Psychotropic Medication Management in Neurodevelopmental Disabilities

Scott M. Myers, MD

Psychopharmacology

- The study and clinical use of compounds that affect the central nervous system, resulting in changes in thinking, behavior, or emotion (psychotropic medications)
Psychopharmacology Timeline:

<table>
<thead>
<tr>
<th>Year</th>
<th>Psychopharmaceuticals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1850</td>
<td>Bromides</td>
</tr>
<tr>
<td>1875</td>
<td>Barbiturates</td>
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<tr>
<td>1900</td>
<td>Lithium</td>
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<tr>
<td>1925</td>
<td>Antidepressants</td>
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<tr>
<td>1950</td>
<td>MAO inhibitors</td>
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<tr>
<td>1975</td>
<td>Antipsychotics</td>
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<tr>
<td>2000</td>
<td>SSRIs</td>
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</tbody>
</table>

Psychogenic Theory-Driven Approaches:

- **Bromides**
  - Introduced in 1857 as anticonvulsants
  - Thought to act by lowering sex drive
  - Excessive masturbation was thought to be the cause of epilepsy
  - Later used for insomnia and anxiety as well as epilepsy

History of Pharmacotherapy in ID and ASD

ID = Intellectual Disability, ASD = Autism Spectrum Disorder

- Psychodynamic theory-driven approaches
- Attempts to raise the IQ of people with ID
- Attempts to modulate serotonin in ASD
- Early symptom-based treatments

Attempts to Raise the IQ of People with ID

- 1940s
  - Glutamic acid (Albert et al., 1946)
- 1950s-1960s (reviewed by Louttit, 1965)
  - Stimulants
  - B vitamins
  - Vitamin E
  - Thyroxine
  - Neuroleptics (low doses)
  - Others

Early Attempts to Modulate Serotonin in ASD

- Tryptophan
  - Sutton et al., 1958; Shaw et al., 1959; Schain & Freedman, 1961
- Elevated whole blood serotonin in 30-50% of patients
  - Schain & Freedman, 1961
- Attempts to reduce whole blood serotonin pharmacologically:
  - LSD
  - Methysergide (Fish et al., 1969)
  - L-dopa
  - Ritvo et al., 1971; Campbell et al., 1976
  - Fenfluramine
    - Studied extensively after NEJM paper in 1982; rev. by Aman & Kern, 1989
Early Symptom-Based Treatment

• Concurrent with psychogenic theory-driven treatment, attempts to increase IQ, and attempts to modulate serotonin
• Based on discovery of the effects of medications on related disorders
• Important Milestones
  – Amphetamine and methylphenidate in ADHD
  – Development of antipsychotics (1950s)

Amphetamines

• Shown by Bradley\(^1\) and Molitch and Eccles\(^2\) in 1937 to reduce hyperactivity and disruptive behaviors and improve academic performance in children
  – Hyperactivity was believed to be related to deficits in inhibitory volition, moral control, and sustained attention caused by early mild, undetected brain damage
• More scientifically rigorous research began to appear in the 1960s (amphetamines and methylphenidate)
• Widespread acceptance 1980s

Antipsychotics

• 1950s: Modern age of psychopharmacology
  – Synthesis of chlorpromazine by molecular manipulation of the antihistamine promethazine (1950)
  – Isolation of reserpine from *Rauwolfia serpentina*
• Chlorpromazine – “psychic penicillin”
  – Beginning in the mid-1950s, the number of institutionalized patients with mental illness fell dramatically
  – Plausible mechanism of action was not proposed until 1963, and not proven until 1970
• Antipsychotics in ID and ASD
  – Reports of use in patients with ID began to appear in 1954, use became widespread, especially in institutions
  – Studies of wide variety of antipsychotics in children with autism (peaked in the 1970s-1980s)
• Reserpine in ASD (Lehman et al., 1957)

Pediatric Psychopharmacology

• Pediatric psychopharmacology is a relatively young clinical and research discipline
• Many psychotropic medications are not FDA approved for use in pediatric patients
• Sources of Evidence:
  – Controlled clinical trials in children and adolescents
  – Controlled clinical trials in adults
  – Open-label trials
  – Case series, anecdotal reports
  – Literature regarding related disorders (with similar target behaviors)
  – Clinical experience
  – Neurobiology

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To see a single daily dose of benzedrine produce a greater improvement in school performance than the combined efforts of a capable staff working in a most favorable setting would have been all but demoralizing to the teachers, had not the improvement been so gratifying from a practical viewpoint.”

