Atypical Antipsychotics in Children and Adolescents
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Introduction

Atypical antipsychotics (AAs) have widely replaced the older, typical antipsychotics (e.g., chlorpromazine, haloperidol) since they were introduced to the United States market. One reason is the AAs, in general, produce fewer movement-related adverse effects (extrapyramidal symptoms or EPS) than older antipsychotics. In addition, they were believed to demonstrate superior efficacy, especially against negative symptoms of schizophrenia. While advantages in terms of EPS risk continue to be demonstrated, the purported advantages in effectiveness have been in question. However, superiority in terms of cognitive effects appears to be valid. In addition, the advantages in terms of EPS-related adverse effects have been tempered by concerns about metabolic adverse effects (i.e. weight gain, lipid abnormalities, glucose regulation, etc.). These metabolic effects raise questions about the long-term tolerability of AAs. This article will provide a general review of the available AAs and review data related to their use in children and adolescents.

Available Atypical Antipsychotics:
There are currently ten AAs available in the United States (Table 1). The first AA to become available was clozapine (Clozaril®). However, due to potential toxicity its use is generally reserved for treatment-resistant patients. The first AA to be used as a first-line agent, risperidone (Risperdal®), is the most “typical” of the atypical agents. In a dose-related manner it is associated with the EPS that were a major disadvantage of the older agents. It was followed by olanzapine (Zyprexa®), which was the first agent to produce very few EPS in clinically recommended doses. Unfortunately, it has become apparent that it is associated with a higher risk of metabolic adverse events than many of the other AAs. Since then, other agents have been developed with varying clinical profiles. Of the first-line AAs, risperidone became available generically in 2008 and as of April, 2012 ziprasidone, olanzapine, and quetiapine immediate-release are all available in generic form.

Table 1: FDA Approved Indications for Atypical Antipsychotics*

<table>
<thead>
<tr>
<th>Available Agents</th>
<th>Indications (Age in years)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Schizophrenia</td>
</tr>
<tr>
<td>Abilify® (aripiprazole)</td>
<td>≥13</td>
</tr>
<tr>
<td>Clozapil® (Clozaril)</td>
<td>≥18</td>
</tr>
<tr>
<td>Fanapt® (iloperidone)</td>
<td>≥18</td>
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<tr>
<td>Geodon® (ziprasidone)</td>
<td>≥18</td>
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<tr>
<td>Invega® (paliperidone)</td>
<td>≥12</td>
</tr>
<tr>
<td>Latuda® (lurasidone)</td>
<td>≥18</td>
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### Available Agents

<table>
<thead>
<tr>
<th>Available Agents</th>
<th>Indications (Age in years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperdal ® (risperidone)</td>
<td></td>
</tr>
<tr>
<td>≥13</td>
<td>≥10</td>
</tr>
<tr>
<td>Saphris ® (asenapine)</td>
<td></td>
</tr>
<tr>
<td>≥18</td>
<td>≥18</td>
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<tr>
<td>Seroquel ®/XR (quetiapine)</td>
<td></td>
</tr>
<tr>
<td>≥13</td>
<td>≥10</td>
</tr>
<tr>
<td>Zyprexa ® (olanzapine)</td>
<td></td>
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<tr>
<td>≥13</td>
<td>≥13</td>
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</tbody>
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*Official prescribing information available by drug at: http://dailymed.nlm.nih.gov/dailymed/about.cfm

#Symbyax is a combination of fluoxetine and olanzapine

All available antipsychotics, both typical and atypical, block dopamine activity at the D₂ receptor. This activity is thought to mediate antipsychotic effects and is the source of movement-related adverse effects. AAs differ from typical agents pharmacologically by being more potent serotonin 5HT₂ receptor blockers than dopamine receptor blockers. This activity modulates adverse effects, especially EPS, and probably contributes to their efficacy. As a class, the AAs share some basic pharmacology, but the individual agents all have unique clinical profiles. As can be seen in Table 1 they also have different Food and Drug Administration (FDA) approved indications.

### Trends in Atypical Antipsychotic Prescribing in Children:

While there are limited FDA approved indications for AAs in children and adolescents (see Table 1), the increasing use of these agents in this population has been well documented. In fact, the issue of widespread use of AAs in youth has become the focus of increasing concern and controversy. At a November 2008 meeting, the Pediatric Advisory Committee to the FDA voted unanimously to recommend that additional information be gathered regarding on-label and off-label use of the AA class of drugs in youth with specific attention to age, indication for use, and adverse effects in pediatric patients.

In the United States, the number of non-institutionalized children and adolescents being treated with antipsychotic medications from 1987 to 1996 remained relatively constant at less than 300 per 100,000. A study published in 2006 found the number of office-based visits by youth under the age of 21 years that resulted in treatment with antipsychotics increased from approximately 275 per 100,000 in 1993 to 1,438 per 100,000 in 2002 (see Figure 1). The absolute number of office visits that resulted in antipsychotic treatment increased from approximately 201,000 in 1993 to 1,224,000 in 2002.

**Figure 1:** National trends in office-based visits by children and adolescents that included antipsychotic treatment, 1993 – 2002. Annualized visit rates per 100,000 population were calculated using National Ambulatory Medical Care Survey and US Census Bureau data.

