REPORT OF THE COUNCIL ON SCIENCE AND PUBLIC HEALTH

CSAPH Report 1-I-12

Subject: Use of Atypical Antipsychotics in Pediatric Patients

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INTRODUCTION

Policy D-120.955 directed the Council on Science and Public Health to prepare a report on the safety and appropriate use of atypical antipsychotic medications in children and adolescents. In 2011, the American Academy of Child and Adolescent Psychiatry (AACAP) published a practice parameter on the use of atypical antipsychotics in pediatric patients.[1] Guidance on the clinical use of these drugs in pediatric patients also has been developed by the Canadian Alliance for Monitoring Effectiveness and Safety of Antipsychotics in Children (CAMESA) Guideline Project Group.[2,3] This report addresses safety and appropriate use and briefly discusses the complex issues surrounding the clinical use of these drugs in pediatric patients, evaluating new data, and referencing clinical recommendations that are intended to improve outcomes when atypical antipsychotics are used in pediatric patients.

METHODS

Information for this report was obtained from English-language reports selected from a PubMed search for article titles for the terms “olanzapine,” “ziprasidone,” “clozapine,” “aripiprazole,” “risperidone,” “paliperidone,” “ asenapine,” “iloperidone,” “lurasidone,” or “quetiapine” combined with the terms “child*,” “adolescent*” or “pediatric*,” in the title or abstract and applying filters corresponding to systematic reviews, randomized controlled trials, clinical trials or case reports. Additionally, the Cochrane Library clinical trial database and the federal registry of clinical trials (www.clinicaltrials.gov) were searched using the same strategy. Further information was obtained from the Internet site of AACAP. Pharmaceutical companies that were original patent holders for atypical antipsychotics were invited to supply bibliographies as well.

ATYPICAL ANTIPSYCHOTIC DRUGS

Definition

Compared with conventional antipsychotic drugs such as haloperidol, atypical antipsychotics have a substantially lower propensity for inducing extrapyramidal nervous system symptoms (EPS) (i.e., parkinsonism, dystonia, akathisia, and tardive dyskinesia). This feature represents the most significant clinical advantage of atypical antipsychotics. Serum prolactin concentrations also are less affected compared with older antipsychotic drugs, except for risperidone.

Action of the AMA House of Delegates 2012 Interim Meeting: Council on Science and Public Health Report 1 Recommendations Adopted, and Remainder of Report Filed.

Currently Marketed Atypical Agents

Atypical agents include clozapine, paliperidone (metabolite of risperidone), olanzapine, quetiapine, ziprasidone, aripiprazole, risperidone, asenapine, iloperidone, and lurasidone (see Table). With the exception of aripiprazole, which is a partial agonist, atypical antipsychotic drugs (like their conventional counterparts) antagonize dopamine 2 receptors but also exhibit variable affinity for blocking other dopamine receptor subtypes. Atypical antipsychotics also generally antagonize serotonin 2A and 2C receptors with variable antagonist activity at histamine, muscarinic, and alpha-adrenergic receptors; some also function as agonists or partial agonists at serotonin 1A receptors. For a summary chart detailing these variable receptor activities see McDonagh et al.[4] As a group, these drugs have diverse pharmacodynamic properties and exhibit variable clinical responses, especially with respect to adverse effects. Little or no information is available on the use of asenapine and iloperidone in pediatric patients and these agents are not further discussed.

Clinical Efficacy and Safety

Atypical agents are similar to conventional drugs in reducing psychotic symptoms (and may be more effective in reducing so-called negative symptoms). Although they produce fewer neurologic side effects, evidence of superior efficacy in adult patients with schizophrenia has been neither consistent nor robust, except for clozapine, which can cause severe hematologic side effects that limit its pattern of use. More recently, even the putative safety advantages of atypical antipsychotics have been questioned because they present their own spectrum of adverse effects including hypotension, seizures, weight gain, increased risk of type II diabetes and hyperlipidemia; some of these drugs may lengthen the QT interval as well.

