

# Atypical Antipsychotics and Pediatrics

**Background and Update on June 9-10, 2009 Psychopharmacological Drugs  
Advisory Committee Meeting**

Mitchell V. Mathis, M.D.  
Deputy Director  
Division of Psychiatry Products  
Office of New Drugs, FDA

# Outline

- Division's perspective on atypical antipsychotics and use in pediatric patients
- Update on the 9-10 June 2009 PDAC
- Conclusions

# Background

- Schizophrenia and bipolar disorder can afflict the pediatric population
- Atypical antipsychotics are first-line treatments (9 approved in adults, 4 of these are approved in the pediatric population)
- FDA has requested manufacturers to submit pediatric data (efficacy, safety, and PK) for drugs approved in adults

# Practice Guidelines: AACAP

- American Academy of Child and Adolescent Psychiatry
  - Pharmacologic intervention is an integral part of treatment of schizophrenia and bipolar disorder.
  - Antipsychotics are recommended as first-line treatment for both schizophrenia and bipolar mania.

American Academy of Child and Adolescent Psychiatry (2001), Practice Parameters for the Assessment and Treatment of Children and Adolescents with Schizophrenia. *J Am Acad Child Adolesc Psychiatry*

American Academy of Child and Adolescent Psychiatry (2007), Practice Parameter for the Assessment and Treatment of Children and Adolescents with Bipolar Disorder. *J. Am Acad Child Adolesc Psychiatry*

# Policy Statement: AACAP

- Use of Psychotropic Medication for Children and Adolescents (2009)
  - Recognizes that informed use of psychotropic drugs has positively impacted children/adolescents, and that these drugs are often used for off-label indications.
  - “To provide the optimal treatment, the child and adolescent psychiatrist must have access to a full range of psychotropic medications. Restrictions and limitations placed upon a physician’s choice among medications expose children and adolescents to unnecessary medical risks and the potential for non-compliance. These complications ultimately impact the quality of the child’s life and result in an overall increase in health care costs.”
  - AACAP opposes practices that interfere with the doctor-patient relationship.

American Academy of Child and Adolescent Psychiatry (2009), Policy Statement for Pharmaceutical Benefit Management and the Use of Psychotropic Medication for Children and Adolescents, *J. Am Acad Child Adolesc Psychiatry*, Jan 12, 2009.

# Approval Requirements for Pediatric Indications

- An existing approval in adults for the same indication(s)
- One adequate and well-controlled trial in pediatric patients demonstrating efficacy
- Pharmacokinetic data to support dosing recommendations
- Longer-term (6 months) safety data in a sufficient number of patients to support safety labeling

# Pediatric Approvals to Date

- Risperdal (risperidone)
  - Schizophrenia (13-17)
  - Bipolar mania (10-17)
  - Irritability associated with autistic disorder (5-16)
- Abilify (aripiprazole)
  - Schizophrenia (13-17)
  - Bipolar mania (10-17)
  - Irritability associated with autistic disorder (6-17)
- Seroquel (quetiapine)
  - Schizophrenia (13-17)
  - Bipolar mania (10-17)
- Zyprexa (olanzapine) [labeling: consider other drugs first]
  - Schizophrenia (13-17)
  - Bipolar mania (13-17)

# Drug Differences

- Limited comparative safety/efficacy data available in pediatric patients
- Generally accepted that more treatment options are better than fewer
  - Differential response not well understood
  - Different safety profiles



## June 9-10 2009 Psychopharmacologic Drugs Advisory Committee (PDAC)

- Safety issues with pediatric applications should be more widely (publicly) discussed
- Differential labeling should be considered

## June 9-10 2009 Psychopharmacologic Drugs Advisory Committee (PDAC)

- Seroquel (quetiapine)
  - Acute treatment of schizophrenia in adolescents (13-17 years of age)
  - Acute treatment of bipolar mania in children and adolescents (10-17 years of age)
- Zyprexa (olanzapine)
  - Acute treatment of schizophrenia in adolescents (13-17 years of age)
  - Acute treatment of manic/mixed episodes of bipolar disorder in adolescents (13-17 years of age)
- Geodon (ziprasidone)
  - Acute treatment of manic/mixed episodes of bipolar disorder in children and adolescents (10-17 years of age)

# Makeup of Committee

- Child and Adolescent Psychiatry: 4
- General Psychiatry: 4
- Geriatric Psychiatry: 1
- Pediatric Advisory Committee Members: 2
- Cardiovascular and Renal Drugs Advisory Committee Members: 2
- Endocrinologic and Metabolic Drugs Advisory Committee Members: 1
- Drug Safety and Risk Management (DSaRM) Advisory Committee Members: 2
- Biostatistics: 1
- Patient Representative: 1
- Industry Representative (non-voting): 1

