Attention-Deficit Hyperactivity Disorder (ADHD)
<table>
<thead>
<tr>
<th>Table 1. Criteria for the Diagnosis of ADHD.*</th>
</tr>
</thead>
<tbody>
<tr>
<td>The diagnosis requires evidence of inattention or hyperactivity and impulsivity or both</td>
</tr>
<tr>
<td>Inattention</td>
</tr>
<tr>
<td>Six or more of the following symptoms of inattention have persisted for at least six months to a degree that is maladaptive and inconsistent with developmental level:</td>
</tr>
<tr>
<td>Often fails to give close attention to details and makes careless mistakes</td>
</tr>
<tr>
<td>Often has difficulty sustaining attention</td>
</tr>
<tr>
<td>Often does not seem to listen</td>
</tr>
<tr>
<td>Often does not seem to follow through</td>
</tr>
<tr>
<td>Often has difficulty organizing tasks</td>
</tr>
<tr>
<td>Often avoids tasks that require sustained attention</td>
</tr>
<tr>
<td>Often loses things necessary for activities</td>
</tr>
<tr>
<td>Often is easily distracted</td>
</tr>
<tr>
<td>Often is forgetful</td>
</tr>
<tr>
<td>Hyperactivity and impulsivity</td>
</tr>
<tr>
<td>Six or more of the following symptoms of hyperactivity and impulsivity have persisted for at least six months to a degree that is maladaptive and inconsistent with developmental level:</td>
</tr>
<tr>
<td>Often fidgets</td>
</tr>
<tr>
<td>Often leaves seat</td>
</tr>
<tr>
<td>Often runs about or climbs excessively</td>
</tr>
<tr>
<td>Often has difficulty with quiet leisure activities</td>
</tr>
<tr>
<td>Often is &quot;on the go&quot; or &quot;driven by a motor&quot;</td>
</tr>
<tr>
<td>Often talks excessively</td>
</tr>
<tr>
<td>Often blurts out answers</td>
</tr>
<tr>
<td>Often has difficulty awaiting turn</td>
</tr>
<tr>
<td>Often interrupts or intrudes</td>
</tr>
<tr>
<td>Symptoms that cause impairment:</td>
</tr>
<tr>
<td>Are present before 7 years of age</td>
</tr>
<tr>
<td>Are present in two or more settings (e.g., home, school, or work)</td>
</tr>
<tr>
<td>Do not occur exclusively during the course of a pervasive developmental disorder, schizophrenia, or another psychotic disorder</td>
</tr>
<tr>
<td>Are not better accounted for by another mental disorder (e.g., a mood disorder or an anxiety disorder)</td>
</tr>
</tbody>
</table>

* The criteria are adapted from the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, revised.
Possible changes in DSM-V  APA, 2010

- For older adolescents and adults (≥17) confirmatory observations by third parties should be obtained whenever possible.

- Fewer symptoms (≥4) required for older adolescents and adults (≥17)

- Symptoms present by age 12.
Course

- Prospective studies of school-aged children (mostly boys):
  - Persistence of symptoms into early adolescence
  - Number of symptoms decreases during mid- to late adolescence
  - Inattention most likely to persist into adulthood (90% of adults report inattention; 50% hyperactivity/impulsivity)
Course

- Adults with persistent symptoms
  - Less schooling, lower-status jobs, more ASP
  - Higher frequency of substance abuse disorder (non-alcoholic)
- Adults whose symptoms decrease in adolescence similar to normals except in academic achievement
Cumulative Risks for Disorders in Girls With ADHD Relative to Comparison Girls for Six Composite Diagnostic Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood Disorders</td>
<td>6.8</td>
<td>3.7—12.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antisocial Disorders</td>
<td>2.1</td>
<td>1.6—2.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Developmental Disorders</td>
<td>7.2</td>
<td>4.0—12.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Substance Dependence Disorders</td>
<td>3.2</td>
<td>2.0—5.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Eating Disorders</td>
<td>2.7</td>
<td>1.6—4.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>3.5</td>
<td>1.6—7.3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Figure Legend:
Course

- Effect of treatments (drugs, therapy, special education) on long-term outcome is controversial
- Multimodal treatment study (Satterfield)
  - Decreased arrests in those treated with psychotherapy and stimulants
Differential Diagnosis

- Attention problems are common in many psychiatric conditions
  - depression
  - anxiety
  - substance abuse
  - psychosocial stress (divorce, abuse)
  - Tourette’s Disorder (chronic motor-vocal tics)
  - Autism Spectrum Disorders
Differential Diagnosis

- Common conditions most frequently misdiagnosed as ADHD
  - Anxiety and depression
- ADHD is a diagnosis of exclusion
  - Made only if not better accounted for by another mental disorder
Comorbid Conditions

