Role of Psychotropic Medications in the Care of Children with ASDs

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Presentation Outline

- Introduction
- Frequency of psychotropic medication use in children and adolescents with ASDs
- Target symptoms of medications
  - Hyperactivity/impulsivity/inattention (HII)
  - Irritability
  - Repetitive behaviors
  - Core symptoms of ASDs
- Summaries of findings regarding use of medications
- New directions
Role of Medications

- Medications are an ancillary treatment in ASDs
- They are to be considered in the context of a comprehensive treatment plan that focuses on educational, psychological and social interventions
Frequency of use

- A survey of IAN, a web-based data registry, revealed 35.3% of respondents used at least one psychotropic drug. Rosenberg, et al., *JADD* 2010; 40(3):342-51.


- Data drawn from commercial claims and encounters databases revealed a rate of 70% in ASD children ≥8. Oswald and Sonnenklar, J Child Adolesc Psychopharm 2007; 17(3): 348-55.
Factors associated with use of psychotropic medication

- Older age
- Presence of intellectual disability (ID)
- Presence of psychiatric co-morbidity
- Greater use of autism services
- Male gender
- White race (in one study)
- Residing in a poorer county
- Residing in the South or Midwest regions of US
Psychotropic Medication Use in ASD

- **Most common agents**
  - Stimulants
  - Neuroleptics
  - Anti-depressants
  - Anti-convulsants
  - Alpha-agonists

- **In IAN survey, medications were prescribed by**
  - Psychiatrists---49%
  - Neurologists---20%
  - Developmental pediatricians---12.5%
  - PCP---10.5%
Only FDA-approved medications for specific use in children with ASDs are risperidone (Risperdal) and aripiprazole (Abilify) for irritability associated with autism.

- Irritability includes:
  - Aggression
  - Self-injurious behavior
  - Severe tantrums
Psychotropic Medication Use in ASDs

In general,

- Medications are used to target associated challenging behaviors rather than core symptoms of ASDs.
- Target symptom clusters are: 1) irritability, 2) ADHD-like symptoms of hyperactivity/impulsivity/inattention (HII), 3) repetitive behavior.
- Medications that are effective in neurotypical children do not always work the same way in ASD children.
- ASD children experience more prominent side effects and less robust positive effects.
- Even well-proven treatments do not work in all individuals.
Psychotropic Medications in ASDs

- Approaches to a medication trial
  - Delineate symptoms
  - Consider causes
    - Medical illness
    - Change in environment
    - Behavior secondary to another symptom, i.e., aggression secondary to rigidity
  - Is there an agent that targets the symptoms?
  - Start with well-studied agents
  - Begin at a low dose
  - Advance the dose slowly, keeping other factors constant
  - Make one change at a time
Irritability

- Includes aggression, self-injurious behavior and severe tantrums
- Treated with anti-psychotics and mood stabilizers
- These medications have been used in children for more than 20 years, though mostly in neurotypicals
- Some of the first generation antipsychotics were used in children with ASDs and other developmental disorders in the 1970s
Risperidone (Risperdal)

- 2002 RUPP Autism Network 8-week, multi-site, randomized, double-blind, placebo-controlled trial
  - 69% were responders compared to 12% on placebo

- 2005, RUPP longer-term, open-label extension phase and double-blind discontinuation study
  - 2/3rd s that responded to the acute phase continued their improvement after six months

- Dose 0.5-3.5 mg per day
Risperidone

- **Adverse effects (AE)**
  - weight gain
  - hyperglycemia
  - dyslipidemia
  - dizziness and sedation
  - acute dystonia
  - tardive dyskinesia
  - prolactin elevation
  - rarely may lower the seizure threshold
  - rarely may lead to neuroleptic malignant syndrome
Aripiprazole (Abilify)

- Marcus et al. 2009, 8-week, placebo-controlled, fixed dose
  - All three doses showed statistically significant improvement on the ABC-Irritability subscale and CGI-I compared to placebo
- Owen et al. 2009 used flexible dosing from 2-15 mg per day, 8-week, randomized, double-blind, placebo-controlled study
  - Improvement on outcome measures from week 1 to 8 on the agent vs. the placebo
- Same AE; although more weight neutral than risperidone, still an issue.
Other Second Generation Anti-Psychotics

- **Clozapine**—case reports, need frequent blood draws, can lower seizure threshold; risk of agranulocytosis and myocarditis
- **Olanzapine**—head-to-head against haloperidol; 6-week, open-label, parallel design favored olanzapine, but weight gain\(^1\) Malone et al. 2001; double-blind, placebo-controlled, 8 week-study favored agent, but weight gain,\(^2\) Hollander et al. 2006
- **Quetiapine**—several open label studies, shows 22-60 % response, very broad dose range used
- **Ziprasidone**—open label study, 6-week; N=12; more weight neutral, but have to do baseline EKG and EKG monitoring secondary to potential QTc increase
- **Paliperidone**—8-week, prospective, open label study; N=25; 20/24 responded; significant weight gain,\(^2\) Stigler, et al. poster 2010 APA
Mood Stabilizers

- Two small randomized controlled studies of valproic acid in children with ASDs---one study showed substantial improvement; the other study showed no difference between active agent and placebo---but there was a very big placebo response
- One randomized controlled study of lamotrigine showed no benefit over placebo
- Small open-label or case reports have indicated some benefit of lithium in manic-like symptoms and aggressive behavior
Mood Stablizers

