

## Impact of Atypical Antipsychotics on Outcomes of Care in Schizophrenia

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### Abstract

**Objective:** To compare persistence, compliance, and psychiatric treatment costs in patients who were initiated on atypical antipsychotics.

**Methods:** Medical and pharmacy claims data were used to compare persistence (days of therapy between first and last prescriptions, allowing therapy gaps <90 days); compliance (ratio of days of medication supplied to total days on therapy); treatment costs in adults with schizophrenia having claims for atypical antipsychotics from March 2001 to August 2003; and enrollment for  $\geq 6$  months before and  $\geq 12$  months after therapy initiation. Psychiatric treatment costs for 1 year were examined before and after therapy initiation. Differences in costs were tested by univariate analyses.

**Results:** Persistence was approximately 30 days longer for patients receiving ziprasidone ( $n = 217$ ; 228 days) than risperidone ( $n = 831$ ; 193 days) or olanzapine ( $n = 762$ ; 201 days). Compliance was significantly ( $P < .05$ ) higher among patients receiving ziprasidone (87%) compared with other treatments (78%-80%). Ziprasidone patients had significantly larger decreases ( $-\$6866$ ) in mean annual psychiatric-related costs following therapy initiation than those on risperidone ( $-\$3353$ ;  $P = .0116$ ) or olanzapine ( $-\$4764$ ;  $P = .0021$ ). The primary driver of cost savings was reduced hospitalization after treatment initiation.

**Conclusion:** Patients initiated on ziprasidone had longer persistence, better compliance, and greater decreases in psychiatric-related costs than those initiated on other atypicals.

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The prevalence of schizophrenia in the United States is approximately 1.1% for those aged  $\geq 18$  years,<sup>1</sup> yet schizophrenia accounts for 2.5% of healthcare expenditures.<sup>2</sup> Management of symptoms and manifestations of schizophrenia with pharmacotherapy is the foundation of treat-

ment. Beginning in 1990, a new generation of antipsychotic medication was introduced. In comparison to the "conventional" antipsychotics, these "atypical" antipsychotic medications have been associated with improved efficacy in treating both positive and negative symptoms of schizophrenia. These medications, which include clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole, have also exhibited a superior safety profile in regard to adverse effects (AEs).<sup>3-6</sup>

Compliance with therapy is an essential component of successful treatment. However, there are many factors that influence poor compliance with antipsychotic treatment. These include patients' beliefs regarding their illness, perceived benefits and AEs of treatment, complex drug regimens, the need to monitor for selected AEs, and access to treatment.<sup>7,8</sup> Compliance with pharmacotherapy treatment greatly impacts the cost of care for patients with schizophrenia.<sup>8-10</sup> Atypical antipsychotics have been associated with greater compliance to treatment compared with conventional antipsychotics and associated improved clinical outcomes including fewer office, hospital, inpatient, and emergency department visits.<sup>9</sup> In addition, in a study of Medicaid patients with schizophrenia, hospitalization rates (both psychiatric and medical) were lower among patients who were more compliant with prescribed therapy compared with less compliant patients.<sup>10</sup>

The goal of this study was to compare compliance with treatment and the potential effects of compliance on psychiatric-related direct costs of care among the currently available atypical therapies in real-world practice. Comparisons of costs of

care for patients with schizophrenia have been conducted for other atypical therapies,<sup>11-13</sup> but have not included ziprasidone in the comparison because of its more recent launch in the United States. The present study examined compliance, duration of therapy, and direct costs of care following initiation of atypical treatment with ziprasidone, olanzapine, and risperidone in a geographically diverse commercially insured population.

## Methods

**Data Source.** Medical and pharmaceutical claims were obtained from the PharMetrics Patient-Centric Database for the period September 1, 2000, to November 30, 2003. At the time of this study, the database included fully adjudicated claims from 70 health plans across the United States. Patients in the database are representative of the national commercially insured population on a variety of demographic measures, including geographic region, age, gender, and health plan type. The data are also longitudinal, with an average member enrollment time of 2 years. Inpatient and outpatient diagnoses (*International Statistical Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM]* format), procedures (Current Procedural Terminology, Version 4 [CPT-4] and Health Care Financing Administration Common Procedural Coding System [HCPCS] formats), as well as standard and mail order prescription records are included in the data set. Reimbursed payments and charged amounts are available for all services rendered, as well as dates of service for all claims. Additional data elements include demographic variables (ie, age, gender, geographic region), plan type (ie, health maintenance organization [HMO], preferred provider organization [PPO]), payer type (ie, commercial, self-pay), provider specialty, and plan enrollment start and stop dates.

