Psychopharmacology Update: Anxiety, Depression and ADHD

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Disclosures

• "My spouse/partner has no relevant financial relationship with a commercial interest to disclose."
• "I have the following relevant financial relationship with a commercial interest to disclose:"
  – Publication of the book “Almost Depressed”
    By Harvard Health Publications

-Please note this presentation may include discussion of “off label” (Non-FDA approved) uses of medications

Normal Anxiety vs Disorder

• Anxiety disorders must be distinguished from developmentally normal anxiety
• Anxiety disorders:
  – Cluster of symptoms that exist together over time
  – Worries are persistent and excessive
  – Avoidance and distress despite lack of threat
  – Cause impairment in functioning
  – May have family heritability

Anxiety Disorders in Youth

• Roughly 1 in 4 Americans will meet lifetime criteria for an anxiety disorder.
• Anxiety disorders are among the earliest psychiatric conditions to manifest, with a median age at onset of 11 years.
• General population prevalence rates among children younger than 18 years are estimated to be between 5.7% and 12.8%.

Angold A et al., Arch Gen Psychiatry. 2002;59(10):893-901.
Costello EJ et al., Arch Gen Psychiatry. 2003;60(8):837-844.

Common Clinical Characteristics of Anxiety Disorders in Teens

• Frequently accompanied by somatic symptoms (e.g., headaches, bellyaches, sleep difficulties & fatigue)
• Receive/require (unnecessary?) medical examinations and laboratory tests
• Exacerbate physical illnesses
• Chronic with waxing and waning pattern
**Etiology**

- Genetics accounts for one-third of the variance
  - Polymorphism in serotonin transporter gene
- Environment accounts for one-third of the variance
  - Parenting (e.g., parental modeling of anxious behavior, insecure attachment, reinforcement of anxious behavior)
- Neural circuits: Fear and reward circuits include amygdala, orbitofrontal cortex, anterior cingulate (highly interconnected)
- Psychological processes: Fear conditioning (development of fear towards previously unsafe stimulus)
- Temperament: Behavioral inhibition; more likely to interpret neutral stimuli as threatening

**Types of Anxiety Disorders**

- Specific Phobia - common
- Social Phobia
- Separation Anxiety Disorder (SAD) - common
- Obsessive Compulsive Disorder (OCD)
- Generalized Anxiety Disorder (GAD) - common
- Post-Traumatic Stress Disorder (PTSD)
- Selective Mutism

**Overview**

1/3 of children with anxiety disorders meet the criteria for two or more anxiety disorders.

A child with separation anxiety disorder, GAD, or social phobia has a 60% chance of having at least one of the other two, and a 30% chance of having all three.

Presence of an anxiety disorder in childhood increases the risk of developing new anxiety disorder, depression and substance abuse later.

References:


**Practice Parameters**

Recommendation 7: SSRIs should be considered for the treatment of youth with anxiety disorders.

Reasons to use medications: insufficient effect from CBT, moderate to severe anxiety, comorbidity, lack of availability of psychotherapy, case where impairment makes psychotherapy impossible.

**SSRIs**

- Fluoxetine (Prozac)
  - Available in 10mg tablets (brand and generic), 10, 20, 40mg capsules (brand and generic), 90mg weekly capsule, and 20mg/5ml solution (generic only)
- Sertraline (Zoloft)
  - Available in 25, 50, 100mg scored tabs (brand and generic), 20mg/ml solution (brand and generic). Note this is equivalent to 20mg per tsp. Can mix with water, ginger ale, sprite, lemonade, OJ only
- Citalopram (Celexa)
  - Available in 10, 20, 40mg tablets (brand and generic), 10mg/ml solution (brand and generic).
- Escitalopram (Lexapro)
  - Available in 5, 10, 20mg tablets (generic only), and 5mg/3ml solution (generic only)
SSRI Studies

- RCTs show short-term efficacy of SSRI medications in GAD, SAD, social phobia, selective mutism
- Bridge et al, 2007:
  - Meta-analysis of 6 RCT trials; 69% rate of response in SSRI-treated kids, 39% in placebo
  - Efficacy greatest for non-OCD anxiety disorders (OCD: 52% rate of response)
  - NNT 3 (compared to depression NNT of 10 and OCD NNT of 6).

