ADHD and Treatment Considerations

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Medical Director, Animo Sano Psychiatry

Content

• What is ADHD
• Epidemiology of ADHD
• Guidelines on ADHD
• ADHD Treatments
  • Stimulant Treatments
  • Non-Stimulant Treatments
Disclaimer

• Advisory work:
  • Holmusk

What is the DSM-5 criteria for ADHD?
DSM-5 Criteria

- 6 or more symptoms for children or 5 or more in those ≥17 years of age
- Prior to age 12*
- Present in 2 or more settings
- Symptoms interfere with or reduce quality of social, academic, or occupational function.
- Not better explained by an alternate disorder

APA, 2013. DSM-5

Inattention

Often fails to give close attention to details or makes careless mistakes in school work
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 school work
Often has difficulty organizing tasks and activities
Often avoids, dislikes, or reluctantly engages in tasks requiring sustained mental effort
Often loses things necessary for activities (e.g. school assignments, pencils, or books)
Often is distracted by extraneous stimuli
Often is forgetful in daily activities

APA, 2013. DSM-5
CADDRA, 2018. Canadian ADHD Practice Guidelines
Inattention

- Organizing
- Initiating
- Staying on Task
  - Distractibility
  - Sustained attention
  - Attention to detail
- Completing Tasks

- Forgetful
- Lose items
- Difficulty listening

Hyperactivity/Impulsivity

Often fidgets with hands or feet or squirms in seat
Often leaves seat in classroom when remaining seated is expected
Often runs about or climbs excessively in situations where it is inappropriate
Often has difficulty playing or engaging in leisure activities quietly
Often is "on the go" or often acts as if "driven by a motor"
Often talks excessively
Often blurs out answers to questions before the questions have been completed
Often has difficulty awaiting turn
Often interrupts or intrudes on others (e.g., butts into conversations/games)

Runs, climbs or restless
Uninhibited in conversation
Not able to play quietly
Fidgets or squirms in seat
Interrupts or intrudes on others
Difficulty waiting his or her turn
Get going or acting as if driven by a motor
Evacuates seat unexpectedly
Talks excessively

APA, 2013. DSM-5
CADDRA, 2018. Canadian ADHD Practice Guidelines
Kadiyala, 2020. General Psychiatry
Specifiers

- Combined
- Predominantly inattentive
- Predominately hyperactive/impulsive
- In partial remission

Severity:
- Mild
- Moderate
- Severe

APA, 2013. DSM-5

Prior to Age 12

- A subset of adults do not recall symptomatology prior to age 12
  - Could be great early life support
  - High IQ to allow compensation
  - Good structure/routine
  - Adult onset
CADDRA

Red Flags for ADHD
[3, 42-44]

- Organizational skill problems (time management difficulties, missed appointments, frequent late and unfinished projects).
- Erratic work/academic performance.
- Anger control problems.
- Family/marital problems.
- Difficulty in maintaining organized household routines, sleeping patterns and other self-regulating activities.
- Difficulty managing finances.
- Addictions such as substance use, compulsive shopping, sexual addiction, overeating, compulsive exercise, video gaming or gambling.
- Frequent accidents either through recklessness or inattention.
- Problems with driving (speeding tickets, serious accidents, license revoked).
- Having a direct relative who has ADHD.
- Having to reduce their course load, or having difficulty completing assignments in school.
- Low self-esteem or chronic under-achievement.

CADDRA, 2018. Canadian ADHD Practice Guidelines

How do you diagnose ADHD?
What Do the Guidelines Say?

