Diagnosis and Pharmacological Treatment of Autism Spectrum Disorder

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Changes in Diagnostic Criteria from DSM-IV-TR to DSM-5

- Autistic disorder
- Asperger’s disorder
- Pervasive developmental disorder – not otherwise specified
- Childhood disintegrative disorder
- Rett syndrome

Autism spectrum disorder
Eliminated as separate disorder
Changes in Diagnostic Criteria

DSM-IV-TR

- Social Interaction
- Restricted & Repetitive Behaviors
- Communication

DSM-5

- Social Interaction
- Restricted & Repetitive Behaviors
- Communication
Comparison of DSM-IV-TR and DSM-5 Diagnostic Criteria

<table>
<thead>
<tr>
<th>DSM-IV-TR Diagnostic Criteria</th>
<th>DSM-5 Diagnostic Criteria</th>
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</thead>
<tbody>
<tr>
<td>Autistic disorder one of five PDD subtypes</td>
<td>Single autism spectrum disorder diagnosis</td>
</tr>
<tr>
<td>Three symptoms domains:</td>
<td>Two symptom domains:</td>
</tr>
<tr>
<td>1. Deficits in social interaction</td>
<td>1. Deficits in social communication and social interaction</td>
</tr>
<tr>
<td>2. Deficits in communication</td>
<td>2. Restricted, repetitive behaviors, interests, or activities</td>
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<tr>
<td>3. Restricted, repetitive, and stereotyped patterns of behavior, interests, and activities</td>
<td></td>
</tr>
<tr>
<td>A minimum of 6 out of 12 possible symptoms</td>
<td>A minimum of 5 out of 7 possible symptoms</td>
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<tr>
<td>Inclusion of language delay subcriterion under domain of communication impairments</td>
<td>Elimination of language delay subcriterion</td>
</tr>
<tr>
<td>Onset of symptoms by age 3</td>
<td>Inclusion of atypical sensory experiences as a subcriterion under domain of restricted, repetitive behaviors</td>
</tr>
<tr>
<td>Exclusion of comorbid diagnosis of attention-deficit/hyperactivity disorder (ADHD)</td>
<td>Presence of symptoms in the early developmental period</td>
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<tr>
<td></td>
<td>Removal of this restriction</td>
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<td>Addition of severity specifiers</td>
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</table>

Autism Spectrum Disorder

MUST HAVE ALL 3 OF THE FOLLOWING:

• Deficits in social-emotional reciprocity
• Deficits in nonverbal social communication behavior
• Deficits in developing, maintaining, & understanding relationships

MUST HAVE 2 OF THE FOLLOWING:

• Stereotyped or repetitive motor movements, use of objects, or speech
• Insistence on sameness, inflexible adherence to routines, or ritualized patterns of behavior
• Highly restricted interests
• Over- or under-reactivity to sensory input or unusual sensory interests
## ASD Severity Grid

<table>
<thead>
<tr>
<th>Severity Level for ASD</th>
<th>Social Communication</th>
<th>Restricted Interests &amp; Repetitive Behaviors</th>
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<tbody>
<tr>
<td><strong>Level 3</strong></td>
<td>Severe deficits in verbal and nonverbal social communication skills cause severe impairments in functioning; very limited initiation of social interactions and minimal response to social overtures from others.</td>
<td>Preoccupations, fixated rituals and/or repetitive behaviors markedly interfere with functioning in all spheres. Marked distress when rituals or routines are interrupted; very difficult to redirect from fixated interest or returns to it quickly.</td>
</tr>
<tr>
<td>‘Requiring very substantial support’</td>
<td>Marked deficits in verbal and nonverbal social communication skills; social impairments apparent even with supports in place; limited initiation of social interactions and reduced or abnormal response to social overtures from others.</td>
<td>RRBs and/or preoccupations or fixated interests appear frequently enough to be obvious to the casual observer and interfere with functioning in a variety of contexts. Distress or frustration is apparent when RRB's are interrupted; difficult to redirect from fixated interest.</td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
<td>Without supports in place, deficits in social communication cause noticeable impairments. Has difficulty initiating social interactions and demonstrates clear examples of atypical or unsuccessful responses to social overtures of others. May appear to have decreased interest in social interactions.</td>
<td>Rituals and repetitive behaviors (RRB’s) cause significant interference with functioning in one or more contexts. Resists attempts by others to interrupt RRB’s or to be redirected from fixated interest.</td>
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<tr>
<td>‘Requiring substantial support’</td>
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<tr>
<td><strong>Level 1</strong></td>
<td></td>
<td></td>
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<tr>
<td>‘Requiring support’</td>
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</table>
Diagnostic Assessment

