Antipsychotics in Children and Adolescents
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Disclosure
1
No financial relationship or conflict of interest to report
2
I will be talking about non FDA approved uses for medications

Questions
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Increase in Antipsychotic Use
- Growth in the concurrent use of antipsychotics with other psychotropic medications in Medicaid in children
  - Kreisker et al. JAACAP, 9/2014
  - Medicaid enrolled children 8-18 years old 2004-2008
    - 22% increase, 85% of use occurred concurrently with other meds
      - Stimulants, antidepressants, mood stabilizers, alpha-agonists
      - Highest use was in foster care, disability programs, or those who had been psychiatrically hospitalized
      - Increased use in those who were income eligible for Medicaid, without ADHD, not hospitalized and did not have intellectual disabilities

Typical Uses
- Psychosis
- Mood disorders
- Adjunctive therapy for depression
- Mood stabilization in bipolar disorder
- Adjunctive treatment for anxiety
- OCD
- Tics and Tourette’s
- Aggression
- Autism/Developmental disabilities

Increase in Number of Children on Atypical Antipsychotics (2001-2010)
TOSCA Trial Update

- Treatment of Severe Childhood Aggression
- Initial study was a 9 week study assessing parent training+stimulant+placebo vs parent training+stimulant+risperidone
- At 9 weeks the augmented group had a greater improvement in ODD and teacher ADHD ratings
- Two thirds of the families were re-evaluated at 52 weeks
- 43% of the augmented group and 36% of the basic group adhered to their original plan
- 23% and 11% were no longer taking any mes
- No behavioral difference at the 52 week FU

Antipsychotic use with Autism

- Antipsychotic use trends in youth with autism spectrum disorder and/or intellectual disability: a meta-analysis
- 39 studies were included, 365,449 subjects, average age 11.4 years
- 10% were diagnosed with either Autism or intellectual disability
- One in six youth with an autism spectrum disorder diagnosis received an antipsychotic

ADHD and Antipsychotics

- No indication for use in ADHD
- Side effects are serious
- May be useful in ADHD with comorbidities

Atypical Antipsychotics and Disruptive Disorder

- Cochrane database review current to 1/2017
- 10 studies: 8 with risperidone, 1 quetiapine, 1 ziprasidone
- Results suggested risperidone decreased aggression (low quality evidence) and conduct problems (moderate quality evidence)
- Had significant weight gain

Atypicals and Mood

- Generally show better efficacy than traditional mood stabilizers when used in children/adolescents with bipolar disorder
- Aripiprazole, risperidone, quetiapine, olanzapine, ziprasidone and asenapine have FDA approval for bipolar disorder in children/adolescents
- No literature about augmenting depression

Atypicals and Tics

- Most of the literature is about the benefit of risperidone which shows value in tic reduction for patients with Tourette’s
- Literature also exists for clozapine, olanzapine, aripiprazole
Augmentation in OCD

- Case reports
  - Aripiprazole augmentation with sertraline in an adolescent
- Case series
  - Four patients with risperidone augmentation of SSRI, all improved
- No double blind trials

Medical Work Up Before Medications and Ongoing Monitoring

- Antipsychotics
  - Weight, fasting lipids and glucose at baseline
  - Weight at every visit
  - Fasting lipids and glucose at 3 months then at least yearly but many practitioners assess lipids every sixth month if there is weight gain or the trend from previous lab testing is elevated
  - EKG depending on the drug used and other medications. Consider for quetiapine and ziprasidone or if on other medications that can cause QTc elongation
  - Prolactin for risperidone only if clinically indicated

Getting Screening Labs

- Antipsychotic Metabolic Screening in Kids Remains Shockingly Low, Fran Lowry, Medscape, 2015
  - 52,407 patients aged 5 to 18 years, (mean age, 13.14 years; 61% male) from a large, nationwide, commercial insurance claims database (United Healthcare) for the period January 1, 2003, through December 31, 2011.
  - By 2011, the proportion of patients starting second-generation antipsychotics who had a glucose test within 6 months of initiation was 17.5%.