- Rule, rather than the exception
- ADHD alone 31%
- Oppositional Defiant Disorder 40%
- Conduct Disorder 14%
- Tic Disorders 11%
- Anxiety and Mood 38%
Stimulants

Birth
Ritalin
Prozac
Viagra
Death
MTA Study of ADHD

- 14-month, multicenter, randomized controlled trial
- 579 children aged 7-9, ADHD combined type
- Not placebo controlled

Jensen et al., 2001
MTA Cooperative Group, 1999
MTA Study of ADHD

- **Treatment Arms**
  - Medication management only
  - Intensive behavioral treatment only
  - Medication management + behavioral treatment (combined)
  - Community-based care
Medication management

- Monthly 30 minute sessions
- MPH TID adjusted for best dose
- General advice and readings
- Regular contact with child’s teacher
- Case management by pharmacotherapist
Results

- All treatments led to improvement
- Medication management = combined treatment > intensive behavioral treatment and community-based treatment
- Higher rate of “excellent” responders in the combined treatment group – Gold Standard
ADHD with comorbid anxiety

- No significant differences between medication management, behavioral, and combined treatment
- All superior to community based treatment
Lessons learned

- Stimulants led to long-term, continuous improvement as long as the drug is taken.
- Measure progress in ADHD core symptoms utilizing Connors’ teacher ratings.
- Push stimulant dose until teacher ratings in the non-clinical range or side effects intolerable.
MTA at 36 months

ADHD Symptoms

ODD Symptoms

Columbia Impairment Scale
MTA at 36 months
What Does It All Mean? (Pliszka, 2008)

- Stimulants work very well in first year of treatment if given systematically
- Gains not maintained if medication not given consistently
What Does It All Mean? (Pliszka, 2008)

- Consistent use may lead to growth suppression (~1 inch)
- Some cases of ADHD will resolve without treatment
- Medication free period?
MTA at 8 (Molina et al., 2009)

- Type or intensity of treatment at 7-9 years does not predict functioning 6-8 years later
- Early ADHD symptom trajectory regardless of treatment type prognostic
MTA at 8 (Molina et al., 2009)

- Children with behavioral and SES advantage, and best response to any treatment have best long-term prognosis
- Despite symptom improvement, significant impairment in adolescence
From: ADHD Pharmacotherapy: Rates of Stimulant Use and Cardiovascular Risk


Figure Legend:

Stimulant Use in the U.S. Pediatric Population, by Age Group
Stimulants and Cardiovascular Events (Olfson et al., 2012)

- Claims data of 171,126 privately insured youth aged 6-21 years
- Cardiovascular events and symptoms rare, not associated with stimulant use
Pre-stimulant Use (Olfson et al., 2012)

- Personal and family cardiovascular history
  - Family history of premature sudden death
  - Personal history of syncope, dizziness, palpitations, chest pain
- Physical exam with careful cardiac exam
Stimulants and Tics

- Stimulants were formerly contraindicated in chronic tic disorders and Tourette’s
- Recent studies support use of stimulants in co-morbid ADHD and Tourette’s
  - Disruptive behavior decreased with no increase in severity of tics
Stimulant Drug Preparations

- Methylphenidate and dextroamphetamine
  - Class II controlled substances
- Equal efficacy, side effects the same
- No predictors of response - if one doesn’t work, try the other
- All of our first-line medications are variants of MPH and dextroamphetamine
  - Strattera, Intuniv and Kapvay are the only important exceptions
Mean Methylphenidate Plasma Concentrations From CONCERTA® and Methylphenidate TID (N=15)¹

- CONCERTA® 36 mg qd (n=15)
- IR MPH 10 mg tid (n=15)

IR MPH = immediate-release methylphenidate; qd = once daily; tid = 3 times daily.

Methylphenidate Patch

- Applied to hip, up to 9 hours
- Lag time
  - Package insert – 2 hours before effect needed
  - Pharmacokinetic studies – 3 hours before detectable in blood stream
For Example:

<table>
<thead>
<tr>
<th>Time</th>
<th>School Day</th>
<th>Weekend</th>
</tr>
</thead>
<tbody>
<tr>
<td>5AM</td>
<td>Apply Patch.</td>
<td>Apply Patch.</td>
</tr>
<tr>
<td>6AM</td>
<td>Ready for school.</td>
<td></td>
</tr>
<tr>
<td>7AM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8AM</td>
<td></td>
<td>Ready for Activity.</td>
</tr>
<tr>
<td>9AM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10AM</td>
<td></td>
<td>Remove Patch. (Effects continue for 3 hours or more.)</td>
</tr>
<tr>
<td>Noon</td>
<td></td>
<td>Ready for dinner.</td>
</tr>
<tr>
<td>1PM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2PM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3PM</td>
<td>Remove Patch. (Effects continue for 3 hours or more.)</td>
<td></td>
</tr>
<tr>
<td>4PM</td>
<td></td>
<td>Ready for dinner.</td>
</tr>
<tr>
<td>5PM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6PM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7PM</td>
<td></td>
<td>Ready for bed.</td>
</tr>
<tr>
<td>8PM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9PM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10PM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Ready for bed.
Methylphenidate Patch

