

Cost Analysis of Atypical Antipsychotic Agents North Dakota Medicaid

Larry E. Bridger, R.Ph., MS
Clinical Education Consultant, Pfizer, Inc.

Background

Schizophrenia is a devastating psychotic disorder that affects a broad spectrum of cognitive and emotional systems in the brain. It can be described as a severe, persistent disease of the brain that manifests with multiple signs and symptoms involving thought, perception, emotion, movement and behavior. Worldwide lifetime prevalence is approximately 0.05% to 1%.ⁱ Lower educational levels, socioeconomic status, and unmarried status correlate with higher prevalence rates.ⁱⁱ

It generally manifests early in life, usually between 15 and 25 years for men and 25 and 33 years for women. Because the disease develops at such a young age, individuals are often unable to reach their full social and occupational potential. Lost potential for employment creates a large economic burden for patients' families, as well as society, who assume the costs associated with living and medical therapy for these patients.ⁱⁱⁱ

Pharmacotherapy is the cornerstone of the treatment and management of schizophrenia. The agents include conventional antipsychotic agents, such as haloperidol and thioridazine, and the atypical antipsychotic agents clozapine, risperidone, olanzapine, quetiapine and ziprasidone. The conventional antipsychotic agents were first introduced in the 1950s and provided a significant advancement in the treatment of this illness. Though the conventional antipsychotics still provide good positive symptom efficacy, they have limited impact on negative symptoms, a high incidence of central nervous system side effects (e.g. extrapyramidal symptoms) and high rates of non-compliance due to tolerability issues.^{iv} Clozapine (Clozapine®) was the first of the atypical antipsychotic agents to be marketed in the US for the management of treatment-resistant schizophrenia in 1990. A number of trials and experience in the US and Europe demonstrated superior efficacy compared to conventional antipsychotic agents in both negative and positive symptoms as well as a low incidence of EPS.^v However the agent sustains a 1% incidence of agranulocytosis which requires monitoring that may be expensive and inconvenient for patients and have limited the use of clozapine.^{vi} The next atypical antipsychotic agent was marketed in 1994, risperidone (Risperdal®), followed by olanzapine (Zyprexa®) in 1996, and quetiapine (Seroquel®) in 1997.^{vii,viii,ix} These agents differ from clozapine relative to the potential for agranulocytosis. Like clozapine the newer agents have a low potential for EPS and are effective for both negative and positive symptoms. In 2001, the newest novel antipsychotic agent was marketed under the brand name of Ziprasidone® (Geodon).^x

Switching between conventional and atypical agents may occur as a result of poor therapeutic response at therapeutic doses or tolerability issues. In addition, patients can be tried on alternative atypicals if they are not tolerating certain side effects associated with a particular antipsychotic agent.

Other issues related to treating Schizophrenia include a poor therapeutic response rate (approximately 30%), non-compliance (approximately 50% at 1 year), and a high relapse rate which has been described as high as 75% for untreated/noncompliant patients and 25% for treated patients.^{xi} In addition these patients have a number of comorbid concerns such as substance/alcohol abuse history, depression and suicide. Schizophrenic patients are also at an increased risk for all-cause mortality compared to the general population, including a 2

times greater risk of cardiovascular related mortality. Risk factors for increased cardiovascular mortality with this population include a higher incidence of obesity, greater risk of developing diabetes, and the high percent of smokers (70-80% compared to 25% in the general population).^{xii}

Schizophrenia is associated with a significant cost burden to the health care system. It is associated with more than \$100 billion spent annually in direct and indirect costs.^{xiii} The disease currently ranks as the seventh highest cause of disability in this country. Much of the cost associated with schizophrenia is related to patient institutionalization due to failure of pharmacotherapy. Antipsychotic medications that are associated with a more favorable side effect profile may improve patient compliance and ultimately increase the success of pharmacotherapy in reducing institutionalization and costs.

