Attention Deficit Hyperactivity Disorder Across The Lifespan

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Disclosure

<table>
<thead>
<tr>
<th></th>
<th>Research Grants</th>
<th>Speaker</th>
<th>Advisory Board</th>
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Learning Objectives
Inform participants regarding:
• Etiology of ADHD
• Prevalence of ADHD
• DSM-IV and DSM-5 diagnostic criteria
• Diagnosis and differential diagnosis
• Comorbidities at different developmental stages
• Treatment of ADHD
  – Pharmacological
  – Psychosocial
• Treatment of ADHD and various comorbidities
  – Pharmacological
  – Psychosocial

Epidemiology
Perceived prevalence of ADHD in Europe and the USA
Chronicity of ADHD: Follow-up Studies


![Graph showing prevalence and duration for various studies](image)

- Feldman (1979): 15.5 y
- Mendelson (1971): 13.4 y
- August (1983): 14.2 y
- Barkley (1990): 14.9 y
- Weiss (1985): 25.1 y
- Borland & Heckman (1976): 30.4 y
- Mannuzza & Gittleman (1984): 17.4 y
- Gittleman (1985): 18.3 y
- Mannuzza (1991): 18.5 y
- Mannuzza (1991): 18.5 y
- Mannuzza (1993): 25.5 y
- Offord (1992): 8-16 y
- Hart (1995): 10.4 y
- Biederman (1996): 14.5 y

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### Estimated ADHD Sufferers in Canada in 2005
How many do you have in your practice?

<table>
<thead>
<tr>
<th></th>
<th>ADHD in children, teens (age 5–19)</th>
<th>ADHD in adults (age 20–59)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Population</td>
<td>6,182,933</td>
<td>18,567,976</td>
</tr>
<tr>
<td>Prevalence [%]</td>
<td>6%</td>
<td>4%</td>
</tr>
<tr>
<td>Patients with ADHD</td>
<td>370,976</td>
<td>742,719</td>
</tr>
<tr>
<td>% diagnosed</td>
<td>33%</td>
<td>7%</td>
</tr>
<tr>
<td>Patients untreated</td>
<td>248,544</td>
<td>690,729</td>
</tr>
</tbody>
</table>

Statistics Canada, 2004 projected to 2005; % diagnosed calculated based on estimate of treated patients in Canada

### ADHD Prevalence By Subtypes and Gender

<table>
<thead>
<tr>
<th></th>
<th>Children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence</td>
<td>6-8%</td>
<td>4.4%</td>
</tr>
<tr>
<td>Subtypes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Combined</td>
<td>50-75%</td>
<td>30-40%</td>
</tr>
<tr>
<td>• Predominantly inattentive</td>
<td>20-30%</td>
<td>50-60%</td>
</tr>
<tr>
<td>• Predominantly hyperactive/impulsive</td>
<td>&lt;15%</td>
<td>5%</td>
</tr>
<tr>
<td>Male-to-female ratio</td>
<td>2.5:1</td>
<td>1:1</td>
</tr>
</tbody>
</table>

ADHD is Most Likely Caused by a Complex Interplay of Factors:

- Neuroanatomic
  - Neurochemical
- Genetic origins
  - origins
- Environmental factors
- CNS insults

References:
ADHD: Genetics

- Twin Studies
- Family Studies
- Adoption Studies
- Molecular Genetics Studies

Genetic Basis of ADHD

ADHD: A Family Affair

- Between 40-60% of parents with ADHD
  - will have a child with the disorder

- 25% of children with ADHD
  - will have parent with the disorder

- Added challenge of raising a child with ADHD
  - when the parent has the disorder

Twin Studies Show ADHD Is a Genetic Disorder

Average genetic contribution of ADHD based on twin studies

<table>
<thead>
<tr>
<th>Study</th>
<th>ADHD Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hudziak, 2000</td>
<td></td>
</tr>
<tr>
<td>Nadder, 1998</td>
<td></td>
</tr>
<tr>
<td>Levy, 1997</td>
<td></td>
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<tr>
<td>Sherman, 1997</td>
<td></td>
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<td>Silberg, 1996</td>
<td></td>
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<td>Gjone, 1996</td>
<td></td>
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<td>Thapar, 1995</td>
<td></td>
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<td>Schmitz, 1995</td>
<td></td>
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<tr>
<td>Edelbrock, 1992</td>
<td></td>
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<tr>
<td>Gillis, 1992</td>
<td></td>
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<tr>
<td>Goodman, 1989</td>
<td></td>
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<tr>
<td>Willerman, 1973</td>
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</tbody>
</table>

Candidate Genes

- Candidate genes include:
  - Dopamine D4 receptor; chromosome 11 (DRD4)\(^1\)
  - Dopamine transporter; chromosome 5 (DAT-I)\(^1\)
  - Monoamine oxidase A (MAOA)\(^2\)
  - Vesicular monoamine transporters 1 and 2 (VMAT-1, VMAT-2)\(^3,4\)
  - Synaptosomal-associated protein 25 (SNAP-25)\(^5,6\)
  - Human thyroid receptor-β gene\(^7\)
- \textit{No Specific X linked gene identified}