- DBPC trial, 270 subjects
- ADHD-RS
  - 18 core symptoms, ranked 1, 2, 3
  - Max score 54
  - Average score for ADHD 30-35
- Patch reduced score by 24.2, Placebo by 9.9
# Methylphenidate Patch
*(from Daytrana package insert)*

<table>
<thead>
<tr>
<th>MPH content</th>
<th>Delivery rate</th>
<th>Dose over 9 hours</th>
</tr>
</thead>
<tbody>
<tr>
<td>27.5 mg</td>
<td>1.1 mg/hour</td>
<td>10 mg</td>
</tr>
<tr>
<td>41.3 mg</td>
<td>1.6 mg/hour</td>
<td>15 mg</td>
</tr>
<tr>
<td>55 mg</td>
<td>2.2 mg/hour</td>
<td>20 mg</td>
</tr>
<tr>
<td>82.5 mg</td>
<td>3.3 mg/hour</td>
<td>30 mg</td>
</tr>
</tbody>
</table>
Lisdexamfetamine (Vyvanse)

- L-lysine conjugated with d-amphetamine
- Activated after hydrolyzed in digestive system
- No euphoria when snorted or injected
Lisdexamfetamine (Vyvanse)

- DBPC of 290 6-12 year olds
- Randomized to 30 mg, 50 mg, 70 mg of drug or placebo
Lisdexamfetamine (Vyvanse) ADHD-RS

- Placebo - 6.2
- 30 mg - 21.8
- 50 mg - 23.4
- 70 mg - 26.7

Side effects
- Anorexia, insomnia, headache, abdominal discomfort
Adverse Effects of Stimulants

- Decreased appetite (80%)
- Substantial weight loss (10-15%)
- Slow growth, but long-term effect minimal (1")
Adverse Effects of Stimulants

- Insomnia (3-85%)
- Increased heart rate and blood pressure
- Abdominal pain, tics, irritability, headaches, dry mouth, dizziness, depression less frequent
Non-stimulant Medications

- Atomoxetine – SNRI
- Bupropion - antidepressant
- Clonidine – Alpha adrenergic agonist
Non-stimulant Medications

- Guanfacine - Alpha 2a agonist
  - Intuniv – guanfacine xr
  - Kapvay - clonidine xr
- Tricyclic antidepressants – Imipramine or Nortriptyline
Atomoxetine

- SNRI
- Four short-term RCT’s with replication
- One RCT lasting nine months; superiority to placebo in relapse-prevention
- Head-to-head trials suggest less efficacy than stimulants
Atomoxetine

- Dosed by body weight
- Start at .5 mg/kg/day and titrate to 1.2 mg/kg/day (max. 1.4)
- Twice daily dosing may be better tolerated
- Onset of action – 1 to 2 weeks, full effect at one month
Clonidine

- Alpha adrenergic agonist, inhibits NE transmission at the synapse
  - RCT’s suggest moderately efficacy in ADHD, but less than stimulants (HA, impulsivity>attention)
  - Requires frequent dosing (up to 4-6 times per day) – patch available
  - Very sedating; start at .025/dose
Guanfacine (Tenex)

- Antihypertensive, alpha 2a agonist
- Uncontrolled studies suggest effectiveness in treatment-refractory ADHD or in patients with co-morbid Tourette’s Disorder
- Twice to three times daily dosing
“Intuniv” (Guanfacine XR)
Biederman et al, Pediatrics 2009, cited by Kratochvil

- DBPC trial at dosages of 2 mg, 3 mg, and 4 mg/day
- N=345, ages 6-17
- All doses led to improvement in hyperactivity, impulsivity, inattention
- Effect sizes: .64, .66, .80
Adverse Effects

Biederman et al, Pediatrics 2009, cited by Kratochvil

- Headache, somnolence, fatigue, upper abdominal pain, sedation
- Discontinuation secondary to AE’s
  - Placebo 1
  - 2 mg - 9
  - 3 mg - 13
  - 4 mg - 20
Guanfacine XR
Sallee et al, JAACAP, 2009 cited by Kratochvil

- 9 week DBPC trial, n 324, ages 6-17
- 1,2,3, and 4 mg doses separated from PBO; effect sizes .43 to .62
- 2-year open-label continuation trial, n = 262, ages 6-17
  - 5 subjects discontinued because of syncope
INTUNIV has a different dissolution curve than GIR²