Charles Bradley, MD
*Am J Psychiatry* (1937)
FDA Approval

- A drug approved for marketing may be labeled, promoted, and advertised by the manufacturer only for those uses for which the drug’s safety and effectiveness have been established.
- According to the FDA, "the FD & C Act does not, however, limit the manner in which a physician may use an approved drug. Once a product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens or patient populations that are not included in approved labeling."
- "Accepted medical practice" often includes drug use that is not reflected in approved drug labeling.

Psychopharmacology

- Gold standard of evidence-based pharmacotherapy:
  - Independently replicated randomized double-blind, placebo-controlled clinical trials with adequate sample sizes and defined study populations
- Sources of Evidence:
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Evidence: 2 Examples

Research Units on Pediatric Psychopharmacology (RUPP Autism Network)

- Randomized, DBPC trial, n = 101, age 5-17, duration 8 weeks
- Risperidone, dose range 0.5-3.5 mg/day, mean dose 1.8 mg/day
- Primary outcome measures:
  - Irritability subscale of the Aberrant Behavior Checklist
  - Clinical Global Impressions – Improvement
- 56.9% reduction in Irritability score in risperidone group vs. 14.1% in placebo group
- Positive response (25% or more reduction in Irritability score and much improved or very much improved on CGI-I) rate:
  - 69% in risperidone group
  - 12% in placebo group
- Side effects: weight gain, increased appetite, fatigue, drowsiness, dizziness, drooling
- In 2/3 of responders, effect maintained at 6 months

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Longer-Term Treatment

- Part I: open-label, n = 63, duration 16 weeks, mean dose 1.96 mg/day, mean wt. gain 5.1 kg, stable dose and ABC Irritability scores
- Part II: RDBPC placebo-substitution study, n = 32, relapse rate 62.5% for gradual placebo substitution vs. 12.5% for continued risperidone
- NIMH Data and Safety Monitoring Board ordered that the discontinuation phase be stopped immediately after interim analysis

ABC Irritability

CGI

RUPP Autism Network; McCracken et al. New Engl J Med, 2002


Impact of Risperidone on the Core Symptoms of Autism

- No significant impact on social interaction and communication deficits
- Improvements in restricted, repetitive, stereotyped behavior
  - RFRLRS sensory motor behaviors, affectual reactions, and sensory responses subscales
  - C-YBOCS
  - Vineland Maladaptive Behavior Domain

Double-Blind, Placebo-Controlled Clinical Trials of Risperidone in ASD

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>McDougle et al. (1998)</td>
<td>31</td>
<td>18-43</td>
</tr>
<tr>
<td>McCracken et al. (2002)</td>
<td>101</td>
<td>5-17</td>
</tr>
<tr>
<td>Shea et al. (2004)</td>
<td>77</td>
<td>5-12</td>
</tr>
<tr>
<td>Hellings et al. (2006)</td>
<td>36</td>
<td>8-56</td>
</tr>
<tr>
<td>Luby et al. (2006)</td>
<td>24</td>
<td>2-6</td>
</tr>
<tr>
<td>Nagaraj et al. (2006)</td>
<td>39</td>
<td>2-9</td>
</tr>
<tr>
<td>Kent et al. (2013)</td>
<td>96</td>
<td>5-17</td>
</tr>
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</table>

Double-Blind, Placebo-Controlled Clinical Trials of Atypical Antipsychotics for Disruptive Behavior in ID

<table>
<thead>
<tr>
<th>Agent</th>
<th>Reference</th>
<th>N</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risperidone</td>
<td>Aman et al. (2002)</td>
<td>118</td>
<td>5-12</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Snyder et al. (2002)</td>
<td>110</td>
<td>5-12</td>
</tr>
<tr>
<td>Risperidone (discontinuation)</td>
<td>Reyes et al. (2006)</td>
<td>193 (IQ 55-84) (of 527 total)</td>
<td>5-17</td>
</tr>
</tbody>
</table>