Getting Screening Labs

  - A total of 5370 children (aged 6-17 years) without diabetes mellitus taking SGA drugs and 15,000 children without diabetes taking albuterol but no SGA drugs.
  - Glucose screening was performed in 31.6% SGA-treated children vs 12.6% control individuals. Lipid testing was performed in 13.4% SGA-treated children vs 1.1% controls.

The Drugs

- Newer drugs
  - Risperidone
  - Aripiprazole
  - Olanzapine
  - Quetiapine
  - Ziprasidone
  - Lurasidone

- Old drugs
FDA Approved Uses

Aripiprazole
- 6 and older for ASD
- 10 and older for mania/mixed bipolar
- 13 and older for schizophrenia

Olanzapine
- 10 and older mania/mixed bipolar
- 13 and older for schizophrenia

Quetiapine
- 10 and older mania/mixed bipolar
- 13 and older for schizophrenia

Risperidone
- 5-16 years old for ASD
- 10 and older for mixed/manic bipolar

Paliperidone
- 12 and older for schizophrenia

The Other Uses

- Non-schizophrenic psychosis and severe mood disorders
- Tics
- Adjunctive treatment in partial responders
  - OCD, major depression and severe anxiety
- Aggression and explosive behavior
- Other developmental disabilities
- Severe intractable disruptive behavior

Side Effects

- Weight gain
- Sedation or activation
- Aripiprazole and ziprasidone tend to be more activating
- Metabolic syndrome
- Sexual dysfunction
- Movement side effects
  - Tardive dyskinesia, extrapyramidal side effects
- Menstrual irregularity
  - Elevated prolactin
  - Risperidone: usually returns to normal in the first year of treatment

Cytochrome P450 Variations may impact Side Effects
Metabolic Syndrome

- All antipsychotics may cause metabolic syndrome
- Patients with schizophrenia have an increased risk for death even before treatment with antipsychotics
- Changes in lipids and glucose can occur even without any change in weight
- Quality of life can be highly impacted with a significant weight gain

In my clinical experience most patients will have some change in their metabolic profile
- Decreased HDL is often first followed by increased triglycerides and finally increased LDL
- Reduce dose to minimal effective dose
- Use this class of medications only when absolutely needed
- Work to get them off meds when possible
- Change to a lower risk antipsychotic if appropriate

Metabolic Syndrome in Drug Naïve Adolescents

Sp et al, JCAP 12/2017
35 SGA drug naïve subjects aged 7-19 with a diagnosis of psychosis
- Significant increase in BMI, waist circumference, triglycerides, fasting blood sugar
- Significant decrease in HDL
- No change in BP

Risk of Diabetes from Antipsychotics

- Risk of diabetes in children and adolescents exposed to antipsychotics: a nationwide 12 year case control study
- Nielsen et al, JACAP 9/2014
  - 48,299 psychiatrically ill youth
  - Of the 7253 youth exposed to antipsychotics 52 developed type two diabetes
  - Of the 41,046 youth without exposure to antipsychotics 111 developed type two diabetes
  - Risk for diabetes was associated with antipsychotic drug exposure, female sex, and older age at first psychiatric diagnosis

Antipsychotics with Metformin in ASD

- Randomized, placebo controlled trial of Metformin for the treatment of Overweight induced by antipsychotic medication in youth with autism spectrum disorder
- Handen et al, JACAP 10/2017
  - 16 week open label extension after the preliminary trial
  - 52 subjects
    - 250 mg bid or 850 mg bid
  - Subjects who had been on placebo during the first phase treated with Metformin in the extension phase
  - Subjects on Metformin in the first phase maintained weight

