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# FOR YOUR INFORMATION



## PHARMACY NEWSLETTER



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### Antipsychotics on the Horizon

#### INTRODUCTION

Quetiapine (Seroquel®) marketed in 1998 was the last novel antipsychotic drug to be released in Canada. Awaiting Notice of Compliance (NOC) from the Health Protection Branch (HPB) are three new atypical agents ziprasidone, amisulpride and aripiprazole. Two of these new antipsychotics are already available in the U.S., with ziprasidone available for over 2 years now. The expected approval of these agents over the next year or two will provide both the client and clinician with an array of alternatives in the treatment of schizophrenia.

#### Ziprasidone (Geodon®)

##### Pharmacology

This agent is a benzisothiozoyl piperazine compound. Similar to other atypical antipsychotic agents, this drug blocks serotonin 5HT<sub>2A</sub> receptors more so than dopamine D<sub>2</sub> receptors, providing activity against both positive and negative symptoms of schizophrenia. It also has two other interesting receptor effects. One is agonism at both pre and post-synaptic 5 HT<sub>1A</sub> receptors, which in vitro has been shown to increase dopamine release. The postsynaptic 5 HT<sub>1A</sub> receptor has been implicated in both depressive and anxiety disorders. Ziprasidone also exhibits weak antagonism at 5-HT and norepinephrine reuptake transporters, a mechanism that may increase these neurotransmitter levels as seen with antidepressants. The extent of this latter effect, however, is much less than that of desipramine and paroxetine.

##### Pharmacokinetics

The half-life of ziprasidone is 6.6 hours and steady state level are achieved in 1-2 days. This drug is usually administered with food starting at an initial dose of 20mg twice daily and increasing thereafter as tolerated to a maximum of 160 mg per day. Liver and kidney dysfunction do not appear to impact serum concentrations significantly, although slower titration and monitoring are warranted in patients with liver dysfunction.

##### Clinical trials

In clinical trials, ziprasidone 160mg has demonstrated comparable efficacy to haloperidol 15mg, with fewer adverse effects. In a study of acutely relapsing inpatients it was found to be as effective at doses of 80 - 160mg as olanzapine 5 - 15mg/day for acute positive symptoms on the BPRS and negative symptoms on the PANSS. It was equally effective on the Calgary Depression Scale for Schizophrenia. Other trials have looked at ziprasidone in doses of 40 to 160mg versus placebo for the treatment of schizophrenia and schizoaffective disorders. Doses of 80mg to 160mg were statistically superior to placebo in reductions on the PANSS and BPRS scales. Efficacy in affective symptoms, although promising, requires further research.

##### Adverse effects

The most commonly reported side effect in trials was headache at 31% on doses of 160mg, which was no different than that reported with placebo at 33%. At a lower dose of 80mg, the incidence of headache was 17%. Other common side effects included somnolence, dizziness, dyspepsia and nausea.

Ziprasidone has modest antagonism of alpha-1 receptors, suggesting low cardiac and hypotensive properties. In studies, the incidence of tachycardia and orthostatic hypotension was reported to be 1-2%. The release of ziprasidone onto both the Canadian and American markets was delayed, due to heightened awareness of QTc interval prolongation and its association with sudden death. Ziprasidone 160 mg prolongs the QTc interval by approximately 20msec. This prolongation is greater than that reported with other atypical agents, but is less than that reported with thioridazine. Since its release in the U.S, there have been no cases of torsade de pointes in over 150,000 patients. In cases of overdose, there have been no significant cardiac sequelae and no QTc intervals > 500 msec. There is no clinically significant increase of QTc at the high end of the dosing range.

The potential for EPS is low although it has been reported. A review of ziprasidone after its release in the U.S. has found the incidence of EPS to approximate that of olanzapine but not to be quite as good as quetiapine or clozapine. Ziprasidone has negligible affinity for muscarinic receptors, so does not cause dry mouth, or blurred vision. The drug appears to have a low potential for weight gain; some patients switching from olanzapine to ziprasidone have experienced weight loss in one trial suggesting that weight gain is less than that seen with olanzapine. Elevations greater than 1.2 x the upper limit of normal of random glucose, cholesterol and triglyceride concentrations have occurred in 14.9%, 13.4% and 24.1% of ziprasidone-treated patients, compared to placebo rates of 12.2%, 14.5% and 16% respectively.