Clinical Uses of Atypical Antipsychotic Drugs in Pediatric Patients

Labeled Indications. Risperidone, olanzapine, aripiprazole, quetiapine, and paliperidone have FDA-approved uses in pediatric patients. All five are approved for the treatment of schizophrenia in adolescents 13 to 17 years of age. Olanzapine is approved for the acute treatment of manic or mixed episodes and maintenance treatment of bipolar I disorder in adolescents. This approval is extended down to the age of 10 years for aripiprazole and risperidone, although risperidone is approved only for short term use. Aripiprazole and risperidone also are approved for the treatment of irritability associated with autistic disorder in pediatric patients 6 to 17 years of age.

Off-Label Uses. Atypical antipsychotics are used off-label to treat Tourette syndrome and tic disorders, attention deficit hyperactivity disorder (ADHD), and pervasive developmental disorder. They also have been increasingly used to treat oppositional behavior, irritability and aggressive behaviors across various diagnostic categories. Case reports and open label trials also indicate they are being used in pediatric patients with borderline personality disorder, obsessive compulsive and other anxiety disorders, anorexia nervosa, mental retardation/developmental delay, Axis I disorders that include psychotic features, as adjunctive therapy in major depressive disorder, and in patients with delirium (references supplied on request).

Trends in Prescribing of Antipsychotics

Based on data obtained from IMS Health, total antipsychotic use (conventional plus atypical) increased from more than 6 million treatment visits* in 1995 to 16.7 million visits in 2006, declining to 14.3 million visits in 2008.[5] By 2011, U.S. spending on prescriptions for all

* A treatment visit is defined as a visit that was concluded with a prescription being issued.

antipsychotic medications was estimated at $18.2 billion, trailing only medications used for diabetes, hyperlipidemia, respiratory disease, and cancer.[6] The proportional use of atypical antipsychotics was 16% of treatment visits in 1995, but such use had surged to 93% of treatment visits by 2008. In two-thirds of these visits, the prescription was for an off-label use.[5]

Antipsychotic treatment rates among privately insured youth ages 6 to 17 increased steadily from 1996 (0.21%) to 2006 (0.90%) with higher rates among those ages 13 to 17.[7] The annualized rate of use in such patients ages 2 to 5 more than doubled between 1999 and 2007 to 0.16%, most commonly to help manage pervasive developmental disorder or mental retardation.[8]

More than 4% of Medicaid youth ages 6 to 17 filled at least one prescription for an antipsychotic in 2004, with 75% of these being for off-label uses.[7] A number of children under 6 years of age enrolled in Medicaid programs receive ongoing treatment with antipsychotic medications.[9,10]

Safety

While all atypical antipsychotics are associated with metabolic changes that may increase cardiovascular risk, each drug has its own risk profile. The chief concerns are weight gain, hyperlipidemia, glucose intolerance, and extrapyramidal side effects. Based on analysis of short term trials (3 to 12 weeks) that examined adverse effects in youths, weight gain was most prominent in olanzapine (~20 lbs), clozapine, quetiapine and risperidone recipients; aripiprazole was the most weight neutral.[11-14] Such weight gain persists during long-term treatment.[15] Clozapine and olanzapine also consistently elevate fasting glucose, insulin and triglycerides.[16] Based on limited comparative data, cholesterol is increased most significantly by olanzapine, quetiapine and risperidone, and triglycerides also are increased by risperidone; the latter also is most likely to increase prolactin levels.[11-14] Children and adolescents may be more sensitive than adults to metabolic changes occurring during long-term treatment, especially weight gain, total cholesterol, and triglycerides.[17] Weight gain may be more likely in autistic children and in those with disruptive behavioral disorders.[18]

Increases in treatment-related adiposity predict insulin resistance. One retrospective analysis indicated that the risk of diabetes may be 4-fold higher in children 5 to 18 years of age who initiated therapy with atypical antipsychotic drugs between 2001 and 2008.[19] The risk of incident diabetes appears higher for users of clozapine and olanzapine.[20] The reported occurrence of EPS has been variable. Although these occur at lower frequencies than in patients treated with conventional antipsychotic drugs, the atypical agents most likely to be associated with EPS are risperidone and olanzapine, and in one study ziprasidone.[21] Atypical antipsychotics also are generally associated with an increased risk of somnolence and sedation.

