Attention Deficit/Hyperactivity Disorder:
Medication Therapy Management

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Objectives

• Review the background and prevalence of Attention Deficit/Hyperactivity Disorder (ADHD)
• Identify common presentation of ADHD
• Examine pharmacologic and non-pharmacologic methods for ADHD treatment
• Review possible adverse effects of pharmacologic therapy for ADHD
• Summarize adult ADHD and identify differences from pediatric diagnosis
Background

• Attention Deficit/Hyperactivity Disorder
  – Chronic disorder
  – Developmentally inappropriate degrees of
    • Inattention or concentration
    • Impulsiveness
    • Excessive motor activity
  – Subtyping
  – More likely in males than females (3:1 to 4:1)
  – Impairs social, academic, and occupational functioning in children, adolescents, and adults
Prevalence

• Worldwide
  – 5.3% (children and adolescents)

• United States
  – Children ages 5 to 12 yrs: 6 to 9%
    • Functionally impairing symptoms into adolescence: 60 to 80%
    • Approximately 50% have functionally impairing symptoms into adulthood
  – Adults: 3 to 5%
    • Varies with number of symptoms and level of impairment
    • Equally divided between men and women

# Differential Diagnosis

<table>
<thead>
<tr>
<th>Medical disorders</th>
<th>Emotional/behavioral disorders</th>
</tr>
</thead>
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<tr>
<td>Tourette syndrome</td>
<td>Anxiety/mood disorders</td>
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<tr>
<td>Seizure disorders</td>
<td>Depression</td>
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<tr>
<td>Fetal alcohol syndrome</td>
<td>Oppositional defiant disorder</td>
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<tr>
<td>Lead poisoning</td>
<td>Conduct disorder</td>
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<tr>
<td>Iron deficiency anemia</td>
<td>Adjustment reaction</td>
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<tr>
<td>Thyroid disorders</td>
<td>Post-traumatic disorder</td>
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<tr>
<td>Substance abuse</td>
<td>Schizophrenic disorder</td>
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<tr>
<td>Medication side effects</td>
<td>Personality disorder</td>
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<tr>
<td>Malnutrition</td>
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<tr>
<td>Neurodegenerative disorders</td>
<td>Development disorders</td>
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<tr>
<td>Sequelae of central nervous system</td>
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<tr>
<td>infection/trauma</td>
<td>- Autism</td>
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<tr>
<td>Vision/hearing impairments</td>
<td>- Pervasive developmental disorder</td>
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<tr>
<td>Sleep disturbances</td>
<td>- Mental retardation</td>
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<tr>
<td>Sensory impairments</td>
<td>- Learning disabilities</td>
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<tr>
<td></td>
<td>- Language disabilities</td>
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<tr>
<td>Environmental disorders</td>
<td>- Communication disorder</td>
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<tr>
<td>- Child abuse/neglect</td>
<td>- Cognitive impairment</td>
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<tr>
<td>- Stressful home environment</td>
<td>- Perceptual/processing disorders</td>
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<tr>
<td>- Inadequate/punitive parenting</td>
<td>- Fragile X syndrome</td>
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<tr>
<td>- Sociocultural difference</td>
<td>- Giftedness</td>
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<tr>
<td>- Inappropriate educational setting</td>
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<tr>
<td>- Parental psychopathology</td>
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</tbody>
</table>

## Associated problems
- Enuresis/encopresis
- Social skills deficit
- Motor coordination disorders
Diagnosis

• ADHD/I
  – 20 to 30%
  – At least 6 symptoms of inattention

• ADHD/HI
  – 5 to 10%
  – At least 6 symptoms of hyperactivity and impulsivity

• ADHD/C
  – 60 to 70%
  – Combined; at least 6 of each type

Symptoms of Inattention

- Often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities
- Often has difficulty sustaining attention in tasks or play activities
- Often does not seem to listen when spoken to directly
- Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace
- Often has difficulty organizing tasks and activities
- Often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort
- Often loses things necessary for tasks or activities
- Is often easily distracted by extraneous stimuli
- Is often forgetful in daily activities

Symptoms of Hyperactivity

- Often fidgets with hands or feet or squirms in seat
- Often leaves seat in classroom or in other situations in which remaining seated is expected
- Often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, feelings of restlessness)
- Often has difficulty laying or engaging in leisure activities quietly
- Is often “on the go” or often acts as if “driven by a motor”
- Often talks excessively

Symptoms of impulsivity

• Often blurts out answers before questions have been completed
• Often has difficulty awaiting turn
• Often interrupts or intrudes on others
DSM-IV Diagnostic Criteria

