Table 2, the group differences were not statistically significant, with a mean time to first hospitalization (or first re-hospitalization for individuals who were inpatients at time of initiation) of 176.1 days vs. 111.0 days, p = 0.107 for the OLZ and RIS groups, respectively. The median time to first hospitalization was also numerically longer for the OLZ treatment group (173.0 days vs. 94.0 days for OLZ and RIS, respectively).

Robustness and sensitivity analysis

In order to assess the robustness and sensitivity of the current findings we (a) pursued an Intent-to-Treat (ITT) analysis for the adherent and non-adherent groups combined, (b) repeated the analyses with adjustment for the duration on a concomitant antipsychotic drug, and (c) investigated the validity of the predicted log transformation values of the Generalized Linear Model and Two Part Model.

Table 2 presents the adjusted and unadjusted results for participants who continued on the index drug for at least 1 year ("Adherent" group) as well as for the ITT population. IIT findings demonstrated that although the adjusted group differences were not statistically significant, results were highly consistent with previous findings from the "Adherent" group analysis. Specifically, the RIS-treated patients had a numerically higher hospitalization rate, a longer hospitalized duration, and a shorter median time to first hospitalization. We also found that following discontinuation of the index drug, a substantial percentage of non-adherent patients switched to the comparator drug, such that 24.3% of the RIS-treatment group switched to OLZ, and 22.5% of the OLZ-treated patients switched to RIS (p = 0.737). This illustrates that when an ITT analytical approach is used, some of the benefits attributed to the index drug may actually be due to the comparator drug. We pursued this issue in more detail for the non-adherent group and found that while on the index drug, the RIS-treated patients were significantly more likely to be hospitalized than the OLZ-treated patients (45.79% vs. 30.43%, p = 0.014). However, after the index drug was discontinued, the treatment groups did not significantly differ on hospitalization rates (38.32% vs. 28.26%, p = 0.096 for the RIS and OLZ treatment groups, respectively). Furthermore, the non-adherent RIS-treated patients were found to experience a significantly greater reduction in hospitalized duration *after* they were switched off RIS, as compared to patients who were switched off OLZ (14.1% (19.0% – 4.9%) reduction in days hospitalized from the period on the index drug to the period following drug discontinuation for RIS vs. 5.9% (13.5% – 7.6%) reduction in days hospitalized from the period on the index drug to the period post drug discontinuation for OLZ, p = 0.010). These findings demonstrate that compared to OLZ, the RIS treatment group benefited more from the discontinuation of RIS by accruing beneficial outcomes that were actually attributable to other drugs, including the comparator drug.

Since the concomitant use of antipsychotic drugs is frequently found in usual practice, we assessed whether such practice may have altered the present results by repeating the analyses with adjustment for the previous covariates in addition to the number of days on concomitant antipsychotic. Results indicated that following adjustment for concomitant use of antipsychotics, the results remained essentially unchanged (not shown). Further, in order to

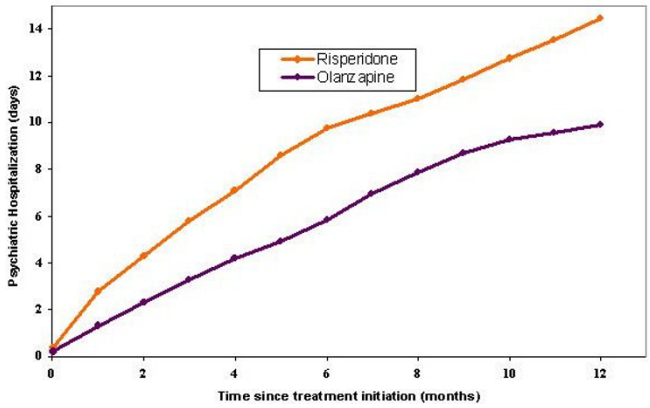

Figure 1
Average cumulative days of psychiatric hospitalization in the 12 months following initiation on olanzapine or risperidone *. * Average cumulative days differed significantly for each month during the 12 months following initiation, p-values range from p = 0.003 to p = 0.025.