SYSTEMATIC REVIEWS

Two recent systematic reviews are relevant. The Drug Effectiveness Review Project (DERP) is an Oregon-based collaboration of public and private organizations, including fifteen states, that have joined together to provide systematic evidence-based reviews of the comparative effectiveness and safety of drugs in many widely used drug classes and to apply the findings to inform public policy and related activities. DERP has conducted an ongoing drug class review of the atypical antipsychotic drugs. The most recent update was published in July 2010.[4] With respect to off-label uses, compared with placebo, risperidone, aripiprazole, and olanzapine improved behavioral symptoms in children and adolescents with pervasive developmental disorders, and risperidone and quetiapine showed efficacy in children and adolescent with disruptive behavior disorders.

Additionally, the Agency for Healthcare Research and Quality commissioned a comparative effectiveness review of the off-label use of atypical antipsychotics.[22] This review evaluated the use of atypical antipsychotics in children (younger than 12 years old) and adolescents (12 to 17 years old) with eating disorders (including anorexia nervosa and bulimia), attention deficit hyperactivity disorder, Tourette syndrome, and insomnia. Evidence of efficacy was noted for risperidone in the treatment of ADHD and Tourette syndrome, while quetiapine and olanzapine were not effective in the treatment of anorexia nervosa, and risperidone was not effective in managing insomnia. These commissioned reviews and the Cochrane library (www.thecochranelibrary.com) are good sources for other systematic reviews on atypical antipsychotic drugs.[4,22]

PRACTICE GUIDELINES

In 2011, AACAP developed a practice parameter for clinicians on the use of atypical antipsychotics in children and adolescents.[1] A previous practice parameter from AACAP on the assessment and treatment of children and adolescents with bipolar disorders also is germane.[23] The former, which covered the literature to 2010 offers guidance on the clinical use of atypical antipsychotics in pediatric patients based on 19 separate recommendations. These recommendations address:

- Principles inherent in using psychotropic medication in children and adolescents;
- Risks associated with these drugs, including recommended history taking, baseline assessments, duration of therapy, and discontinuation;
- Dosing recommendations based on disease target and attendant side effects;
- Issues with the use of multiple psychotropic medications;
- Recommendations for safety monitoring especially weight, body mass index, heart rate, blood pressure, electrocardiogram, blood glucose, and lipid profiles;
- Measurements of movement disorders using structured measures; and
- Drug specific risks.

The reader is referred to the AACAP practice parameter for further information and specific clinical practice recommendations.[1]

Evidence-based recommendations for monitoring the safety of atypical antipsychotics in children and adolescents also have been developed by the CAMESA Guideline Project.[2] These recommendations address the first six atypical antipsychotics that were approved in the U.S. and exclude the newer agents paliperidone, asenapine, iloperidone, and lurasidone. Monitoring recommendations address height, weight, BMI, waist circumference, blood pressure, EPS, fasting blood glucose, insulin, lipid profiles, liver enzymes, prolactin, and thyroid stimulating hormone. The same group also developed clinical advice for addressing emergent metabolic complications associated with the use of atypical antipsychotics in pediatric patients.[3] Treatment recommendations addressed minimizing weight gain and managing abnormal BMI, waist circumference, blood pressure, fasting blood glucose, insulin, lipid profiles, liver function tests, TSH, and prolactin levels.[3]

DISCUSSION

Although certain atypical antipsychotic drugs are FDA-approved for specific uses in pediatric patients, the majority of prescribing (70 to 75%) is off-label for these drugs. Head-to-head comparisons of atypical antipsychotic drugs for off-label uses are few, and evidence from placebo-

controlled trials for off-label use suggests that efficacy differs between drugs. Accordingly, one cannot anticipate that a "class effect" exists for atypical antipsychotics with respect to any specific clinical use or indication.