• Clinical interview
• Historical data
• Direct observation
• Physical and neurological exam
• Standardized cognitive or developmental testing
Additional Diagnostic Tools

• Autism Diagnostic Interview – Revised (ADI-R)
  – Semi-structured caregiver interview

• Autism Diagnostic Observation Schedule, Second Edition (ADOS-2)
  – Semi-structured observation tool
Symptom Rating Scales

- Australian Scale for Asperger’s Syndrome (ASAS)
- Gilliam Asperger’s Disorder Scale (GADS)
- Gilliam Autism Rating Scale—2nd Edition (GARS-2)
- Childhood Autism Rating Scale (CARS)
- Childhood Autism Spectrum Test (CAST)
- Social Responsiveness Scale—2nd Edition (SRS-2)
- Aberrant Behavior Checklist (ABC)
- Repetitive Behavior Scale (RBS)
Pharmacological Treatment

- Pharmacologic interventions target:
  - Reduction of ASD symptoms
  - Management of associated psychiatric symptoms and behaviors
- No medications specifically approved for the treatment of core ASD symptoms
- Relatively few well-designed, controlled trials of psychotropic medications in individuals with ASD to guide evidence-based practice
- Much of today’s discussion will refer to “off-label” use of medications
Target Symptom Domains

- 1. Motor hyperactivity and inattention
- 2. Irritability (aggression, self-injury, tantrums)
- 3. Restricted, repetitive patterns of behavior
- 4. Sleep disturbance
- 5. Mood disorders
- 6. Anxiety disorders
Motor Hyperactivity and Inattention

Level 1: Alpha-2 Agonists (guanfacine, clonidine)

Level 2: Atomoxetine

Level 3: Psychostimulants (methylphenidate, amphetamine compounds)
Level 1: Guanfacine

• Begin dosing at 0.5 mg qAM.

• Increase by 0.5 mg weekly in a BID manner (morning and when the child gets home from daily activities). Continue titrating until ADHD symptoms are adequately controlled, treatment-limiting side effects emerge, or a maximum daily dose is reached.

• Maximum recommended doses:
  – 27 to 40.5 kg: 2 mg/day
  – 40.5 to 45 kg: 3 mg/day
  – >45 kg: 4 mg/day

• Higher doses may necessitate TID dosing, which may require administration of a mid-day dose at school.

• Monitor pulse and blood pressure.

• If guanfacine is not helpful or poorly tolerated, taper by 0.5 mg every 3 days until off. Move on to trial of atomoxetine.

• If guanfacine is of partial benefit, consider combined therapy.
Level 2: Atomoxetine

- Begin dosing at 10 mg qAM.
- Increase by 10mg on a weekly basis until ADHD symptoms are adequately controlled, treatment-limiting side effects emerge, or a maximum daily dose of 1.8 mg/kg or 100 mg is reached.
- Give the dose once daily or on a BID schedule.
- If atomoxetine is not helpful or poorly tolerated, taper by 10 mg every 3 days until off. Move on to a trial of psychostimulant monotherapy.
- If atomoxetine is of partial benefit, consider combined therapy.
Level 3: Short-acting Methylphenidate or Amphetamine Formulations

- Begin dosing at 2.5 mg qAM.
- Increase by 2.5 mg every 3-4 days, administered in BID manner (morning and when the child gets home from daily activities). Continue titrating until ADHD symptoms are adequately controlled, treatment-limiting side effects emerge, or a maximum daily dose is reached.
- Maximum recommended doses:
  - Mehtylphenidate 2mg/kg
  - Amphetamine 1.5 mg/kg
- Monitor weight/height, pulse, blood pressure.
- Discontinue drug if it is not helpful or results in treatment-limiting side effects. Then consider a trial of a psychostimulant from the alternate group (methylphenidate or amphetamine compounds, whichever was not tried first).
Target Symptom Domains

1. Motor hyperactivity and inattention
2. **Irritability** (agression, self-injury, tantrums)
3. Restricted, repetitive patterns of behavior
4. Sleep disturbance
5. Mood disorders
6. Anxiety disorders
Medications for Irritability

• Alpha-agonists
• Antipsychotics
  – Risperidone and aripiprazole have FDA approval for treatment of severe irritability in autism
• Mood Stabilizers
Recommendation: Irritability

Level 1: Alpha agonists

Level 2: Aripiprazole

Level 3: Risperidone

Level 4: Ziprasidone – particularly if significant weight gain

Level 5: Quetiapine

Level 6: Combination therapy
Level 1: Guanfacine

• Begin dosing at 0.5 mg qAM.

• Continue titrating by 0.5mg weekly symptoms are adequately controlled, treatment-limiting side effects emerge, or a maximum daily dose is reached.

• Higher doses may necessitate TID dosing, which may require administration of a mid-day dose at school.

