Antipsychotic Use in Children and Adolescents

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Objectives

At the end of this workshop, the participants will be able to:

- Recognize mental health diagnoses of children and adolescents treated with antipsychotics.
- Determine how the risks and benefits of treatment of children and adolescents with antipsychotics are estimated.
- Interpret response of child or adolescent’s targeted symptoms to treatment with antipsychotics.
- Distinguish between symptoms of side effects and adverse effects that children and adolescents might display while taking antipsychotics.
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Antipsychotics

**Indications:**

• Psychosis
• Aggression/agitation/ self injurious behaviors/autism/
• Autism spectrum disorders and disruptive behavior disorders
• Severe OCD/ severe anxiety
• Mania/severe depression
• Tics/Tourette’s
• Personality disorders/insomnia/delirium etc
Antipsychotics

Behaviors Seen:

- Psychosis
- Aggression/agitation/ self injurious behaviors/autism/
- Autism spectrum disorders and disruptive behavior disorders
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Antipsychotics

Theories regarding psychosis:

• Disruption in flow of Dopamine... like gas flooded car

• Excess of dopamine – positive symptoms of hallucinations...?

• Diseases & drugs that increase dopamine will produce positive symptoms

• All known antipsychotics are blockers of dopamine receptors (esp. D2)

• Negative symptoms / cognitive symptoms may be due to a deficit of dopamine in mesocortical areas

• Neurodegeneration due to excitotoxicity – excess stimulation of
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WHY DO YOU TREAT CHILDREN AND ADOLESCENTS WITH Antipsychotics?

- HARMING SELF
- HARMING OTHERS
- DETERIORATING EMOTIONALLY/BEHAVIORALLY
- CLEARLY PSYCHOTIC
- CLEARLY CYCLING
- INABILITY TO SLEEP
- INABILITY TO FUNCTION IN SCHOOL, HOME, COMMUNITY
- RISK OF HOSPITALIZATION
- MULTIPLE TRIALS OF LESS RISKY MEDS WITHOUT CLEAR BENEFIT OR LIMITED BENEFIT
- SEVERE TRAUMA
<table>
<thead>
<tr>
<th>RISKS</th>
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<tbody>
<tr>
<td>• SIDE EFFECTS</td>
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<td>• WEIGHT GAIN</td>
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<td>• IMPROVED SELF ESTEEM</td>
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<td>• CAN STAY IN HOME VS HOSPITALIZATION</td>
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Typical Antipsychotics

- 1953 Thorazine
- The Single Most Important Advancement in Treatment of Psychotic Illnesses
The Dopaminergic Pathways of the Brain

- Basal Ganglia
- Nigrostriatal Dopamine Pathway
- Mesolimbic Dopamine Pathway
- Substantia Nigra
- Mesocortical Dopamine Pathway
- Hypothalamus
- Tegmentum
- Tubero-infundibular Dopamine Pathway
Some Key Behaviors Hypothetically Linked to Specific Brain Regions

- executive function
- attention
- concentration
- emotions
- impulses
- obsessions
- compulsions
- motor
- fatigue
- ruminations
- worry
- pain
- negative symptoms
- guilt
- suicidality

- delusions
- hallucinations
- pleasure
- interests
- libido
- fatigue
- euphoria
- reward
- motivation

PFC - Pre frontal Cortex

motor
- critical relay site from PFC

pain
- sensory relay to and from cortex
- alertness

- memory
- alertness

- fear
- anxiety
- panic

- memory
- reexperiencing

- sleep
- appetite
- endocrine

Stahl (2008)
Some Key Behaviors Hypothetically Linked to Specific Brain Regions

- delusions
- hallucinations
- pleasure
- interests
- libido
- fatigue
- euphoria
- reward
- motivation

Nucleus Accumbens

(Stahl, 2008)
Typical Antipsychotics

Conventional/typical Antipsychotics:

• AKA Neuroleptics- “seize the neuron”

