

Decline in hospitalization risk and health care cost after initiation of depot antipsychotics in the treatment of schizophrenia

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Purpose: To assess change in hospitalization and cost of care from 6 months pre- to 6 months post-initiation on any depot antipsychotic among schizophrenia patients.

Patients and methods: Using a large United States commercial claims and encounters database, patients younger than 65 years diagnosed with schizophrenia were identified. Patients initiated on a depot antipsychotic were studied in a mirror-image design to assess change in hospitalization rates, mean duration hospitalized, and hospitalization cost. McNemar's test and paired *t*-tests compared the proportions of patients hospitalized and the mean duration. Paired *t*-test and bootstrapping methods compared costs.

Results: In these patients ($n = 147$), psychiatric hospitalizations declined from 49.7% pre-initiation to 22.4% post-initiation ($P < 0.001$), and the mean hospitalized duration for psychiatric purposes numerically declined from 7.3 to 4.7 days ($P = 0.05$). Total health care costs declined from \$11,111 to \$7884 ($P < 0.05$) driven by reduction in costs for psychiatric hospitalizations from \$5384 to \$2538 ($P < 0.05$).

Conclusion: Initiation of depot antipsychotic therapy appeared to be associated with a decline in hospitalization rates and costs. Current findings suggest that treatment with depot antipsychotics may be a cost-effective option for a subgroup of patients with schizophrenia who are at high risk of nonadherence with their oral antipsychotic medication regimen.

Keywords: mirror-image, claims database, treatment outcomes, depot antipsychotics

Introduction

Longer treatment duration with antipsychotics is associated with better clinical and functional outcomes.^{1,2} Despite the benefits, many patients have difficulty sustaining maintenance treatment because of difficulties adhering to daily regimens of oral medications. More than 35% of patients have adherence issues during their first 4 to 6 weeks of treatment³ and by 2 years, 75% are considered only partially adherent.⁴ A 1998 study reported that patients receiving antipsychotics took an average of only 58% of the recommended amount of the medications.⁵

Antipsychotics in long-acting injection form ("depot") were developed in the 1960s to improve long-term schizophrenia treatment.⁶ Depot antipsychotics are often used to treat schizophrenia patients who are at high risk of nonadherence with their oral antipsychotics and, thus, also at a possible high risk of relapse and hospitalization.^{7,8} Treatment with a depot antipsychotic requires the patient to visit the clinic every 1 to 6 weeks to receive an intramuscular injection, which eliminates the patient's need to take the oral antipsychotic medication daily.

Although the efficacy of oral antipsychotic medications has been compared with depot medications by using randomized clinical trials (RCTs), there are difficulties

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using RCTs in this patient group. For example, the patients who are most appropriate for depot treatment tend to have additional problems such as substance abuse and legal issues,⁹ making them less likely to enroll in RCTs. Patients who are switched to depot antipsychotics generally have a history of poor adherence to oral antipsychotics and are frequently coaxed into depot treatment via legal commitments (“compulsory treatment”) and thus unable to give a valid informed consent for a clinical trial. It has also been suggested that RCTs are likely to recruit adherent patients selectively by excluding patients with characteristics that are associated with poor adherence (eg, comorbid substance abuse).¹⁰ Yet these patients with poor adherence are the best candidates for depot treatment.

In contrast with RCTs, retrospective mirror-image studies do not require the patients to enroll in a study, as their medication and use of services in usual care are routinely captured in claims databases. Importantly, the mirror-image study design does not require a parallel active control group, as each patient serves as his or her own control. In these studies, patients maintained on oral medication are switched to depot medications and the outcome before and after the switch is compared. While some researchers reported a decline in the number of hospital admissions after initiation on depot antipsychotics,^{11,12} other researchers reported an increase in hospitalization days and resource utilization.^{13–15} Prior mirror-image research publications have been confined to patients treated in the United Kingdom with one exception: one United States-based publication¹⁶ reported change in hospitalization and resource utilization after initiation of depot antipsychotics. In that study, from the Ohio Veterans Affairs (VA) Healthcare System, 75% of patients experienced a psychiatric-related hospitalization before depot initiation but only 42% were hospitalized during an equal amount of time after initiation. In addition to fewer psychiatric-related hospitalizations, these investigators reported shorter length of stay, fewer inpatient days per month, and one additional outpatient visit per month post-initiation. These researchers expressed a need for further United States studies in a non-VA population.

To fill this information gap and expand on the sparse United States-based research findings, the present mirror-image study aimed to assess change in hospitalization risk from 6 months pre- to 6 months post-initiation on any depot antipsychotic among patients treated for schizophrenia in the United States. Hospitalization risk was defined as the proportion of patients hospitalized and the number of psychiatric hospital admissions. Secondary objectives included assessment of the change in patients’ adherence level, assessment of the change

in utilization of outpatient services (emergency room, day treatment, and other outpatient visits), and assessment of the change in total direct cost and cost components (any inpatient hospitalization, psychiatric hospitalization, outpatient visits, and medication cost).

