Medication Alternatives for Autism Spectrum Disorders

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Nurses: N-407

Target Audience:
Pharmacists, Technicians & Nurses

Program Overview:
This knowledge-based activity will provide an extensive overview of the pharmacological therapy of the associated behaviors of the Autism Spectrum Disorders. The program will provide a broad review of information related to the pervasive development disorders. The focus will then shift to the analysis of available literature for the pharmacotherapy of the associated symptoms.

Objectives:
• List the associated behaviors for ASD that pharmacological therapy is used to treat.
• Describe the pharmacological therapies used for treating the associated behaviors for ASD.
• Discuss the current limitations for making evidence-based pharmacological treatment of the associated behaviors of ASD.
• Given patient information, provide pharmacological recommendations for the treatment of the associated behaviors of ASD.

Case

DS is a 10 yom dx with autism in 2002. Dysfx. primarily in areas of socialization, communication, and restricted and repetitive patterns of behavior.

Primary sx: anxiety, social behavior deficits, stereotypies
Background

- Autism one of 5 pervasive development disorders
- All PDD's characterized by dysfunction in 3 symptom domains:
  - Socialization
  - Communication
  - Stereotypy - behavioral condition characterized by a lack of variation in patterns of thought, motion, and speech; by repetition of these patterns; or both

The Five PDDs

- Autistic disorder (Autism)
  - Autistic spectrum disorder

- Rett’s disorder (Rett syndrome)
  - Almost exclusively females, male fetuses seldom survive to term
  - Deceleration in rate of head growth with or without microcephaly
  - Small hands and feet
  - Repetitive hand movements, GI problems and seizures (up to 80%) common
  - Most have no verbal skills, 50% not ambulatory
  - Caused by genetic mutations (MECP2)

- Childhood Disintegrative Disorder (CDD)
  - Rare
  - Late Onset (>3 yo, up to 10 yo) development of delays in language and social function and motor skills.
  - Fairly normal development may be noted before regression
  - Regression can be very sudden
  - Devastating
The Five PDDs
- Asperger disorder (Asperger’s syndrome)
  - Autistic spectrum disorder
  - Linguistic and cognitive development are preserved
  - Deficits in social interaction and stereotypy
  - Physical clumsiness and atypical use of language also often reported
- PDD-NOS (NOS = not otherwise specified)
  - Autistic spectrum disorder
  - Individuals described by PDD
  - Do not meet criteria for other PDDs

Treatment
- Multi-faceted
  - Non-pharmacological
    - Behavioral interventions
    - Educational interventions
    - Rehabilitation (OT, speech and language therapy)
  - Pharmacological – used primarily to treat associated behaviors
    - Aggression, irritability, inattention, hyperactivity, mood/anxiety symptoms
    - 1/3rd of patients take psychotropic med. or vitamin

Drugs for ADHD-like Symptoms
- Treat hyperactivity, impulsivity, inattention
- Impulsivity – inclination of a person to act on impulse rather than thought
- Inattention – in ADHD, inability to filter out unwanted stimuli, easily distracted

Quality of Evidence Pyramid
Evidence for hyperactivity in PDDs is good
- R, DB, PC trials
- Response in Asperger, PDD-NOS, and autism
- Response rate lower with autism
- Overall, lower response rate than in children with ADHD
- Also, higher rate of ADEs in PDD patients
- ADEs include –
  - Lethargy, social withdrawal, stereotypy, irritability, dysphoria, motor tics, increased hyperactivity, decrease in appetite (most frequent)

Not well studied
- Appears to have lower response rate in ASD
- ADEs
  - GI symptoms
  - Fatigue
  - Appetite changes

ADE profiles and risk of cardiac toxicity – little further study accepted
- Amitriptyline – not studied in ASD
- Desipramine/Clomipramine
  - Two studies in ASD
  - Both improved hyperactivity equally
  - Clomipramine better for aggression and repetitive behaviors
- Imipramine – one study (1971)
- Nortriptyline – one study (1966)
  - Improved symptoms, particularly hyperactivity
  - ADEs – restlessness, confusion, weight gain

