Psychopharmacology of Autism Spectrum Disorder

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Increasing Incidence of Autism

Percent growth in autism in the USA compared with all other disorders tracked in the IDEA legislation (see http://www.fightingautism.org).

Autism on the Rise (Figure 1)
Over the last decade, the number of students diagnosed with autism in America’s schools has increased more than fivefold.

Growth in the Number of Autistic Students Served under the Individuals with Disabilities Education Act

Graph Source: www.Fightingautism.org  Data Source: www.idealdata.org and www.cdc.gov/nchs/  
SOURCE: US Department of Education
Core Domains in Autism Spectrum Disorders

DSM IV

- **Socialization**
  - Qualitative impairment in socialization

- **Communication**
  - Qualitative impairments in communication

- **Activities and interests**
  - Restricted repetitive and stereotyped patterns of behavior, interest, and activities
Core Domains in Autism Spectrum Disorder

DSM 5

- Social Communication and social interaction
- Restricted repetitive patterns of behavior, interests or activities
TREATMENT

• Unclear pathogenesis
  ▪ No definitive neurochemical abnormalities
  ▪ Emerging animal models
• Diagnosis
• Few Animal Models
• Measures of effectiveness
EFFECTIVE TREATMENT

- Evidence based practice
  - Behavioral
  - Medical
  - Other treatments
- Many distressing symptoms
  - ADHD
  - Severe tantrums, mood swings and aggression
  - Anxiety
NATURAL COURSE AND SYMPTOMATOLOGY

• 0-5 Years
  ▪ Hyperactivity, Irritability

• 6-12 Years
  ▪ ODD, Anxiety, OCD

• Teen Years
  ▪ Depression, CD

• Late Teens
  ▪ Bipolar, CD

• Adult
  ▪ Personality D/O, CD
ETIOLOGY OF SYMPTOMS

• Environmental
  ▪ Changes and other stressors

• Physiological
  ▪ Onset of a new treatable medical condition

• Psychiatric
  ▪ Onset of a psychiatric disorder

• Medication associated
MEDICAL TREATMENT

ATN Survey of 2,853 Children

- At least one psychotropic medication 27%
- Usage increased with age
  - 3 to 5 years of age 11%
  - 12 to 17 years of age 66%
- Usage by class
  - Stimulants 13%
  - Second Generation Antipsychotics (SGA) 8%
  - Selective Serotonin Reuptake Inhibitors (SSRI) 8%
  - Alpha-2-a agonists 7%

Coury et al., Pediatrics, 2007, 37:1949
NEUROTRANSMISSION

Dopamine

- Motor function
- Cognitive function
- Many receptor subtypes (D_{1-5})
- Inconsistent neurochemical studies
- Treatment studies in Autism
DOPAMINE
NEUROTRANSMISSION

Serotonin

- Widespread in mammalian brain
- Influences early brain development
  - Enhances proliferation
  - Enhances migration
- Many receptor subtypes (5-HT$_{1-7}$)
- Hyperserotononemia in Autism ~ 1/3
ADHD SYMPTOMS in ASD

- Kanner 1943
  - Described attention deficits
- Attention may be too wide or too narrow
- Presence of attention deficits in core domains
  - Fixation on interests
  - Unusual intensity
**ASD and ADHD**

**DSM IV**

“Attention Deficit/Hyperactivity Disorder is not diagnosed if the symptoms of inattention and hyperactivity occur exclusively during the course of a Pervasive Developmental Disorder…”

**DSM 5**

“Abnormalities of attention (overly focused or easily distracted) are common in individuals with autism spectrum disorder, as is hyperactivity. A diagnosis of attention-deficit disorder (ADHD) should be considered when attentional difficulties or hyperactivity exceeds that typically seen in individuals of comparable mental age.”
ADHD vs. ASD vs. ID

- Important differential diagnosis
- Intellectual disability and ADHD
- ASD and ADHD
  - HFA
  - Asperger disorder
‘FOCUS’ IN ASD AND ADHD

• Distractibility
  - External distractibility
  - Internal (cognitive) distractibility
VISUAL ATTENTION AND SOCIAL INTERACTION

- Eye contact
- Visual attention
- Less time focusing on the eyes
- Social deficits
PREVALENCE?