Seixas et al. 2012 *Journal of Psychopharmacology*

<table>
<thead>
<tr>
<th>Table 5. Rating of methodological quality (AGREE scores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scope and purpose (maximum score 12)</td>
</tr>
<tr>
<td>Stakeholder involvement (maximum score 16)</td>
</tr>
<tr>
<td>Rigour of development (maximum score 28)</td>
</tr>
<tr>
<td>Clarity and presentation (maximum score 16)</td>
</tr>
<tr>
<td>Applicability (maximum score 12)</td>
</tr>
<tr>
<td>Editorial independence (maximum score 8)</td>
</tr>
<tr>
<td>Total score (maximum score 92)</td>
</tr>
</tbody>
</table>

Guidelines for the Diagnosis/Treatment

Seixas et al. 2012 *Journal of Psychopharmacology*
How to Diagnose ADHD

- Gold standard: The clinical interview (review of guideline recommendation)
  - Clinical assessment, mental status exam, assessment of impairment, development, comorbidity and family history, physical exam
  - “the use of rating scales has standardized and improved the reliability, breadth and efficiency of assessments”
  - Collateral in children (parent/teacher rating scale)
  - In adults collateral from someone who lives with them

What Do the Guidelines Say?

Seixas et al. 2012 Journal of Psychopharmacology
Neuropsychiatric Testing

• Discriminative validity of neuropsychiatric tests in diagnosis ADHD in adults

<table>
<thead>
<tr>
<th></th>
<th>ASRS Screener</th>
<th>QBTTest Ace</th>
<th>QBTTest Ins</th>
<th>QBTTest One</th>
<th>QBTTest RT Var</th>
<th>PASAT Test</th>
<th>CPT I Com</th>
<th>CPT II Var</th>
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</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>91.7</td>
<td>90.0</td>
<td>76.7</td>
<td>58.3</td>
<td>73.3</td>
<td>43.3</td>
<td>33.3</td>
<td>33.3</td>
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<tr>
<td>Specificity</td>
<td>27.1</td>
<td>72.9</td>
<td>43.8</td>
<td>66.7</td>
<td>56.3</td>
<td>75.0</td>
<td>77.1</td>
<td>91.7</td>
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<tr>
<td>False positives</td>
<td>38.9</td>
<td>19.4</td>
<td>37.0</td>
<td>31.4</td>
<td>32.3</td>
<td>31.6</td>
<td>35.5</td>
<td>16.7</td>
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<tr>
<td>False negatives</td>
<td>27.8</td>
<td>14.6</td>
<td>40.0</td>
<td>43.9</td>
<td>37.2</td>
<td>48.6</td>
<td>51.9</td>
<td>47.6</td>
</tr>
<tr>
<td>PPV</td>
<td>61.1</td>
<td>80.6</td>
<td>63.0</td>
<td>68.6</td>
<td>67.7</td>
<td>68.4</td>
<td>64.5</td>
<td>83.3</td>
</tr>
<tr>
<td>NPV</td>
<td>72.2</td>
<td>85.4</td>
<td>60.0</td>
<td>56.1</td>
<td>62.8</td>
<td>51.4</td>
<td>48.1</td>
<td>52.4</td>
</tr>
<tr>
<td>Total classification accuracy</td>
<td>63.0</td>
<td>82.4</td>
<td>62.0</td>
<td>62.0</td>
<td>65.7</td>
<td>57.4</td>
<td>52.8</td>
<td>59.3</td>
</tr>
<tr>
<td>AUC</td>
<td>0.739</td>
<td>0.828</td>
<td>0.664</td>
<td>0.673</td>
<td>0.725</td>
<td>0.674</td>
<td>0.663</td>
<td>0.741</td>
</tr>
</tbody>
</table>

Patterson et al. 2018, Journal of Attention Disorders

NICE Guidelines

• “rating scales such as the Conners' rating scales and the Strengths and Difficulties Questionnaire are valuable adjuncts, and observations (for example, at school) are useful when there is doubt about symptoms”
What do you know about the heritability of ADHD?

**Biological Considerations**

Faraone and Larsson, 2019, *Molecular Psychiatry*
Biological Consideration

Generally Accepted to be 77-88% heritable

Comparison of Common SNP’s

What are your thoughts about stimulant prescribing rates?

