Module 3:
Psychopharmacology and ASD in Transitional Age Youth: Evidence and Trends in Practice

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Learning objective

• Identify interfering symptoms for teens with autism
• Consider classes of medications and the data supporting use in ASD/ID
• Understand risks and benefits of medications for ASD
Target symptoms for ASD

• Sleep dysregulation
  – Onset
  – Sustaining sleep

• Symptoms to track: intensity and frequency
  – Hyperactivity and Inattention
  – Irritability
    • Self injurious behaviors
    • Aggression toward others
  – Repetitive behaviors /OCD like behaviors
Symptoms measure

• Outcome measures
  – Aberrant Behavior Checklist – often used in research
    • Developed for ID
    • Used mostly in children
    • Subscales:
      – Irritability
      – Social withdrawal
      – Stereotypy
      – Hyperactivity,
      – Odd speech
  • Subscales for **Irritability**, **Hyperactivity**, **Social withdrawal** seem to be more reliable than total score
Psychotropic Medications Used in Autism

• Hyperactivity
  – Stimulants
  – Atypical ADHD Medications
    • Clonidine
    • Guanfacine
    • Atomoxetine
• Irritability and Aggression
  – Neuroleptics
• Repetitive behaviors/Depression and Anxiety
  – SSRI
  – Chlomipramine
  – Mood stabilizers
• CAM
Stimulants and ASD

- Stimulant medication (methylphenidates, amphetamines) effective in about 50% of cases compared to 80% plus in typically developing children
- Generally higher doses not as well tolerated as in non-comorbid (ASD and ADHD) cases
- Children with ASD and/or ID are more vulnerable to side effects

Davis NO and Kollins SH. *Neurotherapeutics*, 2012.; Antshel K. *Neurotherapeutics*, 2013
# Non-Stimulants

<table>
<thead>
<tr>
<th>Medication</th>
<th>FDA Approved</th>
<th>Common Side Effects</th>
<th>Side Effects Less Common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha agonist: Capvay, Intuniv</td>
<td>Yes</td>
<td>Sedation</td>
<td>HR, dry mouth, nausea, headaches</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Yes</td>
<td>Decr. Appetite Poor sleep</td>
<td>Incr. HR/BP Sweating, wt change, sweating</td>
</tr>
</tbody>
</table>
Uses of Alpha Agonist for ASD Symptoms and Comorbidities

- Clonidine moderately effective in decreasing reactivity, hyperactivity and aggressiveness.
- May be helpful for sleep
- Guanfacine improvement in hyperactivity on ABC hyperactivity scale (only in children)
- Side effects
  - Sedations
  - Decrease blood pressure
  - Decrease heart rate
- Clonidine - oral (short or long acting) or patch
- Guanfacine – short or long-acting (Intuniv)

Atomoxetine

- TCA derivative
- Doses 1.2 - 1.4 mg/kg/day
- Targets symptoms of ADHD medication with possible impact on comorbid anxiety in typically developing population
- Has shown some positive impact on ADHD symptoms in ASD and ADHD (Ages 5-15) (Arnold et al., 2006; Posey et al., 2006)
- Haferkamp et al., 2013, children ages 6-17 yo, noted 81% of subjects experienced AE although some had positive clinical outcome.
- One promising case study in young adult (Neiderhoffer, 2006)
Atypical Antipsychotics and ASD

• Compared to typical neuroleptics, increase impact serotonin receptors
  – Serotonin transporter 5HTT
  – 5-HT2A receptors

• May help mood, anxiety as well as psychotic symptoms

• SGA seem more effective for ASD and Bipolar disorder than typical antipsychotics
First Generation Antipsychotics in Autism

• Typical Neuroleptics (Haldol)
  – Haldol: although effective in children; more effect in adults with ASD
  – Children more likely to have dystonia and SE
  – Improved stereotypies
  – Risperidal is more effective
FDA Approved Atypical Neuroleptics

• Aripiprazole and Risperidonal are the only medication approved for ‘irritability’ and ‘aggression’ and ‘repetitive’ behaviors.

• Abilify has more data for younger ASD patients; less studied in adults

• Noted mild Benefit of Risperidonal for inattention.