**Sample Selection.** All patients  $\geq 18$  years of age with one or more paid pharmacy claims for risperidone, olanzapine, quetiapine, or ziprasidone between March 1, 2001, and August 31, 2003, were first selected

for inclusion in the study sample.\* Only patients with a schizophrenia or schizoaffective disorder diagnosis (*ICD-9-CM 295.XX*) in their claims history were included. The first pharmacy claim for the most recent atypical antipsychotic (ie, risperidone, olanzapine, quetiapine, or ziprasidone) received during the study period (to maximize sample size for recently launched medications) was deemed the "index date"; a preindex period of 6 months' duration was then defined in relation to this date. All medical and pharmacy claims were compiled for these patients for the period from September 1, 2000, to November 30, 2003. Follow-up varied beyond a minimum of 12 months and was terminated either at the end of the patient's enrollment period in the health plan or the study "end date" (November 30, 2003), whichever came first.

Patients not continuously eligible for drug and health benefits during their entire pre-index and follow-up periods were excluded, as were those whose insurance coverage did not include retail pharmacy or whose health plan did not report days supplied or quantity dispensed on pharmacy claims. Members of health plans that "carve out" mental health services were excluded from the sample, as complete utilization data would not be available for these patients. Patients aged  $\geq 65$  years who were not enrolled in a Medicare-Risk plan (as full utilization and cost data on nonrisk patients would not be available for such patients because of coordination of benefits with other payers) were also excluded.

In addition, appropriate dosing ranges for each medication were constructed based in part on the observed distribution of average daily doses for those medications and the recently published guidelines.<sup>14,15</sup> For each atypical therapy of interest, a 5% range was added on either side of each interval (eg, -5% for the lower bound and +5% for the upper bound) in order to capture patients whose calculated initial daily dose was reasonably close to the dosing interval.

- Ziprasidone: Patients started between 40 mg daily and 160 mg daily.

\*Aripiprazole was not approved by the Food and Drug Administration until 2002 so it was not included in this study.

- Olanzapine: Patients started between 2.5 mg daily and 40 mg daily.
- Risperidone: Patients started between 0.5 mg daily and 8 mg daily.
- Quetiapine: Patients started between 100 mg daily and 800 mg daily.

Upon review of the distribution of the daily doses, the vast majority of patients in the quetiapine group were using a daily dose well below that recommended for schizophrenia treatment.<sup>15</sup> This suggested that the majority of quetiapine use was not as a primary antipsychotic and consequently the sample size at therapeutic doses was too small to include in this study.

Patients were stratified based on the atypical therapy received on the index date (ie, ziprasidone vs olanzapine vs risperidone).

**Measures.** Measures of interest included the demographic and clinical characteristics of the study patients, duration of index therapy, compliance with index therapy, and utilization and costs during the preindex and follow-up periods.

Demographic and clinical characteristics of the study sample included age, gender, physician specialty, health plan type, geographic region, number of atypical and typical medications used in the pretreatment period, total healthcare costs (eg, payments by health plans to providers) in the preindex period, comorbidity profile preindex (as defined by the Charlson Comorbidity Index score),<sup>16</sup> and psychiatric comorbidities (other than schizophrenia). Psychiatric diagnoses (ie, mood disorders [296.0-296.1, 296.2-296.3, 296.4-296.9, 300.4], anxiety disorder [300.0X, 309.21], and/or obsessive-compulsive disorder [300.3]) present in the preindex or follow-up periods were included.

Persistence was calculated as the duration of index therapy (in days), from the first to last observed prescription date. Those with no index therapy activity for 90 days or more before the end of follow-up were designated as being “discontinued.” Any patient with a gap in therapy of 90 days or more between the time the previous prescription was exhausted and the subsequent prescription was initiated was also designated as being discontinued.