Material and methods

Data source

The data source for this study was the Thomson Medstat MarketScan commercial claims and encounters databases (January 1, 2004 to March 31, 2008; MarketScan® Databases, Thomson Healthcare, Inc., Ann Arbor, MI). The databases capture person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services from a selection of about 100 payers, including large employers, health plans, and government and public organizations. The MarketScan Databases link paid claims and encounter data over time and to detailed patient information across sites and types of providers, and over time.¹⁷

Study sample selection

The sample selection consisted of patients (<65 years of age) who were diagnosed with schizophrenia (International Classification of Diseases [ICD]-9-CM codes 295.XX) between January 1, 2004 and March 31, 2008 and who had at least 2 outpatient visits or 1 inpatient hospitalization associated with the schizophrenia diagnosis. Patients diagnosed with dementia type disorder were excluded. Patients who were initiated on any depot antipsychotic, who had no depot injection in the 6 months before this injection, and who had continuous enrollment for the 6 months before and 6 months after the depot initiation date (“index date”) were included if the 2 outpatient visits or 1 inpatient hospitalization occurred within 180 days before the depot initiation. The index date was the date of the first depot injection.

Study measures

Patient demographics, including age and gender, were assessed for all patients. The specific antipsychotic depot medication, schizophrenia patients’ related medical comorbidities, and substance use were determined based on ICD-9-CM diagnosis codes during the 6-month pre-index period. During the 6-month pre-index period and 6-month post-index period, data were collected on the proportion of patients hospitalized at least once for any reason, hospitalized at least once with a psychiatric diagnosis, and hospitalized at least once with a schizophrenia diagnosis, the number

of psychiatric hospital admissions, total number of days hospitalized for psychiatric purposes, adherence with antipsychotic medication (defined as the Medication Possession Ratio [MPR] – the proportion of days the patient is in possession of any antipsychotic during each 180-day observation period), outpatient service use (emergency room, day treatment, and other office visits), total direct cost, and cost components (any hospitalization, psychiatric hospitalizations, outpatient services, and medication).

Statistical methods

Patients' baseline characteristics, comorbidities, and drug use disorders in the 6-month pre-index period were summarized. Analyses comparing the pre- vs post-initiation data employed McNemar's test for categorical variables, including the proportion of patients hospitalized for psychiatric reasons and the proportion of patients who used outpatient services, and paired *t*-tests to assess the continuous variables including the mean number of admissions, mean of total hospitalized duration, and MPR. Mean cost comparisons were conducted with paired *t*-tests and bootstrapping methods. Because cost data frequently do not exemplify a typical random distribution (ie, they are usually right-skewed and truncated at zero due to a small number of patients with high costs, a large number of patients with no costs, and the impossibility of costs less than zero¹⁸), bootstrapping methods were used. Nonparametric bootstrapping is a technique where an empirical distribution of the mean cost difference between groups is constructed through resampling with replacement from the observed cost data. Bootstrapping is an alternative for analysis of cost data because it uses a nonparametric approach, which can directly address arithmetic means without making assumptions about the shape of the distribution.¹⁹ Bootstrap resampling (5000 iterations) was used to provide a nonparametric comparison of total cost as well as component costs (eg, any hospitalization cost, psychiatric hospitalization cost, outpatient cost, and medication cost) in the 6-month pre- vs post-index periods. No statistical adjustments were made for the multiple comparisons. Sensitivity analyses include examining the impact of acute care costs occurring just after the medication change, which may be incurred due to the failure on the prior treatment.²⁰

Results

From a total of 674 patients with schizophrenia who were initiated on depot antipsychotics, data from 147 patients met inclusion criteria and were included in the analyses (Figure 1). Their baseline characteristics are presented in

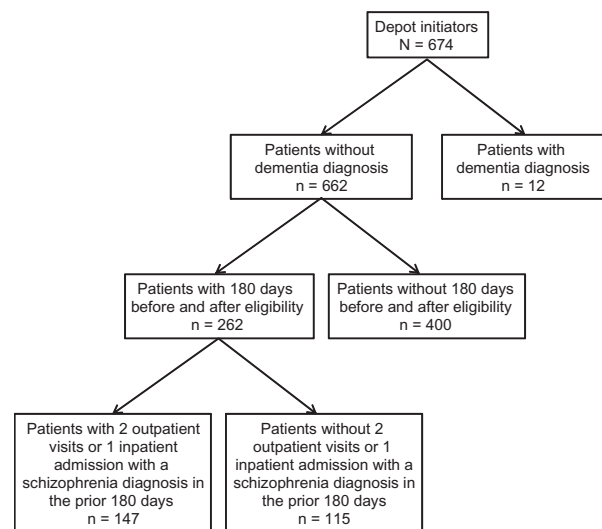


Figure 1 Patient flowchart.

