OREGON DUR BOARD NEWSLETTER©
AN EVIDENCE BASED DRUG THERAPY RESOURCE http://pharmacy.oregonstate.edu/drug_policy/newsletter

April 2010 Volume 12, Issue 3

Answers to Frequently Asked Questions About Atypical Antipsychotics

By Ann Hamer, PharmD, BCPP, OptiumHealth Behavioral Solutions & OSU College of Pharmacy

This article summarizes answers to several commonly asked questions about atypical antipsychotics and their use in both the mental health and primary care settings.

What are the labeled indications for each of the atypical antipsychotics?

Table 1: Food and Drug Administration (FDA) Approved Indications for Atypical Antipsychotics as of March 2010.[1-8]

Indication	*aripiprazole Abilify®*	*risperidone Risperdal®*	*quetiapine Seroquel®*	*olanzepine Zyprexa®*	*ziprasidone Geodon®*	*paiperidone Invega®*	*iloperidone Fanapt®*	*Asenapine Saphris®*
Acute Treatment of Schizophrenia in Adults	X	X	X	X	X	X	X	X
Maintenance Treatment for Schizophrenia in Adults	X	X	X^	X	X	X		
Acute Treatment of Schizophrenia in Adolescents (13-17 yrs)	X	X	X	X±				
Acute Treatment of Bipolar Mania in Adults	X	X	X	X	X			X
Acute Treatment of Bipolar Mania in Adults—Adjunct to Lithium/Valproate	X	X	X	X				
Acute Treatment of Bipolar Mania in Pediatric Patients (10-17 yrs)	X	X		X±				
Acute Treatment of Bipolar Mania in Pediatric Patients (10-17 yrs)—Adjunct to Lithium/Valproate	X							
Maintenance Treatment of Bipolar Mania in Adults	X			X				
Maintenance Treatment of Bipolar Mania in Adults—Adjunct to Lithium/Valproate			X		X			
Acute Treatment of Agitation Associated with Schizophrenia in Adults*	X			X	X			
Treatment of Depressive Episodes Associated with Bipolar Disorder in Adults			X					
Irritability Associated with Autistic Disorder in Children and Adolescents (5-16 yrs)	X	X						
Acute Treatment of Depressive Episodes Associated with Bipolar Disorder in Combination with Fluoxetine				X				
Acute Treatment of Treatment Resistant Depression in Adults in Combination with Fluoxetine				X				
Adjunctive Therapy to Antidepressants for Acute Treatment of Major Depressive Disorder in Adults	X		X^					
Acute Treatment of Schizoaffective Disorder as Monotherapy						X		
Acute Treatment of Schizoaffective Disorder—Adjunct to Mood Stabilizers and/or Antidepressants						X		

±*Zyprexa label suggests trial of other drugs first in adolescents*
**Injectable formulations for IM use only*
^ *XR form only*

What are the major differences between risperidone (Risperdal®) and paliperidone (Invega®)?

Paliperidone is the primary metabolite of risperidone. Both drugs are manufactured by Janssen. Structurally, the only difference between the two chemical compounds is an extra hydroxyl group. There appear to be no differences in efficacy or effectiveness.[9] Adverse effects appear to be identical between the two drugs and include movement disorders, weight gain, elevated prolactin and tachycardia. [9] A comparison of their pharmacokinetic properties reveals that paliperidone is less extensively metabolized by the CYP450 isoenzymes compared to risperidone, potentially leading to fewer drug-drug interactions. [9, 10] Actual clinical significance has not been reported. Because risperidone is available as a generic (brand name Risperdal lost patent exclusivity in December 2007), there is a significant difference is cost.[11]

How do adverse effects compare between the atypical antipsychotics?

Table 2. A relative comparison of some of the adverse effects associated with atypical antipsychotics.[12]

Drug	Anticholinergic Symptoms	EPS	Akathisia	Hypotension	Prolactin Elevation	QT Prolongation	Sedation	Wt Gain
Aripiprazole	+/-	+/-	+++	+/-	+/-	+/-	+/-	+/-
Olanzapine	+	+	+	+/-	+/-	+	+	+++
Quetiapine	++	+/-	+/-	++	+/-	+	++	++
Risperidone	+/-	++	++	+	++	+	+	++
Paliperidone	+/-	++	++	+	++	+	+	++
Iloperidone	+/-	+/-	+/-	++	+	++	+	++
Ziprasidone	+/-	+/-	+	+/-	+/-	++	+/-	+/-
Clozapine	+++	0	++	+++	+/-	+	+++	+++
Haloperidol	+/-	+++	+++	+	++	++	+	+

What are the metabolic monitoring recommendations for the atypical antipsychotics?

