



## Therapeutic Class Review<sup>SM</sup>

### Mental Health – Atypical Antipsychotics Class Update

August 2008

#### Executive Summary

- The atypical antipsychotics have evolved to be the most utilized class of drugs for the treatment of schizophrenia due to:
  - National guidelines recommendations;
  - Practice patterns/trends; and
  - Perception that the atypical antipsychotics have better tolerability and are more efficacious than the older, first generation or “typical” antipsychotics.
- Ziprasidone (Geodon) and aripiprazole (Abilify) were the two most recently approved atypicals.
  - Ziprasidone (Geodon) claims less metabolic effects than other atypicals.
  - Aripiprazole (Abilify) claims once daily dosing and less propensity to increase prolactin levels.
- Both have significant toxicities.
  - Ziprasidone (Geodon) is linked with QTc prolongation.
  - Aripiprazole (Abilify) is linked with postural hypotension.

#### August 2008 Update

- This update included a published systematic review as well as a review of all comparative studies published that were not included in that review (November 2007 to July 21, 2008).
  - A systematic review concluded that the efficacy and safety data were of uncertain usefulness
  - A review of studies published since the systematic review discovered significant flaws, including patient loss to follow-up, lack of ITT analyses, and small study populations.

#### Evidence

##### *Efficacy*

- There is uncertain evidence from systematic reviews and RCTs regarding the efficacy of the newer (atypical) antipsychotic medications other than clozapine when compared to conventional medications for the reduction of symptoms of schizophrenia.
  - There is no useful evidence of comparing the efficacy of atypical antipsychotic medications when used in the reduction of symptoms of schizophrenia or any other indication. However, it appears that all atypical antipsychotics have similar efficacy.
  - While the overall evidence is unreliable, the evidence consistently points to the need for individualized treatment options for patients with schizophrenia and bipolar disorders. Although differences between medication options are difficult to discern in a population, individual patients clearly have different responses to different medications in terms of efficacy and tolerability.
- There is possibly useful evidence of superior efficacy and usefulness for clozapine compared to conventional antipsychotics for the reduction of symptoms of schizophrenia.
  - Risks of blood dyscrasia associated with clozapine may outweigh its benefits of use. Clozapine is generally considered the “option of last resort” for patients unresponsive to other antipsychotics, including the other atypicals.

### Formulary Considerations for Atypical Antipsychotics

Consideration	Impact
Disease Severity	The impact to patients, society and the health-plan is high when patients relapse with uncontrolled disease.
Potential magnitude of clinical benefit	Generally considered efficacious, but long-term impact on quality of life is unknown.
Other treatment options	While often considered inferior, the neuroleptics (e.g., haloperidol, perphenazine, etc) are treatment options for patients with schizophrenia.
Risk of off-label use	There are a number of off-label uses, but the tolerability of this class of medications limits unnecessary use.
Safety	There is a general lack of useful data on the relative safety and tolerability of the atypical antipsychotics. Although no one product has been proven to have an overall safety advantage, the safety profile of individual agents is unique. Generally, treatments are selected based on potential side effect profiles and the impact on the patients existing health status.
Member impact	If these medications were to be removed from formulary there would be tremendous member disruption.
Clinical Practice Guidelines	All of these medications are recommended in clinical practice guidelines.
Expert Opinion	Limited, but current feedback is that agents are selected based on individual response and adverse effect profiles.

#### Decision

- Aripiprazole (Abilify), ziprasidone (Geodon), risperidone, olanzapine (Zyprexa), clozapine and quetiapine (Seroquel) are preferred/formulary because, although the evidence is unreliable, clinical considerations suggest that there is value in having multiple treatment options available.
- Paliperidone (Invega) is non-preferred/non-formulary because there is no useful evidence that paliperidone (Invega) offers a significant advantage over generic risperidone.