Medication possession ratio (MPR) was used as a proxy for compliance. MPR was calculated by comparing the number of days of medication supplied while on therapy with the total number of calendar days persistent on index therapy. Only patients who had 2 or more pharmacy claims on different dates for the same medication during the study period were included in the compliance analysis. MPR was measured as the Total Days Supplied divided by the Total Days of Therapy. The Total Days Supplied was defined as the sum of days supplied for the index drug from therapy initiation to the date the last prescription was filled during the follow-up period while the patient was persistent (excluding the days supplied on the last prescription). The Total Days of Therapy was defined as the number of days from therapy initiation to the date the last prescription was filled during the follow-up period while the patient was persistent. Compliance rates were capped at 100% if total days supplied exceeded total days of therapy (eg, due to early refills).

Annualized utilization and costs of atypical medications, typical medications, all other medications, outpatient care (ie, office visits, emergency room, other outpatient), inpatient care, and laboratory/microbiology were assessed before and following initiation of therapy. Costs were classified as psychiatric-related and unrelated; a grand total was also provided. Costs were categorized as psychiatric-related based on the presence of a prescription claim for an antipsychotic or a psychiatric diagnosis (*ICD-9-CM* 290.XX-319.XX) on the relevant claim.

**Analyses.** All patients meeting study entry criteria were included in these analyses. Direct costs (health plan reimbursements) for all services were calculated separately for the 6-month preindex and 12-month postindex periods. Costs were expressed in 2003 dollars, and were adjusted using the medical care component of the US Consumer Price Index.<sup>17</sup> Preperiod costs were annualized for comparison with the postindex period. Differences in costs following initiation of index therapy were compared among the treatment groups.

**Table 1.** Demographic and Clinical Characteristics of Patients, by Treatment Group

Characteristics	Group A Ziprasidone (n = 217)	Group B Risperidone (n = 831)	Group C Olanzapine (n = 762)	P Value	
				A vs B	A vs C
Age: mean [SD]	40.1 [11.9]	43.4 [14.9]	45.3 [14.6]	.0221	<.0001
Male gender (n, %)	80 (36.9)	349 (42.0)	342 (44.9)	.1710	.0354
Physician specialty (n, %)				.3899	.3134
Psychiatry	132 (60.8)	446 (53.7)	400 (52.5)		
FP/GP	16 (7.4)	77 (9.3)	91 (11.9)		
Internal medicine	18 (8.3)	63 (7.6)	66 (8.7)		
Psychology	5 (2.3)	35 (4.2)	21 (2.8)		
Neurology	0 (0.0)	4 (0.5)	2 (0.3)		
Other	45 (20.7)	198 (23.8)	174 (22.8)		
Unknown	1 (0.5)	8 (1.0)	8 (1.0)		
Plan type (n, %)				.0028	.0461
HMO	117 (53.9)	557 (67.0)	492 (64.6)		
PPO	56 (25.8)	153 (18.4)	161 (21.1)		
POS	26 (12.0)	57 (6.9)	64 (8.4)		
Indemnity	7 (3.2)	17 (2.0)	12 (1.6)		
Unknown	11 (5.1)	47 (5.7)	33 (4.3)		
Geographic region (n, %)				.1996	.1123
Northeast	21 (9.7)	126 (15.2)	122 (16.0)		
South	24 (11.1)	76 (9.1)	68 (8.9)		
Midwest	134 (61.8)	492 (59.2)	453 (59.4)		
West	38 (17.5)	137 (16.5)	119 (15.6)		
Other psychiatric diagnosis (n, %)					
Mood disorders	102 (47.0)	329 (39.6)	327 (42.9)	.0481	.2839
Anxiety disorders	28 (12.9)	99 (11.9)	116 (15.2)	.6907	.3947
Obsessive-compulsive disorder	7 (3.2)	12 (1.4)	13 (1.7)	.0798	.1626
Charlson Comorbidity Index: mean [SD]	0.5 [1.1]	0.6 [0.6]	0.7 [1.4]	.6174	.2074
Six-month preindex total healthcare costs: mean [SD]	10624.9 [16553.9]	7824.2 [17618.0]	9391.3 [22426.9]	<.0001	<.0001
Days of follow-up in postperiod: mean [SD]	561.9 [151.9]	598.0 [164.6]	592.3 [165.2]	.0035	.0199

FP/GP indicates family practitioner, general practitioner; HMO, health maintenance organization; PPO, preferred provider organization; POS, provider of service(s).