Epidemiology

Estimated number of US children who ever had a diagnosis of ADHD

- 2003: 4.4 (Millions)
- 2007: 5.4 (Millions)
- 2011: 6.4 (Millions)
- 2016: 6.1 (9.4%) (Millions)

[cdc.gov/ncbddd/adhd/data.htm (accessed:11.16.20)]
NC Epidemiology

- In 2011 NC: 12.8%
- Treatment in NC: 9.4%

Epidemiology: Adults

- 4.4%
- 2:1 ratio m:f
- Despite females receiving more mental health care fewer received care specifically for ADHD
- Only 10.9% of respondents with adult ADHD received treatment for ADHD in the 12 months before interview (12.1% of females vs. 10.1% of males, \( z = 0.4, p = .657 \)).

Kessler et al. 2006, *American Journal of Psychiatry*
Table 1: Incidence of comorbidities with ADHD in children

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Incidence</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>18%</td>
<td>Larson et al(^{11})</td>
</tr>
<tr>
<td></td>
<td>25%–35%</td>
<td>Geller et al(^{12})</td>
</tr>
<tr>
<td></td>
<td>25%–50%</td>
<td>Sicam et al(^{13})</td>
</tr>
<tr>
<td></td>
<td>27%</td>
<td>Bakken et al(^{14})</td>
</tr>
<tr>
<td>Binge eating</td>
<td>13%</td>
<td>Rainblatt et al(^{15})</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>0%–20%</td>
<td>Taurines et al(^{16})</td>
</tr>
<tr>
<td></td>
<td>7%–22%</td>
<td>Singh et al(^{17})</td>
</tr>
<tr>
<td></td>
<td>5%</td>
<td>Bakken et al(^{14})</td>
</tr>
<tr>
<td>Conduct disorder/ODD</td>
<td>30%–50%</td>
<td>Deppehde and Pilsbury(^{7})</td>
</tr>
<tr>
<td></td>
<td>40%–60%</td>
<td>Biederman et al(^{18})</td>
</tr>
<tr>
<td></td>
<td>24%</td>
<td>Bakken et al(^{14})</td>
</tr>
<tr>
<td>Depression</td>
<td>21%</td>
<td>Bakken et al(^{14})</td>
</tr>
<tr>
<td></td>
<td>16%–26%</td>
<td>Glibberg et al(^{19})</td>
</tr>
<tr>
<td>Learning and language</td>
<td>23%</td>
<td>Bakken et al(^{14})</td>
</tr>
<tr>
<td>disorders</td>
<td>46%</td>
<td>Larson et al(^{20})</td>
</tr>
<tr>
<td>Obsessive compulsive disorder</td>
<td>2%</td>
<td>Jensen and Steinhausen(^{9})</td>
</tr>
<tr>
<td>Pervasive developmental</td>
<td>12%</td>
<td>Jensen and Steinhausen(^{9})</td>
</tr>
<tr>
<td>disorders/ASD</td>
<td>30%–50%</td>
<td>Reichow et al(^{20})</td>
</tr>
<tr>
<td>Substance abuse disorders</td>
<td>22%</td>
<td>Kolins(^{11})</td>
</tr>
<tr>
<td>Tic disorders/Tourette's</td>
<td>7%</td>
<td>Bakken et al(^{14})</td>
</tr>
<tr>
<td>syndrome</td>
<td>20%–30%</td>
<td>Taurines et al(^{16})</td>
</tr>
</tbody>
</table>

Note: No data were found in the literature for ADHD and antisocial personality disorder in children (<18 years of age).

Abbreviation: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; ODD, oppositional defiant disorder.

Percentage of children with ADHD and another disorder

- Any mental, emotional, or behavioral disorder: 64%
- Behavior or conduct problem: 52%
- Anxiety: 33%
- Depression: 17%
- Autism spectrum disorder: 14%
- Tourette syndrome: 1%