There are a number of metabolic side effects that have been linked to the atypical antipsychotics. Weight gain is a common adverse effect of using antipsychotic medications, and can be rapid and difficult to control.[13] Weight gain does not seem to be dose dependent within the normal therapeutic range. It is worse with clozapine and olanzapine, minimal with aripiprazole and ziprasidone, and intermediate with the others, including low-potency FGAs.[14]

Antipsychotic medications can contribute to a wide range of glycemic abnormalities, ranging from mild insulin resistance to diabetic ketoacidosis,[15] as well as worsening of glycemic control in patients with preexisting diabetes. Risk is again variable with the greatest risk linked to clozapine and olanzapine. Risk is somewhat difficult to quantify because so many other diabetes risk factors are present in this population. Although the weight gain associated with antipsychotics clearly contributes, there appear to be other independent effects as well.[16,17]

Dyslipidemia is also associated with several of the antipsychotic medications, with increases noted primarily in triglyceride levels. The atypical antipsychotics olanzapine, clozapine and quetiapine, are associated with a higher risk of hyperlipidemia.[18-21]

Overall, metabolic disturbances appear to be greatest with clozapine and olanzapine, intermediate with quetiapine , and lowest with aripiprazole, risperidone, and ziprasidone. Baseline and routine monitoring are critical to detect metabolic changes and increasing risk for cardiovascular disease. The following table devised by the American Psychiatric Association (APA) and American Diabetes Association (ADA) Consensus Panel provides recommendations for routine monitoring.[22]

Table 3. Recommended Monitoring Schedule for Patients Taking Atypical Antipsychotics

	Initial	4 Weeks	8 Weeks	12 Weeks	Quarterly	Annually	5 Years
Personal/family history	X					X	
Weight (BMI)	X	X	X	X	X		
Waist Circumference	X			X		X	
Blood Pressure	X			X		X	
Fasting Plasma Glucose	X			X		X	
Fasting Lipid Profile	X			X			X

***More frequent monitoring may be warranted in certain patients based on clinical presentation/status*

In late 2003, the FDA announced that it was requiring that class warnings be added to the labeling of atypical antipsychotic drugs describing increased risk of hyperglycemia and diabetes. Concurrently, the recommendations from the APA and ADA listed in Table 3 were released. A recently published study evaluated the impact of the monitoring recommendations on metabolic testing and treatment selection of lower risk antipsychotics.[23] This study found that testing rates prior to the FDA warning were low (glucose, 27%; lipids, 10%). The warning, however, was not associated with an increase in glucose testing among atypical-treated patients and was associated with only a marginal increase in lipid testing rates (1.7%; P=.02). Testing rates and trends in atypical-treated patients were not different from background rates in the control group (control group included patients starting an albuterol prescription and no antipsychotic). The study did find that new prescriptions for olanzapine (associated with a higher metabolic risk) declined during the warning period (annual share decline, 19.9%; P<.001). This study demonstrates the need for enhanced awareness of the monitoring guidelines recommended by the APA and ADA.

Are atypical antipsychotics safer than traditional antipsychotics in terms of risk of sudden death?

A recent study published in the New England Journal of Medicine demonstrated that the risk for sudden death with atypical antipsychotics is at least as high with the atypicals compared to the older antipsychotics, and that the risk is dose-dependent for all agents.[24] The incidence rate reported by Ray et al. was 478 events per 166,324 patient-years of use, or 2.9 events per 1000 patient-years. Among patients given higher doses, the rate was 3.3 events per 1000, a level of risk that would be described as between “moderate” and “low,” but not “rare.”[25] Although this risk might initially appear low, the rate of death from clozapine due to agranulocytosis is about 0.2 per 1000 patient-years, much less than the risk of sudden cardiac death in patients taking antipsychotic medications. [26]

What are the preferred atypical antipsychotics for the Oregon Health Plan (OHP)?

The Oregon Medicaid program (aka OHP) has identified and listed preferred drugs for two mental health drug classes (newer antidepressants and atypical antipsychotics). Use of preferred products in these classes remains voluntary. This policy is expected to avoid approximately $3 million in OHP drug costs and assumes 66% use of preferred products.[27] The copay will be waived for preferred mental health drugs. Preferred atypical antipsychotics are: clozapine, risperidone, Geodon®, Seroquel® and Seroquel XR®.

Reviewed by Joseph Arnold, MD, Psychiatrist, Yamhill County Mental Health

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Oregon DUR Board Newsletter Produced by OSU COLLEGE of PHARMACY
DRUG USE RESEARCH & MANAGEMENT
Managing Editor: Kathy L. Ketchum
Kathy.l.ketchum@state.or.us 503-947-5220