The results were stratified by index therapy. Data were presented as descriptive statistics (eg, means and standard deviations) for each treatment group. Univariate comparisons between ziprasidone and the other atypical therapies (eg, ziprasidone vs risperidone, ziprasidone vs olanzapine) were conducted using Wilcoxon rank-sum tests.

All analyses were conducted using Statistical Analysis Software (SAS<sup>®</sup>), version 8.2.

## Results

**Patient Population.** Patients initiating ziprasidone therapy (n = 217; mean [±SD] age: 40.1 [±11.9] years) were significantly ( $P < .05$ ) younger than those in the risperidone (n = 831; 43.4 [±14.9] years) and olanzapine (n = 762; 45.3 [±14.6] years) groups (Table 1). A significantly ( $P < .05$ ) smaller proportion of patients in the ziprasidone group were male compared with the olan-

**Table 2.** Compliance and Persistence for Patients New to Therapy, by Treatment Group

Characteristics	Group A Ziprasidone	Group B Risperidone	Group C Olanzapine	P value	
				A vs B	A vs C
Number of prescriptions (index therapy)					
n	1683	5130	5074		
Mean [SD]	7.8 [5.5]	6.2 [5.0]	6.7 [5.5]	.0536	.1182
Median	8.0	5.0	5.0		
Persistence (days): Patients with 1 Rx for index therapy					
Number of patients	217	831	762		
Mean [SD]	227.7 [140.8]	192.5 [140.9]	201.3 [143.7]	.1703	.0657
Median	299.0	161.0	183.0		
Compliance: Patients with 2 Rxs for index therapy					
Number of patients	178	628	587		
Mean [SD]	86.7 [19.3]	78.3 [23.9]	79.9 [23.3]	.0059	.0057
Median	96.4	87.7	89.1		

Note: Persistence and compliance were measured over a 12-month period for the subset of patients with at least 1 year of follow-up. P values calculated using Wilcoxon rank-sum year.

zapine group (36.9% vs 42.0% vs 44.9% for ziprasidone, risperidone, and olanzapine, respectively). More than half of the patients in each therapy group were seen by a psychiatrist at the time of initiation of atypical therapy. Approximately 85% of the population belonged to an HMO or a PPO plan. The overall regional distribution reflects the distribution of patients in the data source utilized in these analyses. Approximately 2 in 5 patients across treatment groups had a psychiatric comorbidity of a mood disorder (42%), 13% had a diagnosis of anxiety disorder, and 2% had a diagnosis of obsessive-compulsive disorder. Patient severity as defined by the Charlson Comorbidity Index Score was similar among the 3 treatment groups (range: 0.5-0.7).

**Compliance and Persistence.** Compliance was significantly ( $P < .01$ ) higher among patients receiving ziprasidone (87% [ $\pm 19$ ]) therapy compared with the other treatment groups (78% [ $\pm 24$ ] for risperidone and 80% [ $\pm 23$ ] for olanzapine) (Table 2). Persistence in the first year following initiation of ther-

apy was approximately 30 days longer on average (albeit not statistically significant) among patients receiving ziprasidone (228 [ $\pm 141$ ] days) compared with risperidone (193 [ $\pm 141$ ] days;  $P = .1703$ ), and olanzapine (201 [ $\pm 144$ ] days;  $P = .0657$ ).

During this period, the average number of prescriptions for index therapy was higher in the ziprasidone group (7.8 [ $\pm 5.5$ ]) compared with the risperidone (6.2 [ $\pm 5.0$ ];  $P = .0536$ ) and olanzapine (6.7 [ $\pm 5.5$ ];  $P = .1182$ ) groups.

**Direct Costs.** Mean annualized preindex total costs were highest in the ziprasidone treatment group (\$21 277) compared with the risperidone (\$15 674) and olanzapine (\$18 717) groups. Psychiatric-related costs constituted the majority of the costs in each treatment group (\$17 145 vs \$11 538 vs \$14 092 for ziprasidone, risperidone, and olanzapine, respectively).

The change in total costs from the pre- to postindex periods was not significantly different among the treatment groups (-\$4656 vs -\$3041 vs -\$4942 for ziprasidone, risperidone, and olanzapine, respectively) (Table 3).

