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Atypical Antipsychotic Drug Class Review Summary of Findings

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With the relatively recent approval of three new atypical antipsychotics, there are now ten different atypical agents available. Some have a variety of dosage forms (orally disintegrating tablets or long-acting injectables) and many have an assortment of approved indications (ranging from the irritability associated with autistic disorder in children and adolescents to the maintenance treatment for schizophrenia in adults). This article will cover a summary of findings from the most recent Drug Effectiveness Review Project (DERP) drug class review on atypical antipsychotics and a brief review of the three newest atypical antipsychotics.

Summary of DERP Atypical Antipsychotics Review Findings (July 2010)[1]

Schizophrenia and Related Psychoses:

- In patients with schizophrenia, differences in short-term efficacy are not apparent among the atypical antipsychotics.
- In patients with schizophrenia, clozapine reduces suicidal behavior in patients at high risk, but results in more discontinuations due to adverse events compared to other atypical antipsychotics.
- Clozapine and olanzapine treatment result in lower rates of drug discontinuation for any reason over periods of up to 2 years.
- While risperidone and extended-release paliperidone resulted in higher rates of extrapyramidal symptoms in some studies, the majority of studies found no differences among the drugs.
- Risperidone was found to result in more frequent or more severe sexual dysfunction symptoms than quetiapine, but was similar to extended-release paliperidone or ziprasidone.
- Very limited evidence existed regarding atypical antipsychotics used for the treatment of schizophrenia in subgroup populations. Among adolescents with schizophrenia, quetiapine was not superior to placebo based on response rate, but was superior based on improvements measured by the Positive and Negative Syndrome Scale. There were no differences by race were found. Compared with men, women had greater improvements with clozapine on a global impression scale, and with olanzapine on a quality of life scale.

Bipolar Affective Disorder:

- In adults with bipolar disorder, no significant differences were found between risperidone and olanzapine or asenapine and olanzapine in quality of life, remission, or response outcomes.
- Olanzapine resulted in greater mean weight gain compared with asenapine and risperidone, respectively.
- Asenapine appears to have a higher risk of drug discontinuations due to adverse events than olanzapine.
- There were no significant differences between risperidone and olanzapine or between asenapine and olanzapine in extrapyramidal symptoms or between risperidone and olanzapine in discontinuations due to adverse events.
- Evidence is limited in children and adolescents with bipolar disorder.

Major Depressive Disorder:

- In adults with major depressive disorder, the majority of studies evaluated the adjunctive use of atypical antipsychotics in patients with an inadequate response to prior standard antidepressants. These studies provided insufficient evidence for determining their comparative effectiveness and efficacy.
- Evidence from both observational studies and randomized controlled trials of atypical use in major depressive disorder have indicated that weight gain was greatest with adjunctive olanzapine.

Behavioral and Psychological Symptoms of Dementia:

- The best evidence found similar rates of response and withdrawal, and no differences in clinical outcome measures for olanzapine, risperidone, and quetiapine in patients with behavioral and psychological symptoms of dementia.

Children and Adolescents with Pervasive Developmental Disorders or Disruptive Behavior Disorders:

- Compared to placebo, risperidone, aripiprazole, and olanzapine improved behavioral symptoms in children and adolescents with pervasive developmental disorders.
- Compared to placebo, risperidone and quetiapine showed efficacy in children and adolescents with disruptive behavior disorders.

Serious Harms:

- Based on randomized controlled trials and observational studies, olanzapine demonstrated greater weight gain than other drugs (6-13 pounds more) and a 16% increased risk of new-onset diabetes.
- In the review, risperidone was identified as having an increased risk of new-onset tardive dyskinesia.
- While clozapine has been shown to be associated with increased risk of seizures and agranulocytosis, differences among the drugs in other serious harms have not been clearly shown.
- Evidence on the long-term harms for the newest drugs is lacking.

Newest Atypical Antipsychotics

The following section provides a brief overview of the newest atypical antipsychotics. A review of clinical findings (Positive and Negative Syndrome Scale—PANSS) from published trials are available in Table 1.

Asenapine[2,3]

Brand Name: Saphris

Indications: Asenapine is approved for the treatment of schizophrenia and as monotherapy or as an adjunct to lithium or valproate for the treatment of bipolar manic or mixed episodes.

Overview: Asenapine is only available as a sublingual (SL) tablet due to its bioavailability (bioavailability is 35% when taken sublingually, but < 2% if ingested). Similar to other second-generation antipsychotics, asenapine's binding profile includes serotonin type 2A (5-HT2A) and dopamine type 2 (D2) antagonism. Binding at the alpha-1 adrenergic and histamine H1 receptors predicts asenapine's propensity to cause orthostasis and sedation in some patients.

Side Effects: Commonly occurring adverse events reported with asenapine (incidence ≥ 5% and at least twice that for placebo) were: akathisia, oral hypoesthesia and somnolence in schizophrenia trials, and dizziness, and extrapyramidal symptoms (other than akathisia) in bipolar trials. Weight gain was greater than placebo, but less than with risperidone and olanzapine in short 6-week trials. In addition, increases in the QTc interval ranging from 2 to 5 milliseconds have occurred. Per the package insert, concomitant use of asenapine with other drugs known to prolong the QTc interval should be avoided.[8]

Dosing: The recommended starting and target dose is 5 mg twice daily sublingually for schizophrenia and 10 mg SL twice daily for bipolar affective disorder (dose should be reduced to 5 mg twice daily if adverse effects occur). The dose should be allowed to dissolve within seconds, but food and drink should be avoided for 10 minutes after ingesting. Use should be avoided in severe hepatic impairment (Child-Pugh C) as asenapine drug concentrations can increase dramatically when used in this population.