- Challenging to use in children with ASDs
- Lithium and valproic acid require frequent blood draws to be used safely and effectively
- Lithium has the potential for toxicity, severe AE (problems concentrating urine, excessive thirst, cardiac arrhythmias, ataxia) and numerous milder AE (hypothyroidism, tremor, GI upset, sedation, blurred vision)
- Lamotrigine has to be managed carefully secondary to rare, but serious, even fatal, Stevens-Johnson syndrome, a hypersensitivity reaction affecting skin and mucus membranes
Hyperactivity/Impulsivity/Inattention (HII)

- The similarity in these symptoms to those of ADHD led to the hope that treatments effective for ADHD might be successful in children with ASDs
- In neurotypical children, treatment of ADHD is highly effective with a 70-80% response rate
Methylphenidate (MPH)

- Large, randomized, controlled study showed 49% were “much or very much improved” \( \text{RUPP, 2005} \)
  - Compared to about 70% of neurotypical children
- In a retrospective chart review, only 24.6% of ASD children responded to their first stimulant trial \( \text{Stigler, et al., 2004} \)
  - Compared to about 60-70% of neurotypical children
- AE (57%)
  - Agitation
  - Depression
  - Aggression
  - Increased stereotypies
  - Insomnia
  - Anorexia
HII/α-agonists

- Clonidine (Catapres) and guanfacine (Intuniv)
  - Small, open-label trial of guanfacine in ASD children showed hyperactivity dropped in 48% during 8-week trial Scahill et al., 2006
  - Small, randomized, double-blind, placebo-controlled, crossover trial of guanfacine in children with ASD and/or DD, hyperactivity dropped by 50% in 45% of the subjects Handen et al., 2008
  - AE:
    - Sedation
    - Rebound hypertension or hypotension
    - Headache
    - Dry mouth
    - Constipation
Atomoxetine (Strattera)
- Selective norepinephrine reuptake inhibitor
- Placebo-controlled, crossover pilot trial showed same effect size as MPH in the RUPP study, with fewer AE (Arnold et al., 2006)
- 8-week, open-label trial in HFA subjects showed improvement with fewer AE (Posey et al., 2006)
- AE
  - Sedation and fatigue
  - Increased heart rate and blood pressure
  - Anorexia
  - Sleep disruption
  - Irritability
Repetitive Behaviors

- This set of behaviors has significant overlap with another psychiatric disorder, obsessive-compulsive disorder
- The clinical overlap led to experimentation with the group of agents effective in OCD, namely selective serotonergic reuptake inhibitors (SSRIs)
SSRIs

- **Fluoxetine (Prozac)**
  - 16-week, double-blind, placebo-controlled, crossover study showed a *marginal decrease in repetitive behaviors* and no differences in AE between agent and placebo  
    Hollander et al., 2005
  - Autism Clinical Trials Network 14-week, randomized, placebo-controlled trial showed *no effect* (2009)

- **Citalopram (Celexa)**
  - The Studies to Advance Autism Research and Treatment (STAART) Network, sponsored by NIH 12-week, multisite, double-blind, placebo-controlled trial showed *no difference*
### SSRIs

<table>
<thead>
<tr>
<th>AE found in studies</th>
<th>AE reported in general population</th>
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<tbody>
<tr>
<td>- Increased energy level</td>
<td>- Sexual dysfunction</td>
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<tr>
<td>- Impulsivity</td>
<td>- GI upset</td>
</tr>
<tr>
<td>- Decreased concentration</td>
<td>- Insomnia</td>
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<tr>
<td>- Hyperactivity</td>
<td>- Anorexia</td>
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<tr>
<td>- Stereotypic behavior</td>
<td>- Induction of mania</td>
</tr>
<tr>
<td>- Diarrhea</td>
<td>- Seizures</td>
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<tr>
<td>- Insomnia</td>
<td>- Suicidal ideation</td>
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<td>- Dry skin</td>
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Trials of risperidone and aripiprazole demonstrated statistically significant decrease in stereotypic behaviors.
Core Social Impairment

- **D-cycloserine**
  - FDA-approved antibiotic used in TB
  - Partial agonist of NMDA subtype of glutamate, major excitatory neurotransmitter in the brain
  - Showed promise in a single-blind pilot study, but no effect in a larger, double-blind, placebo-controlled study

- **Memantine**
  - FDA-approved for Alzheimer’s disease
  - A glutamatergic antagonist
  - Retrospective review demonstrated clinical improvement in social withdrawal [Erickson et al., 2007]
  - Open label, add-on therapy showed improvement in CGI-I scale for language [Chez et al., 2007]
Core Social Impairment

- Oxytocin
  - A peptide thought to modulate social behavior in humans
  - Approved by the FDA in IV and IM forms only for use in labor induction
  - IV infusion of oxytocin in adults with autism showed promise in social relatedness *Hollander et al., 2005*
  - Intranasal oxytocin in adults with Asperger’s or HFA showed improved nonverbal communication and social relatedness *Andari et al., 2010*
The lessons from Fragile X

- Fragile X syndrome is the most common cause of inherited intellectual disability and the most common known cause of autism
- Fragile X syndrome is a single gene defect caused by a trinucleotide repeat disorder
- A protein, fragile X mental retardation protein (FMRP) is not made
- This lack of FMRP affects the mGluR5 pathway, which becomes overly active
The lessons from Fragile X

- Blocking this pathway may help restore functioning and relieve the symptoms of Fragile X.
- The hope is that there are commonalities in the pathophysiology of Fragile X-associated autism and autism unrelated to Fragile X. Potentially, treatments for Fragile X could be effective for other autisms.
- mGluR5 antagonists or blockers are in clinical trials for patients with fragile X syndrome and for patients with autism unrelated to fragile X syndrome.
Thank you