• Monitor pulse and blood pressure.

• If guanfacine is not helpful or poorly tolerated, taper by 0.5 mg every 3 days until off. Move on to a trial of an atypical antipsychotic.

• If guanfacine is of partial benefit, consider combined therapy.
Level 2: Aripiprazole

• Obtain a baseline fasting glucose and lipid panel along with height and weight. Repeat lab studies after 12 weeks.

• If lab studies are WNL, they can then be repeated annually. Height and weight should be obtained at each office visit.

• Begin aripiprazole at 2 mg daily, then increase to 5mg daily.

• Continue titrating by 2.5mg every 1-2 weeks, in a once daily dose, until irritability is adequately controlled, treatment-limiting side effects emerge, or a maximum daily dose is reached.

• If aripiprazole is ineffective or poorly tolerated, reduce by 2.5-5 mg every 3 days until off. Move on to a trial of risperidone monotherapy.
Level 3: Risperidone

- Obtain a baseline fasting glucose and lipid panel, along with height and weight. Repeat lab studies after 12 weeks.

- If the lab results are WNL, they can then be repeated annually. Height and weight should be obtained at each office visit.

- Begin risperidone at 0.25 mg qHS.

- Increase by 0.25 mg weekly in a once daily or BID dosing regimen until irritability is adequately controlled, treatment-limiting side effects emerge, or a maximum daily dose is reached.

- If risperidone is ineffective or poorly tolerated, taper by 0.25 – 0.5 mg every 3 days until off. Move on to a trial of a different second-generation antipsychotic.
# Metabolic Monitoring for Second-Generation Antipsychotics

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>4 weeks</th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>Annually</th>
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<td>Weight (BMI)</td>
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<td>Waist circumference</td>
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<td>Blood pressure</td>
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<tr>
<td>Fasting plasma glucose</td>
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<tr>
<td>Fasting lipid profile (HDL, LDL, TG, total cholesterol)</td>
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<td></td>
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</tbody>
</table>

Target Symptom Domains

1. Motor hyperactivity and inattention
2. Irritability (aggression, self-injury, tantrums)
3. Restricted, repetitive patterns of behavior
4. Sleep disturbance
5. Mood disorders
6. Anxiety disorders
Medications for Restricted, Repetitive Patterns of Behavior

- SSRIs
- Antipsychotics
Restricted, Repetitive Patterns of Behavior

• Restricted, repetitive patterns of behavior are a core diagnostic feature of ASD.
• Individuals often engage in such behavior in an effort to self-regulate anxiety, frustration, and agitation.
• It should not be a target of treatment unless it is interfering with the individual’s functioning and/or producing significant distress.
• Parent/family education may be needed (e.g., differentiating from symptoms of obsessive compulsive disorder).
Recommendation: Restricted, Repetitive Patterns of Behavior

Level 1: Low-dose SSRI

Level 2: Risperidone monotherapy

Level 3: Combination therapy
Level 1: Low-Dose Fluoxetine

• Fluoxetine Liquid (20 mg/5 mL): Begin fluoxetine at 2mg qAM.

• Increase by 2mg every 2 weeks until the interfering repetitive behavior is adequately controlled, treatment-limiting side effects emerge, or a maximum daily dose is reached.

• If fluoxetine monotherapy is ineffective or poorly tolerated, first consider a trial of another SSRI and then move on to risperidone monotherapy.

• If fluoxetine provides partial benefit for interfering repetitive behavior, consider adding risperidone.
Level 2 : Risperidone Monotherapy

• Obtain baseline fasting glucose and lipid panel, along with height and weight. Lab studies should be repeated at 12 weeks.

• If the lab studies are WNL, they can then be repeated annually. Height and weight should be obtained at each office visit.

• Begin risperidone at 0.25 mg qHS.

• Increase by 0.25 mg on a weekly basis in a once daily or BID dosing regimen until symptoms are adequately controlled, treatment-limiting side effects emerge, or a maximum daily dose is reached.

• Risperidone should be reserved for those with severe compulsions or associated irritability or agitation.
Target Symptom Domains

1. Motor hyperactivity and inattention
2. Irritability (aggression, self-injury, tantrums)
3. Restricted, repetitive patterns of behavior
4. **Sleep disturbance**
5. Mood disorders
6. Anxiety disorders
Medications for Sleep Disturbance

- Melatonin
- Trazodone
- Clonidine
- Mirtazapine
- Amitriptyline
- Diphenhydramine and benzodiazepines
Recommendation: Sleep Disturbance

- Level 1 - Melatonin
- Level 2 - Clonidine
- Level 3 - Trazodone
- Level 4 - Mirtazapine
- Level 5 - Amitriptyline
Level 1 - Melatonin

• Begin at 1mg qHS for 1 week.
• If no significant improvement in sleep, continue increasing dose by 1-3mg weekly, until reaching a dose of 9mg qHS.
• Consider time-release preparation for mid-cycle or early-morning awakenings.
• If no significant improvement in sleep at a dose of 9mg qHS, discontinue and move on to a trial of clonididine monotherapy.
Level 2 - Clonidine

• Begin at 0.05 mg (1/2 tab) qHS.