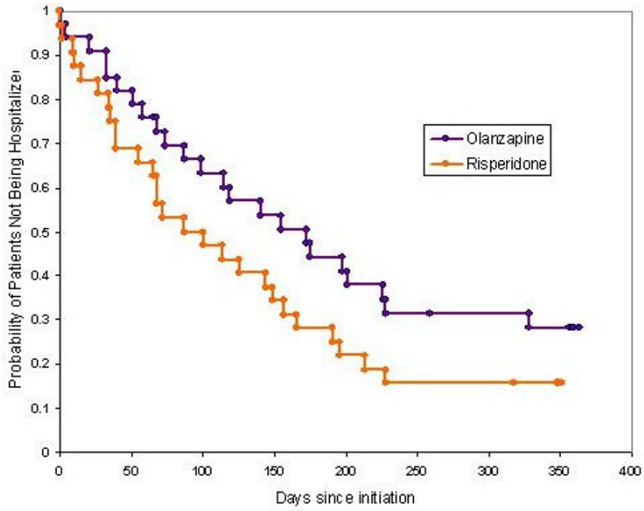

Figure 2
Time to first psychiatric hospitalization for patients initiated on olanzapine or risperidone who were hospitalized during the 1-year following initiation. * p = 0.107; Olanzapine (n = 33) and risperidone (n = 32). For outpatients: time to first hospitalization following initiation on the index drug. For inpatients at time of initiation on the drug, it was the first re-hospitalization following discharge from the index hospitalization.

demonstrate a valid transformation of the log predicted values of the Generalized Linear Model and Two Part Model, we assessed goodness of fit and heteroskedasticity. Using F-test, the comparison of the variances between the treatment groups indicated comparability (p = 0.118) and assessment of the goodness of fit demonstrated a reasonable fit to data (adjusted R square 0.23 for days hospitalized; 0.19 for hospitalization rate).

Discussion

This study compared olanzapine and risperidone on the risk of psychiatric hospitalization for patients with schizophrenia who were treated in usual care settings. Current findings complement prior findings from clinical trial research, thus providing clinicians and mental health decision makers with information to help guide their resource allocation decisions at a time of growing budgetary constraints in the mental health care delivery system. Specifically, this study was intended to investigate in usual care settings whether the two most widely used second-generation antipsychotics, olanzapine and risperidone, differ in a meaningful fashion on the risk of psychiatric hospitalization, the costliest of all service components in the treatment of patients with schizophrenia. Our findings demonstrated that compared to risperidone-treated patients, the olanzapine treatment group had a clinically meaningful and a statistically significant lower rate of hospitalization and fewer hospitalized days during the year following initiation. We found a mean group difference in days hospitalized translated to $2,502 in psychiatric hospitalization cost savings per olanzapine-treated patient per year, on the average. These cost savings more than offset the higher annual acquisition cost of olanzapine and can help maintain more patients in the community. If psychiatric hospitalization is to be viewed as a marker or a proxy for effectiveness [16], the current findings suggest that olanzapine should be a preferred therapeutic option since patients receiving olanzapine may require less psychiatric inpatient care. In addition to having economic implications, the current findings are clinically meaningful to treatment providers, to patients, and to patients' relatives because inpatient hospitalizations cause a substantial societal burden, including personal suffering, disruption of peoples' lives, and interruptions of patients' mental health treatments in the community.

Our findings documented the consistency with which treatment with olanzapine was associated with a lower risk of hospitalization as indicated by lower rates of hospitalization, shorter total hospitalization time, and a longer time to first hospitalization. It is noteworthy that findings were consistent with results from the sensitivity analysis using intent-to-treat approach in which the risperidone-treated patients had a numerically higher hospitalization rate, a longer hospitalized duration, and a shorter median time to first hospitalization. Overall, the findings provide a cohesive picture in which the

olanzapine-treated patients were not only hospitalized at a lower rate and for fewer days, but their median time to hospitalization was longer than that for patients treated with risperidone. Longer stay in the community, as observed with olanzapine, may provide the patients and their treatment teams with greater opportunities to pursue psychosocial and vocational rehabilitation and to improve the therapeutic alliance, all of which are linked to better long-term prognosis [24].

The current findings are consistent with two previous randomized double-blind clinical studies of olanzapine and risperidone in the treatment of schizophrenia [12,13]. Interestingly, at the end of the first study, which was 6-months long, the olanzapine-treated group was hospitalized for 3.6 fewer days than the risperidone-treated patients, and at 6-months in the current study the group difference was almost identical, with 3.9 fewer hospitalization days for the olanzapine than the risperidone treatment group. Our findings are similarly consistent with those found in another randomized double-blind study of patients with schizophrenia [13] in which olanzapine-treated patients had a significantly lower rate of psychiatric hospitalization than patients treated with risperidone in the year post initiation. The lower risk of hospitalization in that study was also translated into meaningful cost savings for the olanzapine-treated patients [24].