Table 1, showing that the mean age was the early 40s and slightly more than half of patients were male.

After initiation of depot antipsychotics, patients improved their medication adherence. Mean antipsychotic MPR increased from 36.8% in the 6 months preceding depot initiation to 60.0% in the 6 months after initiation ($P < 0.001$). After depot initiation, patients were less likely to be hospitalized for any reason, for any psychiatric reason, and for schizophrenia specifically (Table 2). During the 6 months preceding initiation, 79 patients (53.7%) were hospitalized for any reason compared with 44 patients (29.9%) in the 6 months after initiation ($P < 0.001$). Hospitalization for any psychiatric reason decreased from 73 patients (49.7%) to 33 patients (22.4%; $P < 0.001$). Hospitalization for schizophrenia decreased from 63 patients (42.9%) to 30 patients (20.4%; $P < 0.001$).

Table 1 Patient baseline characteristics

No. of patients who initiated depot, n	147
Specific depot medication, n (%)	
Risperidone long-acting	38 (25.9)
Haloperidol decanoate	69 (46.9)
Fluphenazine decanoate	40 (27.2)
Age at initiation, mean (SD)	42.6 (14.7)
Male, n (%)	79 (53.7)
Medical comorbidities, n (%)	
Congestive heart failure	3 (2.0)
Chronic pulmonary disease	13 (8.8)
Mild liver disease	4 (2.7)
Diabetes	20 (13.6)
Diabetes with chronic complications	1 (0.7)
Substance use disorder, n (%)	17 (11.6)
Alcohol use, n (%)	4 (2.7)
Drug use, n (%)	14 (9.5)

Abbreviation: SD, standard deviation.

Table 2 Change in hospitalization parameters in the 6 months pre- vs 6 months post-depot initiation

	Before initiation	After initiation	P-value ^a
Proportion of patients hospitalized at least once for any reason, n (%)	79 (53.7)	44 (29.9)	<0.001
Proportion of patients hospitalized at least once for psychiatric reasons, n (%)	73 (49.7)	33 (22.4)	<0.001
Proportion of patients hospitalized at least once for schizophrenia, n (%)	63 (42.9)	30 (20.4)	<0.001
Inpatient psychiatric admissions, mean (SD)	0.67 (0.80)	0.31 (0.65)	<0.001
Days hospitalized for any reason, mean (SD)	8.0 (12.2)	5.3 (13.2)	0.067
Days hospitalized for psychiatric reasons, mean (SD)	7.27 (11.6)	4.73 (13.1)	0.054
Days hospitalized for schizophrenia, mean (SD)	5.7 (9.2)	4.0 (11.7)	0.190

Note: ^aPaired *t*-test for continuous variable and McNemar's test for categorical variable.

Abbreviation: SD, standard deviation.

The mean number of hospitalizations for any reason decreased from 0.78 to 0.41 ($P < 0.001$). The mean number of inpatient psychiatric admissions decreased from 0.67 to 0.31 ($P < 0.001$). The mean number of hospitalizations for schizophrenia decreased from 0.53 to 0.29 ($P = 0.002$). There were nonsignificant trends for decreases in the mean number of days of hospitalization for any reason (from 8.0 to 5.3; $P = 0.067$) and for psychiatric hospitalization (from 7.3 to 4.7; $P = 0.054$). The mean number of days of hospitalization for schizophrenia decreased from 5.7 to 4.0 but this change was not significant ($P = 0.190$).

During the 6 months preceding initiation, 36.1% of patients had 1 hospitalization for any reason, 12.2% had 2, and 5.5% had 3 or more. In the 6 months after initiation, 21.8% had 1 hospitalization for any reason, 5.4% had 2, and 2.7% had 3 or more. During the 6 months preceding initiation, 35.4% of patients had 1 hospitalization for psychiatric reasons, 12.2% had 2, and 2.1% had 3 or more. In the 6 months after

initiation, 16.3% had 1 hospitalization for psychiatric reasons, 4.1% had 2, and 2.0% had 3 or more. During the 6 months preceding initiation, 34.0% of patients had 1 hospitalization for schizophrenia, 7.5% had 2, and 1.4% had 3 or more. In the 6 months after initiation, 14.3% had 1 hospitalization for schizophrenia, 4.1% had 2, and 2.0% had 3 or more.