cdc.gov/ncbddd/adhd/data.htm (accessed: 11.16.20)
Co-morbidities

<table>
<thead>
<tr>
<th>Condition</th>
<th>Adults with ADHD (n = 89)</th>
<th>Adults without ADHD (n = 94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>54 (60.7)</td>
<td>18 (19.1)</td>
</tr>
<tr>
<td>Insomnia or other sleep disorders</td>
<td>41 (46.1)</td>
<td>7 (7.4)</td>
</tr>
<tr>
<td>Anxiety disorder(s)</td>
<td>36 (40.4)</td>
<td>5 (5.3)</td>
</tr>
<tr>
<td>Personality disorder</td>
<td>27 (30.3)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>20 (22.5)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Alcohol or drug abuse or dependence</td>
<td>19 (21.3)</td>
<td>6 (6.4)</td>
</tr>
<tr>
<td>Oppositional defiant disorder</td>
<td>15 (16.9)</td>
<td>0</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>15 (16.9)</td>
<td>0</td>
</tr>
<tr>
<td>Decline to answer</td>
<td>0</td>
<td>4 (4.3)</td>
</tr>
<tr>
<td>None of these</td>
<td>0</td>
<td>65 (69.1)</td>
</tr>
</tbody>
</table>

Note: ADHD, attention-deficit/hyperactivity disorder.

Pitts et al. 2014, Archives of Psychiatric Nursing

Gender Differences in Co-morbidity

Education and Social/Psychiatric Well Being

Harpin, 2005. Archives of Disease in Childhood

Driving

Harpin, 2005. Archives of Disease in Childhood
Social Life

Pitts et al. 2014, Archives of Psychiatric Nursing

Romantic Relationships

Pitts et al. 2014, Archives of Psychiatric Nursing
Work Function

Pitts et al. 2014, Archives of Psychiatric Nursing

Financial Life

Pitts et al. 2014, Archives of Psychiatric Nursing
What is the first line treatment for ADHD in children? Adults?
Treatment

- Psychosocial intervention
  - Parent training
  - Therapy
  - School intervention
  - Workplace intervention
- Focus on psychopharmacology
Stimulant Therapy First Line

• Unanimous agreement about stimulant therapy.

Seixas et al. 2012 *Journal of Psychopharmacology*

Stimulant Therapy First Line

• Mixed amphetamines not suggested by 4 groups.

Seixas et al. 2012 *Journal of Psychopharmacology*
What do you know about stimulant medication?

Pharmacologic Treatments

- Stimulants:
  - Methylphenidate
  - Amphetamine Salts
- Non-stimulant:
  - Atomoxetine
  - Alpha-agonists
  - Bupropion
  - Modafinil
  - Venlafaxine
  - Desipramine/Nortriptyline
Stimulants

- 87% response rate to one agent or the other.

![Venn diagram illustrating response rates to stimulants.](Arnold, 2000. *Journal of Attention Disorders*

Comparative Effect Sizes

- By comparison bzd has 0.38 +/- 0.15 effect size GAD

![Graphs showing comparative effect sizes.](Bitter et al. 2012, *Current Opinion in Psychiatry* (Figure to right)
Meszaros et al. 2009, *International Journal of Neuropharmacology* (Figure to left)
Hidalgo et al. 2007, *Journal of Psychopharmacology*
A  Mean change in ADHD symptoms—-rated by clinicians

<table>
<thead>
<tr>
<th></th>
<th>Children and adolescents</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>-0.02 (-0.15 to -0.01)</td>
<td>-0.29 (-0.49 to -0.09)</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>-0.05 (-0.12 to -0.02)</td>
<td>-0.19 (-0.28 to -0.11)</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>-0.03 (-0.14 to -0.01)</td>
<td>-0.04 (-0.14 to 0.06)</td>
</tr>
<tr>
<td>Clonidine</td>
<td>-0.01 (-0.06 to -0.04)</td>
<td>-0.04 (-0.05 to -0.03)</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>-0.05 (-0.07 to -0.03)</td>
<td>-0.05 (-0.06 to -0.04)</td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>-0.04 (-0.05 to -0.03)</td>
<td>-0.04 (-0.05 to -0.03)</td>
</tr>
<tr>
<td>Modafinil</td>
<td>-0.02 (-0.05 to -0.01)</td>
<td>-0.04 (-0.05 to -0.03)</td>
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</table>

