



The Bulletin of Medicaid Drug Utilization Review in Iowa

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Are Non-Benzodiazepine Sedative Hypnotics Less Addictive Than Benzodiazepines?

By Ashley Butt, Pharm.D. Candidate

The Iowa Medicaid Drug Utilization Review Commission has recently noticed an increasing trend toward the concomitant use of non-benzodiazepine (non-BZD) sedative hypnotics with benzodiazepines. The Commission recommends that the following DUR intervention letter be sent to providers of members treated with the above mentioned combination:

According to the profile, this patient is taking both a benzodiazepine and a non-benzodiazepine hypnotic agent. Could the non-benzodiazepine hypnotic be replaced by a higher dose of the patient's current benzodiazepine at bedtime?

Many providers have responded back with a preference for the combination because they believe non-BZD sedative hypnotics are not addictive and therefore safe for their patients.

Zolpidem, Ambien CR™, and Lunesta™ are the main drugs being targeted with this initiative. Each of their package inserts state that clinical trial experience revealed no clear evidence either way of serious withdrawal syndrome when discussing abuse, dependence, and tolerance^{1, 2, 3}. While zolpidem and eszopiclone are hypnotic agents with chemical structures unrelated to benzodiazepines, they share some of the same pharmacologic properties. It is known that benzodiazepines may lead to physical and psychological dependence¹.

Published reviews of the literature are inconclusive on the true addictive potential of non-BZD sedative hypnotics and the incidence of abuse is currently unknown. Case reports document the abuse and withdrawal of these agents⁴. Many studies conclude that addiction is more common in patients with a history of drug abuse or psychiatric illness, but others must also take caution⁵. The risk of abuse and dependence also rises with increased dose and duration of treatment and concomitant use of other psychoactive drugs, which applies to many patients on current non-BZD sedative/hypnotic therapy.

The Iowa Medicaid Drug Utilization Review Commission suggests considering replacing a non-benzodiazepine sedative hypnotic with a higher dose of a patient's current benzodiazepine for those on concomitant therapy. There is evidence of improper and increased use of non-benzodiazepine sedative hypnotics, which prompted this intervention, and is continuing to be followed.

References:

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2. Ambien package insert. Accessed 3/21/08. <http://www.fda.gov/cder/foi/label/2007/019908s022lbl.pdf>
3. Ambien CR package insert. Accessed 3/24/08. http://products.sanofi-aventis.us/ambien_cr/ambienr.html
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The Use of Atypical Antipsychotics in Preschool Aged Children

By Erica Pearce, Pharm.D.

The use of the atypical antipsychotics in preschool age children is increasing.¹ Currently in the United States, risperidone is the only atypical antipsychotic FDA approved for patients as young as five years of age and only for the treatment of autism.² Therefore, the use of these agents in preschool aged children for mental health reasons is considered “off-label”. While the FDA has developed incentives to encourage manufacturers to test their drugs in pediatric patients, there has been little progress in this area.³ With the recent addition of a black box warning to the labeling of antidepressants, some health care professionals and patients have increasing concerns about the safety of psychotropic medications in children.⁴

Prevalence

In Texas, the number of pediatric Medicaid patients prescribed an atypical antipsychotic medication increased 494% between 1996 and 2000.⁵ From 1996-2001, the use of typical and atypical antipsychotics in American children between 2-4 years of age increased 2-fold and 24-fold, respectively.⁶ Of all children receiving antipsychotics, 92.3% were for an atypical antipsychotic.¹ Male children have nearly a 3-fold greater chance of being prescribed an antipsychotic when compared to female children. Pediatric patients prescribed antipsychotics were more frequently covered under a public health insurance plan than private health insurance plan.⁶

Guidelines

Recently the American Academy of Child and Adolescent Psychiatry (AACAP) developed clinical algorithms for treatment of very young children with mental health disorders.⁴ All of the treatment algorithms contained the following five factors:

1. Assessment and diagnosis - the diagnostic process can be more complex with very young children and reassessment of the diagnosis and clinical picture should occur frequently due to the rapid development in preschool aged children.
2. Psychotherapy - psychotherapeutic interventions are an essential part of treatment for patients with mental health disorders.
3. Evidenced based practice - clinicians should consider the body of evidence and tailor treatment to include the patient-specific needs.
4. Discontinuation - after a successful psychopharmacologic trial, recommendations are to discontinue medications to reassess patient's need.
5. Referral - If the patient arrives at the end of the treatment algorithm and has failed all recommended treatments, the patient should then be referred to a specialist in that disorder.