Objective

The objective of this project was to assist the State of North Dakota in the evaluation of current utilization patterns of atypical antipsychotic medications for Medicaid. Secondly, the objective was to evaluate the potential budgetary impact of changing market shares of selected therapeutic agents.

Methods/Results

Atypical antipsychotic drug utilization patterns for Medicaid recipients for six months (January through June) of calendar year 2002 were obtained from North Dakota Medicaid utilization data. These data were converted into a Microsoft Access database for analytical purposes. The following tables and graphs represent the utilization data obtained.

Results

Table 1. Utilization by Drug: Risperidone is the highest utilized atypical antipsychotic in terms of prescriptions at 35.6% (n = 7791) , followed by Olanzapine at 25.1% (n = 5501). Quetiapine accounts for 18.8% (n = 4113) and Clozapine is 14.9% (n = 3272). Ziprasidone is the least utilized antipsychotic at 4.3% (n = 948) other than Zydis® (1.2%, n = 262).

Drug	Total Rx per Drug	% Utilization
Clozapine	3272	14.9%
Ziprasidone	948	4.3%
Risperidone	7791	35.6%
Quetiapine	4113	18.8%
Olanzapine	5501	25.1%
Olanzapine (Zydis)	262	1.2%
Total	21887	100%

Graph 1: Utilization by Drug and Strength: Graph 1 displays the utilization of the atypical antipsychotic utilization by strength. Risperidone 1mg is the highest utilized dose (12%) of all the atypicals, followed by Risperidone 0.5mg (9.6%) and Clozapine 100mg (9.3%). Quetiapine 25mg, and Olanzapine 5mg, and Olanzapine 10mg are at 7.9%,7.2%, and 7.0% respectively.

Table 2. Total and Percent Cost by Drug: Although Olanzapine accounts for 25.4% of the utilization by prescription, it is 37% of the cost. Risperidone accounts for 36% of the utilization and 28.1% of the cost. Quetiapine is 17% of the cost and 19% of the utilization.

Drug	Total Cost	% Cost
CLOZAPINE	\$436,954.95	12.48%
ZIPRASIDONE	\$136,270.97	3.89%
RISPERIDONE	\$983,779.69	28.09%
QUETIAPINE	\$603,787.60	17.24%
OLANZAPINE	\$1,271,778.99	36.31%
OLANZAPINE (ZYDIS®)	\$69,556.56	1.99%
	\$3,502,128.76	100.00%

Graph 3. Total Cost by Drug: Graph 3 graphically compares the total Medicaid cost of each of the atypical antipsychotics.

Graph 4. Breakdown by Diagnosis: A total of 3,401 patients were in the database. Based on diagnoses codes, only 27.8% (n = 946) of the patients were diagnosed as having schizophrenia. Another 21.9% (n = 745) were diagnosed with Depression, and 17.1% (n = 581) with Psychosis. A combination of Psychosis and Schizophrenia accounted for approximately 45% (n = 1,527) of the patients.

Table 3. Average Number of Prescriptions: The average number of prescriptions per patient is slightly over one per month.

Total # of Rx's	Total # of Patients	Average # of Rx's per Patient	Annualized # of Rx's per Patient
21,887	3,401	6.43	12.87

Graph 5. Cost per Prescription: Olanzapine is the highest cost per prescription at \$232.75, followed by Quetiapine at \$146.80. Risperidone is the least expensive on a cost per prescription basis at \$126.27.

Graph 6. Clozapine and Concurrent Medications (> 30 days): There were one hundred and six prescriptions (3.2%) for Clozapine that had concomitant medications prescribed. 41.5% (n = 44) had concomitant novel antipsychotics, 23.6% (n = 25) had concomitant mood stabilizers, and 16% had concomitant antidepressants prescribed.

Graph 7. Ziprasidone and Concurrent Medications (> 30 days): There were one hundred fifty-six prescriptions (16%) for Ziprasidone that had concurrent medications prescribed. The majority (32.69%, n = 51) had antidepressants prescribed concurrently.