Bridge JA et al JAMA. 2007;297:1683-1696

Use of SSRIs

- Choose SSRI based on side effects, PK profile, history of positive response in family member. SSRI may take 2-6 weeks for effect
- Typically, dose for anxiety is lower than dose for depression. Consider increasing dose if significant improvement not apparent by week 4 of treatment
- Do a pre-drug symptom checklist so SEs not confused with anxiety sx
- Screen for bipolar disorder and assess family history of bipolar disorder
- Monitor for agitation and suicidality
- Consider medication-free trial period (during low stress period) after 1 year if patient asymptomatic

Practice Parameters

Recommendation 8: Medications other than SSRIs may be considered for the treatment of youths with anxiety disorders

Note that other than for OCD, there are no FDA-approved medications for pediatric anxiety disorders

Other Anxiety Meds

- SNRIs
- TCAs
- Benzodiazepines
- Buspirone
- Beta-Blockers
- Gabapentin
- Antihistamines
- Alpha-Adrenergic Agents
- Anticonvulsants – Depakote, Tegretol, Topamax, Neurontin
- Atypical Antipsychotics
- Atomoxetine

SNRIs for Anxiety

Venlafaxine (Effexor):
- Available in 75, 150mg ER capsule, 37.5, 75, 150, 225mg ER tablets, and 25, 37.5, 50, 75, 150 scored IR tablets
- Start at 12.5-37.5mg, increase up to 225mg
- Side Effects: diastolic hypertension (monitor BP), HA, GI, sweating, +/- sleep. Discontinuation. Rare seizures.
- Two of three studies looking at venlafaxine for pediatric anxiety disorders were positive

TCAs for Anxiety

- Clomipramine is FDA-approved for OCD but not for non-OCD anxiety disorders.
- 5 randomized controlled studies looking at TCAs in pediatric non-OCD anxiety disorders: mixed results with some positive and some negative
- Not used frequently due to increased side effects, need for monitoring, dangerousness in overdose
- These, or atomoxetine, have a role if comorbid ADHD
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Benzodiazepines for Anxiety

Lorazepam
- Available in 0.5, 1, 2mg tablets and 0.5mg/5mL, 2mg/mL liquid
- Start at 0.25-0.5mg HS, titrate as necessary to 4mg, dose HS-TID
- Can mix liquid with water, soda, applesauce, pudding

Clonazepam
- Available in 0.5mg scored tablets; 1, 2mg tablets; 0.125, 0.25, 0.5, 1, 2mg disintegrating wafers
- Start at 0.125-0.25mg HS, titrate as necessary up to 3mg, dose HS-BID

Side Effects: disinhibition (worse in younger kids), rebound insomnia, ataxia, cognitive effects. Use short-term. Must taper to avoid withdrawal seizures. Don't use in adolescents with substance abuse probs. Efficacy: no RCTs for pediatric anxiety disorders; three negative studies.

Buspirone for Anxiety

Buspirone (Buspar):
- Available in 5, 10mg scored tablets, 15, 30mg multiscored tablets
- Start at 2.5-5mg BID x week, increase by 2.5-5mg q 3-7 days to max of 40mg (modification for adolescents: start at 5-10mg, increase by 5-10mg up to max of 60mg).
- Side Effects: HA, nausea, dizziness, lightheadedness, somnolence
- Efficacy: no pediatric RCTs; open-label studies have demonstrated efficacy in kids. Approved for anxiety in adults.

Beta Blockers for Anxiety

Propranolol (Inderal):
- Nonselective beta-blocker (B1 & B2)
- Available as 10, 20, 40, 60, 80mg tablets
- Start 10mg daily to BID, can increase by 10mg q 3 days to 2.5 mg/kg/day given BID-QID
- Side Effects: bradycardia, hypotension, rebound hypertension, bronchospiration, sedation, dizziness, sleep disruption, potential neuroendocrine effects (e.g., glucose, growth hormone). May worsen depression.
- Warning: Do not use with clonidine
- Monitoring: blood pressure

