ACP Brief - Fall 2006 prioritization

Atypical antipsychotics in bipolar disease

Background
- This topic was approved by ACP members in 2005 and stems from another HTA project assessing atypical antipsychotics in patients with schizophrenia.
- Olanzapine (Zyprexa®), risperidone (Risperdal®), quetiapine (Seroquel®), clozapine (Clozaril®), and aripiprazole (Abilify®) are atypical antipsychotics used in the treatment of bipolar disorder, although aripiprazole is only available in Canada through Health Canada Special Access Program.¹
- The research question identified is: What is the comparative effectiveness between the atypical antipsychotic agents in terms of clinical outcomes and cost-effectiveness when used to treat bipolar disease?

Disease Burden
- The prevalence of bipolar disorder is about 1% of the general adult population. Therefore, based on a population of 26 million adults, approximately 260,000 Canadians are affected with this disorder. The onset is typically between 15 and 30 years of age.²,³
- Bipolar disorder is the 6th leading cause of disability-adjusted life years.²,³
- The lifetime risk for bipolar disorder is between 0.5% to 1.5%, whereas first degree relatives of individuals with bipolar disorder have a lifetime risk of 5% to 10%.²
- The total annual costs for bipolar disorder is estimated at US$45 billion.³,⁴

Alternatives
- Medications used in the treatment for bipolar disorder include mood stabilizers such as lithium and valproate, as well as carbamazepine, oxcarbazepine, lamotrigine, and atypical antipsychotics.⁴
- Non-pharmacologic treatments include psychoeducational programs, counselling, psychotherapy, cognitive behavioural therapy, stress reduction techniques, nutrition and exercise.⁴
- Electroconvulsive therapy may be recommended for patients who are non-responsive to other therapies.⁴

Clinical Impact
- Aripiprazole, olanzapine, quetiapine and risperidone are effective in the treatment of bipolar mania, and there are no significant differences in efficacy.⁵
- A recent DERP report found that the atypical antipsychotics had comparable efficacy using indirect comparisons from placebo controlled trials.⁶
- Olanzapine was shown to be more effective than placebo for acute and maintenance monotherapy and combination therapy for manic and mixed episodes and monotherapy for depressed episodes.⁶
- Quetiapine and risperidone were more effective for acute and maintenance monotherapy for mixed or manic episodes, alone and in combination with lithium and mood stabilizers, compared to placebo.⁶
- Aripiprazole was found to be more effective than haloperidol for maintenance therapy, and more effective than placebo for manic or mixed episodes.⁶
- Olanzapine has been shown to be more effective than placebo, and as effective as lithium, valproate, haloperidol and risperidone for treatment of bipolar mania.⁷
One recent review reported less extrapyramidal symptoms (EPS) with atypical antipsychotics than with classical antipsychotics.\(^8\) The DERP review also found no differences in the frequency of EPS between olanzapine, quetiapine, and risperidone when used at midpoint doses. Higher doses of risperidone may however be associated with more EPS than low to medium doses of clozapine and olanzapine.\(^6\)

Adverse effects such as weight gain and metabolic effects are associated with atypical antipsychotics. Olanzapine and clozapine have the highest risk of these adverse effects, whereas the risk is moderate with risperidone and quetiapine and low with aripiprazole.\(^9\)

The DERP report had similar findings with regarding weight gain and aripiprazole, but slight differences with the other atypical antipsychotics. Aripiprazole had a similar risk of weight gain compared to placebo, whereas quetiapine had a significantly greater risk for weight gain. Olanzapine and risperidone were associated with a similarly high risk for weight gain compared to placebo.\(^6\)

**Budget Impact**

- Assuming all Canadians with bipolar disease are treated with recommended doses\(^10\)-\(^13\) of atypical antipsychotics, daily treatment costs may be estimated to be:
  - Olanzapine: C$876,200 to C$2,632,500
  - Risperidone: C$995,800 to C$1,991,600
  - Quetiapine: C$332,800 to C$2,672,800

**Economic Impact**

- No studies evaluating the comparative cost effectiveness between atypical antipsychotics were identified. Comparisons with other drugs used for bipolar disease exist however.

- One study compared total monthly costs of treatment for one year of an undescribed treatment before conversion to olanzapine. Total monthly costs of treatment with olanzapine were US$649, compared to US$1533 for the previous treatment period.\(^14\) Inpatient and outpatient costs were US$248 and US$73 for the olanzapine treatment phase, compared to US$1179 and US$354 for the previous treatment phase.\(^14\)

- Comparing treatment with olanzapine with divalproex sodium, the difference in total medical costs was not significant. Total costs associated with the olanzapine treatment were US$15,180 while they were $13,703 with divalproex. The outpatient medical costs, however, were significantly lower in the divalproex group (US$540) compared to the olanzapine group (US$1080).\(^15\)

- Another study comparing costs of olanzapine and divalproex found similar results. Total yearly costs per patient for olanzapine (US$14,967) and total costs for divalproex (US$15,801) were not significantly different.\(^16\)

**Evidence**

- A recent DERP drug class review on atypical antipsychotics used for the following conditions was released in April 2006: schizophrenia, bipolar disease, dementia, and autism.\(^6\)

- A systematic review conducted in 2004 regarding the effectiveness of the atypical antipsychotics for bipolar mania was conducted, and found no significant differences in efficacy between the atypical antipsychotics.\(^5\)