B  Mean change in ADHD symptoms—rated by teachers

<table>
<thead>
<tr>
<th></th>
<th>Children and adolescents</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>-0.02 (-0.12 to 0.08)</td>
<td></td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>-0.05 (-0.21 to 0.11)</td>
<td></td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>-0.03 (-0.11 to 0.05)</td>
<td></td>
</tr>
<tr>
<td>Clonidine</td>
<td>-0.01 (-0.04 to 0.03)</td>
<td></td>
</tr>
<tr>
<td>Guanfacine</td>
<td>-0.05 (-0.14 to 0.04)</td>
<td></td>
</tr>
<tr>
<td>Methylphenidate</td>
<td>-0.04 (-0.05 to 0.01)</td>
<td></td>
</tr>
<tr>
<td>Modafinil</td>
<td>-0.02 (-0.04 to 0.00)</td>
<td></td>
</tr>
</tbody>
</table>

C  Dropouts due to adverse events

<table>
<thead>
<tr>
<th></th>
<th>Children and adolescents</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamines</td>
<td>2.36 (1.36 to 3.89)</td>
<td>3.26 (1.54 to 6.97)</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>1.48 (0.64 to 3.26)</td>
<td>2.33 (0.28 to 4.25)</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>1.13 (0.42 to 3.27)</td>
<td>2.55 (0.13 to 2.99)</td>
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<tr>
<td>Clonidine</td>
<td>4.82 (0.79 to 27.03)</td>
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</tr>
<tr>
<td>Guanfacine</td>
<td>2.24 (1.20 to 4.18)</td>
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<tr>
<td>Methylphenidate</td>
<td>1.44 (0.95 to 2.13)</td>
<td></td>
</tr>
<tr>
<td>Modafinil</td>
<td>1.34 (0.52 to 3.38)</td>
<td></td>
</tr>
</tbody>
</table>

Cortese et al. 2018, *The Lancet Psychiatry*
Response

- **Bold is significant**
- **Negative favors row**

Cortese et al. 2018, *The Lancet Psychiatry*
Tolerability

Cortese et al. 2018, The Lancet Psychiatry

Cortese et al. 2018, The Lancet Psychiatry
Moral of the Story

- Stimulants are first line agents
- Guidelines vary:
  - Children use methylphenidate as first option
  - Adults use amphetamine salt as first option
  - Generally preferable to try long acting agent first
  - Failure: try alternate stimulant class of medication

Stimulants

Hodgkins et al. 2012, European Child and Adolescent Psychiatry
Note to residents.

- I had hoped to take you through the up to date table entitled “Drugs for adult ADHD” at this point. Table can be found in article titled “Treatment of Attention Deficit Hyperactivity Disorder in Adults”

Methylphenidate

- Dexamethasone
  - Short and long acting formulations
  - Oral (tablet and capsule only)
- Methylphenidate (short and long acting formulations)
  - Oral (tablet, chewable, capsule, suspension, and patch)
Methylphenidate

- Usually comes in combination dl-methylphenidate
- Recognized that l-methylphenidate is an inactive isomer
- Animal models demonstrate attenuation of d-mph motor response in rats when l-mph supplied.
- Still l-mph attenuation on d-mph in humans not demonstrated.
- Metabolized by carboxylesterase 1.

Amphetamine Salts

- Dextroamphetamine
  - Short and long acting.
  - Tablet and capsule
- Dextroamphetamine and amphetamine (mixed salts)
  - Short and long acting
  - Tablet, ODT, and capsule
- Lisdexamfetamine
Amphetamine Salts

- Usually comes in combination dl-amphetamine
- Both are active, though, l isomer less potent
- Metabolized through oxidative deamination (FMO3) to an inactive product.