Gabapentin for Anxiety

Gabapentin (Neurontin):
- Available in 100, 300, 400mg capsule (generic and brand), 600, 800mg scored tablet (generic only), and 250mg/5mL liquid (brand only)
- Start at 100-300mg daily; increase by 100-300mg q 3-5 days; generally therapeutic at 900-1800mg/day; can go as high as 2400+
- Side Effects: sedation, dizziness, ataxia, nystagmus. Disinhibition in young kids has been reported.
- Efficacy: no RCTs, open-label showed efficacy

Antihistamines for Anxiety

Diphenhydramine (Benadryl)
- Available in 25, 50mg tablets and capsules, 12.5mg/5mL liquid, 2mg strip
- Start at 12.5-25mg at bedtime
- increase by 12.5-25mg every 3 days as needed
- usual dose range 25-75mg (NTE 300mg/day or 5mg/kg/day whichever is less)

Side Effects: sedation, daytime drowsiness, cognitive and psychomotor slowing, dizziness, anticholinergic effects, paradoxical excitation

Lifetime Prevalence of Depression in Adolescents

- National Comorbidity Survey–Adolescent Supplement
- Face-to-face study of 10,123 US adolescents, ages 13 to 18 years
- Modified version of World Health Organization Composite International Diagnostic Interview

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age</th>
<th>Total</th>
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<tr>
<td></td>
<td>Female %</td>
<td>Male %</td>
<td>13-14</td>
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<tr>
<td>MDD or Dysthymia</td>
<td>15.9</td>
<td>7.7</td>
<td>8.4</td>
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</table>

**Etiology**

- **Genetics**
  - 50% of the variance in the transmission of mood disorders is genetic
  - Evidence for MAOA gene and serotonin transporter gene

- **Biologic**
  - MRI scans show low frontal lobe volume and high ventricular volume

- **Environment**
  - Having one depressed parent doubles the risk for child (both parents depressed quadruples the risk)
  - Family conflict or divorce, abuse or neglect, more rejection and less expression of affect, less support, communication problems, family SES, recent stressor or loss

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**Clinical Presentation of Depressive Disorders in Youth**

- **Irritable mood and dysphoria (vs. sadness in adult depression)**
- **Inability to enjoy favorite activities ("bored")**
- **Social withdrawal**
- **Blame/worthlessness/guilt**
- **Suicidal preoccupation**
- **“Mood reactive” similar to atypical adult depression**
- **Abnormal sleep patterns** (i.e., nightmares)
- **Fatigue**
- **Diminished ability to concentrate**

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**Negative Cognitive Style**

- **Low self-esteem**
- **High self-criticism**
- **Cognitive distortions**
- **Negative attributions**

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**Sequelae**

- Increased risks for later adolescence and adulthood:
  - Suicidal behavior
  - Aggression
  - Tobacco use
  - Alcohol and drug use
  - Impaired interpersonal relationships
  - School problems
  - Increased physical problems
  - Early pregnancy
  - Impairment in global functioning

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**Comorbidity**

- 40% to 70% have comorbid disorders
- Most common comorbid disorders are:
  - Dysthymic Disorder
  - Anxiety Disorders
  - Disruptive Disorders
  - Substance Abuse

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**Selective serotonin reuptake inhibitors (SSRIs) include**

- citalopram (Celexa), escitalopram (Lexapro),
- fluoxetine (Prozac),
- fluvoxamine (Luvox), fluvoxamine CR (Luvox CR),
- paroxetine (Paxil), paroxetine CR (Paxil CR),
- sertraline (Zoloft).

*SSRIs help to alleviate symptoms of Depression & Anxiety by blocking the reabsorption or reuptake of serotonin in the brain.*
## Serotonin norepinephrine reuptake inhibitors (SNRIs)

- venlafaxine (Effexor), venlafaxine XR (Effexor XR),
- desvenlafaxine (Pristiq),
- duloxetine (Cymbalta),
- milnacipran (Savella),
- levomilnacipran (Fetzima).

*(SNRIs) work by blocking the reabsorption of the neurotransmitters serotonin and norepinephrine in the brain*

## Side effects most common to SSRIs & SNRIs include …

- Nausea, dizziness, and sweating.
- Sexual dysfunction.
- Tiredness, constipation, insomnia, anxiety, headache, dry mouth and loss of appetite.