### **Drug interactions**

Ziprasidone is metabolized by aldehyde oxidase and by cytochrome CYP3A4. Potential inhibitors of aldehyde oxidase include chlorpromazine, hydralazine, methadone and d-propoxyphene, while fluvoxamine, norfluoxetine, nefazodone, macrolide antibiotics, protease inhibitors and azole antifungals are among the inhibitors of the CYP3A4 enzyme. Although CYP3A4 inhibitors have been shown to increase ziprasidone levels, the effect of aldehyde inhibitors on ziprasidone levels is not known. Ziprasidone also exhibits protein binding > 99% suggesting the potential for protein-binding displacement interactions.

### **Sulpiride (Dogmatil®)**

In the past several years sulpiride has been available only through a special access via Health Canada. Many patients non-responsive to other antipsychotic agents continue to be successfully treated with this agent, however there are no plans to market this drug in Canada or the U.S. (See For Your Information – December 2001).

### **Amisulpride (Solian®)**

#### **Pharmacology**

Amisulpride is a substituted benzamide related to sulpiride also marketed by Sanofi of France. At low doses, it enhances dopamine transmission by blocking presynaptic dopamine D2 and D3 autoreceptors, preferentially in the limbic system. At higher doses, it antagonizes postsynaptic D2 and D3 receptors in the limbic system, thereby reducing dopaminergic transmission. It has little affinity for serotonin, histamine, muscarinic or adrenergic receptors.

#### **Clinical trials**

In comparative trials it was as effective as haloperidol, flupenthixol and risperidone in patients with acute exacerbations with predominantly positive symptoms. It was more effective than haloperidol but equally effective as risperidone in controlling negative symptoms and more effective than all three in controlling affective symptoms. In double-blind randomized trials it was more effective than placebo at doses of 50-300mg for negative symptoms.

#### **Pharmacokinetics**

Amisulpride is unusual in that it undergoes minimal metabolism and relies mostly on the kidneys for excretion. Its half-life is 12 hours. Doses of 400-800mg/day are recommended for acute psychotic episodes in schizophrenia, with a maximum recommended dose of 1200mg/day. Doses above 400mg/day should be administered twice daily. In patients with predominantly negative symptoms who are not acutely psychotic, low doses of amisulpride 50-300mg/day are suggested. As this drug undergoes renal excretion, dose reductions are required when creatinine clearance is less than

60ml/min. Since it undergoes minimal metabolism the potential for drug interactions is much less than with other anti-psychotics.

### **Adverse effects**

At low doses, the incidence of adverse events was similar to placebo. The most commonly reported adverse events associated with higher doses of amisulpride were extrapyramidal symptoms, insomnia, hyperkinesia, anxiety, bodyweight increase and agitation. EPS side effects are dose-related and similar to risperidone, although less than that of haloperidol or flupenthixol. Weight gain was more than that of haloperidol but less than risperidone. Prolactin levels increase 3-fold after 12 months of therapy, similar to the effects seen in patients treated with haloperidol or risperidone. Isolated cases of QT prolongation have been identified.

### **Aripiprazole (Abilify®)**

#### **Pharmacology**

Aripiprazole is the most recent antipsychotic to be released in the U.S. and is waiting for approval in Canada. Aripiprazole has shown to be effective in treating the positive and negative symptoms of schizophrenia. It has a relatively new mechanism of action.

It shows partial agonist activity at dopamine D<sub>2</sub> receptors and serotonin 5HT<sub>1A</sub> receptors, and antagonist activity at serotonin 5HT<sub>2A</sub> receptors. This partial agonist activity at dopamine receptors means that where dopamine activity is low, the net effect is an increase in dopamine neurotransmission, and where dopamine activity is high, the net effect is an inhibition of dopamine activity. This mode of action on the dopamine system results in dopamine system stabilization without the side effects of high dopamine blockade such as EPS.

#### **Pharmacokinetics**

Aripiprazole has a half-life of 75 hours and its major active metabolite 94 hours such that steady state takes approximately 2 weeks.

### **Adverse effects**

The most common adverse events reported in trials were headache, anxiety, and insomnia. Akathisia was noted to be greater than risperidone but less than haloperidol. Clinical trials report minimal weight change and minimal extrapyramidal symptoms. Sedation was more common with this drug relative to placebo (11 percent vs. 8 percent). The incidence of QTc interval prolongation with aripiprazole treatment is not different from placebo.

### **Drug Interactions**

CYP3A4 and 2D6 are the major enzymes involved in the metabolism suggesting the potential for drug interactions. 8% of Caucasians are poor metabolizers of 2D6 achieving much higher levels of active drug and even higher with known inhibitors of 2D6 such as quinidine.