Weight Gain with Atypical Antipsychotics in Children

<table>
<thead>
<tr>
<th>Medication</th>
<th>Number of Patients</th>
<th>Weight Gain, kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>85</td>
<td>3.3 to 3.4</td>
</tr>
<tr>
<td>Clozapine</td>
<td>9</td>
<td>6.9 to 8.1</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>1</td>
<td>3.9 to 4.2</td>
</tr>
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</tbody>
</table>

Source: Pardridge, 2006 and Foursab
Weight Gain

- Check weight and BMI before starting medications
- Discuss side effects thoroughly with families
  - Weight gain can be managed better if families know weight gain is very likely to happen

Weight Gain: Risperidone and Autism

- Weight Gain and Metabolic Consequences of Risperidone in Young Children with ASD
  - JAACAP May 2016 Scahill et al
  - 24 week study of 124 children mean age 6.9 years
  - 5.4 +/- 3.4 kg weight gain over the 24 weeks
  - At baseline 60.8% were normal weight, only 24.9% at 24 weeks were normal weight
  - BMI increases were the greatest for those who reported significant appetite increase in the first eight weeks
  - 19 subjects met the criteria for metabolic syndrome by week 16

Extrapyramidal Side Effects

- Acute dyskinesias
- Acute dystonias
- Tardive dyskinesia
- Parkinsonism
- Akinesia
- Akathisia
- Neuroleptic malignant syndrome

Akathisia

- Motor restlessness with the subjective feeling of inner tension and discomfort
  - Pseudoakathisia if no sense of inner restlessness
  - Usually in the limbs
    - Rocking from foot to foot, swinging legs, pacing
  - May exist with other EPS such as Parkinsonism
  - Usually occurs in the first few days of treatment
    - May be chronic
  - May occur more often when doses are increased rapidly

Treatment of Akathisia

- Lower the dose
- Not typically helped by the use of anticholinergic agents
- Clonidine has been associated with benefit
- Propranolol may be helpful
Acute Dystonia
- Characterized by intermittent or sustained muscle action
- Torticollis, trismus, limb dystonias, blepharospasm, ocular spasm, otolaryngological spasm of respiratory stridor
- Usually peak 24-48 hours after starting therapy
- Treat with IM benzotropine or diphenhydramine for emergencies, oral if less severe or less urgent

Parkinsonism
- Muscle rigidity, tremor, bradykinesia, postural changes, salivation
- Treat by reducing the dose
- May add an anticholinergic medication if needed
- Amantadine maybe helpful
- Severe refractory Parkinsonism may increase the risk for NMS

Tardive Dyskinesia
- Late onset
- Involuntary movements mainly of the tongue and mouth but may include limbs and trunk
- Increased risk in older and female
- Other risks include presence of mood disorder, brain injury, increased total drug exposure, pre-existing Parkinsonism, or a child

Withdrawal Dyskinesia
- Withdrawal dyskinesia is very common when stopping or decreasing antipsychotics in children
- Slow decrease can minimize dyskinesia
- They may last for weeks but do resolve

Extrapyramidal Side Effects
- Neuromotor adverse effects in 340 youth during 12 weeks of naturalistic treatment with five second-generation antipsychotics
- Carbon et al, JACAP, 9/2015
- 340 subjects, average age 13.6 years, 65.8% antipsychotic naïve, 58.2% male
- 15.2% developed a drug-induced parkinsonism
  - Quetiapine 1.5%
  - Chlorpromazine 13.8%
  - Risperidone 16.1%
  - Ziprasidone 20.0%
  - Aripiprazole 27.3%

Movement Disorders
- Visconti et al, JCAP, 12/2017
- Population based study of all residents in Manitoba who received risperidone or quetiapine 4/96-3/2011
- 23,888 subjects were prescribed an antipsychotic
- 2594 of those were using risperidone or quetiapine
- Quetiapine was associated with a lower risk of EPS
Rates of TD with SGAs in Children