Little evidence exists on how treatment efficacy varies among populations, including how clinical responses may be influenced by sex, race, ethnicity, or medical co-morbidities. The metabolic effects of atypical antipsychotics are concerning. Because the risk of childhood obesity is inversely related to socioeconomic status, low-income children who are already at high risk for obesity and related metabolic disorders may be especially vulnerable to the adverse effects of weight gain from atypical antipsychotics.[24]

Improving Health Outcomes

In order to improve outcomes in pediatric patients who are candidates for treatment with atypical antipsychotics, treatment must include appropriate baseline assessments, examination of risks and benefits, adequate ongoing monitoring of key metabolic and neurologic variables, and management of emergent metabolic and physiologic conditions. Clinical guidance is available from AACAP and CAMESA. Nothing in the recently published literature significantly affects the basis from which these recommendations were derived; however, additional study, especially further long term measures of safety and efficacy would be helpful to inform clinical decision-making.

RECOMMENDATIONS

The Council on Science and Public Health recommends that the following statements be adopted and the remainder of the report be filed.

That our AMA:

1. Urge the National Institute of Mental Health to assist in developing guidance for physicians on the use of atypical antipsychotic drugs in pediatric patients. (Directive to Take Action)

2. Encourage and support ongoing federally funded research, with a focus on long term efficacy and safety studies, on the use of antipsychotic medication in the pediatric population. (Directive to Take Action)

3. Rescind Policy D-120.955 as it has been accomplished by preparation of this report. (Rescind HOD Policy)

Fiscal Note: Less than $500

REFERENCES

1. Practice Parameter for the use of Atypical Antipsychotic Medications in Children and Adolescents http://www.aacap.org/galleries/PracticeParameters/Atypical_Antipsychotic_Medications_Web.pdf

2. Pringsheim T, Panagiotopoulos C, Davidson J, Ho J for the CAMESA Guideline Group. Evidence-based recommendation for monitoring safety of second generation antipsychotics in children and youth. *J Can Acad Child Adolesc Psychiatry*. 2011;20:218-233. http://www.ncbi.nlm.nih.gov/pmc/articles/pmid/21804853/?tool=pubmed. Accessed July 30, 2012.

3. Ho J, Panagiotopoulos C, McCrindle B, Grisaru S, Pringsheim T for the CAMESA Guideline Group. Management recommendations for metabolic complications associated with second generation antipsychotic use in children and youth. *J Can Acad Child Adolesc Psychiatry*. 2011;20:234-241. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3143701/?tool=pubmed. Accessed July 30, 2012.

4. McDonagh MS, Peterson K, Carson S, Fu R, Thakurta S. Drug class review: Atypical antipsychotic drugs. Update 3. http://derp.ohsu.edu/final/AAP_final_update_3_version%202_JUL_10.pdf. Accessed July 23, 2012.

5. Alexander GC, Gallagher SA, Mascola A, Moloney RM, Stafford RS. Increasing off-label use of antipsychotic medication in the United States, 1995-2008. *Pharmacoepidemiol Drug Saf.* 2011;20:177-184.

6. IMS Health. Top Therapeutic Classes by U.S. Spending. http://www.imshealth.com/ims/Global/Content/Corporate/Press%20Room/Top-Line%20Market%20Data%20&%20Trends/2011%20Top-line%20Market%20Data/Top_Therapy_Classes_by_Sales.pdf. Accessed July 23, 2012.

7. Crystal S, Olfson M, Huang C, Pincus H, Gerhard T. Broadened use of atypical antipsychotics: Safety, effectiveness, and policy challenges. *Health Aff*. 2009;28:770-781.

8. Olfson M, Crystal S, Huang C, Gerhard T. Trends in antipsychotic drug use by very young, privately insured children. *J Am Acad Child Adolescent Psychiatry*. 2010;49:13-23.

9. Constadine RJ, Tandon R, McPhwerson M, Andel R. Early diagnosis and psychotherapeutic medication treatment experiences of a cohort of children under 6 years of age who received antipsychotic treatment in Florida's Medicaid program. *J Chil Adolesc Psychopharmacol.* 2011;21:79-84.