Patrick et al. 2008 Human Psychopharmacology
Amphetamine Salts

<table>
<thead>
<tr>
<th>Name</th>
<th>Mode of Delivery</th>
<th>Duration of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ritalin SR, Metadate ER, Methyl ER</td>
<td>Gradual release</td>
<td>4-8 h</td>
</tr>
<tr>
<td>Metadate CD</td>
<td>30% IR, 70% 3 h later</td>
<td>7-9 h</td>
</tr>
<tr>
<td>Ritalin LA</td>
<td>50% IR, 50% 4 h later</td>
<td>7-9 h</td>
</tr>
<tr>
<td>Quillivant XR</td>
<td>20% IR, 80% gradual release</td>
<td>8-10 h</td>
</tr>
<tr>
<td>Focalin XR</td>
<td>50% IR, 50% 4 h later</td>
<td>Up to 12 h</td>
</tr>
<tr>
<td>Concerta</td>
<td>22% IR, pump</td>
<td>Up to 12 h</td>
</tr>
<tr>
<td>Daytrana patch</td>
<td>Gradual release</td>
<td>3-5 h after removal</td>
</tr>
<tr>
<td>Adderall XR</td>
<td>50% IR, 50% 4 h later</td>
<td>8-12 h</td>
</tr>
<tr>
<td>Dextedrine spanule</td>
<td>50% IR, 50% gradual</td>
<td>10 h</td>
</tr>
<tr>
<td>Vyvanse</td>
<td>Activated in GI tract</td>
<td>10 h</td>
</tr>
</tbody>
</table>
A Note on Authorized Generic Concerta

- Not all Concerta is made equal.
- Some patients seem to have a less favorable response to generic vs brand Concerta. This may be due to subtle variations in the laser hole and tablet structure.
- In those cases you should have note on the patient script authorized generic only.
- If you have a chance you should read on the difference between authorized generic vs generic medication.
Stimulant Precautions

- Cardiac disease in patient (family history of sudden death <40 y/o)
- Bipolar disorder/Psychosis
- Substance abuse (particular attention to alcohol/sedative hypnotics and stimulant abuse)
- Pregnancy Category C (new study this year may result in this changed to category D)

Additional Considerations:
- Anxiety (start SSRI)
- Tic Disorders

Stimulant Medications

- Black Box Warning:
  - High abuse potential and dependance: All
  - Psychosis/Tolerance: Concerta
  - Sudden Death: Adderall and Dexedrine
- Common Side Effects: Anxiety, decreased appetite and weight loss, insomnia, dry mouth, headache, upset stomach
Monitoring

- Blood pressure and heart rate
- Weight
- Height in children
- SUD
- Manic/psychotic symptoms
- Anxiety, sleep, appetite

Does stimulant treatment influence substance abuse risk?
SUD and ADHD Treatment

Biederman et al. 1999, Pediatrics

Thoughts on stimulant treatment and growth?
Growth and Stimulant Treatment

We have previously believed that kids on long term treatment eventually “catch-up” this does not appear entirely the case for consistent treatment. None the less, the chronic effects of treatment may outweigh this convenience and parents should be advised of the finding.

Severe Cardiovascular Event (Children/Young Adults)

<table>
<thead>
<tr>
<th>End Point</th>
<th>Person-Yr</th>
<th>Events</th>
<th>Rate per 100,000 Person-Yr</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden cardiac death</td>
<td>1,597,962</td>
<td>17</td>
<td>1.06</td>
<td>1.00</td>
</tr>
<tr>
<td>Former user</td>
<td>607,475</td>
<td>13</td>
<td>2.14</td>
<td>1.52 (0.65–3.56)</td>
</tr>
<tr>
<td>Current user</td>
<td>373,667</td>
<td>3</td>
<td>0.80</td>
<td>0.88 (0.23–3.35)</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1,597,962</td>
<td>6</td>
<td>0.38</td>
<td>1.00</td>
</tr>
<tr>
<td>Former user</td>
<td>607,475</td>
<td>3</td>
<td>0.49</td>
<td>0.88 (0.26–4.71)</td>
</tr>
<tr>
<td>Current user</td>
<td>373,667</td>
<td>0</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1,597,962</td>
<td>26</td>
<td>1.63</td>
<td>1.00</td>
</tr>
<tr>
<td>Former user</td>
<td>607,475</td>
<td>9</td>
<td>1.48</td>
<td>0.80 (0.33–1.96)</td>
</tr>
<tr>
<td>Current user</td>
<td>373,667</td>
<td>4</td>
<td>1.07</td>
<td>0.93 (0.29–2.97)</td>
</tr>
</tbody>
</table>