At present, there are no published findings from any head to head double-blind controlled studies of olanzapine versus risperidone demonstrating that risperidone-treated patients have a lower or even a comparable risk of hospitalization compared with patients treated with olanzapine. There is, however, a growing body of retrospective studies using intent-to-treat (ITT) methodology, comparing olanzapine and risperidone on the risk of hospitalization [6,26-32]. These studies provided a mixed picture and reported either a lower risk of hospitalization for olanzapine than for risperidone-treated patients [30,31], fewer hospitalizations for risperidone-treated patients [32], or similar rates of psychiatric hospitalization for olanzapine and risperidone-treated patients [6,26-29].

Unlike previous ITT retrospective studies, the current study aimed to avoid the potential pitfalls associated with an ITT methodology. As we have demonstrated, the bias can be introduced when there are changes in patients' medication regimens, a frequent phenomenon in the dynamic and complex treatment of patients with schizophrenia [37].

Our findings may help clinicians in choosing between olanzapine and risperidone or assist decision makers when considering the need to maintain open and unrestricted formulary access to olanzapine. Decision makers will need to balance the higher price of olanzapine compared with risperidone and the cost savings attributed to reduced psychiatric hospitalization. While we aimed to minimize potential economic bias from the payer perspective, the inclusion of patients who were continuously treated with the index antipsychotic drug during the study period also provided for a more optimal comparison between the two treatment groups by attempting to level the potentially confounding impact of non-adherence with medication, the best predictor of future psychiatric hospitalization. Furthermore, the exclusion of the non-adherent group can be construed as a more conservative approach and also as "raising of the effectiveness bar" because compared to olanzapine, the risperidone-treated patients were previously shown to have a significantly shorter time to all-cause drug discontinuation [33-36].

In this study, the two treatment groups were continuously treated with the index antipsychotic drug during the year following initiation. Based on patients' self-reports of medication adherence the treatment groups were assumed to be comparable on adherence with medication regimens. If one accepts the comparability of the two groups on adherence with medication, then the observed differences on psychiatric hospitalization parameters between the olanzapine and the risperidone-treated groups are likely to reflect differences in the effectiveness of the two antipsychotics. Based on prior research [3], about 40% of schizophrenia patients' hospitalizations are attributable to medication non-adherence whereas about 60% is due to medication efficacy factors. Differential efficacy between olanzapine and risperidone was previously demonstrated in randomized controlled trials of patients with schizophrenia, such that olanzapine therapy was found to provide patients with a more robust therapeutic response [13,38], particularly in the treatment of negative symptoms [13,38-41]. A significantly greater proportion of olanzapine-treated patients were found to achieve 20%, 40%, and 50% improvement on a general measure of psychopathology and on specific measures of negative symptoms. The differential efficacy found in randomized controlled trials was replicated in a recent naturalistic study [42] in which treatment with olanzapine provided patients with a greater improvement on negative symptoms than treatment with risperidone. Importantly, negative symptoms, such as apathy, poverty of speech, and lack of motivation are part of the schizophrenia syndrome and their presence was found to predict a longer duration of psychiatric hospitalization [43].

Results of the current study need to be evaluated in the context of their limitations. First, this study was a non-randomized observational study in which potential selection bias, particularly due to differences in illness severity, could not be ruled out because information about

patients' clinical status was unavailable at the time of initiation on the index drug. Further, the comparability of the treatment groups on adherence with medication regimens was based on prescription and self-report data, which may not reflect patients' medication adherence in an accurate fashion. However, previous research [44] has demonstrated a very high concordance rate between the presence of a prescription for psychotropic medications such as an antipsychotic, and the fill of the prescription in a patient population that resembles SCAP participants (severely mentally ill patients, diagnosed primarily with schizophrenia, covered by Medicaid). Another limitation is the generalizability of the findings due to the inclusion of participants who continued on the index antipsychotic for at least 1 year. This inclusion criterion reduced by one half the number of participants eligible for the current analysis. Consequently, results may not generalize to patient treated with olanzapine or risperidone who discontinued the index drug regimen prior to the end of the first year. In addition, results may not generalize to patients treated in the private sector because public payers covered almost all SCAP participants.

In conclusion, results of our naturalistic study are consistent with prior clinical trial research, demonstrating that among treatment-adherent patients olanzapine conferred a lower risk of psychiatric hospitalization than risperidone, thus reducing the costliest service component in the treatment of schizophrenia. Although olanzapine therapy was found to have a lower hospitalization risk than treatment with risperidone on each of the three studied hospitalization parameters, there is a need to replicate the current findings in other clinical care settings. Optimally, future comparative studies would incorporate assessments at the time of initiation on the index drug, use direct measures of medication adherence, and recognize that an intent-to-treat methodology may obscure the true economic impact of the studied antipsychotic drugs.

Competing interests

Drs. Ascher-Svanum, Zhu, Faries and Ernst are employees of and minor stockholders in Eli Lilly and Company

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