**Table 3.** Annualized Change in Cost of Healthcare Services Following Index Date, by Treatment Group

Medication & Services	Group A Ziprasidone (n = 217)		Group B Risperidone (n = 831)		Group C Olanzapine (n = 762)		P Value	
	Mean (\$)	SD	Mean (\$)	SD	Mean (\$)	SD	A vs B	A vs C
<b>Psychiatric-related cost</b>								
Pharmacy claims:								
Atypical medications	662	1981	843	1482	1812	2002	.0983	<.0001
Typical medications	-18	265	-13	136	-15	192	.4137	.5858
Other medications	5	96	-5	119	1	20	.7869	.4310
Outpatient claims:								
Outpatient management	-425	2919	177	1548	171	1739	.0004	.0011
Outpatient ED	-109	939	-77	1312	-124	1110	.6760	.3527
Partial hospitalization	-48	580	-20	943	-42	776	.5659	.5191
Laboratory/diagnostic tests	-14	327	-8	319	-14	295	.0217	.1534
Outpatient procedures	5	56	0	13	0	147	.9895	.7310
All other outpatient	-169	4767	-532	5487	-215	5296	.7978	.8312
Inpatient claims:								
Hospitalization costs	-6754	28 227	-3718	33 248	-6337	43 536	.1119	.9596
<b>Total psychiatric-related cost</b>	<b>-6866*</b>	<b>30 051</b>	<b>-3353</b>	<b>33 720</b>	<b>-4764*</b>	<b>43 299</b>	<b>.0116</b>	<b>.0021</b>
<b>Other-related cost</b>								
Pharmacy claims:								
Other medications	309	1822	322	1155	318	1816	.3283	.5685
Outpatient claims:								
Outpatient management	72	719	-24	528	-22	698	.2973	.3407
Outpatient ED	99	654	-90	1265	-83	1180	.1088	.0895
Partial hospitalization	-9	138	14	560	-2	193	.6955	.5406
Laboratory/diagnostic tests	95	997	-21	989	-11	994	.9100	.8087
Outpatient procedures	40	1023	-9	747	-61	1234	.4511	.3172
All other outpatient	191	2432	-109	3516	-265	4163	.2733	.1403
Inpatient claims:								
Hospitalization costs	1412	14 219	229	12 735	-52	7304	.8189	.8097
<b>Total other-related cost</b>	<b>2210*</b>	<b>16 171</b>	<b>312</b>	<b>14 319</b>	<b>-178</b>	<b>8864</b>	<b>.4575</b>	<b>.2376</b>
<b>Total costs</b>	<b>-4656</b>	<b>36 019</b>	<b>-3041</b>	<b>35 861</b>	<b>-4942</b>	<b>44 355</b>	<b>.1717</b>	<b>.1321</b>

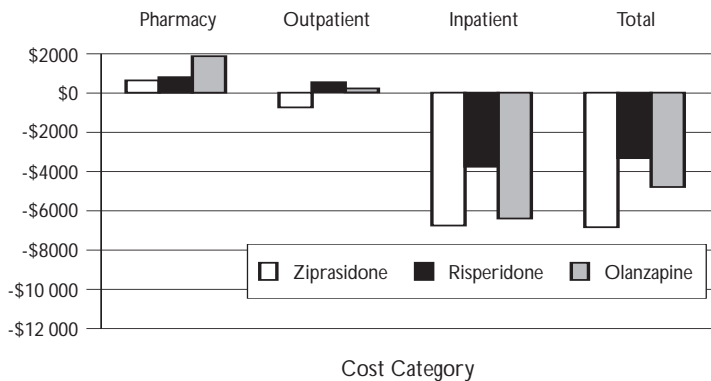
\*Numbers rounded up.

ED indicates emergency department.

However, the mean change in annual psychiatric-related costs was significantly greater among the patients initiating treatment with ziprasidone (-\$6866) compared with the risperidone (-\$3353;  $P = .0116$ ) and olanzapine (-\$4764;  $P = .0021$ ) treatment groups (Figure). The largest decrease in costs for each group was because of a decrease in hospitalization costs (-\$6754 vs

-\$3718 vs -\$6337 for ziprasidone, risperidone, and olanzapine, respectively). As expected, medication treatment costs increased among each of the treatment groups, although the mean annual atypical medication cost for ziprasidone patients was significantly lower than that of olanzapine patients (\$662 vs \$1812;  $P < .0001$ ). The costs of outpatient management visits de-

**Figure.** Comparison of Change in Psychiatric-related Costs by Treatment Group



Total psychiatric-related cost:  $P = .0116$  vs risperidone;  $P = .0021$  vs olanzapine.

creased by approximately \$400 in the ziprasidone group while increasing by almost \$200 in the other treatment groups (ziprasidone vs risperidone:  $P = .0004$ ; ziprasidone vs olanzapine:  $P = .0011$ ).

