



Indiana Medicaid Drug Utilization Review Board Newsletter

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Atypical Antipsychotics: Monitoring the Metabolic Effects

Antipsychotics are widely used in the medical management of many psychiatric conditions. Atypical antipsychotics are considered more effective in treating certain symptoms of psychotic illness and are better tolerated than the first-generation antipsychotics. However, these newer antipsychotics are associated with serious adverse effects including weight gain, hyperglycemia and new-onset diabetes, and dyslipidemia. Since these metabolic side effects are associated with the development of cardiovascular disease, early interventions are imperative for the safety of the patient.

It is difficult to determine whether the incidence of obesity, diabetes, or dyslipidemia are increased in patients with psychiatric illnesses independent of antipsychotic use. Studies suggest that the prevalence of obesity and diabetes among patients with schizophrenia and affective disorders is approximately 1.5 to 2 times higher than the general population. In addition, patients may be prone to obesity and dyslipidemia due to poor lifestyle habits. Limited data also suggest that drug-naïve schizophrenic patients have an increased prevalence of impaired fasting glucose and insulin resistance and higher glucose, insulin, and cortisol levels than patients without psychiatric illnesses. Available evidence suggests these patients have an increased prevalence of obesity, impaired glucose tolerance, and type 2 diabetes. Whether this is due to the illness itself as opposed to drug treatment is still unknown.¹ A joint panel of the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endo-

crinologists, and the North American Association for the Study of Obesity published a consensus statement in February 2004 examining the relationship of atypical antipsychotics with obesity, diabetes, and dyslipidemia (Table 1). The following are some conclusions of the consensus.

Obesity

Obesity was determined to be strongly associated with the use of atypical antipsychotics. Rapid weight gain is usually seen in the first few months of therapy, but weight can still increase in patients even after one year of therapy. Weight gain and subsequent changes in body composition may precipitate other metabolic complications such as insulin resistance, diabetes, and dyslipidemia. Clozapine and olanzapine are associated with the highest incidence of weight gain, followed by risperidone and quetiapine, with aripiprazole and ziprasidone having little effect on weight, though studies are limited with the latter agents.¹

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Physician education addressing the important adverse effects of atypical antipsychotics and their effects on obesity, diabetes, and dyslipidemia can hopefully prevent future patient complications and decrease overall health care costs. Baseline screening, ongoing monitoring, and appropriate adjustment (or switching) of medication is necessary to decrease the likelihood of developing or worsening cardiovascular diseases, diabetes, or other complications.

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Table 1. Second-generation antipsychotics and metabolic abnormalities¹

Drug	Weight Gain	Risk for Diabetes	Worsening Lipid Profile
Clozapine	+++	+	+
Olanzapine	+++	+	+
Risperidone	++	D	D
Quetiapine	++	D	D
Aripiprazole*	+/-	-	-
Ziprasidone*	+/-	-	-

+ = increase effect; - = no effect; D= discrepant results. *Newer drugs with limited long-term data.

Diabetes

The onset or exacerbation of diabetes has been documented following initiation of atypical antipsychotics. Data from studies consistently show that patients on clozapine or olanzapine have an increased risk for diabetes compared with patients on first-generation or other second-generation antipsychotics. There is some evidence that risperidone and quetiapine can increase risk, but additional studies are warranted. Aripiprazole and ziprasidone have not shown significant effects on glucose because long-term data are limited. Impairment of insulin action (eg, insulin resistance) may be one possible mechanism for hyperglycemia. Drug-induced insulin resistance may be due to weight gain, change in body fat distribution, or a direct effect on insulin-sensitive target tissues. The Food and Drug Administration has requested that labeling for all atypical agents carry a warning on the potential risk for developing diabetes.¹

Dyslipidemia

Dyslipidemia, associated with atypi-

cal antipsychotics, is evident by increases in total cholesterol, LDL cholesterol, and triglycerides, and decreases in HDL cholesterol. Evidence indicates that changes in serum lipids are concordant with changes in body weight. Therefore, clozapine and olanzapine have the greatest increases in lipids, with risperidone and quetiapine having an intermediate effect on lipids. Again, aripiprazole and ziprasidone have limited data, which do not show a significant effect on lipids.¹

Monitoring:

With potentially serious adverse effects of atypical antipsychotics, the panel recommends appropriate baseline screening and ongoing monitoring of patients receiving these medications. Baseline measurements include personal and family history of obesity, diabetes, dyslipidemia, hypertension or cardiovascular disease, body mass index (BMI), waist circumference, blood pressure, fasting plasma glucose, and fasting lipid profile. These measures are used to determine if a patient is overweight (BMI 25–29.9) or obese (BMI ≥ 30),

has pre-diabetes (fasting plasma glucose 100–125 mg/dL or diabetes (fasting plasma glucose 126 mg/dL), hypertension (blood pressure >140–90 mmHg), or dyslipidemia.¹ Weight should be reassessed at 4, 8, and 12 weeks after initiation or change of atypical antipsychotic therapy. Fasting plasma glucose, lipid levels, and blood pressure should also be reassessed 3 months after initiation. Blood pressure and plasma glucose should be checked annually or more frequently in patients at higher risk for developing diabetes or hypertension. Repeat testing of lipid levels should be reassessed at 12 weeks and every 5 years or more frequently if indicated (Table 2).¹

If a patient gains 5% of his or her initial weight or develops worsening of glycemia or dyslipidemia, the panel recommends considering switching the second-generation antipsychotic. If this is necessary, cross-titration is the safest approach; antipsychotic drugs should never be abruptly discontinued.¹

Of note, paliperidone has been approved since the development of these guidelines; however, patients receiving paliperidone should adhere to the monitoring protocol for all atypical antipsychotics.

References:

¹ Barrett E, Blonde L, Clement S, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Diabetes Care*. 2004; 27:596-601.

² Marder SR, Essock SM, Miller AL, et al. Physical health monitoring of patients with schizophrenia. *Am J Psych*. 2004;161(8):1334-1349.

Table 2. Monitoring protocol for patients on second-generation antipsychot-

	Baseline	4 weeks	8 weeks	12 weeks	Quarterly	Annually	Every 5 years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist circumference	X					X	
Blood pressure	X			X		X	
Fasting plasma glucose	X			X		X	
Fasting lipid profile	X			X			X

Program Assistance

All prior authorization requests or questions regarding the PDL should be directed to the ACS Clinical Call Center at 1-866-879-0106.

PDL Listing

The fee-for-service PDL listing may be found at the following Web site:

<http://www.indianapbm.com/>

Top 20 Drugs for 2Q 2007

**Top 20 Drugs 2nd Quarter 2007
Ranked by Total Amount Paid**

Drug	Total Paid	Total Claims
Antihemophilic factor	\$3,624,026.33	115
Risperidone	\$3,533,549.32	13,630
Olanzapine	\$2,933,766.30	6,399
Quetiapine	\$2,921,786.28	11,744
Aripiprazole	\$2,895,019.91	7,536
Divalproex sodium	\$1,638,936.65	10,813
Insulin	\$1,429,197.34	12,416
Topiramate	\$1,429,027.05	5,803
Lamotrigine	\$1,268,518.80	5,659
Fentanyl	\$1,137,147.16	3,667
Oxycodone	\$1,095,376.57	4,835
Ziprasidone	\$1,016,047.23	3,693
Atorvastatin	\$1,003,825.22	9,730
Fluticasone/salmeterol	\$876,543.48	4,990
Oxcarbazepine	\$869,726.00	4,283
Levetiracetam	\$805,015.09	3,426
Anti-inhibitor Coagulant Comp	\$797,787.44	19
Duloxetine	\$775,908.71	5,799
Amphetamine salts	\$761,987.07	7,770
Pantoprazole	\$741,060.44	6,064

**Top 20 Drugs 2nd Quarter 2007
Ranked by Total Claims Paid**

Drug	Total Claims	Total Paid
Hydrocodone/APAP	42,676	\$367,199.92
Aspirin	38,240	\$30,894.76
Docusate sodium	36,596	\$75,893.90
Alprazolam	31,221	\$234,016.41
Calcium/Vit D	30,574	\$63,088.05
Acetaminophen	30,455	\$75,859.09
Multivitamins	25,042	\$36,482.90
Loratadine	24,867	\$240,608.52
Clonazepam	21,510	\$115,615.57
Lorazepam	20,536	\$123,824.27
Multivitamins with minerals	19,216	\$53,271.15
Omeprazole	18,665	\$524,668.94
Albuterol	16,291	\$318,026.22
Risperidone	13,630	\$3,533,549.32
Insulin	12,416	\$1,429,197.34
Levothyroxine	12,197	\$107,274.60
Diazepam	12,059	\$236,307.61
Quetiapine	11,744	\$2,921,786.28
Lisinopril	11,698	\$76,574.11
Furosemide	10,999	\$42,723.19