• Neurolepsis= Slowing/affective indifference

• Block all D2 receptors in the brain (including the Mesocortical pathway which worsens negative symptoms
Typical Antipsychotics

Typical Antipsychotics: tightly adhered to neuron

- Haldol (haloperidol) (depot, IM, liquid forms)
- Orap (pimozide)
- Prolixin (fluphenazine) (depot form)
- Moban (molindone)
- Navane (thiothixene)
- Thorazine (chlorpromazine) (IM form)
- Mellaril (thioridazine)
- Stelazine (trifluoperazine)
Atypical Antipsychotics

Atypical Antipsychotics: Less tightly bound at D2

• Dopamine has rapid dissociation off of neuron

• Block serotonin receptors (esp. 5HT 2A)

• Serotonin blockade in nigrostratum reduces EPS

• Serotonin blockade in mesocortical areas may improve negative symptoms
Atypical Antipsychotics

Antipsychotics Novel/Atypical:

• Clozaril (clozapine) – agranulocytosis!
• Zyprexa (olanzapine) – weight gain
• Risperidal (risperidone) EPS at higher doses
  • Invega (paliperidone) - active metabolite of risperidone
• Seroquel (quetiapine) – no prolactin increase/galactorrea
• Abilify (aripiprazole) – partial agonist, less weight gain
  • Rexulti (brexpiprazola)
• Geodon (ziprasidone) – EKG changes but less weight gain
• Latuda (lurasidone)
• Fanapt (iloperidone)
• Saphris (asenapine maleate)
Clozaril (clozapine)

• The first atypical
• Agranulocytosis (low white count) limits use
• Need for weekly then biweekly blood draws
• Effective for recalcitrant conditions
• Dose range is 50 to 800mg/day
• SE: weight gain, seizures, sedation
Zyproxa (olanzapine)

FDA approved for **Schizophrenia and Bipolar mania/mixed** (13 and up)

Dosage range 2.5mg to 20mg/day

**Zydis form** – orally disintegrating tablet

Q day or BID

**Weight gain/metabolic syndrome**

Mood stabilizing
Risperdal (risperidone)

FDA approved for **treatment of *autism related irritability*** (5 to 16),
**schizophrenia** (13 and up) and
**bipolar mania or mixed state** (10 and up)

Dosage range 0.25 – 6mg

**Atypical** at lower doses

Becomes **typical at higher doses**

Liquid form and injectable form (Consta)
Seroquel (quetiapine)

FDA approved to treat

**Schizophrenia** (13 and up),

**Mania** (10 and up)

Dosage range 25mg to 800mg/day

Highly **sedating**

Requires slow dosage titration

? Anxiolytic

**Mood stabilizing** effects

QD, BID or TID dosing especially in children

**Minimal EPS and no elevation of prolactin**
Abilify (aripiprazole)

FDA approved for treatment of *autism related irritability* (6-18),

*schizophrenia* (13-18), *bipolar disorder* – manic and mixed episodes (10 and above)

Partial agonist at D2 and 5HT1A

Dosage range 2.5mg/day to 30mg/day

Q day or BID dosing

? Less robust as antipsychotic

**Mood stabilizing**

Less weight gain/No EKG changes,
Geodon (ziprasidone)

5HT and norepinephrine reuptake inhibition
Dosage range 40mg/day to 160mg/day
BID dosing
Effects on EKG Potential QTc prolongation
Less weight gain
Figure 1. FDA-Approved Pediatric Age Ranges and Indications for Atypical Antipsychotics

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- Red: schizophrenia
- Blue: bipolar I disorder: manic or mixed
- Yellow: irritability with autistic disorder

*Risperidone should not be used by patients older than age 16 who have been diagnosed with irritability with autistic disorder.*
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TARGETED SYMPTOM RESPONSE

• Follow up closely with child over phone with mother and in person either weekly or every other week due to dangerousness (intensity and frequency) of symptoms
  
  • Eg. ”Recommended aripiprazole 2.5 mg daily targeting severe impulsivity and aggression (tried to choke brother). Mother has to monitor closely as episodes of aggression towards brother (hitting, pushing, choking) occur daily and his tantrums last up to 20 minutes”