- Onset before age 7
- Symptoms persisting for at least 6 months
- Impairment in at least 2 settings
  - With multiple informants (teachers, parents, etc.)
- Clinically significant impairment in social, academic, or occupational functioning
- Symptoms not accounted for by another mental disorder
  - Two-thirds of children with ADHD have additional diagnosis
- Standardized questionnaires
  - Vanderbilt scale, Achenbach behavior checklist, ADD II, Connors Rating Scale

Psychostimulant Therapy

- Consistently have shown to improve core symptoms of ADHD
- Improves oppositional behavior, impulsive aggression, and social interactions
- Increased academic productivity and accuracy
- BUT... without psychosocial intervention, psychostimulants have not been shown to alone yield genuine academic gains

Non-pharmacologic Therapy

- Behavioral modification has been shown effective
- Parent and teacher training
  - Increase ability to respond appropriately to child’s behavior
  - Clear, concrete, and specific goal/target setting
  - Application of rewards and negative consequences
  - Daily report cards
  - Individual versus group settings

Non-pharmacologic Therapy

Stimulant Therapy

• Most effective drug therapy for ADHD

• Mechanism of action
  – Methylphenidate and amphetamines block pre-synaptic reuptake of dopamine and norepinephrine and inhibit monoamine oxidase (MAO)
  – Amphetamines increase dopamine release and have more potent MAO inhibition

• At least 80% of children will respond to one type of stimulant

Pharmacokinetics of Stimulants

• Every patient has a unique dose response curve
• Start low and titrate to effect
• Consider “Drug Holidays”
• Pulsatile dosing was once best
  – Extended-release preparations offer
    • Equal efficacy as immediate release
    • Convenience for patient and family
    • Enhanced confidentiality

# FDA Approved ADHD Medications

<table>
<thead>
<tr>
<th>Generic Class/Brand Name</th>
<th>Dose Form</th>
<th>Typical Starting Dose</th>
<th>FDA Max/Day</th>
<th>Off-Label Max/Day</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine preparations</td>
<td></td>
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<tr>
<td>Short-acting</td>
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</tr>
<tr>
<td>Adderall&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5, 7.5, 10, 12.5, 15, 20, 30 mg tab</td>
<td>3–5 y: 2.5 mg q.d.; ≥6 y: 5 mg q.d.–b.i.d.</td>
<td>40 mg</td>
<td>&gt;50 kg; 60 mg</td>
<td>Short-acting stimulants often used as initial treatment in small children (&lt;16 kg), but have disadvantage of b.i.d.–t.i.d. dosing to control symptoms throughout day</td>
</tr>
<tr>
<td>Dextedrine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 mg cap</td>
<td>3–5 y: 2.5 mg q.d.</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>DextroStat&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5, 10 mg cap</td>
<td>≥6 y: 5 mg q.d.–b.i.d.</td>
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<tr>
<td>Long-acting</td>
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<td></td>
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<tr>
<td>Dextedrine Spansule</td>
<td>5, 10, 15 mg cap</td>
<td>≥6 y: 5–10 mg q.d.–b.i.d.</td>
<td>40 mg</td>
<td>&gt;50 kg; 60 mg</td>
<td>Longer acting stimulants offer greater convenience, confidentiality, and compliance with single daily dosing but may have greater problematic effects on evening appetite and sleep Adderall XR cap may be opened and sprinkled on soft foods</td>
</tr>
<tr>
<td>Adderall XR</td>
<td>5, 10, 15, 20, 25, 30 mg cap</td>
<td>≥6 y: 10 mg q.d.</td>
<td>30 mg</td>
<td>&gt;50 kg; 60 mg</td>
<td></td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td>30, 50, 70 mg cap</td>
<td>30 mg q.d.</td>
<td>70 mg</td>
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</tbody>
</table>

*Note: FDA = U.S. Food and Drug Administration; ADHD = attention-deficit/hyperactivity disorder.

*<sup>a</sup> Generic formulation available.*
Lisdexamfetamine (Vyvanse)

- Prodrug activated by rate-limited enzymatic hydrolysis
- Approved for use in adults and children ages 6-12
- Initially 30 mg qAM, increase by 10-20 mg weekly to max of 70 mg
  - 70 mg of Vyvanse = 30 mg of mixed amphetamine salts
- Less abuse potential and euphoria due to rate limited activation
- Increased insomnia
- Long Tmax (3.5 hours); may need IR preparation in morning