## Serious Side effects of SSRIs & SNRIs include …

- Bleeding
- ‘Suicidality’
- Activation
- Serotonin Syndrome
  - Symptoms of serotonin syndrome may include anxiety, restlessness, sweating, muscle spasms, shaking, fever, rapid heartbeat, vomiting, and diarrhea.

## Atypical antidepressants

- bupropion (Wellbutrin), mirtazapine (Remeron), nefazodone (Serzone), trazodone (Desyrel, Oleptro), vilazodone (Viibryd), and vortioxetine (Brintellix).
- Each has a unique mechanism of action

## Important to recognize that

- Mirtazapine and trazodone cause drowsiness and are usually taken at bedtime.
- Bupropion generally does not cause weight gain or sexual problems. Bupropion may also be used to help quit smoking.
- Viibryd is not associated with significant weight gain or sexual dysfunction.

## DRUG-GENE TESTING

- AKA pharmacogenomics or pharmacogenetics.
- A small blood or saliva sample can help determine:
  - How well certain medications may be tolerated and effective
  - Best dose range
Current limitations of pharmacogenomics testing

• cannot be used to determine how you will respond to all medications.
• No tests for aspirin and many over-the-counter pain relievers.
• In my hands better for guiding what not to take rather than what is/may be most effective.

ADHD in the United States

Prevalence of ADHD among 8- to 15-year-olds: 8.7%
Prevalence of ADHD among 18- to 44-year-olds: 4.4%

Only 1 in 10 adults with ADHD surveyed in the National Comorbidity Survey Replication had received treatment during the prior 12 months.

*According to results from the National Comorbidity Survey Replication, N = 3199 respondents ages 18 to 44 years.

Available Guidelines & Reviews


Helpful Recent Reviews


The ABC's of ADHD

Signs and Symptoms of ADHD Across the Lifespan
ADHD Core Symptom Areas

- Hyperactivity Impulsivity
- Inattention

Age

Childhood  Adolescence  Adulthood

ADHD Variation in Symptoms

- Pervasiveness
- Frequency of Occurrence
- Degree of Impairment

The Persistence of ADHD in the U.S.

- 75% persist into adolescence
- 50% persist into adulthood

Prevalence ages 8 to 11: 10%
Prevalence ages 12 to 15: 7.5%
Prevalence in adults: 3% to 5%

The ABC’s of ADHD

Assessment and Diagnosis of ADHD in Children & Adolescents

Rating Scales of Children and Adolescents with ADHD

- Academic Performance Rating Scale
- ADHD Rating Scale (Parent and Teacher versions)
- Barkley Home and School Situations Questionnaires
- Brown ADD Rating Scales for Child, Adolescents and Adults
- Child Behavior Checklist (CBCL) Parent, Teacher and Self (if >13 years old) Report Forms
- Connors Parent, Teacher Rating Scales-Revised (CPRS-R, CTRS-R)
- Connors Wells Adolescent Self-Report Scale
- Inattention/Overactivity With Aggression (IOWA) Connors Teacher Rating Scale
- SNAP-IV (Parent and Teacher versions)
- Vanderbilt ADHD Rating Scale (Parent and Teacher versions)

www.schoolpsychiatry.org or http://www.help4adhd.org/en/treatment/scales

Assessment of ADHD

- Life history with information from parents (and teachers or school records if available) for children and adolescents
- Self report for adults
- Mental status exam
- Rating scales—measuring core and broad features
- Medical history review; cardiac and neurologic status, blood pressure/pulse, growth.
- Additional assessment, if indicated
  - Psychological/neuropsychological battery
  - Lab tests (eg, toxicology screen, thyroid function)

Pliszka et al., JACAP 2007;46(7):894-921.

Treatment of ADHD

Recommendation 6

- A well-thought-out and comprehensive treatment plan should be developed for the patient with ADHD [MS].
- Such a treatment plan may include:
  - Education about ADHD.
  - Medication for ADHD and comorbid disorders.
  - Psychosocial treatments.