## Products

Drug Products	FDA approval <sup>a</sup>	Patent Expiration(s) <sup>d</sup>	FDA approved indications	Usual Dose/Route	Potential Off-label Uses <sup>c</sup>
clozapine (Clozaril <sup>®</sup> , generic)	09/1989	N/A	- Tx resistant schizophrenia - Suicidal behavior, recurrent	400 mg daily PO	- Aggressive behavior - Bipolar disorder - Borderline personality disorder - Dementia - Excessive thirst - HIV psychosis disorder - Involuntary movement disorder - Parkinson's disease – psychotic disorder - Schizoaffective disorder, Refractory
risperidone (Risperdal <sup>®</sup> , generic)	12/1993	12/2007	- Schizophrenia - Bipolar mania - Irritability in autism	4 - 8 mg daily PO  25 mg/q 2wk IM	- Behavioral syndrome – Dementia - Behavioral syndrome - Mental retardation - Bipolar disorder - Borderline personality disorder - Cocaine dependence - Cognitive function finding - Delusional disorder - Dementia - Psychotic disorder - Depression, Refractory - Drug-induced psychosis - Levodopa adverse reaction - Gilles de la Tourette's syndrome - Huntington's disease - Obsessive-compulsive disorder, Refractory - Organic psychotic condition - Parkinson's disease - Psychotic disorder - Pervasive developmental disorder - Posttraumatic stress disorder - Schizotypal personality disorder - Stuttering - Trichotillomania
olanzapine (Zyprexa <sup>®</sup> )	09/1996	04/2011	- Schizophrenia - Bipolar mania	5 mg – 20 mg daily PO  2.5-10 mg IM	- Cannabis induced psychotic disorder - Alzheimer's disease - Psychotic disorder - Anorexia nervosa - Anxiety – Dementia - Borderline personality disorder - Cancer – Nausea - Cocaine dependence - Delirium - Depressed bipolar I disorder - Drug-induced psychosis - Methamphetamine adverse reaction - Essential tremor - Gilles de la Tourette's syndrome - Headache - Huntington's disease - Neuroleptic adverse reaction – Tremor - Obsessive-compulsive disorder, Refractory - Parkinson's disease - Psychotic disorder - Pervasive developmental disorder - Posttraumatic stress disorder - Repetitive self-excoriation - Schizophrenic prodrome

Drug Products	FDA approval <sup>a</sup>	Patent Expiration(s) <sup>d</sup>	FDA approved indications	Usual Dose/Route	Potential Off-label Uses <sup>c</sup>
olanzapine (Zyprexa <sup>®</sup> ) - continued					- Senile dementia of the Lewy body type - Severe major depression with psychotic features - Trichotillomania
quetiapine (Seroquel <sup>®</sup> , Seroquel XR <sup>®</sup> )	09/1997	09/2011	- Schizophrenia - Bi-polar mania	400 mg – 800 mg daily PO	- Bipolar disorder - Delirium - Diffuse Lewy body disease - Psychotic disorder - Gilles de la Tourette's syndrome - Obsessive-compulsive disorder - Parkinson's disease - Psychotic disorder - Tardive dyskinesia
ziprasidone (Geodon <sup>®</sup> )	02/2001	03/2012	- Schizophrenia - Bi-polar mania	20 mg – 80 mg BID PO  10-20 mg/day IM	- Major depressive disorder, Treatment-resistant; Adjunct - Schizoaffective disorder
aripiprazole (Abilify <sup>®</sup> )	11/2002	10/2014	- Schizophrenia - Bi-polar mania	10 mg – 30 mg daily PO	- Asperger's disorder
paliperidone (Invega <sup>®</sup> )	12/2006	10/2009	- Schizophrenia	3 mg to 12 mg daily PO	- None identified
<b>For Comparison</b>					
haloperidol (Haldol, generic)	04/1967	N/A	- Schizophrenia	0.5 mg to 10 mg BID to TID	- Numerous
perphenazine (Trilafon, generic)	02/1957	N/A	- Schizophrenia - Nausea/vomiting	4 mg to 16 mg TID	- Numerous

<sup>a</sup> Date applies to approval date for the original brand name medication where there are now generics available.

<sup>c</sup> As listed in © 1974 - 2007 Thomson MICROMEDEX database or as referenced.

<sup>d</sup> Based on patents listed in Orange Book as of August 2008

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