

Atypical Antipsychotics in the Pediatric Population

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- Past speakers' bureau participation:
 - Janssen
 - Pfizer
 - Schering-Plough

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Outline

- Brief review of antipsychotics and their usage
- Present data indicating trends in use
- Describe current best practice guidelines
- Discuss recommendations for this class of medications

What Are Antipsychotics?

- Also called, in the past, neuroleptics or major tranquilizers
- Class of medications developed to treat schizophrenia and other psychotic disorders
- First appeared in 1950s
- Second generation or "atypical" medications began to be used in 1990s
 - Thought to be less likely to cause certain side effects related to movement problems including extrapyramidal symptoms (EPS) and tardive dyskinesia (TD)
 - More likely to cause metabolic side effects

FDA Approved Atypical Antipsychotic for Schizophrenia

- Cases of schizophrenia in children younger than 13 are very rare
- Prevalence rises in adolescence, peak onset is between ages 15 and 30
- Outcome is generally poor with onset in childhood
- Olanzapine (ages 13 and up)
- Risperidone (ages 13 and up)
- Aripiprazole (ages 13 and up)
- Quetiapine (ages 13 and up)
- Paliperidone ER (ages 12 and up)

FDA Approved Atypical Antipsychotic for Bipolar Disorder

- Prevalence of bipolar disorder in community sample is approximately 1% of adolescents
- Often exhibit mixed mania and rapid cycling
- Meds with FDA approval for acute treatment of bipolar I disorder, mixed or manic episodes:
 - Non-antipsychotic: Lithium for ages 12 and up
 - Aripiprazole (ages 10 and up)
 - Asenapine (ages 10 and up)
 - Clanzapine (ages 13 and up)
 - Risperidone (ages 10 and up)
 - Quetiapine (ages 10 and up)

Combination Treatment for Bipolar Disorder

- Treatment of bipolar disorder often requires combination of treatment
- FDA has approved the following medications as an adjunct to lithium or valproate for treatment of bipolar I disorder, mixed or manic episode:
 - Quetiapine (ages 10 and up)
 - Aripiprazole (ages 10 and up)

Autism Spectrum Disorder (ASD)

- DSM-5 has combined the previous categories of autistic disorder (autism), Asperger's disorder, and pervasive developmental disorder not otherwise specified into this diagnosis of ASD
- Two core domains of symptoms: deficits in social communication and social interaction and restricted repetitive patterns of behavior, interests, and activities
- Associated symptoms include hyperactivity, stereotypies, attentional problems, self-injurious behavior, aggression, mood lability, anxiety, obsessions and compulsions
- Prevalence of approximately 18.7 per 10,000 individuals in the population.

FDA Approved Atypical Antipsychotics for ASD

- Treatment of irritability associated with ASD
- No evidence that pharmacotherapy is effective in treating the core social and communication deficits but may be helpful in treating associated symptoms
- Approved meds:
 - Risperidone (ages 5 and up)
 - Aripiprazole (ages 6 and up)

Trends in Atypical Antipsychotics: Study in Kentucky Medicaid population

- Studies indicate increasing use of antipsychotics in preschoolers for treatment of disruptive behavior and aggression
- Kentucky Medicaid prescription claims between 2001 and 2010 for all children ≤ 6 years old
- Use peaked in 2004 at about 1%
- Older male children were more likely recipients
- Diagnoses: mood disorders, primarily bipolar disorder, accounted for nearly 75%
- Only 32% of prescriptions were written by child psychiatrists

Lohr et al., *J of Child and Adol Psychopharm*, 2015; 25 (5):440-443.

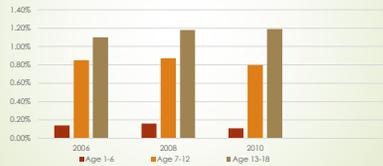
Trends in Office-Based Treatment with Antipsychotics

- Survey and not claims based
- Dramatic increase in antipsychotic usage in children and adolescence from mid 1990s to mid 2000s
- Disruptive behavioral diagnosis was the most common diagnostic category
- Often no diagnosis was given
- Risperidone was most common antipsychotic medication

Olsson et al., *Arch Gen Psych*, 2012; 69(12):1247-1256.