Graph 8. Risperidone and Concurrent Medications (> 30 days): Eight hundred thirty eight (10.7%) of Risperidone prescriptions had concurrent medications prescribed. Forty two percent (n = 356) of those were prescribed a concurrent antidepressant.

Graph 9. Quetiapine and Concurrent Medications (> 30 days): Thirteen percent (n = 532) Quetiapine prescriptions had concurrent medications prescribed. The majority (38%, n = 202) were concurrent antidepressants.

Graph 10. Olanzapine and Concurrent Medications (> 30 days): Seven hundred twenty (12.5%) of Olanzapine prescriptions had concurrent medications prescribed. A majority (33.5%) were antidepressants, followed closely by mood stabilizers (29.6%).

THERAPY COST: The following images are from a floating Markov transition matrix technology called Therapy Cost®. This models the perpetual movement of patients between therapeutic treatment arms and demonstrates the economic impact of changing market shares.

Scenario One: Decreasing Olanzapine by 5% and increasing Ziprasidone by 5% will produce cost savings for North Dakota State Medicaid \$165,937 per year or \$48.79 per patient.

THERAPY OPTIONS (Double click for costs) \$	CURRENT		NEW		Current \$	New \$
	% patients	n current	% patients	n new		
Olanzapine	26.30	894.5	21.30	724.4	2553613	2068135
Risperidone	35.60	1210.8	35.60	1210.8	1894996	1894996
Quetiapine	18.80	639.4	18.80	639.4	1152747	1152747
Ziprasidone	4.30	146.2	9.30	316.3	255014	551542
Clozapine	15.00	510.2	15.00	510.2	837950	860963
	0.00	0.0	0.00	0.0	0	0
	0.00	0.0	0.00	0.0	0	0
	0.00	0.0	0.00	0.0	0	0
	0.00	0.0	0.00	0.0	0	0
Lost to follow-up	0.00	0.0	0.00	0.0	0	0
	100	3401.1	100	3401.1	6694320	6528383
					Difference	165937
					1968.28	1919.49
					Per patient	48.79
					Total	
					0.0	3401.0
					0.0	3401.0 100.0%

HORIZON
 1

Cumulative costs
 Current cycle costs

INTENT TO TREAT ANALYSIS

Scenario Two: Decreasing Olanzapine utilization by 10% and increasing Ziprasidone by 10%, the cost savings to North Dakota Medicaid would be \$354, 888 per year and \$104.34 per patient.

THERAPY OPTIONS (Double click for costs) \$	CURRENT		NEW		Current \$	New \$
	% patients	n current	% patients	n new		
Olanzapine	26.30	894.5	16.30	554.4	2553613	1582657
Risperidone	35.60	1210.8	35.60	1210.8	1894996	1894996
Quetiapine	18.80	639.4	18.80	639.4	1152747	1152747
Ziprasidone	4.30	146.2	14.30	486.3	255014	848069
Clozapine	15.00	510.2	15.00	510.2	837950	860963
	0.00	0.0	0.00	0.0	0	0
	0.00	0.0	0.00	0.0	0	0
	0.00	0.0	0.00	0.0	0	0
	0.00	0.0	0.00	0.0	0	0
Lost to follow-up	0.00	0.0	0.00	0.0	0	0
	100	3401.1	100	3401.1	6694320	6339432
HORIZON 1					Difference	354888
Init <input checked="" type="radio"/> Cumulative costs <input type="radio"/> Current cycle costs					1968.28	1863.94
INTENT TO TREAT ANALYSIS					Per patient	104.34
					Total	
					0.0	3401.0
					0.0	3401.0 100.0%

Scenario Three: Decreasing Olanzapine utilization by 15% and increasing Ziprasidone by 15%, the cost savings to North Dakota Medicaid would be \$543,837 per year and \$159.90 per patient.