Change in outpatient service use was not significant. From the 6 months before depot initiation to the 6 months after initiation, the percent of patients who used emergency room services changed from 25.2% to 19.1%, the percentage of patients who used day treatment changed from 56.5% to 53.7%, and the percentage of patients having office visits changed from 88.4% to 86.4%.

Mean total direct costs of treatment decreased from \$11,111.30 in the 6 months before depot initiation to \$7883.80 in the 6 months after initiation ($P < 0.05$; Table 3). Median total direct costs decreased from \$7089.40 to \$4051.93. Mean total inpatient costs decreased from \$6696.40 to \$3593.20 ($P < 0.05$) and psychiatric-related inpatient costs decreased from \$5384.20 to \$2537.70 ($P < 0.05$). Total outpatient costs and total medication costs did not change significantly. Median total outpatient costs decreased from \$1591.05 to \$1297.62. Median total medication costs were slightly changed (\$853.04 before depot initiation and \$851.46 after initiation). The sensitivity analyses indicated that mean total direct costs of treatment decreased from \$10,615.60 in the 6 months before depot initiation to \$8379.50 in the 6 months after initiation ($P < 0.05$).

Discussion

This study used a mirror-image design to assess and compare hospitalization risk and health care costs during the 6 months before and 6 months after initiation of depot antipsychotics for the treatment of patients with schizophrenia in the United States. This study found an improvement in medication adherence, a decrease in the rate of psychiatric hospitalization for any reason, for any psychiatric reason, and for schizophrenia specifically, and a decrease in health care costs after patients initiated depot antipsychotics. These results suggest that

Table 3 Change in total cost (US\$) and cost component in the 6 months pre- vs 6 months post-depot initiation

Mean (SD)	Six months pre-depot initiation	Six months post-depot initiation	P-value
Total cost	\$11,111.30 (\$12,551.70)	\$7883.80 (\$9481.30)	0.003
Total inpatient cost	\$6696.40 (\$10,620.40)	\$3593.20 (\$7806.20)	0.002
Psychiatric inpatient cost	\$5384.20 (\$8703.40)	\$2537.70 (\$6678.70)	<0.001
Schizophrenia inpatient cost	\$4143.30 (\$7568.00)	\$2377.30 (\$6561.50)	0.017
Total outpatient cost	\$2862.16 (\$3681.64)	\$2557.77 (\$2919.90)	0.300
Total medication cost	\$1552.82 (\$2047.31)	\$1732.78 (\$2713.65)	0.220

Abbreviation: SD, standard deviation.

depot antipsychotic therapy may be a cost-effective option for a subgroup of patients typically at high risk of nonadherence with their oral antipsychotic regimen.⁹

Current findings are consistent with prior research in and outside the United States. A study in a VA population in the United States by Fuller et al¹⁶ found decreases in psychiatric-related hospitalization from 75% to 42% after initiation of depot antipsychotics. In addition to fewer psychiatric-related hospitalizations, these researchers reported shorter length of stay, fewer inpatient days/month, and one additional outpatient visit/month post-initiation. Our results are also consistent with two United Kingdom studies that reported a decline in the proportion of patients requiring hospital admissions after initiation of depot antipsychotics.^{11,12} The Taylor et al¹¹ study reported a decline in hospital admission rate from 62% before to 22% after initiation of depot. Similarly, the study by Niaz and Haddad¹² found a reduction in hospital admissions, compulsory admissions, and total inpatient days.

Our study expanded on prior research by demonstrating an increase in medication adherence after initiating depot antipsychotics. This is important because patients being treated for schizophrenia often have problems with adherence to medications, and stopping medication often has serious consequences.²¹ Increased adherence with depot antipsychotics has the additional benefit of allowing clinicians to differentiate compliance failure from efficacy failure which can reduce the use of rescue medications and the need for switching to a second-choice antipsychotic.²² Our study also demonstrated potential cost savings following depot initiation. Cost analyses found a significant decline in total cost of treatment, driven by decline in hospitalization cost from pre- to post-depot initiation.

Results need to be considered in the context of the study limitations. The sample size was rather small (n = 147). Also, the study design is devoid of a control group. In this mirror-image study, each patient served as his or her own control. As such, observed changes from pre- to post-depot initiation may reflect regression to the mean. Thus, we cannot determine if similar or even better results would have occurred with a different intervention. In addition, we used data from a large United States commercial claims and encounters database. Findings may not be generalizable to patients with schizophrenia who lack commercial insurance, which is a large segment of the schizophrenia population in the United States.

Conclusion

In summary, results from this study suggest that initiating depot antipsychotic therapy is associated with declines in hospitalization rates and related costs, compared with the

prior treatment periods. These findings also suggest that treatment with depot antipsychotics may be a cost-effective option for a subgroup of patients with schizophrenia who are at high risk of nonadherence with their oral antipsychotic medication regimen.

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