Organize Targets for Intervention

- Inattentive/Disorganized & Impulsive/Hyperactive Behaviors
- Academic Specific Skills
- Daily Life Functioning
- Emotional Dysregulation
- Distress Intolerance
- Social Relationships

Prioritize Targets and Structure Interventions

Principles of Clinical Intervention

- Educate, educate, educate
- Understand patient’s & family’s explanatory models (frameworks) and seek to find common ground
- Respectfully challenge misconceptions and unrealistic expectations – emphasize a Socratic approach
- Encourage patients and families to focus on positive coping strategies rather than just reducing symptoms
- If parents have ADHD, encourage them to get help for themselves
- Emphasize collaborative teamwork among family members, educators and professional helpers

Resources for Patient Education

- American Academy of Child and Adolescent Psychiatry www.aacap.org
- American Academy of Pediatrics www.aap.org
- CHADD, Children and Adults with Attention Deficit/Hyperactivity Disorder (information, local support groups and online communities) www.chadd.org
- Attention Deficit Disorder Association, an organization for adults with ADHD www.add.org
- ADHD Coaches Organization www.adhdcoaches.org
- ADD Warehouse, a source for books and tools www.addwarehouse.com
- National Resource Center on ADHD, a Program of CHADD, for scientific and medical information www.help4adhd.org
- LDOnline, for information about learning disorders and ADHD www.ldonline.org
- School Psychiatry www.schoolpsychiatry.org

Recommendation 7

- The initial psychopharmacologic treatment of ADHD should be a trial with an agent approved by the Food and Drug Administration for the treatment of ADHD [MS].

Methylphenidate

- Low bioavailability (~20-25%)
  - (+)-MPH isomer much greater bioavailability than the (-)-MPH isomer
- Typical therapeutic doses provide
  - Tmax = 1.5 – 2.5 h
  - Cmax = 6 – 15 ng/mL
  - T1/2 = 2 – 3.5 h
- Primarily de-esterified; extrahepatic metabolism (plasma based)
- Prominent metabolism (L-MPH) in intestinal wall
- Stereo-isomeric metabolism (L>D)
- Linear pharmacokinetics at moderate doses
- No pharmacokinetic drug interactions

Amphetamine

- High bioavailability (~75%)
- Typical therapeutic doses of dextroamphetamine provide
  - Tmax = 2 – 3 h
  - Cmax = 40 – 70 ng/mL
  - T1/2 = 7 h
- Redundant hepatic metabolism
- Linear pharmacokinetics
- No pharmacokinetic drug interactions


Conceptualization of Synapse With Dopaminergic Neuron


FDA Approved Medications for ADHD

<table>
<thead>
<tr>
<th>Medication</th>
<th>Usual Starting Dose</th>
<th>FDA Approved Daily Dose</th>
<th>Off-LABEL Max per Day*</th>
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</thead>
<tbody>
<tr>
<td>Methylphenidate Preparations</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting</td>
<td>5 mg bid</td>
<td>20 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td>Intermediate-acting</td>
<td>10 mg bid</td>
<td>30 mg</td>
<td>75 mg</td>
</tr>
<tr>
<td>Long-acting</td>
<td>20 mg bid</td>
<td>60 mg</td>
<td>150 mg</td>
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<tr>
<td>Atomoxetine</td>
<td>0.5 mg/kg/day</td>
<td>1 mg/kg/day</td>
<td>1.4 mg/kg/day</td>
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<tr>
<td>Guanfacine</td>
<td>1 mg</td>
<td>4 mg</td>
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</tr>
<tr>
<td>Clonidine</td>
<td>0.1 mg</td>
<td>0.4 mg</td>
<td>Not yet known</td>
</tr>
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</table>

*recommended max daily dose.

Approved Ages of Medications for ADHD

<table>
<thead>
<tr>
<th>Medication</th>
<th>&gt; 3 years</th>
<th>&gt; 5 years</th>
<th>Adolescents</th>
<th>Adults</th>
</tr>
</thead>
</table>

- Short-acting
- Intermediate-acting
- Long-acting

AMPH Vesicular release
Reverse transport


Amphetamine Preparations

Short-acting
- D-amphetamine or MAS

Long-acting
- MAS XR
- LDX
- Dexedrine Spansule

Conceptualization of Synapse With Dopaminergic Neuron (cont’ d.)