Large, Informative Open-Label Clinical Trials

<table>
<thead>
<tr>
<th>Reference</th>
<th>N</th>
<th>Duration</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turgay et al. (2002)</td>
<td>77</td>
<td>48 wks</td>
<td>5-12</td>
</tr>
<tr>
<td>Findling et al. (2004)</td>
<td>107</td>
<td>48 wks</td>
<td>5-12</td>
</tr>
<tr>
<td>Croonenberghs et al. (2005)</td>
<td>504</td>
<td>52 wks</td>
<td>5-14</td>
</tr>
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</table>

Psychopharmacologic Interventions

- **Risperidone** and aripiprazole are the only medications with FDA-approved labeling specific to autism spectrum disorder
  - for the symptomatic treatment of irritability, including aggressive behavior, deliberate self-injury, and temper tantrums in children and adolescents with autism

Medication + Behavioral Intervention

- RUPP Autism Network
- RCT, n=124, age 4-13, duration 24 weeks
- Medication (risperidone) + parent training (COMB) vs. medication alone (MED)
  - COMB n=75, MED n=49
  - Parent training based on principles of ABA
- Risperidone + parent training (COMB) resulted in greater reduction of serious maladaptive behavior than risperidone alone
  - ABC Irritability, Hyperactivity/Noncompliance, Stereotypy
- COMB group risperidone dose was lower (mean 1.98 mg/day vs. 2.26 mg/day for MED alone group)
### Double-Blind, Placebo-Controlled Clinical Trials

**Agent** | **Reference** | **N** | **Age**
--- | --- | --- | ---
Clomipramine | Remington et al. (2001) | 36 | 10-36
Fluvoxamine | McDougle et al. (1996) | 30 | 18-53
Fluvoxamine | McDougle et al. (2000) | 34 | 5-18
Fluvoxamine | Sugie et al. (2005) | 18 | 3-8
Fluoxetine | Hollander et al. (2005) | 39 | 5-17
Citalopram | King et al. (2009) | 149 | 5-17
Fluoxetine | SOFIA trial | 158 | 5-17

*(red = negative trial)*

### Citalopram for Repetitive Behavior in ASD

N=73 (citalopram) N=76 (placebo)

- **CGI**
- **CYBOCS - PDD**

Significantly more adverse effects on citalopram vs placebo: increased energy level, impulsiveness, hyperactivity, stereotypy, insomnia, decreased concentration

King BH et al., Arch Gen Psychiatry 2009;66:583

### Psychopharmacology in Neurodevelopmental Disabilities: General Approaches

- Coexisting psychiatric diagnosis (categorical)
  - Depression, anxiety disorder, OCD, bipolar disorder, ADHD, etc.
  - Modified diagnostic criteria, unknown validity
- Target symptom approach (dimensional, spectrum)
  - Treat amenable target symptoms
- Neurobiology/Pathophysiology
  - Primarily theoretical until recently
  - Clinical trials in Fragile X, tuberous sclerosis, Rett, others

### Common Challenging Behaviors

- Inattentiveness, distractibility
- Hyperactivity
- Impulsivity
- Aggression
- Self-injury
- Repetitive behaviors
  - stereotypy
  - ritualistic behavior
  - obsessions
  - compulsions
  - perseveration
- Depression
- Mood lability
- Sleep disturbance
- Anxiety
- Irritability
- Tantrums
- Destructive behavior
- Other disruptive behavior

### Applied Behavior Analysis: Efficacy for the Treatment of Problem Behaviors

- Extensive body of literature over >45 years
- Effective for assessing and treating problem behavior and increasing appropriate skills

- Variety of settings
  - Hospital, Clinic
  - School
  - Home
- Variety of behaviors
  - Self-injurious behavior
  - Aggression
  - Stereotypic behavior
  - Pica
  - Property destruction
  - Noncompliance
  - Others
- Variety of diagnoses
  - Intellectual disability
  - Autism spectrum disorder
  - Stereotypic movement disorder with self-injury
  - Various neurogenetic syndromes
  - ADHD
  - Feeding disorders
  - Schizophrenia
  - Anxiety disorders
  - Sleep disorders
Applied Behavior Analysis

• Meta-analyses
  – Harvey ST et al., J Intellect Dev Disabil 2009;34:67
  – Didden R et al., Am J Ment Retard 1997;101:387

