



# THERAPEUTICS INITIATIVE

Evidence Based Drug Therapy

## Increasing use of newer antipsychotics in children: A cause for concern?

Newer antipsychotics have been called 'atypical' and 'second generation', but both terms are misleading. In this article the term "newer" is used except when making direct quotations. Currently older and newer antipsychotics in Canada are only licensed to treat adults (>18 years), but there is evidence that non-licensed prescribing of newer antipsychotics to children and adolescents is growing. The use of antipsychotics in children and adolescents remains controversial. For example in June 2009, an advisory panel to the US Food and Drug Association (FDA) recommended expanding the indications for quetiapine (Seroquel), olanzapine (Zyprexa) and ziprasidone (Geodon) to include treating schizophrenia and bipolar disorder in adolescents aged 13 to 17. To date the FDA has not granted approval for these indications.

**Understanding the effects of early and possibly long-term exposure to antipsychotics in children is vital given their potential effects on brain and social development.**

### Does prescribing of antipsychotics to children vary around the world?

Antipsychotic drugs are prescribed to children and adolescents around the world albeit at remarkably different rates. American children are approximately three times more likely to be prescribed psychotropic medications in general than children in Europe. Antidepressant and stimulant prescribing are three times greater in the US than in the Netherlands and Germany, while antipsychotic prescribing in the US is 1.5 to 2.2 times greater.<sup>1</sup> Some of the differences may be due to differing cultural beliefs about the role of medication in emotional and behavioral problems but these differences beg the question: is the prescription of antipsychotics to children appropriate?

### What are BC trends in prescribing of newer antipsychotics to children?

BC PharmaNet data shows considerable growth of the prescribing of psychotropic drugs to children and adolescents. **However, the most striking change between 1997 and 2007 is a tenfold increase in newer antipsychotics (olanzapine, quetiapine and risperidone) for children under 14 years in BC (see Figure).**

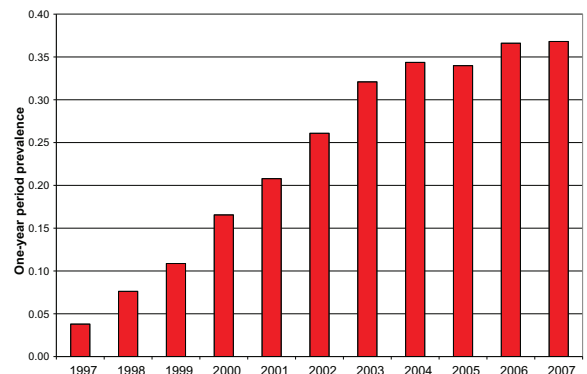


## What is known about the benefits and harms of newer antipsychotics in children?

Schizophrenia in children (<14 years of age) is difficult to diagnose and occurs much less commonly than in adults, about 1/40,000 versus 1/100, respectively.<sup>2</sup> In terms of bipolar disorder, there is widespread disagreement among psychiatrists about this diagnosis in children, some saying that it is impossible to diagnose it at all.

A Cochrane systematic review of antipsychotic treatment in childhood onset schizophrenia (prior to 13 years of age) found 6 relevant RCTs of 6 to 12 weeks in duration and concluded "There are few relevant trials and, presently, there is little conclusive evidence regarding the effects of antipsychotic medication for those with early onset schizophrenia. Some benefits were identified in using the atypical antipsychotic clozapine

**Trends in Percentage of British Columbians ≤14 Years of Age Treated with Newer Antipsychotic Medications**



compared with haloperidol but the benefits were offset by an increased risk of serious adverse effects. Larger, more robust, trials are required.”<sup>3</sup>

A non-Cochrane systematic review of Early Onset Schizophrenia Spectrum Disorder (EOSS) (up to 18 years of age) included 10 RCTs in a qualitative review that did not make any conclusions regarding the relative effectiveness of currently available antipsychotic treatments. They did however state that “the emerging data indicate that adolescents might be particularly vulnerable to side effects (weight gain, metabolic problems, elevation in prolactin levels, sedation) suggesting limited generalizability of adult studies to younger patients.”<sup>4</sup> The concluding comment by researchers from the Centre for Reviews and Dissemination about this review is “Although the conclusions appear to be supported by the data presented, it is difficult to assess their reliability given the rather limited search, poor reporting of review methods and lack of information about study validity.”<sup>5</sup>

A study, published since these two systematic reviews, compared risperidone and olanzapine to an older antipsychotic, molindone, in an 8 week trial in 119 youths with early-onset schizophrenia.<sup>6</sup> They showed no significant differences among treatment groups in response rates (molindone, 50%; olanzapine, 34%; risperidone, 46%) or magnitude of symptom reduction. Weight gain was greater with olanzapine (6 kg) and risperidone (4 kg) as compared to molindone (0 kg). Olanzapine also caused significant increases in fasting cholesterol, low-density lipoprotein, insulin, and liver transaminase levels. Molindone led to more self-reports of akathisia.

### References

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The authors concluded: “The results question the nearly exclusive use of atypical antipsychotics to treat early-onset schizophrenia and schizoaffective disorder. **The safety findings related to weight gain and metabolic problems raise important public health concerns, given the widespread use of atypical antipsychotics in youth for nonpsychotic disorders.**”<sup>6</sup> These concerns have been substantiated in a recent JAMA study showing mean weight gains of 8.5 kg with olanzapine, 6.1 kg with quetiapine, 5.3 kg with risperidone and 4.4 kg with aripiprazole during 11 weeks of first-time use in children and adolescents.<sup>7</sup>

### Is there evidence for use of antipsychotics in behavioural conditions?

A study in the United States on antipsychotic prescribing in children found that much of the increase in prescribing was primarily for behavioural indications such as attention deficit disorder and hyperactivity.<sup>8</sup> No controlled trial evidence supports the use of any antipsychotics for behavioural conditions such as ADHD.<sup>9</sup>

### What are the implications of these findings for practitioners?

Based on a far larger albeit poor quality body of evidence in adults, previous Therapeutics Letters about olanzapine<sup>10</sup> and quetiapine<sup>11</sup> concluded that “More and better evidence is required to demonstrate the long-term effectiveness and safety of new antipsychotics” and that “Long-term effectiveness and safety remain to be established”. Clearly these conclusions apply even more to children. In children, early development of obesity or type 2 diabetes may be irreversible. **Physicians and parents should be especially cautious and concerned when considering using these drugs in children.**

The draft of this Therapeutics Letter was submitted for review to 50 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.