# PDAC June 2009

- All three drugs discussed had already been approved to treat schizophrenia and bipolar mania in adults
- Each sponsor conducted one short-term placebo-controlled efficacy and safety trial for each indication sought
- Pharmacokinetic data and longer-term safety data in the pediatric population were obtained
- Effectiveness was supported in each trial for each drug
- Safety profiles were qualitatively similar between pediatric and adult patients although some quantitative differences were noted

# PDAC June 2009

- Significant risks are associated with this drug class
  - Somnolence
  - Neuroleptic Malignant Syndrome
  - Seizures
  - Weight Gain
  - Hyperlipidemia
  - Hyperglycemia
  - Extrapyramidal Symptoms
  - Tardive Dyskinesia

# PDAC June 2009

- Risks of these disorders in pediatric patients of particular concern
  - Schizophrenia and bipolar disorder are lifelong illnesses
    - Potentially a decade more of exposure when first treated in childhood/adolescence
  - Growth and Development must be factored into risk/benefit decisions
- Many of the pediatric safety findings had already been incorporated into labeling.

# Overview of the Disorders\*

- Pediatric Schizophrenia
  - Early onset schizophrenia before age 18 represents about 1/3 of all schizophrenia
    - Median age of onset
      - Males: early 20s
      - Females: late 20s
    - Same diagnostic criteria/same symptoms as in adults
      - Delusions/hallucinations/disorganized speech and behavior (positive symptoms)
      - Changes in affect and avolition (negative symptoms)
      - Dysfunction
    - Impact on adolescents is devastating
      - Education is disrupted
      - Social development impaired
      - Severe functional impairment in all realms
      - Severe impact on cognitive functioning
    - Data are consistent that antipsychotic treatment is superior to placebo, especially for positive symptoms

\*Ben Vitiello, M.D., Chief, Child and Adolescent Treatment and Preventative Intervention Research Branch, NIMH

# Overview Continued

- Impact on adolescents is devastating
  - Education is disrupted
  - Social development impaired
  - Severe functional impairment in all realms
  - Severe impact on cognitive functioning
- Data are consistent that antipsychotic treatment is superior to placebo, especially for positive symptoms



# Overview Continued

- Pediatric Bipolar I Disorder
  - Defined as in the adult: mania
    - Grandiosity, decreased need for sleep, pressured speech, flight of ideas, distractibility, increased activity
    - Psychosis in the most severe form
    - Disability and dysfunction
  - Median age of onset is 19 years
    - Highest risk between 15-19 years
    - Detectable risk between 5-9 years
  - Antipsychotics considered first-line for the acute treatment of manic symptoms

# Discussion at PDAC

- General agreement
  - Schizophrenia and bipolar disorder in pediatric patients must be treated
  - Atypical antipsychotics are necessary for standard of care treatment
  - Risks with these medications are monitorable and labeling can address safety issues
  - Having multiple drug treatment options available is best for pediatric patients

# Questions to the Committee

- Has (drug name) been shown to be effective for the treatment of (indication) in pediatric patients (age)?
- Has (drug name) been shown to be acceptably safe for the treatment of (indication) in pediatric patients (age)?

# Votes

- Seroquel
  - Schizophrenia
    - Effective? 17 yes; 1 no
    - Safe? 16 yes; 0 no; 2 abstain
  - Bipolar Mania
    - Effective? 17 yes; 0 no; 1 abstain
    - Safe? 13 yes; 0 no; 5 abstain

# Votes

- Zyprexa
  - Schizophrenia
    - Effective? 11 yes; 5 no, 2 abstain
    - Safe? 10 yes; 4 no; 4 abstain
  - Bipolar mania
    - Effective? 17 yes; 0 no; 1 abstain
    - Safe? 11 yes; 4 no; 2 abstain

# Votes

- Geodon
  - Bipolar Mania
    - Effective? 12 yes; 2 no; 4 abstain
    - Safe? 8 yes; 1 no; 9 abstain

# Conclusions

- Schizophrenia and bipolar disorder are devastating diseases that often onset early in life.
- Antipsychotic drugs are the cornerstone of treatment and are considered first line for pediatric patients.
- Atypical antipsychotics have serious side effects, but these are monitorable and can be managed with careful labeling.
- A comparative trial in children/adolescents would advance our understanding of drug differences in pediatric patients.