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# Indiana Medicaid Drug Utilization Review Board Newsletter

## 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 first generation antipsychotics. However, these newer agents are associated with serious adverse effects including weight gain, hyperglycemia, new onset diabetes, and dyslipidemia. Since these metabolic side effects are associated with the development of cardiovascular disease, early intervention is imperative for the safety of the patient.

It is difficult to determine whether obesity, diabetes, or dyslipidemia is increased in these psychiatric populations 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, people with these disorders may be prone to obesity and dyslipidemia due to poor lifestyle habits. Limited data also suggests that drug-naïve schizophrenic patients have an increased prevalence of impaired fasting glucose and insulin resistance, and have higher glucose, insulin, and cortisol levels than control subjects. From the evidence thus far, these patients have an increased prevalence of obesity, impaired glucose tolerance, and type 2 diabetes. Whether this

is due to the illness itself or to drug treatment is still unknown.<sup>1</sup>

A joint panel of the American Diabetes Association, the American Psychiatric Association, the American Association of Clinical Endocrinologists, 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. The following are some conclusions of the panel.

**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 disease, diabetes, or other complications.**

### 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 seem to have the highest incidence of weight gain, followed

by risperidone and quetiapine, with aripiprazole and ziprasidone having little effect on weight (long-term studies are limited for aripiprazole and ziprasidone).<sup>1</sup>

**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 antipsychotics or other atypical antipsychotics. There is some evidence that risperidone and quetiapine can increase risk, but more studies are warranted. Aripiprazole and ziprasidone have not shown significant effects on glucose because long-term data is limited. Impairment of insulin action (i.e., 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 by a direct effect on insulin-sensitive target tissues. Currently, the FDA has requested that labeling for ALL atypical agents carry a warning on the potential risk for developing diabetes.<sup>1</sup>

**Dyslipidemia**

Dyslipidemia associated with atypical antipsychotics can be seen by increases in total cholesterol, LDL cholesterol, triglycerides, and decreases in HDL cholesterol. Available evidence shows 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 and do not show a significant effect on lipids.<sup>1</sup>

**Monitoring**

With the potentially serious adverse effects of atypical antipsychotics, the panel recommends appropriate baseline screening and ongoing monitoring of patients on 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 can determine whether a patient is overweight (BMI 25.0-29.9) 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.<sup>1</sup>

Weight should be reassessed at 4, 8, and 12 weeks after initiation or following a change of 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. Lipid levels should be reassessed at 12 weeks and every 5 years or more frequently if indicated (Table 1 – see next page).<sup>1</sup>

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 disease, diabetes, or other complications.

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

**Table 1. Monitoring for patients on second generation antipsychotics.<sup>1</sup>**

	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

**Top 25 Drugs for Fourth Quarter 2004**

<b>Top 25 Drugs 4th Quarter 2004 By Total Amount Paid</b>		
<b>Drug</b>	<b>Total Paid</b>	<b>Total Claims</b>
Zyprexa	\$10,574,015	31,038
Risperdal	\$8,203,330	38,908
Seroquel	\$6,099,872	29,493
Depakote	\$4,118,546	31,391
Abilify	\$3,969,813	12,181
Lipitor	\$3,781,154	42,948
Zoloft	\$3,391,667	37,147
Duragesic	\$3,255,734	15,288
Novoseven	\$3,109,307	13
Plavix	\$2,831,208	23,555
Protonix	\$2,588,093	22,997
Topamax	\$2,447,049	11,873
Zocor	\$2,455,620	19,304
Effexor	\$2,264,065	18,279
Neurontin	\$2,247,409	13,737
Lexapro	\$2,091,760	30,793
Oxycontin	\$2,064,272	8,959
Aricept	\$2,051,891	15,778
Advair	\$1,952,360	13,552
Geodon	\$1,794,801	7,210
Singulair	\$1,699,622	19,871
Lamictal	\$1,607,321	7,336
Actos	\$1,520,032	9,252
Norvasc	\$1,481,369	26,258
Trileptal	\$1,473,276	9,608

<b>Top 25 Drugs 4th Quarter 2004 Ranked by Claims Paid</b>		
<b>Drug</b>	<b>Total Claims</b>	<b>Total Paid</b>
Hydrocodone/APAP	99,987	\$1,111,110
Furosemide	60,249	\$316,609
Albuterol	49,803	\$662,254
Ranitidine	43,747	\$408,881
Lipitor	42,948	\$3,781,154
Lisinopril	41,980	\$463,762
Risperdal	38,908	\$8,203,330
Aspirin	37,174	\$25,726
Zoloft	37,147	\$3,391,667
Alprazolam	35,550	\$196,542
Amoxicillin	35,279	\$336,395
Docusate	33,487	\$66,716
Depakote	31,391	\$4,118,546
Zyprexa	31,038	\$10,574,015
Lexapro	30,793	\$2,091,760
Zithromax	30,397	\$1,284,227
Potassium	29,561	\$493,201
Seroquel	29,493	\$6,099,872
Propoxyphene N/APAP	28,559	\$248,061
Loratadine	28,431	\$365,443
Levothyroxine	26,829	\$296,700
Norvasc	26,258	\$1,481,369
Toprol	23,576	\$774,577
Plavix	23,555	\$2,831,208
Clonazepam	23,020	\$139,889

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

Barrett E, Blonde L, Clement S, et al. Consensus development conference on antipsychotic drugs and obesity and diabetes. *Journal of Clinical Psychiatry* 2004; 65(2): 267-272

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