Two studies, numerous case reports
- Fast improvement of ADHD-like symptoms in pts with ASD
  - Inattention
  - Hyperactivity
Medication Treatment Alternatives for Autism Spectrum Disorder

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### Alpha-2 Adrenergic Agonists

- **Clonidine**
  - Some benefit in treating hyperactivity in autism
  - Also shown benefit for social relationships, irritability, stereotypy, inappropriate speech and oppositional behavior
  - Transdermal used primarily
  - ADEs – can be significant
    - Sedation, fatigue, decreased activity

- **Guanfacine**
  - One prospective, one retrospective trial
  - Decreases hyperactivity
  - ADEs include sedation and constipation
    - Also increased irritability, aggression and sleep disruption
    - Decreased appetite

### Alzheimer’s Disease Agents

- **Donepezil (Aricept)**
  - Used only as adjunct therapy
  - Retrospective chart reviews only
  - Reduced overall ADHD-like symptoms
  - Improved PDD severity overall
  - Well tolerated

- **Galantamine (Razadyne, formerly Reminyl)**
  - Prospective, open label trial
  - Reduction in aggression and inattention
  - Well tolerated
  - Larger, randomized, placebo-controlled studies in the future
Memantine (Namenda)
- Open-label study
- Improved cognitive aspects of ASD
  - Executive function
  - Working memory
- Increased hyperactivity in some patients

Symptoms may significantly interrupt other treatments and interventions, especially aggression.
Risperidone (Risperdal) is most extensively studied for these symptoms.
Risperidone is FDA approved to treat irritability associated with autism (including concomitant aggressive behaviors).

Memantine (Namenda)
- Open-label study
- Improved cognitive aspects of ASD
  - Executive function
  - Working memory
- Increased hyperactivity in some patients

Haloperidol – others have similar benefits and risks.
- Well studied
- Double-blind, placebo-controlled trials exist
- Improved temper tantrums, aggression, hyperactivity, withdrawal, and stereotypies
- Increased social relatedness
- Mean dose about 1.1 mg/day
- ADEs above this dose
  - Sedation, irritability, dystonic reactions
  - Dystinesias at 1.75 mg/day in about 1/3rd of patients
- More attention now to atypical antipsychotics.

Clozapine (Clozaril)
- Case studies
- Improves aggression, hyperactivity and social aspects at 200 mg/day
- ADEs – sedation, enuresis
- Useful for treatment refractory cases
- Limited use for others
  - Reduces seizure threshold
  - Hematologic monitoring
## Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Medication</th>
<th>Key Points</th>
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<tbody>
<tr>
<td><strong>Risperidone</strong></td>
<td>Well studied for aggression, children and adults</td>
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<tr>
<td><strong>Olanzapine (Zyprexa, Zydis)</strong></td>
<td>Case studies and open-label mainly</td>
</tr>
<tr>
<td><strong>Quetiapine (Seroquel)</strong></td>
<td>Open label and retrospective chart review</td>
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<tr>
<td><strong>Ziprasidone (Geodon)</strong></td>
<td>Little study</td>
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**Atypical Antipsychotics**

- **Aripiprazole (Abilify)**
  - Case series, low patient number
  - Improved aggression, agitation, self-injurious behavior
  - Response not as good with concomitant mental retardation
  - ADE – more prevalent in younger patients
    - Sedation, weight gain

**Antiepileptics – Comorbid seizure rate is high**

- **Topiramate (Topomax)**
  - Retrospective chart review
  - Used as adjunct
  - Improvements in irritability, hyperactivity, inattention
  - ADEs – mild sedation, skin rash, disorientation, speech problems

**Antiepileptics**

- **Divalproex sodium (Depakote)**
  - DB, PC trial
  - Improved repetitive behaviors, social relatedness, aggression, and mood stability
  - Significant improvement in repetitive behaviors
  - ADEs – irritability, weight gain, anxiety, aggression
    - No subjects dropped out due to ADEs