10. Constadine RJ, Jentz S, Bengston M, McPherson M, Andel R, Jones MB. Exposure to antipsychotic medications over a 4-year period among children who imitated antipsychotic treatment before their sixth birthday. *Pharmacoepidemiol Drug Saf.* 2012;21:152-160.

11. Roke Y, van Harten PN, Boot AM, Buitelaar JK. *J Child Adolesc Psychopharmacol*. 2009;19:403-414.

12. DeHert M. Dobbelaere M, Sheridan EM, Cohen D, Correll CU. Metabolic and endrocrine adverse effects of second-generation antipsychotics in children and adolescents: A systematic review of randomized, placebo-controlled trials and guidelines for clinical practice. *Eur Psychiatry*. 2011;26:144-158

13. Correl CU, Lencz T, Malhotra AK. Cardiometabolic risk of second-generation antipsychotic medications during first-time use in children and adolescents. *JAMA.* 2009;302:1765-1773.

14. Amor B. Antipsychotics in pediatric and adolescent patients: a review of comparative safety data. *J Affect Disord*. 2012;138(Suppl S22-30).

15. Findling RL, Johnson JI, McClellan J et al. Double blind maintenance safety and effectiveness findings from the Treatment of Early Onset Schizophrenia Spectrum (TEOSS) study. *J Am Acad Child Adolesc Psychiatry*. 2010;49:583-594.

16. Gohlke JM, Dhurandhar EJ, Correll CU, et al. Recent advances in understanding amd mitigating adipogenic and metabolic effects of antipsychotic drugs. *Frontiers Psychiatry.* 2012;3(62):1-12.

17. Kryzhanovskaya LA, Xu Millen BA, Acharya N, Jen KY, Osuntokun O. Comparison of long-term (at least 24 weeks) weight gain and metabolic changes between adolescents and adults treated with olanzapine. *J Child Adolesc Psychopharmacol*. 2012;22:157-165.

18. Maayan L, Correll CU. Weight gain and metabolic risks associated with antipsychotic medications in children and adolescents. *J Child Adolesc Psychopharmacol*. 2011;21:517-535.

19. Andrade SE, Lo jC, Roblin D, et al. Antipsychotic medication use among children and risk of diabetes mellitus. *Pediatrics*. 2011;128:1135-1141.

20. Yood MU, Delorenz G, Quesenberry C, et al. The incidence of diabetes in atypical antipsychotic users differs according to agent-results from a multisite epidemiologic study. *Pharmacoepidemiol Drug Saf*. 2009;18:791-799.

21. Cohen D, Bonnot O, Bodeau N, Consoli A, Laurent C. Adverse effects of second-generation antipsychotics in children and adolescents: A Bayesian meta analysis. *J Clin Psychopharmacol.* 2012;32:309-316.

22. Maglione M, Ruelaz Maher A, Hu J, et al. Off-Label Use of Atypical Antipsychotics: An Update. Comparative Effectiveness Review No. 43. (Prepared by the Southern California Evidence-based Practice Center under Contract No. HHSA290-2007-10062-Rockville, MD: Agency for Healthcare Research and Quality. September 2011. Available at: http://www.effectivehealthcare.ahrq.gov/ehc/products/150/778/CER43_Off-LabelAntipsychotics_20110928.pdf.

23. Practice Parameter for the Assessment and Treatment of Children and Adolescents With Bipolar Disorder. 2007 http://www.aacap.org/galleries/PracticeParameters/JAACAP_Bipolar_2007.pdf. Accessed July 24, 2012

24. Shrewsbury V, Wardle J. Socioeconomic status and adiposity in childhood: A systematic review of cross-sectional studies, 1990-2005. *Obesity.* 2008;16:275-284.

Table. Atypical Antipsychotic Drugs Marketed in the United States

Generic Name	Trade Name
Aripiprazole	Abilify®
Asenapine	Saphris®
Clozapine*	N/A
Iloperidone	Fanapt®
Lurasidone	Latuda®
Olanzapine*	Zyprexa®
Paliperidone	Invega®
Quetiapine*	Seroquel®
Risperidone*	Risperdal®
Ziprasidone	Geodon®

*Available as a generic equivalent