- One year incident rates of tardive dyskinesia in children and adolescents treated with second-generation antipsychotics: a systematic review
- Cornell et al., JCAP, 3/2007
- 10 studies, 783 subjects, mean age 8.74 years
- 777 risperidone, 27 quetiapine, 19 olanzapine
- Mean days of treatment: 329.6 days, diagnoses included disruptive behavior disorder, bipolar disorder, schizophrenia, and autism spectrum disorder
- Three new cases of tardive dyskinesia emerged with up to three years of treatment resulting in an annualized TD rate of 0.38%

Prolactin Elevation

- Menstrual irregularity
- Osteoporosis
- Hair loss
- Gynecomastia
- Galactorrhea

Prolactin During 1-Year Risperidone Treatment in Youth

- Findling et al., J Clin Psychiatry 2003;64: 1362

Review of Prolactin Elevations

- Role et al., JCAP, 2009
- Review of 29 studies including haloperidol, pimozide, olanzapine, clozapine, ziprasidone, quetiapine
- All showed increase in prolactin except clozapine, ziprasidone, and quetiapine
- Mean baseline of 8ng/ml increased to 25-28 ng/ml after 4 weeks of treatment
- Side effect related to elevated prolactin included gynecomastia, galactorrhea, irregular menses, and sexual dysfunction and occurred in 4.8% of children
- Two studies investigated the impact on puberty and found no progression of Tanner stages

More Prolactin

- Elevated prolactin may increase the risk for osteopenia
- Studies with stimulants added to SGA did not further impact prolactin
- Increased copies of CYP2D6 leading to increased rate of metabolism of risperidone increased prolactin levels further

Cardiac Impact of SGA’s

- Absence of change in corrected QT interval in children and adolescents receiving antipsychotic treatment
- Aida et al., JCAP, 6/2016
- 211 children and adolescents who were prescribed quetiapine, risperidone, or olanzapine
- No significant QTc variations on 12 month follow-up
Risperidone and Iron Deficiency
- Chadi Albert Calarge and Ekhard E. Ziegler.
- 115 patients, 87% male, mean age 11.6 years. Had taken Risperidone for 2.4 years.
- 45% had iron depletion and 14% had iron deficiency.
- Not related to dose of meds or symptoms severity.
- Was associated with elevated prolactin.

Dosing
- **Risperidone**
  - 0.25 mg-6 mg
  - Start with bid dosing in young kids
    - 0.25 mg bid-0.5 mg bid
- **Olanzapine**
  - 2.5-20 mg
- **Aripiprazole**
  - 2.5-20 mg

**Latuda®**
- Lurasidone
- Dosages available 20 mg, 40 mg, 80 mg.
- Target dose 40 with max recommended dose 80 mg.
- Average cost $536 for one month at target dose.
- Does not seem to cause weight gain, increase lipids or glucose, increase prolactin, or cause QTC prolongation.
- Must be taken after a meal to get adequate absorption.

**Saphris®**
- Asenapine
- Sublingual tablets: 5 mg and 10 mg.
- Target dos for acute treatment of schizophrenia in adults, recommended dose 5 mg twice daily; maximum dose 10 mg twice daily; for treatment of bipolar disorder in adults, 10 mg twice daily.
- Average cost $676 for one month at target dose.
- Seems to cause fewer metabolic problems than other atypicals.
- Must be sublingual or no bioavailability.
- Must not eat/drink at all for 10 minutes and then avoid food for 4 hours or bioavailability decreases by 20%.
- Metabolized by 1A2 and inhibits 2D6 so has drug interactions.
- Increased sedation.
- May cause reflex tachycardia which can be frightening to patients.

**FANAPT®**
- Iloperidone
- Dosages available 1 mg, 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, 12 mg.
- Target dose 12 to 24 mg/day administered twice daily.
- Average cost $515 for one month target dose.
- Lower risk of EPS than haloperidol, less akathisia than ziprasidone.