**Beta-blockers**

- **Open trial**
  - Methodologically weak
  - Adults only
  - Adjunctive therapy only
  - Improved aggression and socialization
Buspirone (Buspar)
- In ASD, anxiety may lead to aggression and irritability
- Case reports and open label trial
- Safe, modest ADEs
- Limited efficacy for anxiety, irritability, hyperactivity, aggression, temper outbursts, and self-injurious behaviors

Drugs for Stereotypy/Repetitive Behaviors
- Perseverative/repetitive behaviors – stereotypies
  - May hinder other treatments
- Similar to obsessions and compulsions in OCD patients
- Antidepressants used most commonly

Selective Serotonin Reuptake Inhibitors (SSRIs)
- Fluoxetine (Prozac)
  - Open-label trial – on other medications
    - Highly positive effects on language, cognition, social relatedness, and affect
    - Improvements in irritability, lethargy, stereotypy, and inappropriate speech
  - DB, PC trial
    - Reduction in repetitive behaviors
  - ADEs – insomnia, hyperactivity, irritability, lethargy

SSRIs
- Fluvoxamine (Luvox) – 3 investigations
  - Open-label trial
    - Little improvement noted overall
    - All females responded
    - ADEs – akathisia, agitation, behavioral activation
  - DB, PC trial
    - Significant clinical improvement in 1 of 34 children
  - DB, PC trial
    - Clinical response in half of 30 adults
    - Reduction in repetitive behaviors and thoughts, maladaptive behaviors, and aggression
    - ADEs – mild sedation, nausea
Sertraline (Zoloft)
- Open label study in adults
  - 57% showed improvement in repetitive behaviors and aggression
  - Patients with autism and PDD-NOS responded better than those with Asperger
  - Minimal ADEs
- Open label – adults with ASD and mental retardation
  - Improvement in aggression and self-injurious behavior
  - No randomized, controlled trials
  - Children and adolescents often react differently than adults

Paroxetine (Paxil)
- Existing data is not strong
- Open, prospective trial of 15 patients with aggression and self-injurious behavior
  - 7 patients had PDD
  - Reduction in aggression severity
  - Two case reports, 7 yo, 15 yo
  - Improvement in irritability and preoccupation – 7 yo
  - Improvement in self-injurious behavior and anxiety – 15 yo
  - Well tolerated in all studies

Citalopram (Celexa) and Escitalopram (Lexapro)
- Citalopram – not extensively studied
  - Chart reviews indicate safety and efficacy
- Escitalopram
  - Open-label trial
  - Improvements in some symptom domains
  - Minimal side effects

Clomipramine (Anafranil)
- TCA and serotonin reuptake inhibitor
- Several trials
- DB, PC trial – children and adolescents with ASD
  - Superior to placebo for:
    - Obsessive-compulsive symptoms
    - Abnormal reciprocal interaction
    - Motor stereotypes
    - Self-injurious behaviors
Clomipramine (Anafranil)
- Open pilot study – 8 children
  - Not therapeutic
  - Serious ADEs – urinary retention, severe constipation, insomnia, behavioral problems, drowsiness
- DB, PC comparison to haloperidol
  - 36 patients with autism
  - More dropouts with clomipramine – ADEs and behavioral problems
  - Comparable improvements in irritability and stereotypy

Drugs for Deficits in Social Behavior
- Deficits in social relatedness and social reciprocity very important
- Focus of recent attempts to identify drug treatments

D-Cycloserine
- Partial NMDA-receptor agonist
- Single-blind pilot study – 12 patients with autism
  - Improvement in social withdrawal
  - No significant differences in social responsiveness or obsessive-compulsive behaviors
  - Minimal ADEs

Tetrahydrobiopterin
- Essential cofactor for the synthesis of melatonin, serotonin, dopamine, epi, NE, dopamine, and nitric oxide
- DB, PC trial – 12 children
  - Statistically significant improvement in social interaction ability
  - Minimal ADEs – agitation, difficult sleeping
Conclusions

- Numerous options
- Literature very limited
- Additional trials badly needed
- You can assist other HCP’s in making informed decisions

What about DS?

Questions?

Notes