### **Dosing**

Aripiprazole is administered as a once-daily oral tablet starting at 10 or 15mg daily. Dose increases should be made a minimum of 2 weeks apart to allow for time to reach steady state. The effective dose range is 10 to 30 mg. Tablets may be administered at any time of the day, with or without food.

### **INJECTABLE FORMULATIONS**

#### **Risperidone (Risperdal Consta®) long-acting injection**

Thus far, this is the only atypical antipsychotic for which a long-acting injection will be made available. The injection uses different technology than the traditional suspension in sesame oil. The active drug is encapsulated in biodegradable microspheres suspended in a water-based solution. Oral supplementation is suggested for the first three weeks after the initial injection with tapering over the fourth week since plasma concentrations do not start to increase until week three. Single injections achieve optimal levels between 4 and 6 weeks, declining thereafter. The recommended interval of injections is every two weeks. Daily doses of 4mg orally are equivalent to 25mg IM Q2W and doses over 4mg equivalent to 37.5mg Q2W. The maximum recommended dose is 75mg Q2W. This

product requires reconstitution and refrigeration. In two controlled trials, adverse events over 5% included anxiety, drowsiness, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash and tachycardia. One study found that patients stabilized on a typical long-acting injection could be easily switched over to risperidone with no need for oral supplementation. Most were effectively treated with 25mg Q2W regardless of their previous dose of antipsychotic.

### **Olanzapine (Zyprexa IM) short-acting injection**

Targeted for the treatment of agitation rather than specifically schizophrenia, it has been studied in patients with schizophrenia, bipolar mania and dementia. The excited component of the Positive and Negative Syndrome Scale (PANSS) scale was used as a measure of efficacy in all trials. In addition the Agitation-Calmness Evaluation Scale (ACES) and the Agitated Behaviour Scale were used in the schizophrenia and bipolar mania studies and the Cohen-Mansfield Agitation Inventory in the dementia study. Olanzapine in all doses (2.5mg, 5.0mg, 7.5mg and 10mg) was statistically superior to placebo at 2 hours and equivalent to comparators of haloperidol and lorazepam on the PANSS. In the three studies not involving dementia, olanzapine was superior at 15 minutes in at least one of the dosage arms. This short-acting injection was safe and well-tolerated, although bradycardia was noted in 64 of 850 patients, 40 of whom experienced a reduction in resting blood pressure and orthostatic drop. This effect occurred more often than with active treatment patients than those in the non-agitated control group. The manufacturer recommends that patients experiencing dizziness or drowsiness remain lying down until vital signs return to normal.

### **Ziprasidone (Geodon IM) short-acting injection**

Although this agent has been ready for several years before IM olanzapine, concerns over QTc interval prolongation held up its release. The mean QTc change with ziprasidone in doses up to 160mg/day did not exceed that demonstrated with the oral form (see above). Also targeted for the treatment of agitation, initial trials showed it to be rapidly effective in the treatment of agitation at initial doses of 10 or 20mg. An open-label study presented at the APA in May 2002 reported that this drug had comparable improvement in agitation when compared to haloperidol and greater improvements in psychotic symptoms in schizophrenic patients in emergency settings. Patients were switched to oral dosing and maintained for 6 weeks with improvements sustained or increased. Patients taking ziprasidone were less likely to experience EPS in the oral or IM phase of the study. The most common side effect was insomnia. A study evaluating safety and tolerability reviewed the clinical trials to date where patients were doses at 20mg up to four times daily. Discontinuation rates ranged from 1.1% to 6.1% with the most common adverse events being headache, nausea, dizziness, insomnia and anxiety.

### **SUMMARY**

All of the above agents are awaiting Health Protection Branch approval. It is expected that ziprasidone oral and IM and olanzapine IM will be the first agents to be approved since both have been pending for some time and Ziprasidone oral has been available in the U.S. for two years. The injectable products will be much more expensive than what we have available currently since they offer the first atypical class injectables. The oral products are likely to cost somewhere between risperidone at the low end of the scale and olanzapine and clozapine at the high end.

Generic name and form	Brand (U.S.) name	Manufacturer	Available in the U.S.	Special Release	HPB application
ziprasidone capsules	Geodon®	Pfizer	√ 2001 IM 2002		√
amisulpiride tablets	Solian®	Sanofi		√	√
Sulpiride	Dogmatil®	Sanofi		√	
aripiprazole tablets	Abilify®	Bristol Myers - Squibb	√ 2002		√
<b><u>INJECTIONS</u></b>					
risperidone long-acting	Risperdal Consta®	Janssen			√
olanzapine short-acting	Zyprexa IM®	Eli Lilly			√
ziprasidone short-acting	Geodon IM®	Pfizer	√		√

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