Trends in the Use of Antipsychotics

- Claims based: Retrospective descriptive analysis of antipsychotic prescriptions in patients ages 1 to 24 for calendar years 2006, 2008, and 2010.
- Rates:



Olfson et al., JAMA Psychiatry, 2015; 72(9):867-874.

Trends from the Olfson 2015 Study

- Antipsychotic use increased for 2006 to 2010 for adolescents but not for children aged 12 and under
- Peak antipsychotic use occurred in adolescence
- Boys were more likely than girls to be prescribed antipsychotics
- Many claims didn't have a mental health diagnosis, but those that did had the following diagnoses:
 - Most common diagnosis was ADHD
 - Next, depending on age group were autism or mental retardation and disruptive behavioral disorders
 - Third tier were bipolar disorder, anxiety, depression
 - Lowest tier adjustment-related disorders, substance use, and schizophrenia

Olfson et al., JAMA Psychiatry, 2015; 72(9):867-874.

Potential Side Effects

- Metabolic:** Weight gain, hyperlipidemia, diabetes
- Sedation:** Cognitive dulling
- Cardiovascular:** tachycardia, orthostatic hypotension, QTc prolongation
- Agranulocytosis and neutropenia:** especially clozapine but case reports with others
- Hepatic dysfunction:** rare but may be related to rapid weight gain
- Prolactin elevation and gynecomastia:** related to D2 blockade
- Seizures:** especially clozapine and olanzapine
- EPS and tardive dyskinesia:** less with atypicals but still possible
- Neuroleptic Malignant Syndrome**
- Cataracts:** animal literature for quetiapine

Recommendations from the American Academy of Child and Adolescent Psychiatry

- 19 Recommendations, 27 pages
- Need to follow guidelines prior to use ("careful" diagnostic assessment, "thorough" discussion of potential risks and benefits) (#1)
- Need to follow most current scientific evidence (#1)

AACAP Recommendations

- "In the absence of specific FDA indications or substantial empirical support for the use of AAAs for other specific problems (e.g., disruptive behavior disorders), clinicians should consider other pharmacological or psychosocial treatment modalities with more established efficacy and safety profiles prior to the onset of AAA use." - #2
- "There are almost no data about the use of AAAs in pre-school aged children. As this group is one that may be particularly vulnerable, a marked amount of caution is advised before prescribing an AAA to a preschooler." - #2

AACAP Recommendations

- Obtain personal and family history of diabetes, hyperlipidemia, seizures, cardiac abnormalities - #3
- Obtain baseline vitals, BMI, glucose, lipids (per ADA) - #3
- Target dose based on literature and indication - #5
- Polypharmacy should be avoided if possible - #7
- "the use of more than one agent is not recommended and is not supported in the scientific literature" - #8
- Careful monitoring of metabolic status - #12
- "Measurements of movement disorders utilizing structured measures, such as the Abnormal Involuntary Movement Scale, should be done at baseline and at regular intervals during treatment and during tapering." - #14

AACAP Recommendations

- While routine EKGs may not be needed for all patients, in those with a family history of cardiac abnormalities or sudden death, or a personal history of syncope, palpitations, or cardiovascular abnormalities, a baseline EKG and subsequent monitoring should be carefully considered - #15
- The indefinite use of the AAA should not be assumed. Regular assessments of the continued need for the AAA should be done. - #18

Antipsychotic Medication Prescribing in Children Enrolled in Medicaid

- Prior authorization survey that assessed multiple domains
- Best practice followed 50% of time
 - Lack of lab work #1 reason
- FDA indication followed 27% of time
- Aggression and mood instability top reasons for prescriptions
- High percentage of clinicians now responsible for antipsychotic medications didn't start them originally
- Few children received evidence-based therapy prior to initiation
- Clinicians often did not know prior medication history

Rettew et al., Pediatrics, 2015;135(4):658-665.

Practical Recommendations for Prescribers

- Consider other classes of medications for behavioral problems
 - Alpha adrenergic agents, stimulants, SSRIs
- Talk to the child's counselors/therapists and try to utilize them as you would other health specialists.
- Refer for therapy including family therapy
- Avoid starting these medications without a child psychiatry consultation
- More active collaboration regarding metabolic monitoring and management
- Stay alert for excessive or premature uses of these medications by others
- Consider slow tapers of these medications if patient is generally stable

Thank you

QUESTIONS?