Iloperidone[4,5]

Brand Name: Fanapt

Indications: Iloperidone is approved for the treatment of schizophrenia in adults.

Overview: Iloperidone is chemically related to risperidone and its proposed mechanism of action is thought to be mediated through a combination of D2

and 5-HT2 antagonisms. The manufacturer warns that the medication may not be first-line due to (1) its risk to prolong the QT and (2) its slow dose titration that can delay the control of symptoms in the first couple of weeks. Based on current evidence, the DERP summary reported that discontinuation rates are higher with iloperidone compared to risperidone.[1]

Side Effects: Reported adverse effects occurring in at least 5% of patients and at least twice as often as placebo were: dizziness, dry mouth, somnolence, fatigue, nasal congestion, orthostatic hypotension, somnolence, tachycardia, and weight gain.

Due to risks of QTc prolongation, it is also recommended to avoid using iloperidone with other drugs known to prolong the QTc interval. Monitoring of serum potassium and magnesium in patients at risk for electrolyte disturbances should be considered.[2]

Dosing: Dose titration must occur slowly in order to avoid orthostatic hypotension and should begin with 1 mg twice daily on day 1 with subsequent doubling of the daily dose everyday thereafter to reach a target dose after 1 week of 10-12 mg twice daily. Dosing in hepatic impairment has not been evaluated.

Lurasidone[6,7]

Brand Name: Latuda

Indications: Lurasidone is approved for the treatment of adult schizophrenia.

Overview: Lurasidone is a benzoisothiazol derivative thought to work through D2 and 5HT2A antagonism. Comparative data are lacking, but it appears to be effective in the treatment of schizophrenia and in short-term trials it appears to be well tolerated with minimal metabolic effects. Longer-term trials are needed to further assess long-term efficacy and harms.

Side Effects: Commonly observed adverse effects include: somnolence, akathisia, nausea, parkinsonism, and agitation. Electrocardiogram changes exceeding 500 milliseconds were not reported. Weight gain in short-term trials appears to be similar to placebo.

Dosing: Although dose titration is not required, the recommended starting dose is 40 mg once daily with food (minimum of 350 calories). The maximum recommended daily dose is 80 mg. Maximum daily dosing in patients with hepatic or renal impairment is 40 mg daily.

Treatment Selection:

The findings from the DERP Drug Class Review on Atypical Antipsychotics demonstrate that in terms of short-term efficacy, few differences exist among the atypical antipsychotics.[1] Aside from comparative effectiveness and the quality and quantity of clinical trial data, the American Psychiatric Association's guidelines for the treatment of schizophrenia also recommend considering side effects and co-morbid psychiatric and medical diagnoses.[8,9] A comparison of side effects associated with second-generation antipsychotics are included in Table 2.[6]

Table 1. Change in Total PANSS Score from Published Trials

Study	Treatment	Change in PANSS Total
Asenapine[10,11]		
6 weeks N=458	5mg BID	-16.2 (SS)
	10mg BID	Not SS
	Placebo	-10.7 (SS)
	Haloperidol 4mg BID	-15.4 (SS)
6 weeks N=174	5mg BID	-15.9 (SS)
	Placebo	-5.3 (SS)
	Risperidone 3mg BID	-10.9
Iloperidone[12,13]		
4 weeks N=593	12mg/day BID	-12.0 (SS)
	Placebo	-7.1
	Ziprasidone 80mg BID	-12.3 (SS)
6 weeks N=621	2mg BID	-9.0
	4mg BID	-7.8
	6mg BID	-9.9 (SS)
	Haloperidol 15mg*	-13.9
	Placebo	-4.6
6 weeks N=616	2-4mg BID	-9.5 (SS)
	5-8mg BID	-11.1 (SS)
	Risperidone 2-4mg BID	-16.6 (SS)
	Placebo	-3.5
6 weeks N=706	6-8mg BID	-11.0 (SS)
	10-12mg BID	-14.0 (SS)
	Risperidone 3-4mg BID	-18.8 (SS)
	Placebo	-7.6
Lurasidone[14]		
6 weeks N=180	80mg QD	-14.1 (SS)
	Placebo	-5.5

* Given as two divided doses, SS=statistically significant

Table 2. Adverse Effects Comparison Atypical Antipsychotics[6]

Drug	Diabetes	EPS	Elevated Prolactin	QTc Prolongation	Weight Gain
Aripiprazole	+/-	+	+/-	+/-	+
Asenapine	+	+++	++	+	++
Clozapine	++++	+/-	+/-	+	++++
Iloperidone	++	+	+/-	++	++
Lurasidone	+/-	++	+	+/-	+/-
Olanzapine	++++	+	+	+	++++
Paliperidone	++	+++	+++	+	+++
Quetiapine	++	+/-	+/-	+	+++
Risperidone	++	+++	+++	+	+++
Ziprasidone	+/-	+	+	++	+/-

Conclusion:

While relatively few differences exist between the atypical antipsychotics in terms of clinical efficacy, side effects are often key differentiators in treatment selection. The three newest atypical antipsychotics appear to offer little clinical advantage over the other atypical antipsychotics, but longer-term studies are needed.

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