• ASD with ADHD
• Little available data
• Wide range of findings
  ▪ 37% to 83%
PHARMACOTHERAPY

- Psychostimulants
- Atomoxetine
- Adrenergic agonists
PSYCHOSTIMULANTS

• FDA approved for ADHD symptoms
• Precise mechanism of action is unknown
• Class includes methylphenidate and amphetamine compounds
• Less well studied in ASD
PSYCHOSTIMULANTS

- Bad Reputation
  - Intellectual disability
  - ASD
- Side/adverse effects
  - Stereotypic behavior
  - Irritability
  - Anxiety
- Equivocal results
PSYCHOSTIMULANTS AND SIDE EFFECTS


<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Methylphenidate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repetitive movements</td>
<td>45.5</td>
<td>36.4%</td>
</tr>
<tr>
<td>Sad, unhappy, depressed</td>
<td>36.4%</td>
<td>45.5%</td>
</tr>
<tr>
<td>Social withdrawal</td>
<td>54.5%</td>
<td>54.5%</td>
</tr>
<tr>
<td>Irritable, crabby, whiny</td>
<td>63.6%</td>
<td>54.5%</td>
</tr>
<tr>
<td>Poor appetite</td>
<td>63.6%</td>
<td>72.7%</td>
</tr>
<tr>
<td>Dizzy, balance unstable</td>
<td>18.2%</td>
<td>0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>45.5%</td>
<td>9.1%</td>
</tr>
<tr>
<td>Restless, high activity level</td>
<td>63.6%</td>
<td>45.5%</td>
</tr>
</tbody>
</table>
METHYLPHENIDATE EFFECTS

- (RUPP) Autism Network
  - Double-blind, placebo-controlled crossover
  - 72 children (5-14 years old)
  - Low, medium, & high doses
- Superior to placebo (49%)
  - Inattention
  - Hyperactivity
- Irritability

- Retrospective population based (124) study
- Of 398 treatment episodes 69.4 % positive
- 16.8% of episodes had side effects
- 66% of subjects had at least one side effect
ATOMOXETINE

- A non-stimulant
- Selective norepinephrine reuptake inhibitor
- Enhances dopamine in the frontal lobes
ATOMOXETINE EFFECTS


- Double-blind, placebo-controlled, crossover
- 16 children, aged 5-15 years
- 12 weeks (six weeks in each treatment arm)
- Significant improvement
  - Hyperactivity
  - Impulsivity
  - Inattention just short of significance
- Side effects
  - GI, fatigue, increased heart rate
  - Only one dropped out (aggression)
ATOMOXETINE EFFECTS


- Double-blind, placebo-controlled
- 97 children aged 6 to 17 years
- Fixed dose, 8 weeks
- Significant improvement
  - 8.2 pt. drop on 54 pt. ADHD scale
- Side effects
  - GI, fatigue, early morning awakening
ADRENERGIC AGONISTS

- Hyperarousal suggests an adrenergic-system component
- Alpha-2 adrenergic agonists block sympathetic discharge
  - Decreases catecholamines
- Clonidine improves inattention in typical children with ADHD
CLONIDINE EFFECTS

  - Placebo-controlled, crossover in 8 males
  - Improvement with parents and teachers
  - No improvement by clinicians
  - Extension showed no lasting effects

  - Placebo-controlled in 9 males
  - No effect on hyperactivity
  - Global ratings improved

(GHS Children's Hospital
Greenville Health System)
GUANFACINE EFFECTS

  - Open-label, retrospective
  - 80 with ASD, 3-18 years
  - 0.25 - 9 mg/day (ave.2.6 mg/day)
  - 24% responders.
    - Global improvement scores.
  - 27% improvement for ADHD.
  - 21% improvement for inattention
IRRITABILITY AND TANTRUMS

- Irritability
- Tantrums
- Mood swings
TYPICAL ANTIPSYCHOTICS

Potent Dopamine Blockers

- Used in autism for many decades
- Haloperidol is very efficacious
- High frequency of adverse effects:
  - Dystonic reactions
  - Withdrawal dyskinesias
  - Tardive dyskinesia
DOPAMINERGIC ANTAGONISTS

- Second-generation antipsychotics
  - Blockade of postsynaptic dopamine and serotonin receptors
  - Risperidone and aripiprazole
    - FDA indication for irritability and aggression
SECOND GENERATION ANTIPSYCHOTICS

Advantage Over Typical

- Antagonism at serotonin receptors
- Decreased propensity for EPS
- Improving negative symptoms
  - Apathy
  - Avolition
  - Anhedonia
RISPERIDONE EFFECTS