THERAPY OPTIONS (Double click for costs) \$	CURRENT		NEW		Current \$	New \$
	% patients	n current	% patients	n new		
Olanzapine	26.30	894.5	11.30	384.3	2553613	1097180
Risperidone	35.60	1210.8	35.60	1210.8	1894996	1894996
Quetiapine	18.80	639.4	18.80	639.4	1152747	1152747
Ziprasidone	4.30	146.2	19.30	656.4	255014	1144597
Clozapine	15.00	510.2	15.00	510.2	837950	860963
	0.00	0.0	0.00	0.0	0	0
	0.00	0.0	0.00	0.0	0	0
	0.00	0.0	0.00	0.0	0	0
	0.00	0.0	0.00	0.0	0	0
Lost to follow-up	0.00	0.0	0.00	0.0	0	0
	100	3401.1	100	3401.1	6694320	6150483
HORIZON 1					Difference	543837
Init <input checked="" type="radio"/> Cumulative costs <input type="radio"/> Current cycle costs					1968.28	1808.38
INTENT TO TREAT ANALYSIS					Per patient	159.90
					Total	
					0.0	3401.0
					0.0	3401.0 100.0%

scenario Four: Decreasing Olanzapine utilization by 15%, Quetiapine by 5%, and increasing Ziprasidone by 20%, the cost savings to North Dakota Medicaid would be \$553,890 per year and \$162.80 per patient.

THERAPY OPTIONS (Double click for costs) \$	CURRENT		NEW		Current \$	New \$
	% patients	n current	% patients	n new		
Olanzapine	26.30	894.5	11.30	384.3	2553613	1097180
Risperidone	35.60	1210.8	35.60	1210.8	1894996	1894996
Quetiapine	18.80	639.4	13.80	469.3	1152747	846166
Ziprasidone	4.30	146.2	24.30	826.4	255014	1441125
Clozapine	15.00	510.2	15.00	510.2	837950	860963
	0.00	0.0	0.00	0.0	0	0
	0.00	0.0	0.00	0.0	0	0
	0.00	0.0	0.00	0.0	0	0
	0.00	0.0	0.00	0.0	0	0
Lost to follow-up	0.00	0.0	0.00	0.0	0	0
	100	3401.1	100	3401	6694320	6140430
HORIZON					Difference	553890
1					1968.28	1805.48
INTENT TO TREAT ANALYSIS					Per patient	162.80
					Total	3401.0
					0.0	3401.0 100.0%
					0.0	

Discussion:

This analysis evaluated the utilization of atypical antipsychotic agents based on six months of data from January through June 2002. Risperidone has the highest utilization (35.6%) in number of prescriptions than the other agents. The distribution of the utilization of Risperidone is heavily weighted toward the lower dosages and accounts for a lower percent of the total costs(28.1%). Eighty-four percent of the prescriptions are for the dosage forms from 0.25mg to 2mg with the remainder (15.6%) in the higher dose ranges of 3 and 4 mg. This weighted distribution toward the lower doses has a positive effect on the total cost of therapy, but would beg the question of whether these lower doses are being used for the treatment of Schizophrenia or some other disorder such as depression, bi-polar or dementia. If being used for another disorder, there may be lesser expensive alternatives than the atypical antipsychotic agents. Overall, Risperidone is being used cost-effectively relative to the other atypicals due to the lower dosing regimens, but the actual daily cost for treating schizophrenia may be underestimated. .

Olanzapine is only slightly weighted toward the lower dosage range (58.4% are for 2.5mg to 7.5mg) whereas 41.6% of the prescriptions are for 10mg and above. However, although Olanzapine accounts for 26% of the utilization it accounts for 38% of the costs. It is also the highest cost agent on a per prescription basis at \$232.75 compared to \$126.27 for Risperidone.

Clozapine utilization is in the higher end of the dosage range (79% at 100mg). Quetiapine 100mg and 200mg are 54% of the utilization versus 46% for the 25mg dose. Ziprasidone

60mg and 80mg doses account for 35% of the dosing, whereas 20mg and 40mg account for 65% of the doses used.