• May increase agitation and increase aggression

• Maximum doses for this indication are LOWER than for psychotic disorders
  – Risperidonal: 3 mg
  – Abilify: 15 mg
Other Atypical Antipsychotics

• Clozapine
  – Improved aggression
  – Weight gain significant: 14 kg

• Olanzapine:
  – more improvement than placebo in children and adolescents
  – Open label studies including children thru adults demonstrated improvements in hyperactivity, aggression, SIB, with no change in repetitive behavior.
  – Double blind study (Hollander, 2006) found improvement in behavior but no change in repetitive behaviors

• Quentiapine, Ziprasadone:
  – less well studied; variable results in open trial
  – Mild to moderate response in open studies
<table>
<thead>
<tr>
<th>GENERIC NAME</th>
<th>FDA APPROVED (pediatric age range in years)</th>
<th>TARGET SYMPTOMS</th>
<th>USUAL DAILY DOSAGE RANGE</th>
<th>SUGGESTED TOP END OF DAILY DOSAGE RANGE</th>
<th>SUGGESTED MEDICAL MONITORING</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ATYPICAL ANTIPOSTICHTICS</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>Bipolar (10-17) Schizophrenia (13-17)</td>
<td>Mania Psychosis Irritability</td>
<td>2-30 mg</td>
<td>30 mg (Autism: 15 mg)</td>
<td>BMI, BP, P, fasting glucose &amp; lipids, abnormal movements; EKG if CV history</td>
</tr>
<tr>
<td></td>
<td>Irritability in Autism (6-17)</td>
<td>Agitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risperidone</td>
<td>Bipolar (10-17) Schizophrenia (13-17)</td>
<td>Mania Psychosis Irritability</td>
<td>Bipolar/Schizophrenia: 0.5-6 mg Autism: &lt;20 kg: 0.25-0.5 mg ≥20 kg: 0.5-1 mg</td>
<td>Bipolar &amp; Schizophrenia: 6 mg Autism: 3 mg</td>
<td>BMI, BP, P, fasting glucose &amp; lipids, abnormal movements; EKG if CV history</td>
</tr>
<tr>
<td></td>
<td>Irritability in Autism (5-17)</td>
<td>Agitation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>Bipolar (13-17) Schizophrenia (13-17)</td>
<td>Mania Psychosis Agitation</td>
<td>2.5-10 mg</td>
<td>20 mg</td>
<td>BMI, BP, P, fasting glucose &amp; lipids, abnormal movements; EKG if CV history</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Bipolar (10-17) Schizophrenia (13-17)</td>
<td>Mania Psychosis Agitation</td>
<td>Bipolar: 400-600 mg Schizophrenia: 400-800 mg</td>
<td>Bipolar: 600 mg Schizophrenia: 800 mg</td>
<td>BMI, BP, P, fasting glucose &amp; lipids, abnormal movements; ophthalmological exam; EKG if CV history</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>None</td>
<td>Mania Psychosis Agitation</td>
<td>40-160 mg</td>
<td>200 mg</td>
<td>BMI, BP, P, fasting glucose &amp; lipids, abnormal movements, EKG</td>
</tr>
</tbody>
</table>
Monitoring Neuroleptics

- Monitor weight before starting medications
  - 1 month, 3 months and then Quarterly
  - If gain more than 5 kg; consider change of medications
  - Lipid panel initially, 3 months and then every 6 months
  - CBC and renal and liver panel every 12 months
- Monitor for AIMS and Extrapyramidal symptoms every 3 Months
Antidepressants: Transition from Teen to Adult

- SSRI’s for anxiety and depression improved outcomes with older patients as with general population
- Metabolism generally slows with age
- ASD population is more sensitive to physiological and behavioral side effects than typically developing population
- More likely to see aggression, increase in irritability, sleep disturbance
FDA Approved Antidepressants for Children and Adolescents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Ages</th>
<th>Starting dose</th>
<th>Max dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoxetine</td>
<td>MDD</td>
<td>7 yo +</td>
<td>Child: 5 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td></td>
<td>OCD</td>
<td></td>
<td>Adol: 10 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>MDD</td>
<td>12 yo +</td>
<td>10 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td>Sertraline</td>
<td>OCD (good data for MDD/GAD - no FDA approval)</td>
<td>6 yo +</td>
<td>12.5 mg – child 25 mg - adolescent</td>
<td>200 mg</td>
</tr>
<tr>
<td>Fluvoxamine</td>
<td>OCD</td>
<td>8 yo +</td>
<td>50 mg</td>
<td>100 mg bid</td>
</tr>
<tr>
<td>Duloxetine (SNRI)</td>
<td>GAD</td>
<td>7-17 yo</td>
<td>30 mg</td>
<td>60 mg (120)</td>
</tr>
</tbody>
</table>
SSRI and ASD

• Most commonly prescribed medication for anxiety associated with autism
• First choice for children and adolescents with anxiety and depression but effects are moderate
• In adults with ASD and anxiety or depression, better effects of Fluoxetine and Sertraline than in children
• Outcomes over age span, similar to typically developing population
SSRI’s and OCD type behavior in ASD