McCracken, et al. (2002) NEJM

- Multisite, randomized, double-blind, placebo-controlled
- Average dose 1.8 mg/day (0.5 mg/day-2.5 mg/day).
- Irritability, decreased significantly.
- Hyperactivity decreased significantly.
- 69% more likely than placebo.
- Weight gain
ARIPIPIRAZOLE EFFECTS


- Randomized, double blind, placebo controlled.
- 5 mg-10mg
- Irritability, decreased significantly.
- Weight gain
ADVERSE EFFECTS OF SGA

- Numerous adverse effects in adults
- Heart disease number one cause of death

ADVERSE EFFECTS OF SGA

Risperidone in Children

- **Neurologic effects:**
  - Somnolence 67%, fatigue 42%, increased salivation 22%, Parkinsonian/extrapyramidal 8-12%, confusion 5% [Pre-marketing studies]

- **Weight gain:**
ADVERSE EFFECTS OF SGA

Risperidone in Children

- **Hyperprolactinemia:**
  - RUPP- 10.1+/−8.8 ng/mL
  - v. 39.0+/−19.2 ng/mL

- **Metabolic**
  - Diabetes
ADVERSE EFFECTS OF SGA

Hyperprolactinemia

- Delayed puberty
- Galactorrhea
- Gynecomastia
- Amenorrhea and other sexual problems
- Osteoporosis

Dickson, et al., 1999, Schizophr Res, 35:S75
ADVERSE EFFECTS OF SGA

Extrapyramidal Symptoms

- EPS are related to:
  - $D_2$ receptor occupancy
    - Higher occupancy = higher risk
  - Higher doses associated with higher risk
  - Lower overall risk and pediatric population
ADVERSE EFFECTS OF SGA

Monitoring Extrapyramidal Symptoms

• Simpson-Angus Scale
• Barnes Akathesia Rating Scale
• Abnormal Involuntary Movement Scale
<table>
<thead>
<tr>
<th>Movements</th>
<th>RATER 1</th>
<th>RATER 2</th>
<th>RATER 3</th>
<th>RATER 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facial and Oral Movements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Muscles of Facial Expression</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>e.g., movements of forehead, eyebrows, periorbital area, cheeks, including frowning, blinking, smiling, grinning</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Lips and Perioral Area</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>e.g., puckering, pouting, sucking</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3. Jaw e.g., biting, clenching, chewing, mouth opening, lateral movement</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Tongue Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Extremity Movements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Upper (arms, wrists, hands, fingers):</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Include choreic movements (i.e., rapid, objectively purposeless, irregular, spontaneous) stereotyped movements (i.e., slow, irregular, complex, stereotyped). DO NOT INCLUDE TREMOR (i.e., repetitive, regular, rhythmic)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6. Lower (legs, knees, ankles, toes):</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>e.g., lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and evasion of foot.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trunk Movements</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7. Neck, shoulders, hips e.g., rocking, twisting, squirming, pelvic rhythms</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Global Judgment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8. Severity of abnormal movements overall</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Incapacitation due to abnormal movements</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>10. Patient's awareness of abnormal movements. Rate only patient's report</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>No awareness</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Aware, no distress</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Aware, mild distress</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Aware, moderate distress</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Aware, severe distress</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Dental Status</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11. Current problems with teeth and/or dentures</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>12. Are dentures usually worn?</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>13. Edentia?</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>14. Do movements disappear in sleep?</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Final: 9/2000
ADVERSE EFFECTS OF SGA

Weight Gain

- Shown to be related to receptor binding affinity

CLO>OLZ>QUE>RIS>ARI>ZIP>HAL
## Consensus Statement on Antipsychotic Drugs, Obesity, and Diabetes: Monitoring Protocol for Patients on Second-Generation Antipsychotics

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 Weeks</th>
<th>8 Weeks</th>
<th>12 Weeks</th>
<th>Quarterly</th>
<th>Annually</th>
<th>5Years</th>
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<tbody>
<tr>
<td><strong>Personal/Family Hx</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Weight (BMI)</strong></td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Waist Circum.</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Blood Pressure</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Fasting Glucose</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td><strong>Fasting Lipid Profile</strong></td>
<td>X</td>
<td></td>
<td></td>
<td></td>
<td>X</td>
<td>X</td>
<td>[X]</td>
</tr>
</tbody>
</table>