Methylphenidate preparations

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<tbody>
<tr>
<td><strong>Short-acting</strong></td>
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</tr>
<tr>
<td>Focalin</td>
<td>2.5, 5, 10 mg</td>
<td>2.5 mg</td>
<td>b.i.d.</td>
<td>20 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td>Methylin(^a)</td>
<td>5, 10, 20 mg</td>
<td>5 mg</td>
<td>b.i.d.</td>
<td>60 mg</td>
<td>&gt;50 kg 100 mg</td>
</tr>
<tr>
<td>Ritalin(^a)</td>
<td>5, 10, 20 mg</td>
<td>5 mg</td>
<td>b.i.d.</td>
<td>60 mg</td>
<td>&gt;50 kg 100 mg</td>
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<tr>
<td><strong>Intermediate-acting</strong></td>
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<tr>
<td>Metadate ER</td>
<td>10, 20 mg</td>
<td>10 mg</td>
<td>q.a.m.</td>
<td>60 mg</td>
<td>&gt;50 kg 100 mg</td>
</tr>
<tr>
<td>Methylin ER</td>
<td>10, 20 mg</td>
<td>10 mg</td>
<td>q.a.m.</td>
<td>60 mg</td>
<td>&gt;50 kg 100 mg</td>
</tr>
<tr>
<td>Ritalin SR(^a)</td>
<td>20 mg</td>
<td>10 mg</td>
<td>q.a.m.</td>
<td>60 mg</td>
<td>&gt;50 kg 100 mg</td>
</tr>
<tr>
<td>Metadate CD</td>
<td>10, 20, 30, 40, 50, 60 mg</td>
<td>20 mg</td>
<td>q.a.m.</td>
<td>60 mg</td>
<td>&gt;50 kg 100 mg</td>
</tr>
<tr>
<td>Ritalin LA</td>
<td>10, 20, 30, 40 mg</td>
<td>20 mg</td>
<td>q.a.m.</td>
<td>60 mg</td>
<td>&gt;50 kg 100 mg</td>
</tr>
<tr>
<td><strong>Long-acting</strong></td>
<td></td>
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</tr>
<tr>
<td>Concerta</td>
<td>18, 27, 36, 54 mg cap</td>
<td>18 mg</td>
<td>q.a.m.</td>
<td>72 mg</td>
<td>108 mg</td>
</tr>
<tr>
<td>Daytrana patch</td>
<td>10, 15, 20, 30 mg patches</td>
<td>Begin with 10 mg patch q.d., then titrate up by patch strength</td>
<td>30 mg</td>
<td>Not yet known</td>
<td></td>
</tr>
<tr>
<td>Focalin XR</td>
<td>5, 10, 15, 20 mg cap</td>
<td>5 mg</td>
<td>q.a.m.</td>
<td>30 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td>Selective norepinephrine reuptake inhibitor</td>
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<tr>
<td>Atomoxetine</td>
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<tr>
<td>Strattera</td>
<td>10, 18, 25, 40, 60, 80, 100 mg cap</td>
<td>Children and adolescents &lt;70 kg: 0.5 mg/kg/day for 4 days; then 1 mg/kg/day for 4 days; then 1.2 mg/kg/day</td>
<td>Lesser of 1.4 mg/kg or 100 mg</td>
<td>Lesser of 1.8 mg/kg or 100 mg</td>
<td></td>
</tr>
</tbody>
</table>

Short-acting stimulants often used as initial treatment in small children (<16 kg) but have disadvantage of b.i.d.-t.i.d. dosing to control symptoms throughout day. Longer acting stimulants offer greater convenience, confidentiality, and compliance with single daily dosing but may have greater problematic effects on evening appetite and sleep.

Metadate CD and Ritalin LA caps may be opened and sprinkled on soft food.

Swallow whole with liquids. Nonabsorbable tablet shell may be seen in stool.

Not a schedule II medication.

Consider if active substance abuse or severe side effects of stimulants (mood lability, tics); give q.a.m. or divided doses b.i.d. (effects on late evening behavior); do not open capsule; monitor closely for suicidal thinking and behavior, clinical worsening, or unusual changes in behavior.

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**Note:** FDA = U.S. Food and Drug Administration; ADHD = attention-deficit/hyperactivity disorder.