**Discussion**

Overall, findings from this study suggest that compliance with atypical antipsychotic treatment when patients are persistent on therapy is better with ziprasidone treatment compared with olanzapine and risperidone. Patients receiving ziprasidone treatment are also likely to remain on treatment longer than patients receiving the other 2 atypical therapies.

Mean annual direct costs of care for patients undergoing treatment for schizophrenia or schizoaffective disorder are substantial (\$13 592). Patients initiating ziprasidone treatment had a significantly greater decrease in annual costs of care as compared with patients initiating treatment with olanzapine or risperidone. Similar results were observed in a study conducted in Spain using an economic model comparing the tolerability and direct medical costs for patients initiating antipsychotic treatment. This study found that annual costs of care for patients initiating ziprasidone treatment were \$500 lower than for risperidone or olanzapine.<sup>18</sup>

Patients initiating treatment with ziprasidone had higher total and mental health

costs in the preindex period. This suggests that these patients may have had more severe psychiatric illness or been treatment refractory, leading to the choice of a newer agent for their treatment. Claims databases do not contain direct measures of illness severity, so it is not possible to test this hypothesis with this data set.

Most of the decrease in the annual costs was attributed to a reduction in hospitalization costs. In this study, patients initiating ziprasidone treatment had an average rate of 5 hospitalizations per 100 person-years following initiation of therapy compared with 7 hospitalizations per 100 person-years for both the olanzapine and risperidone groups. Hospitalization rates in this study were similar to those reported by Whitehorn and colleagues in a study of newly diagnosed patients.<sup>19</sup> Their analysis revealed that the overall rate of hospitalization in the first year of treatment was 17%; however, among the patients diagnosed in an outpatient setting, the hospitalization rate was 7%. The association between compliance and hospitalization rates has been documented in a recently published study by Weiden and colleagues.<sup>20</sup> Among California Medicaid patients with schizophrenia, risk of hospitalization was significantly correlated with compliance. Lower compliance was associated with a significantly greater risk of hospitalization, and the risk increased as the number of days between prescription refills increased.

There are some important limitations to this study. Compliance and persistence for patients receiving therapy has been assessed using administrative claims data. Prescription claims data cannot verify administration or that patients took the drug as prescribed, but can verify drug availability at the time of dispensing. Also, the majority of patients included in the study were enrolled in commercial insurance plans and few were managed Medicaid participants. Consequently, our study may not be truly representative of the schizophrenia population in the United States. Third, for patients 65 years of age and older, our sample was restricted to include only patients who were enrolled in a Medicare-Risk plan. Patients who are enrolled in a managed Medicare

benefit may differ in certain respects from the overall elderly population in the United States (eg, demographics, severity).

As optimal dosing is an integral component of persistence with treatment, stratified analyses were also completed for each medication by dosing group (ie, low, medium, high). Among each of the therapies, persistence with therapy was highest among patients receiving the highest dose (ziprasidone: 120-160 mg/day, risperidone: 6-8 mg/day, olanzapine: 30-40 mg/day). However, even among the highest dosing group, patients receiving ziprasidone were on therapy an average of 40 days longer than patients receiving high-dose risperidone and 30 days longer than those receiving high-dose olanzapine. However, compliance with treatment did not improve as the dosing level increased for any of the studied medications.

Costs were categorized as psychiatric-related or other-related based on a hierarchy. Consequently, costs were not partitioned between the 2 categories within an individual claim. Psychiatric-related costs may have been overstated if other-related costs were attributed to a claim assigned as psychiatric-related.

Despite these limitations, these findings suggest that patients initiating treatment with ziprasidone have better compliance with treatment and a larger decrease in associated psychiatric-related treatment costs compared with risperidone and olanzapine. The findings of this study have substantial implications for managed care since the relationship between compliance and prevention of hospitalization and relapse are key drivers of increased costs to third-party payers.

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