• Selected Reviews
  – Paclawskyj T in Shapiro & Accardo (Eds.) 'Neurogenetic Syndromes: Behavioral Issues and Their Treatment' (in press)
  – Matson JL et al., Behav Mod 2006;52:61
  – Hanley GP et al., J Appl Behav Anal 2003;36:147
  – Odom et al., Focus Autism Devel Disabil 2003;10:166
  – Homer RH et al., J Autism Devel Disc 2002;32:423
  – Foxx RM, Behav Anal 1996;19:225
  – Matson JL et al., Res Dev Disabil 1996;17:433

Psychopharmacologic Interventions

• May effectively alleviate or modify certain behavioral symptoms or co-existing disorders but have not been shown to correct the core deficits
• Effective medical treatment may allow a child to benefit more optimally from educational and behavioral interventions

Common Target Symptom Clusters

• ADHD symptoms
  – hyperactivity, impulsivity, inattention, distractibility
• Irritability
  – tantrums, aggression, self-injury
• Repetitive behavior, behavioral rigidity
  – obsessions, compulsions, perseveration, ritualistic behavior, motor stereotypy, insistence on sameness
• Sleep dysfunction (Insomnia)

Medication Options for Common Target Symptoms

(Supported by at least 1 double-blind, placebo controlled study in ASD)

<table>
<thead>
<tr>
<th>Target Symptoms</th>
<th>Medication Class</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD symptoms</td>
<td>Psychostimulants</td>
<td>Methylphenidate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atomoxetine</td>
</tr>
<tr>
<td>Irritability</td>
<td>Alpha-2 Agonists</td>
<td>Clonidine</td>
</tr>
<tr>
<td>Repetitive</td>
<td>Selective Norepinephrine Reuptake Inhibitors</td>
<td>Guanfacine</td>
</tr>
<tr>
<td>Sleep dysfunction</td>
<td>Anticonvulsants</td>
<td>Valproate</td>
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<tr>
<td>Repetitive behavior, behavioral rigidity, obsessive-compulsive symptoms</td>
<td>Atypical Antipsychotics</td>
<td>Aripiprazole, Olanzapine, Risperidone</td>
</tr>
<tr>
<td>Sleep dysfunction</td>
<td>Anticonvulsants</td>
<td>Valproate, Fluvoxamine, Melatonin</td>
</tr>
<tr>
<td>Endogenous chronobiotic hormone with hypnotic properties</td>
<td>Selective Serotonin Reuptake Inhibitors</td>
<td>Fluoxetine, Fluvoxamine, Melatonin</td>
</tr>
</tbody>
</table>

Approach to Psychopharmacologic Management

• Evaluation of target symptoms
• Initiation of therapy
• Monitoring and Adjustment of therapy
Evaluation of Target Symptoms

- Identify and assess target behaviors
  - Parent/caregiver interview, input from school staff and other caregivers
    - Frequency, Intensity, Duration
    - Exacerbating factors/triggers (time, setting/location, demand situations, denials, transitions, etc)
    - Ameliorating factors and response to behavioral interventions
    - Time trends (increasing, decreasing, stable)
    - Degree of interference with functioning
  - Baseline behavior rating scales and/or baseline direct observational data (e.g., collect data on number of episodes of aggression or self-injury in a given time period)
  - Consider formal functional analysis of behavior

- Search for medical factors that may be causing or exacerbating target behavior(s)
  - Consider sources of pain or discomfort
  - Consider other medical causes or contributors (obstructive sleep apnea, seizures, menstrual cycle, etc.)

- Assess existing and available supports
  - Behavioral supports and services
  - Educational program, habilitative therapies
  - Family psychosocial supports, respite care

- Complete any medical tests that may have a bearing on treatment choice
  - e.g., EEG if possible seizures

Problem Behaviors

- Medical factors may cause or exacerbate maladaptive behaviors
  - Consider sources of pain or discomfort
  - Consider other medical causes or contributors
    - obstructive sleep apnea
    - seizures
    - menstrual cycle
    - others

Medical Conditions That May Cause or Exacerbate Problem Behaviors

- Allergies
  - atopic dermatitis
  - environmental (rhinitis, conjunctivitis)
  - food

- Dental Discomfort
  - abscesses, caries
  - quinsy, impaction
  - trauma

- Endocrine Disorders
  - hypothyroidism, hyperthyroidism
  - premenstrual discomfort or dysphoria

- Gastrointestinal Disorders
  - constipation
  - diarrhea, cramping
  - esophagitis, gastroesophageal reflux
  - gastritis