Amphetamine

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**Treatment of ADHD with Medications**

- How to measure response?
  - Rating Scales or Anchor Points (functioning)
- How to ensure safe storage?
- Sources of Information?
  - Patient or Patient Plus
- Dosing to cover schedule from AM thru PM
  - Combining Immediate Release and Extended Delivery Stimulants
  - Regular Schedule vs. “as needed”
  - Adapting Dosing to Various Contexts

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**Stimulants – Additional Considerations**

- Dietary caffeine: recommend decrease in consumption to avoid over-stimulation
- Nicotine: similar caution
- Alcohol: toxic interactions not usually seen at mild/moderate doses, but normal response to alcohol may be altered
- Decongestants (e.g., pseudoephedrine): should reduce dosage or stop stimulant for duration of use
- Diet: should be adjusted to avoid significant weight loss [i.e., not good diet medications!]
- Sleep is Necessary

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**Controversies with FDA-Approved Treatments for ADHD**

- Adverse cardiovascular outcomes
- Psychiatric side effects
- Growth suppression
- Development of tics
- Substance abuse

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**Role of Complimentary Treatments**

All Off Label Use: Non-FDA Approved

- Omega-3 Fatty Acids (10 trials, 699 subjects, mild)\(^1\)
- Zinc Glycinate 15 mg QD or BID (equivocal)\(^2\)
- Serum Ferritin (α/min on SNAP; 23%< 7ng/mL)\(^3\)
- Physical Activity (pilot program)\(^4\)
- Sleep Disturbances greatest in ADHD + Anxiety\(^5\)
- Diet (comprehensive overview)\(^6\)

\(^1\) Bloch & Qawasami (2011) JAACAP 50(10): 991-1000
\(^3\) Calarge C et al., J Child Adolesc Psychoph. 2010 20(6):495-502
\(^4\) Verrett C et al., J Atten Disord. 2012 Jan;16(1):71-80
\(^6\) Millichap JC, Yee MM. Pediatrics. 2012 129(2):330-7

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**Recommendation 5**

- The clinician must evaluate the patient with ADHD for the presence of comorbid psychiatric disorders [MS].

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**Comorbidit**: **A Diagnostic Consideration**

**Lifetime Prevalence of Comorbid Conditions in Pediatric Population With ADHD**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Boys (N = 140)</th>
<th>Girls (N = 140)</th>
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<tbody>
<tr>
<td>ODD</td>
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<td>11</td>
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<tr>
<td>Enuresis</td>
<td>25</td>
<td>29</td>
</tr>
<tr>
<td>Major Depression</td>
<td>18</td>
<td>16</td>
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<tr>
<td>ODD + Anxiety</td>
<td>11</td>
<td>13</td>
</tr>
<tr>
<td>Conduct Disorder</td>
<td>12</td>
<td>13</td>
</tr>
<tr>
<td>Bipolar Disorder</td>
<td>15</td>
<td>12</td>
</tr>
</tbody>
</table>

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Misuse of ADHD Prescription

- 45% reported misusing medication for ADHD; M=F
- Alternative route of administration (27.9%)
- Higher dose than prescribed (62.8%)
- Mixing with drugs/alcohol to feel intoxicated (23.3%)
- Giving away and/or selling their medication (48.8%)
- Prescription for Amphetamine (69%) or MPH (31%)
- Prescribed
  - extended release capsules (68%)
  - immediate release tablets (32%)
  

Effectiveness in Daily Life

- Sleep
- Nutrition
- Physical Activity
- Medication Adherence
- Addictive Behaviors
- Social Relationships
- External Supports

Cultivating Healthy Functioning in Students with ADHD

- Sleep
  - DFA, Restless sleep, Periodic leg mvts, sleep-disordered breathing; SE of Stimulants; SUD
  - Sleep Hygiene; CBT-Insomnia; Melatonin;

- Physical Activity
  - Regular vigorous activity improves EF, with or without Stimulants.

Medina, JA et al. (2010) Attention Deficit and Hyperactivity Disorders, 2, 49-58

Recommendation 12

- Patients should be assessed periodically to determine whether there is continued need for treatment or if symptoms have remitted.
- Treatment of ADHD should continue as long as symptoms remain present and cause impairment [MS].

Looking at the Landscape

The ABC’s of ADHD

“If you hold a cat by the tail you learn things you cannot learn any other way.”

-Mark Twain