Severe Cardiovascular Event (Adult)

Habel et al. 2011, The Journal of the American Medical Association

Stimulants and Pregnancy

Anderson et al. 2020, Journal of Attention Disorders
Stimulants and Pregnancy

Anderson et al. 2020, Journal of Attention Disorders

Stimulant Failure

CADDRA, 2018. Canadian ADHD Practice Guidelines
Non-stimulants

- Atomoxetine
- Bupropion
- Guanfacine/Clonidine
- Modafinil
- Venlafaxine
- Desipramine/Nortriptyline

cover bupropion, venlafaxine, desipramine/nortriptyline as I figure you will hear about them elsewhere.

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Atomoxetine

When to Use:

- High substance abuse risk
- As adjunct or solo agent for those who have partial response/failure to stimulants

Michelson et al. 2002, American Journal of Psychiatry
Atomoxetine

- SNRI
- DAT inhibition in the prefrontal cortex
- Metabolism: CYP2D6
- Inhibit: CYP2D6
- ½ life of 5 hours, can be dosed once or twice a day
- Adults: start 40mg and titrate to max dose 100mg
- Children: weight based

Atomoxetine

- Black Box Warning: Increased suicidal ideation
**Atomoxetine**

- Concern for hepatotoxicity (avoid in those with liver injury)
- Concern for cardiovascular events (consult cardiology)

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**Guanfacine**

- **When to Use:**
  - Reserve for second/third line or augmentation
  - Good adjunct for hyperactivity, impulsivity, sleep disturbance
  - Co-morbid tic disorder, ODD

Guanfacine

- MOA:
  - Alpha2a agonist, presynaptic in brainstem resulting in reduced peripheral sympathetic tone (low systolic/diastolic bp)
  - Postsynaptic agonism of alpha2a (prefrontal cortex)
- SE’s: sleepiness, tiredness, headache, and stomachache
- IR and XR formulation
- Dosing: Start at 1mg and titrate in 1mg increments
- Taper at 1mg every 3 to 7 days
- Metabolism: Renal excretion of ~50% and Remainder CYP3A4
- Pregnancy category B
Clonidine

**MOA:**
- Alpha2a agonist, presynaptic in brainstem resulting in reduced peripheral sympathetic tone (low systolic/diastolic bp)
- Postsynaptic agonism of alpha2a (prefrontal cortex)
- Less selective than Guanfacine (binds 2a, 2b, 2c) may be why more sedative

**SE’s:** sleepiness, tiredness, headache, and stomachache

**IR, XR, and patch formulation**

**Dosing:** Start at 0.1mg and titrate in 0.1mg increments (max 0.4mg)

**Taper at 0.1mg every 3 to 7 days**

**Metabolism:** Renal excretion/Some liver metabolism

**Pregnancy category C**
Combo Stimulant Treatment and Alpha2 Agonist

Kollins et al. 2011, Pediatrics

Modafinil
How does modafinil work?

Modafinil

- Uses:
  - Reserve as 2\textsuperscript{nd} or 3\textsuperscript{rd} line
  - Evidence does not show efficacious as adjunct

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure.png}
\caption{Comparison of modafinil and placebo effects over time.}
\end{figure}

Biederman et al. 2005, *Pediatrics*
Schmitz et al. 2012, *Frontiers in Psychiatry*
Modafinil

- MOA:
  - DAT blockade, partial alpha-1-b blockade, demonstrated to increase 5-HT2 receptor activity
- SE’s: sleepiness, tiredness, headache, and stomachache
- Dosing: 200-425mg once daily (depending on weight)
- Metabolism: CYP3A4
  - Inhibits 2C19
  - Induces 3A4
- Pregnancy category C
- SE/Adverse Events: SJS, headache, nausea, anxiety, insomnia

Provigil [Package Insert], 2015

Questions