- Infectious Diseases
  - otitis media, otitis externa
  - sinusitis
  - pharyngitis

- Musculoskeletal Problems
  - headache (including migraine)
  - arthritis
  - neck, back, and limb pain
  - muscle strain
  - joint pain

- Neurological Disorders
  - seizures
  - stroke

- Nutritional Deficiencies
  - iron deficiency
  - protein-calorie malnutrition
  - zinc deficiency

- Ophthalmologic Problems
  - corneal abrasion
  - strabismus

- Sleep Disorders
  - obstructive sleep apnea
  - other sleep-disordered breathing

- Medication Side Effects
  - prescription medications
  - diet supplements
  - over-the-counter medications

- Musculoskeletal Problems
  - arthritis
  - strain or sprain
  - neck, back, and limb pain

- Neurological Disorders
  - headache (including migraine)

- Nutritional Deficiencies
  - iron deficiency
  - protein-calorie malnutrition
  - zinc deficiency

- Ophthalmologic Problems
  - corneal abrasion

Adapted from Myers, SM. Pediatr Ann. 2003

Initiation of Psychopharmacologic Therapy

- Consider psychotropic medication based on the presence of:
  - Evidence that the target symptoms are interfering substantially with learning/academic progress, socialization, health/safety, or quality of life
  - Suboptimal response to appropriate available behavioral interventions and environmental modifications
  - Research evidence that the target behavioral symptoms or coexisting psychiatric diagnoses are potentially amenable to pharmacologic intervention
Initiation of Psychopharmacologic Therapy

• Choose a medication on the basis of:
  – Likely efficacy for the specific target symptoms
  – Potential adverse effects
  – Practical considerations, such as formulations available, dosing schedule, cost, and requirement for laboratory or EKG monitoring
  – Patient’s other medical conditions (e.g., obesity, asthma, etc.) that might be exacerbated by certain medications
  – Informed consent (verbal or written) from parent/guardian and, when possible, assent from the patient

Initiation of Psychopharmacologic Therapy

• Establish a plan for monitoring of effects
  – Identify outcome measures for the target behaviors/symptoms
  – Discuss time course of expected effects and appropriate timing of follow-up telephone contact, completion of rating scales, reassessment of behavioral data, and office visits
  – Obtain baseline laboratory data if necessary for the drug being prescribed and plan appropriate future lab monitoring

Initiation of Psychopharmacologic Therapy

• Outline a plan regarding what might be tried next if there is a negative or suboptimal response or to address additional target symptoms
  • Change to a different medication
  • Add another medication to augment a partial or suboptimal therapeutic response to the initial medication (same target symptoms)
  • Add a different medication to address additional target symptoms that remain problematic

Monitoring of Psychopharmacologic Therapy

• Explore the reasonable dose range for a single medication for an adequate length of time before changing to or adding a different medication
• Titrate to optimal effect without intolerable side effects
• Monitor for adverse effects systematically
• Consider careful withdrawal of the medication after 6-12 months of therapy to determine whether it is still needed

Neurological disorders
  - Successful therapies
    - Clinical trials
    - Preclinical trials
  - Candidate pathways for therapeutic intervention
  - Basic neurobiology

Gene identification
Animal models
Pathogenesis studies
Basic neurobiology

Zoghbi & Bear, Cold Spring Harbor Perspectives in Biology 2012
Fragile X Syndrome

Fragile X syndrome is caused by a deficiency in the protein (FRMP) encoded by the gene FMR1

**FMR1 inactivation**

**FMRP deficiency** \(\rightarrow\) **Altered synaptic plasticity** \(\rightarrow\) **Abnormal learning, behavior**

• Metabotropic glutamate receptor 5 (mGluR5)
  – Positive regulator of protein synthesis at the synapse

Fragile X syndrome:

- **DNA** → **mRNA** → **Protein**
- **mGluR5** → **FMRP**

Altered synaptic plasticity

• de Vrij, et al. (2008): Rescue of behavioral phenotype and neuronal protrusion morphology in FMR1 knockout mice:
  – The use of a mGluR5 receptor blocker corrected abnormal behavioral features in Fragile X mice, and also corrected abnormal neuronal appearance

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<thead>
<tr>
<th>Target</th>
<th>Design</th>
<th>Action</th>
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<td>mGluR5</td>
<td>Positive regulator of protein synthesis at the synapse</td>
<td>FMRP block</td>
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