AAs were prescribed in 92.3% of the visits in 2002 that included antipsychotic treatment. It was found that office visits to psychiatrists included antipsychotic treatment 18% of the time while mental health related visits
in general resulted in antipsychotic treatment 9% of the time. This analysis also found that antipsychotic treatment was significantly more likely for males compared to females, even when controlling for diagnosis. It was also noted that the majority of the antipsychotic treatment in youth occurred among those publicly rather than privately insured.\(^6\)

A second study involving antipsychotic use in children and adolescents, covering the years of 1995 to 2002, reported there were 5,762,193 outpatient visits in that time frame in which an antipsychotic was prescribed.\(^7\) The number of prescriptions increased from 493,510 in 1995-1996 to 2,490,720 in 2001-2002. The number of U.S. children during those same time periods increased slightly from 61,249,041 and 63,270,000. The mean age of children receiving such treatment was 12.9 years old and two-thirds of them were male. Mental health providers accounted for over 67% of the antipsychotic prescriptions, but frequencies of antipsychotic prescriptions increased for both mental health and non-mental health providers during the study period.\(^7\)

**Indications for Atypical Antipsychotics in Children:**

While little is known about the clinical characteristics of the children who receive AAs, there is concern that they are being used more commonly for aggression and other behavioral disturbances than to treat psychosis, which is the most studied indication for their use.

In the first study described above the majority of the office visits resulting in antipsychotic treatment were for a disruptive behavior disorder, mood disorder, or other mental disorder; only 14% were for a psychotic disorder.\(^6\) In the second study, the most common diagnosis associated with antipsychotic treatment was attention-deficit/hyperactivity disorder (ADHD) or conduct disorder (29%).\(^7\) ADHD is not a well-established indication for antipsychotic medications and is one of the areas of use singled out by committee members during the November Pediatric Advisory Committee meeting.\(^10,11\) Following ADHD/conduct disorder in the Cooper study were mood disorders, which accounted for 23.6% of antipsychotic use.\(^7\) A non-psychiatric diagnosis resulted in almost 14% of the antipsychotic use in this study, while anxiety or other psychiatric conditions accounted for almost 8% of the use. Schizophrenia (13.5%), autism or other pervasive developmental disorders (7.5%), and Tourette’s syndrome (5%) all well established uses of antipsychotic agents, accounted for 26% of all antipsychotic use.

**Concerns about Atypical Antipsychotic Use in Children:**

The limited empiric data related to the use of AAs in youth makes it difficult to assess their risk-benefit ratio. While movement-related adverse effects in youth appear to be less common with AAs than with typical antipsychotics, the same as for adults, a major concern with the use of AAs is the risk for adverse metabolic effects.\(^4\) Unfortunately, there is growing evidence available that suggests the risk for metabolic problems may be more severe in children and adolescents than in adults.\(^12-14\) Data made available by the manufacturer more specifically documents this concern for one of the AAs.\(^15\) In this assessment of the overall adolescent data base with olanzapine weight gain was the most common adverse effect, occurring in 31.7% of the exposed population. In addition, when compared with the adult database, adolescents gained statistically significantly more weight (7.4 kg vs. 3.2 kg, p < 0.001) in short term trials. In additions, adolescents experienced statistically significant within-group baseline-to-endpoint changes in fasting glucose (p < 0.001), total cholesterol (p < 0.002), and triglycerides (p < 0.007).

Other areas also exist where adverse event incidences and concerns are potentially different in children and adolescents than in adults.\(^12\) These include elevated serum prolactin levels, cardiac concerns, and sedation. All of these appear to be more problematic in youth compared to the adult population where most of the data about their incidence exists. In children and adolescents hyperprolactinemia with AAs appears to be more common than in adults. It may result in gynecomastia, menstrual irregularities, and other effects in both adults and a younger population, but may be of particular concern in a younger population because the effect of hypogonadism-induced osteoporosis may have more severe consequences. The potential cardiac effects of AAs in children and adolescents remain an area where data are too limited to allow conclusions. All of the AAs have some activity that results in prolongation of the QT interval and may result in cardiac dysrhythmias. How different this risk is in the young compared to adults, where most of the available data is, remains unknown. These and other areas of potential risk must all be further investigated as called for by the FDA advisory committee.
In 2007, during an Agency for Healthcare Research and Quality (AHRQ) supported Medicaid Medical Directors Learning Network meeting, a plan was developed for a collaborative project to examine the use of AAs for children and adolescents in Medicaid. Indiana Medicaid participated in this study that explored rates and trends of AA use in children and adolescents in fee-for-service Medicaid. An upcoming Retrospective DUR educational mailing will re-look at the issues examined in this original study: use of AAs in children 5 years of age or younger, use of higher than recommended doses, use of multiple AAs, and use of multiple psychotropic agents; in the Indiana Medicaid fee-for-service population.

Conclusion:

In recent years, AAs have become common in the office-based mental health treatment of young people. Some AAs have received FDA approval for use in children for selected indications and the results of recently published clinical trials provide limited support for the short-term safety and efficacy of some AAs for additional indications. However, there remains an apparent disconnect between the documented community practice patterns and the available empiric data related to AA use in children and adolescents. These medications are apparently being used to treat a variety of disorders, many of which require more controlled research before such use can be regarded as both safe and effective. There is a pressing need for this research, especially as related to potential long-term consequences of the widespread use of these potent medications in a young population.

References:


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