In vitro dissolution of INTUNIV and GIR

- **INTUNIV 1 mg**
  - >85% of drug released over 12 hours
  - Slow, sustained release
  - Once-daily formulation

- **GIR 1 mg**
  - ≥75% of drug released within first 45 minutes
  - Burstlike release
  - Plasma-level fluctuations and repeated daily dosing

Adapted from Shojaei et al.²
Clinical significance of these data has not been demonstrated.
Bupropion

- Controlled studies suggest efficacy in ADHD in children and adolescents
- May lower seizure threshold
- ADHD and depression – Two birds with one stone?
Antidepressants

- Tricyclics - imipramine and nortriptyline
  - Effective, but less so than stimulants
  - Useful because of longer half-life, minimal risk of abuse, minimal risk of tics
  - Sudden death; six cases with desipramine, one with imipramine – death rate lower than population background death rate

- SSRI’s – Not effective
Preschoolers with ADHD

- MPH not approved under age 6
- Dextroamphetamine approved to age 3, but no data
- MPH most popular, despite lack of approval
- Zito (2000) found 1.2% of preschoolers on MPH
Preschool ADHD Treatment Study (PATS)

- 303 children, 3 to 5.5 years
- Parent training – still meet ADHD criteria post 10 weeks of parent training [261 completed]
- Open-label lead-in – tolerate all study doses (1.25, 2.5, 5.0, 7.5 mg tid) [183 entered, 169 completed]
Preschool ADHD Treatment Study (PATS)

- Mean optimal dose $14.22 \pm 8.1$mg/day
- Effect sizes smaller in PAT than in MTA
  - PAT 0.35 parents, 0.43 teachers
  - MTA 0.52 parents, 0.75 teachers
Preschool ADHD Treatment Study (PATS)

- Dosage range on PAT lower than MTA
  - PAT 3.75 – 30mg/day
  - MTA 15 – 50 mg/day
- Efficacy lower because of lower dose?
PATS Clinical Implications

- Start with low doses
  - 2.5 mg bid titrated over the course of one week to 7.5mg tid
- Side effects – more frequent at doses of ≥ 5.5 mg tid
  - Loss of appetite, sleeping problems, stomach aches, social withdrawal, lethargy
Diet and ADHD (Nigg et al., 2012)

- Restriction diets in which synthetic food colors and/or other additives eliminated
- Dietary restriction produces reliable and clinically meaningful benefit in children with ADHD
- Effect size .29 (vs. medication .9)
Omega-3 fatty acid supplementation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Weight</th>
<th>Std. Mean Difference</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voigt 2001</td>
<td>8.0%</td>
<td>0.04 [-0.49, 0.58]</td>
<td>2001</td>
</tr>
<tr>
<td>Richardson 2002</td>
<td>4.1%</td>
<td>0.38 [-0.37, 1.13]</td>
<td>2002</td>
</tr>
<tr>
<td>Stevens 2003</td>
<td>4.8%</td>
<td>0.40 [-0.29, 1.09]</td>
<td>2003</td>
</tr>
<tr>
<td>Richardson 2005</td>
<td>17.3%</td>
<td>0.36 [-0.00, 0.73]</td>
<td>2005</td>
</tr>
<tr>
<td>Sinn 2007</td>
<td>11.6%</td>
<td>0.58 [0.13, 1.02]</td>
<td>2007</td>
</tr>
<tr>
<td>Vaisman 2008 fishoil</td>
<td>6.3%</td>
<td>0.17 [-0.44, 0.77]</td>
<td>2008</td>
</tr>
<tr>
<td>Johnson 2008</td>
<td>11.1%</td>
<td>0.35 [-0.11, 0.81]</td>
<td>2008</td>
</tr>
<tr>
<td>Vaisman 2008 omega-3</td>
<td>5.7%</td>
<td>0.41 [-0.22, 1.05]</td>
<td>2008</td>
</tr>
<tr>
<td>Raz 2009</td>
<td>9.6%</td>
<td>0.13 [-0.36, 0.62]</td>
<td>2009</td>
</tr>
<tr>
<td>Gustafsson 2009</td>
<td>13.8%</td>
<td>0.22 [-0.19, 0.62]</td>
<td>2009</td>
</tr>
<tr>
<td>Belanger 2010</td>
<td>7.7%</td>
<td>0.40 [-0.15, 0.95]</td>
<td>2010</td>
</tr>
</tbody>
</table>

Total (95% CI) 100.0% 0.31 [0.16, 0.47]

Heterogeneity: $\chi^2 = 3.68, \text{df} = 10 (P = 0.95); I^2 = 0$

Test for overall effect: $Z = 4.04 (P < 0.0001)$