\(^a\) Generic formulation available.
Pearls of Prescribing Stimulants

- Transdermal methylphenidate (Daytrana)
  - 20 mg Daytrana = 20 mg TID immediate release MPH
  - FDA approved for ages 6 - 17

- Extended release products are more expensive

- Consider risk of abuse

- Watch for class effects
  - Appetite suppression, nausea
  - Insomnia (65% short term; 30% long term)
    - Melatonin 2 - 6 mg QHS
    - Clonidine 0.05 – 0.1 mg QHS
  - Development of tolerance

Uncommon Side Effects

- Transient motor tics in up to 9% of children treated with stimulants
  - Usually not chronic
  - Intervention: lower dosage or change agents
- Over-focused (“zombie-like”)
  - Intervention: lower dosage
- Hallucinations
  - Intervention: discontinue stimulant therapy
- Mood lability, dysphoria, irritability
  - Intervention: re-evaluate diagnosis
Cardiovascular Effects

• Risk of sudden unexplained death per 100,000 patient <16 years old and exposed to ADHD medications (expressed as hazard ratios)
  – Dextroamphetamine and amphetamines = 0.7
  – Atomoxetine = 1.5
  – Methylphenidate = 0.2

• FDA advisory committee determined rate is NO higher than in the general population
  – 0.6-6 cases per 100,000 non-treated children

• Recommendation for EKG monitoring in children with family cardiac history, symptoms of shortness of breath, dizziness, or chest pain

Nonstimulant Therapy

<table>
<thead>
<tr>
<th>Medications Used for ADHD, Not Approved by FDA</th>
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<tbody>
<tr>
<td><strong>Generic Class/Brand Name</strong></td>
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<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
</tr>
<tr>
<td>Bupropion</td>
</tr>
<tr>
<td>Wellbutrin SR</td>
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<tr>
<td>Wellbutrin XL</td>
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<tr>
<td>Imipramine</td>
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<tr>
<td>Tofranil</td>
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<tr>
<td><strong>Noriatricyline</strong></td>
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<tr>
<td>Pamelo, Aventil</td>
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<tr>
<td><strong>α2-Adrenergic agonists</strong></td>
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<tr>
<td>Clonidine</td>
</tr>
<tr>
<td>Catapres</td>
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<tr>
<td>Guanfacine</td>
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</tbody>
</table>

**Note:** ECG = electrocardiogram.  
* Generic formulation available.
Nonstimulant Therapy

- Atomoxetine (Strattera)
  - Selective norepinephrine reuptake inhibitor
  - Advantages
    - No abuse potential
    - Less insomnia and growth effects than stimulants
  - Disadvantages
    - Delayed onset of therapeutic effects (2 – 4 weeks)
    - Lower efficacy rates when compared to stimulants
    - Adverse reactions: nausea, sedation, tachycardia
  - Dosage based on weight
  - Black box warning for new-onset suicidality

Nonstimulant Therapy

• Buproprion
  – Norepinephrine and dopamine reuptake inhibitor (NE > DA); antidepressant
  – Third line treatment
  – Advantages
    • Supporting trials in children, adolescents, and adults with ADHD
    • No abuse potential
  – Disadvantages
    • Delayed onset of therapeutic effects (2 weeks)
    • Do not use in patients with seizure or eating disorders
    • Adverse reactions: nausea, vomiting, rash

Nonstimulant Therapy

- Clonidine and guanfacine (Intuniv)
  - $\alpha_2$-Adrenergic agonist
  - Guanfacine is more selective for $\alpha_2$ receptor
  - Mechanism and therapeutic effects are not well understood in ADHD
    - Less effective than stimulants, atomoxetine, and bupropion
  - May be used as an adjunct to stimulant therapy to improve aggressive behavior, tics, and insomnia
- Disadvantages
  - Adverse reactions: sedation, dizziness, dry mouth, constipation, hypotension

Adult ADHD

- ADHD does not remit with puberty
- Criteria for diagnosis of children may not be appropriate for adults
  - Adults may have significant impairment despite suffering from less than 6 of the 9 symptoms of inattention or hyperactivity/impulsiveness
  - Biederman and colleagues found that rates of ADHD in adults varied according to number of symptoms and level of impairment for diagnosis
    - 40% of 18 to 20 year old “grown up” ADHD patients met full criteria for ADHD
    - 90% had at least 5 symptoms of ADHD and low Global Assessment of Functioning scores

Adult ADHD

- Effective treatment in randomized controlled trials
  - Immediate release and once daily stimulants
    - Adults frequently need higher doses of these agents
    - Atomoxetine
    - Bupropion
- Adverse effects are similar to ADRs in children
- Monitor blood pressure and heart rate in patients with underlying cardiovascular disease or metabolic disease
Conclusions

• ADHD is a complex diagnosis and requires detailed history and examination for diagnosis
• A combination of multiple therapies (pharmacologic, non-pharmacologic, behavioral, etc.) offers the best opportunity for success
• Medication therapy options for ADHD treatment are numerous and include both stimulants and non-stimulants
• Diagnosis and treatment methods for adult ADHD vary from pediatric ADHD
Attention Deficit/Hyperactivity Disorder:
Medication Therapy Management

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