• If no benefit after 1 week, increase by 0.05 mg weekly until sleep improves, treatment-limiting side effects emerge, or a maximum total daily dose is reached.

• If clonidine is ineffective or poorly tolerated, reduce by 0.05 mg every three days until off. Move on to a trial of trazodone monotherapy.
Level 3 - Trazodone

• Begin at 25 mg (1/2 tab) qHS for a week.
• If no benefit after 1 week, titrate by 25mg weekly until sleep improves, treatment-limiting side effects emerge, or a total daily dose of 200 mg is reached.
• If trazodone is ineffective or poorly tolerated, reduce by 25-50 mg every 3 days until off. Move on to a trial of mirtazapine monotherapy.
Level 4 - Mirtazapine

- Begin at 3.75mg (1/4 tab) qHS.
- If no benefit after 1 week, increase by 3.75mg weekly until sleep improves, treatment-limiting side effects emerge, or a total daily dose of 45 mg is reached.
- If mirtazapine is ineffective or poorly tolerated, reduce by 7.5 mg every 3 days until off. Move on to a trial of amitriptyline monotherapy.
Level 5 - Amitriptyline

- Consider baseline EKG.
- Begin at 10mg qHS for a week.
- If no benefit after 1 week, increase by 10mg weekly until sleep improves, treatment-limiting side effects emerge, or a total daily dose of 200 mg is reached.
- If amitriptyline is ineffective or poorly tolerated, reduce by 10 mg every 3 days until off.
Target Symptom Domains

1. Motor hyperactivity and inattention
2. Irritability (aggression, self-injury, tantrums)
3. Restricted, repetitive patterns of behavior
4. Sleep disturbance
5. Mood disorders
6. Anxiety disorders
Medications for Mood Disorders

• Antidepressants
• Antipsychotics
• Mood Stabilizers
Recommendation: Depression

Level 1 - Follow guidelines already developed for assessment and treatment of children and adolescents with depression (AACAP Practice Parameter, 2007; Guidelines for adolescent depression in primary care (GLAD-PC), 2007)
SSRIs in Depression

- SSRIs with FDA approval for treatment of pediatric/adolescent depression: fluoxetine (age 8 or older), escitalopram (age 12 or older)
- “Black box” warning about increased risk of suicidality in children, adolescents, and young adults treated with antidepressants
- Risk of behavioral activation
Recommendation: Bipolar Disorder

Level 1 – Follow the guidelines already developed for the assessment and treatment of children and adolescents with bipolar disorder (AACAP Practice Paramater, 2007)
Target Symptom Domains

1. Motor hyperactivity and inattention
2. Irritability (aggression, self-injury, tantrums)
3. Restricted, repetitive patterns of behavior
4. Sleep disturbance
5. Mood disorders
6. Anxiety disorders
Recommendation: Anxiety Disorders

Level 1 - Buspirone

Level 2 - Low-dose SSRIs

Level 3 - Mirtazapine
Level 1 - Buspirone

- Begin 2.5 mg (1/2 tab) qAM.
- Increase by 2.5mg weekly until interfering anxiety symptoms are adequately controlled, treatment-limiting side effects emerge, or a maximum daily dose of 60 mg is reached.
- Administer in a BID manner up to 20 mg BID, then switch to TID dosing.
- If buspirone is ineffective or poorly tolerated, reduce by 2.5 mg every 3 days until off. Move on to a trial of mirtazapine.
Level 2 - Sertraline

• Begin sertraline 12.5mg. Increase by 12.5 mg every 2 weeks until interfering anxiety symptoms are adequately controlled, treatment-limiting side effects emerge, or a maximum daily dose is reached.

• If sertraline monotherapy is ineffective or poorly tolerated, reduce by 12.5-25 mg every 3 days. Consider a trial of another SSRI or move on to a trial of mirtazapine.
Level 3 - Mirtazapine

• Begin at 3.75 mg (1/4 tab) qHS.

• If no significant improvement in anxiety after 1 week, increase by 3.75mg weekly until there is a satisfactory improvement in anxiety, treatment-limiting side effects emerge, or a total daily dose of 45 mg is reached.

• If mirtazapine is ineffective or poorly tolerated, reduce by 7.5 mg every 3 days until off.
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