• Citalopram – no impact on repetitive behaviors (King, 2009)
• Lexapro: Some positive outcomes in open label study at low doses, 10mg/day
  – More likely to have side effects
• Fluoxetine: Placebo controlled study of children and adults show decrease in repetitive behaviors and anxiety.
  – Adults can tolerate higher doses without activation
  – Decrease in repetitive behaviors: compulsions, stereotypies and hoarding
• Sertraline: may have more side effects with less clear positive impact
  – One open label study, adults with ASD, showed some response with difference by diagnosis
  • ASD / PDD NOS >>>>>Aspergers disorder
• Fluvoxamine
  – No data to support use in children
  – In adults, studies demonstrate positive benefit in randomized control study
• SNRI: Venlafaxine – open label, 60% response rate at low doses (Max 50mg )

(Hollander, 2005, 2012; Koshes, 1997; McDougle, 1990; McDougle, 1996)
Other options for OCD-like behaviors

- Chlomipramine (TCA):
  - Interfering symptoms of repetitive behaviors improved: 33%-66% for Asperger's, PPD-NOS, Autism Spectrum (Brodkin, 1997)
  - Difficult to tolerate side effects

- Riluzole (Glutamate antagonist)
  - Some improvement in 3 individuals (Wink et al., 2011)
  - Ages 15-20 yo
Atypical Antidepressants

• Buspar
  – Minimal data for effect for ADHD
  – May be helpful in adults for Self-insurance behaviors

• Mirtazapine: alpha-2 /5HT antagonistic
  – Promising case reports that demonstrate decrease in self stimulating behavior (Coskun & Mukaddes, 2008 and Nguyen & Murphy, 2001)
  – In open label study, may also be helpful for anxiety, depression, insomnia (Posey, et. al. 2001)

(Volkmar, Reichow, and McPartland, eds. 2014)
Mood Stabilizers: Lithium and Antiepileptics

- Lithium: Case reports that Lithium helps with mood instability in ASD and Bipolar disorder and Depression with psychotic features; no controlled studies (Kerbeshian et al., 1990; Steingard & Biederman, 1987)

- Lamictal/Keppra: negative studies to date

- Topiramate:
  - No data for adults
  - Positive data for children and adolescents targeting hyperactivity and irritability. (Harden et al., 2004; Rezaei et al., 2010)

- VPA: targeted on aggression, repetitive behaviors affective instability
  - Side effects: irritability, hyperactivity, weight gain
NMDA receptors: Future possibilities

• Memantine: NMDA antagonist- comparable to Risperdal for dysregulated/irritable behavior. (Nikvarz, Pharmacopsychiatry, Jan, 2017)

• Amantadine: non competitive NMDA antagonist
  – Trend to improvement in behavior

• D-Cycloserine: NMDA partial agonist
  – used for negative symptoms of schizophrenia
  – Small study (Posey et al., Am J Psychiatry, 2004) some improvement on ABC social withdrawal scale
Miscellaneous trial for TAYS/ASD

- **N-Acetylcysteine (Mucomist)** (Hardan, 2012)
  - Improved social cognition, motivation and decreased stereotypies
  - Study in children 3-10 yo
- **L-carnitine**: Mild response in children, 3-10 yo (Geier, 2011)
- **Oxytocin**: intranasal
  - Suggestion of improvement in social skill (Andari et al., Proc Nat Acad Science, 2010)
- **Naltrexone**: generally poor outcome and not well tolerated
Melatonin

• Helps with ONSET of sleep in young children and adults  (Galli-Carminati, et al. 2009; Malow, et al., 2012)

• Melatonin: more than 10mg is generally not helpful

• Effective in reducing sleep onset, less nocturnal wakenings and increase in total sleep time

• Few side effects
Complementary and Alternative Medications/CAM

• Secretin: no clear impact on behavior

• Omega-3’s:
  – may have value in decreasing hyperactivity and/or repetitive behaviors in young children (Brent, 2011)
  – data is poor for adults.
  – Studies look at dose and EPA/DHA ratio
Summary: Medication management for interfering symptoms of ADHD

• Only FDA approved medications for the irritability of autism: Risperidal and Abilify; monitor for side effects including metabolic abnormalities.
• Melatonin is drug of choice for sleep disorders in neurodevelopmental delays.
• Data supports use of stimulants and atypical ADHD medications for symptoms of hyperactivity.
• SSRI’s may be useful for anxiety/depression in ASD, increase effect in teens and adults with careful monitoring of side effects including increase suicidal ideation.
• Repetitive behaviors may be decreased by use of SSRI’s (e.g. Fluoxetine), particularly in older teens and young adults.
• Look for new studies: vitamin supplements, NMDA, NAC.
References


References