MEASUREMENT OF OUTCOMES

• **AAP recommends:**
  - "Quantifiable" assessment
  - Variety of input
  - Consistent use of validated treatment sensitive rating scales
    - Aberrant Behavior Checklist
    - Clinical Global Impression-Improvement
    - Clinical Global Improvement

www.pediatrics.org/cgi/doi/10.1542/peds.2007-2362
ABERRANT BEHAVIOR CHECKLIST

- Irritability
- Lethargy
- Stereotypy
- Hyperactivity
- Inappropriate Speech
CLINICAL GLOBAL SCALES

- **Clinical Global Impression of Severity**
- **Clinical Global Impression of Improvement**

<table>
<thead>
<tr>
<th>CGI Severity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Normal, not ill</td>
</tr>
<tr>
<td>2</td>
<td>Borderline ill</td>
</tr>
<tr>
<td>3</td>
<td>Mildly ill</td>
</tr>
<tr>
<td>4</td>
<td>Moderately ill</td>
</tr>
<tr>
<td>5</td>
<td>Markedly ill</td>
</tr>
<tr>
<td>6</td>
<td>Severely ill</td>
</tr>
<tr>
<td>7</td>
<td>Among the most extremely ill</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CGI Improvement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Very much improved</td>
</tr>
<tr>
<td>2</td>
<td>Much improved</td>
</tr>
<tr>
<td>3</td>
<td>Minimally improved</td>
</tr>
<tr>
<td>4</td>
<td>No change</td>
</tr>
<tr>
<td>5</td>
<td>Minimally worse</td>
</tr>
<tr>
<td>6</td>
<td>Much worse</td>
</tr>
<tr>
<td>7</td>
<td>Very much worse</td>
</tr>
</tbody>
</table>
SEROTONIN REUPTAKE INHIBITORS

- Schain & Friedman (1961)
- 1/3 have hyperserotonemia
- Anxiety
- Repetitive behaviors
- Few studies on ADHD
FLUOXETINE EFFECTS

- Retrospective chart review
- 7 patients (9-20 years old) treated for depression
- Not significant trend for increased hyperactivity

- Open label study
- 37 children (2-7 years)
- Hyperactivity worsened in some
- Main cause of drop out

- RDBPC
- Adults 22-T, 15-P with OCD
- Significant improvement
CITALOPRAM EFFECTS


• RDBPC crossover
• 149 patients 5-17 yrs.
• No difference in repetitive behaviors
• Significant adverse effects
ESCITALOPRAM EFFECTS

Owley et al. (2005) J. A. A. Child & Adolesc. Psychiatry

- Open label prospective trial
- 28 subjects (6-17 years)
- Significant improvement in 61%
- All outcome measures including hyperactivity
- 6 became hyperactive

- Randomized, controlled, crossover with placebo
- 24 children and adults (6-23 years)
- 25 mg/day-to 250 mg/day (5 mg/kg/day)
- Both were efficacious for hyperactivity
- Cardiac side effects, & durability, temper outbursts, and uncharacteristic aggression
OTHER MEDICATIONS

- Amantadine
- Opiate antagonists
- Divalproex sodium
- Lamotrigine
- Galantamine
- Rvastigmine
- Memantine
AMANTADINE

- N-methyl-D-aspartate receptor antagonist
- May suppress neuronal development
- NMDA-system abnormalities in Rett’s disorder
- A well controlled study showed improvement
OPIATE ANTAGONISTS

NALTREXONE

- Endogenous opioid system in autism
- Elevated beta endorphins
- Several well-controlled studies
- Conflicting results
DIVALPROEX SODIUM & LAMOTRIGINE

- Open label studies have shown promise
- Few specific measures of inattention and hyperactivity
DEMENTIA MEDICATIONS

- Galantamine
- Rivastigmine
- Memantine
SUMMARY

• Behaviors should be assessed in the context of the individual and the environment

• Despite the number of medications used to treat behaviors in ASD, very little evidence exists to support the use of most

• Always use medication as part of a comprehensive treatment program i.e., medication is adjunctive treatment

• Medications used to treat ADHD in typical children are also efficacious for ADHD symptoms in ASD (~50%)
SUMMARY

- Symptoms of hyperactivity and impulsivity are more responsive than symptoms of inattention.
- Second generation antipsychotics have demonstrated efficacy, but should be used with caution.
- There is very little evidence for the use of SSRI and other psychotropic medications in ASD.
- Start low and go slow.
- The benefits of medication must always be weighed against the potential risks.