• Identify whether those symptoms are improved, worse or the same
  
  • “Follow up after 1 week on aripiprazole 2.5 mg daily and aggressive episodes have reduced in frequency from daily to 2 x per week and have reduced to episodes of 5 minutes of tantrumming.”
TARGETED SYMPTOM RESPONSE

• Follow up closely with child over phone with mother and in person either weekly or every other week according to acuity (intensity and frequency) of symptoms
  
  • Eg. “Recommended 0.25 mg risperidone bid targeting daily, almost constant, auditory hallucinations of father telling him he is a bad boy and should be punished. Can’t focus in school, the voice won’t let him concentrate”
  
  • Identify whether those symptoms are improved, worse or the same
  
  • “Follow up after 1 week on 0.25 mg bid of risperidone for auditory hallucinations which have reduced to 2 x per day, when he awakens and when he tries to go to sleep.”
What you might see in the classroom or your office

• Child is calmer, more coherent in their conversations and behavior with you and others
• Less irritable
• More focused, less distracted
• Tired, less energetic
• More attentive
• More cooperative and possibly engaged
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Different antipsychotics have **different receptor binding profiles** and thus differ in SE profile.
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Antipsychotic Side Effects

Mechanism of action:
Dopamine (D2) receptor blockade as with conventional antipsychotics

Side Effects:
• D2 blockade in the **nigrostriatum causes EPS** (extrapyramidal symptoms), chronic D2 blockade causes **tardive dyskinesia**
• D2 blockade in the **tuberoinfundibular pathway** cause increase in prolactin: **galactorrea** (breast liquid secretion) which in turn effects causes **amenorrhea** (no menses)
Antipsychotic Side Effects

Muscarinic cholinergic blockade: Dry mouth, blurry vision, cognitive blunting, constipation; Prevents EPS

$\alpha_1$ (alpha 1) adrenergic blockade: Cardiovascular effects, decrease in blood pressure

H1 (histaminic) blockade: weight gain, sedation
Antipsychotic Side Effects

Other side effects

• Reduced seizure threshold
• Anergia- abnormal lack of energy
• Metabolic syndrome
  • Weight gain “central obesity”
  • Insulin resistance
  • Elevated triglycerides
Antipsychotics

Extrapyramidal symptoms (EPS)

• **Dystonia** Brief or prolonged contractions of muscles (oculogyric crisis, torticollis, trismus) Parkinsonism – tremor, stiffness, slow movements, shuffling gait, cogwheeling, mask like face, **blepharospasm**

• **Akathisia**— extreme motoric restlessness that may be localized to legs
Antipsychotics

**Tardive dyskinesia**—Caused by **chronic D2 blockade** in the NS pathway: receptors become “**super sensitive**” and up-regulate –

Facial & tongue movements, chewing, tongue protrusions, grimacing, limb movements (quick jerks, choreoathetoid movements)…withdrawal dyskinesia
Potentially Life Threatening Adverse Effect
Antipsychotics

Neuroleptic Malignant Syndrome (life threatening)

- Muscular rigidity
- Fever
- Encephalopathy – confusion, stupor, coma
- Vital sign instability
- Muscle enzyme elevation
Atypical Antipsychotics

Medications given with antipsychotics:

Indications: to prevent or treat EPS

- Cogentin (benztropine)
- Benadryl (diphenhydramine)
- Symmetrel (amantadine)
- Inderal (propranolol)
SUMMARY: What to watch for in the classroom or office

SIDE EFFECTS
• Fatigue
• Dry mouth
• Akathisia
• Extra pyramidal symptoms
• Weight gain
• Decreased blood pressure

ADVERSE EFFECTS
• Neuroleptic Malignant Syndrome
• Tardive Dyskinesia
• Oculogyric Crisis
Antipsychotics

Monitoring:

• AIMS test
• Weight/vitals
• Lipids/triglycerides
• Glucose
• ?EKG
References