Efficacy

Common disorders that may require medication management with atypical antipsychotics in preschoolers include disruptive behavior disorders (e.g., violent and defiant behaviors), pervasive developmental disorders (e.g., autism), tic disorders (e.g., Tourette's syndrome), schizophrenia and bipolar disorders.⁷

Risperidone is considered the drug of choice for treatment of children with mental health disorders.⁴ Olanzapine is the second most commonly studied atypical antipsychotic in children.⁷

There are currently no controlled trials of atypical antipsychotics in preschool aged children with disruptive behavior disorders.⁴ In one retrospective case study, eight children with aggressive behavior disorders showed an average decrease in symptom severity of 36% with risperidone.⁸

There are two risperidone controlled trials in children with pervasive developmental disorders, particularly autism. One randomized, placebo-controlled, double-blind 6-month study of 40 children aged 2-9 years with a diagnosis of autism, designated a 20% improvement of symptoms from baseline as clinically significant.⁹ This response target was achieved in 63% and 20% of children receiving risperidone and placebo, respectively. In an 8-week, randomized placebo-controlled trial of 101 children between the ages of 5-17 years, treatment with risperidone was associated with a statistically significant decrease in tantrums, aggression, repetitive behaviors, and self-injury.¹⁰

There has only been one study of atypical antipsychotics in preschool aged children with manic disorders. In the open label trial, 31 children ages 4-6 years old with a history of manic episodes were treated with either risperidone or olanzapine.¹¹ A 30% decrease in the Young Mania Rating Scale score was considered significant, which occurred in 69% and 53% of the risperidone and olanzapine patients, respectively.

Safety and Tolerability

Atypical antipsychotics were generally well tolerated as 2.6-8.3% of patients discontinued treatment due to adverse effects.⁷ The most commonly reported adverse effects included sedation, weight gain and hyperprolactinemia. Sedation was typically mild to moderate in severity and was often reduced by decreasing the dosage, using divided dosing, or switching the dosing from morning to night. Weight gain in pediatric trials averaged between 1 kg in 16 weeks of treatment to 12.8 kg over a year of treatment.⁷ In one study, olanzapine increased prolactin levels by 23.7 ng/ml; however, the elevation in prolactin was not correlated with gynecomastia in males.¹²

Most studies in this age group have a maximum duration of two years.⁷ In preschool aged children the long-term effects of antipsychotics on their physical health and the developing brain are unknown.⁴

The American Academy of Child and Adolescent Psychiatry has recommended that all patients, regardless of age, taking atypical antipsychotics have vital signs, body mass index, fasting blood glucose, extrapyramidal symptoms, lipid profile, and electrocardiography monitoring. They also suggest monitoring prolactin levels.⁴

Conclusion

The use of atypical antipsychotics in preschool aged children has increased dramatically over the past decade. The AACAP clinical algorithms offer suggestions for the treatment of very young children with mental health disorders; however, many of these children may need to be referred to a specialist. Though multiple antipsychotics have been commonly used in younger patients, results of clinical trials provide a limited body of evidence on the short-term safety and efficacy. Additional large-scale randomized controlled trials are needed to strengthen this evidence base and evaluate the long-term safety of these agents.

Endnotes

- ¹ Petal NC, et al. Trends in the use of typical and atypical antipsychotic in children and adolescents. *J Am Acad Child Psychiatry*. 2005; 44(6):548-556.
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- ¹¹ Biederman J, et al. Open-label, 8-week trial of olanzapine and risperidone for the treatment of bipolar disorder in preschool-aged children. *Biol Psychiatry*. 2005;58:589-594
- ¹² Wudarksy M et al. Elevated prolactin in pediatric patients on typical and atypical antipsychotics. *J Child Adolesc Psychopharmacol*. 1999;9:239-245.



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I-MERS

The Iowa Medicaid Electronic Record System (I-Mers) is a web-based tool that will give providers up-to-date information about what services have been paid for by Iowa Medicaid. I-MERS will allow treating providers to view Medicaid members' medical procedures, prescriptions, and other services that are currently in the Medicaid computer system.

I-MERS is NOT a complete medical record. Sensitive information, such as AIDS/HIV, substance abuse, and mental health-related issues is not currently available through I-MERS because of legal impediments.

How to Register for Access

Registration is accomplished on an organizational basis (e.g. Clinic, Group Practice, Hospital, etc). To register your organization and users:

1. **Send a letter.** The Iowa Medicaid provider requesting access to the I-MERS system must send a letter on the organization's letterhead. **The provider sending the letter requesting access to I-MERS will be responsible for assuring appropriate staff usage under HIPAA.** Indicate "I-MERS Registration" in the subject line of the letter and send the letter to:

IME Provider Services
IMERS Access
100 Army Post Rd
Des Moines, Iowa 50315
2. **Include in the letter:**
 - a. Your Provider Number (7 digit Medicaid provider number or NPI)
 - b. Your Provider Type (MD, DO, ARNP, R.Ph, Pharm.D, Hospital, FQHC, RHC, CMHC, Clinic, or PMIC)
 - c. Tax ID Number
 - d. The name and address of the organization (e.g., Northwest Community Hospital, Grand Avenue Clinic, etc)
 - e. The primary point of contact for the organization, a telephone number, an e-mail address, and your role within the organization (e.g., Director of Medical Services, Managing Partner, etc)
 - f. Signature
3. IME personnel will then contact you to discuss user names, passwords and provide you with additional instructions.

Additional information on I-MERS can be found at the Iowa Medicaid Enterprise website; <http://www.ime.state.ia.us>. Please click on providers, quick links on the right side of the page, and then key elements of I-MERS to access this additional information.

You are encouraged to take this opportunity to register for I-MERS so that you can improve coordination of care for your patients.