Concomitant utilization with other Central Nervous System medications for more than 30 days was a common finding with all of the atypical agents. Clozapine had the highest concomitant utilization with other atypical agents at 41.5%. Risperidone had the highest concomitant utilization with antidepressants (42.5%), although Quetiapine, Olanzapine, and Ziprasidone were above 30% concomitant use. Olanzapine had a slightly higher utilization of concomitant mood stabilizers (29.6%) compared to Ziprasidone at 28.2%.

The diagnosis of Schizophrenia occurred in only 27.8% of the patients based on diagnostic codes. The high rate of utilization of atypical antipsychotic agents would seem to demand a higher rate of diagnosis of schizophrenia. As mentioned above, there appears to be a substantial amount of usage for atypical antipsychotics for other than schizophrenia.

The Therapy Cost Scenario's One through Three analyses estimates possible switch rates from Olanzapine to Ziprasidone at different percentages based, first on comparative efficacy, safety, and ultimately, on its cost effectiveness. Scenario Four also included Quetiapine in the switch calculation. A market switch for patients currently taking Clozapine was not considered in this analysis since those patients have usually failed all other therapy. Ziprasidone, because it is considered to be weight neutral, can be expected to be used in those individuals who have significant weight gain (defined as $\geq 7\%$ increase in body weight) or have failed therapy with Olanzapine or Quetiapine. In short-term trials 29% of Olanzapine patients and 23% of Quetiapine had significant weight gain according to the above-defined criteria. In the Olanzapine long-term clinical trials the incidence of weight gain $\geq 7\%$ in body weight was noted in 56% of patients. The most common reason for discontinuation of Risperidone is EPS. The incidence of EPS with Risperidone is dose-dependent and was noted to occur in 17% of patients at doses ≤ 10 and 34% at 16 mg/day. Since the majority of the Risperidone doses are in the low range and are cost effective, no switch rates were considered in this analysis.

It is worth noting that the safety data collected to date with Ziprasidone suggests that there is less potential for body weight, serum insulin, and blood glucose changes compared to other atypical antipsychotics and therefore presents a lower risk of diabetes and coronary heart disease to patients. Both of these diseases are obvious significant cost drivers to the overall cost of healthcare. Also of note, is the availability of intramuscular Ziprasidone as the first available parenteral formulation of an atypical antipsychotic. It has been well accepted as an alternative to treat acute psychotic episodes. The availability of both intramuscular and oral step-down preparations of Ziprasidone enhances current treatment approaches to this disorder.

Conclusion/Recommendation

This pharmacoeconomic analysis looked at cost from the Medicaid perspective. This analysis assumed that all other costs for therapy were equal (e.g. laboratory monitoring, cost for managing adverse drug events, etc.) and all the medications were being used for the same diagnosis.

1. Consider market share switch of patients who are not responding or having side effects from Olanzapine to Ziprasidone for a conservative cost savings of over \$500,000. A higher switch rate as well as beginning new patients on Ziprasidone could yield additional savings.

2. Consider further analysis to determine the actual utilization of Risperidone and Quetiapine in schizophrenia patients and determine if a positive economic outcome exists from a market switch to another agent.

ⁱ National Advisory Mental Health Council. Healthcare reform for Americans with severe mental illnesses: report of the National Advisory Mental Health Council. *Am J Psychiatry* 1993; 150:1447.

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ⁱⁱⁱ National Advisory Mental Health Council. Healthcare reform for Americans with severe mental illnesses: report of the National Advisory Mental Health Council. *Am J Psychiatry* 1993; 150:1447.

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^{vi} Clozapine Package Insert. Novartis; September 1999

^{vii} Risperidone Package Insert. Janssen; May 1999.

^{viii} Olanzapine Package Insert. Lilly; March 2000

^{ix} Quetiapine Package Insert. AstraZeneca; May 1999

^x Ziprasidone Package Insert. Pfizer; June 2002

^{xi} American Psychiatric Association. Practice Guideline for the treatment of patients with schizophrenia. *Am J Psychiatry* 1997; 154(Suppl):1.

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