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Neural Networks of Attention

- Prefrontal cortex
- Parietal cortex
- Cingulate gyrus
- Limbic structures (amygdala-hippocampus)
- Basal ganglia
- Thalamus
- Brainstem (reticular formation)
- Cerebellum
- Nucleus Accumbens


Neuroimaging Studies

- Smaller brains
- Smaller cortical areas, e.g., prefrontal cortex, cerebellum
- Smaller subcortical areas, e.g., corpus colossum, thalamus
- Hypoperfusion in these areas corrected by stimulant medication

ADHD: MRI Studies

- Basal ganglia
- Cerebellum
- Frontal lobes (rich in dopamine receptors)

All 3 found to be smaller in individuals with ADHD compared with controls

MRI studies
- ~10% decrease in size of ADHD-associated areas

Functional imaging studies
- Decreased striatal perfusion in ADHD subjects

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Anterior Cingulate Cortex Cognitive Division Fails to Activate in ADHD

Normal Controls | ADHD

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Cerebral Glucose Metabolism in Adults with Hyperactivity of Childhood Onset

- Global and regional glucose metabolism by PET scan reduced in adults who have been hyperactive since childhood

- Largest reductions in:
  - Premotor cortex
  - Superior prefrontal cortex

Delayed brain growth in ADHD (3 years)

Ns: ADHD=223; Controls = 223

Kaplan–Meier curves illustrating the proportion of cortical points that had attained peak thickness at each age for all cerebral cortical points (Left) and the prefrontal cortex (Right). The median age by which 50% of cortical points had attained their peak differed significantly between the groups (all $P \leq 10^{-20}$). Shaw et al (2007) PNAS, 104 (49)

**DIAGNOSIS**
### ADHD – DSM-IV Definition

**DSM-5**

Attention Deficit Hyperactivity Disorder (ADHD) is a neurobiological condition characterized by developmentally inappropriate levels of:

- Inattention (concentration, distractibility)
- Hyperactivity
- Impulsivity

in various combinations across school, work, home, and social settings.


### Symptoms

- Pervasive – many settings
- Persistent – duration 6 months
- Onset before age 7 (DSM-IV); age 12 (DSM-5)
- Severe
  - Maladaptive, affect functioning
  - Inconsistent with developmental level
  - Clinical significant impairment, social, academic, occupational
Impairment

- DSM-IV-TR; DSM-5: ADHD symptoms must be consistently and persistently impairing in at least 2 areas of life functioning
- Much more than personality traits and quirks
- Must significantly impair major aspects of day-to-day life

Diagnostic and Statistical Manual of Mental Disorders. Fourth ed. Text Revision, 2000

Course of ADHD

Hyperactivity: Pediatric to Adult Symptom Migration

- **Childhood DSM-IV-TR®; DSM-5 symptoms**¹
  - Squirms and fidgets
  - Runs or climbs excessively
  - Cannot play or work quietly
  - “On the go,” driven by a motor
  - Talks excessively

- **Common adult symptoms**²
  - Inner restlessness
  - Overwhelmed
  - Self-selects active jobs
  - Talks excessively
  - Fidgets when seated

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Impulsivity: Pediatric to Adult Symptom Migration

- Childhood DSM-IV-TR®, DSM-5 symptoms
  - Blurs out answers
  - Cannot wait his or her turn
  - Intrudes on or interrupts others

- Common adult symptoms
  - Impulsive job changes
  - Drives too fast, has traffic accidents
  - Irritability or quickness to anger


Inattention: Pediatric to Adult Symptom Migration

- Childhood DSM-IV-TR®, DSM-5 symptoms
  - Difficulty sustaining attention
  - Does not listen
  - Difficulty following instructions
  - Cannot organize
  - Loses things
  - Easily distracted/forgetful

- Common adult symptoms
  - Difficulty sustaining attention to reading or paperwork
  - Easily distracted and forgetful
  - Poor concentration
  - Poor time management
  - Difficulty finishing tasks
  - Misplaces things

Changes in DSM - 5

1. Name DSM-5 not DSM-V
2. ADHD under neurodevelopmental disorders not disruptive disorders
3. Autism spectrum exclusion removed
4. Age of onset before 12 years vs. impairment by age 7
   Still need childhood onset
5. Subtypes – renamed presentations due to longitudinal instability

Changes in DSM-5
New Symptoms
More appropriate for adolescents and adults
a) Often impatient
b) Acting without thinking
c) Uncomfortable doing things slowly and systematically
d) Difficult to resist temptation or opportunity
Often Impatient

- Feeling restless when waiting for others
- Wanting people to get to the point
- Wanting to be faster than others
  - Speeding while driving
  - Cutting into traffic

Tending to Act without Thinking

- Starting a task without adequate preparation
- Avoiding reading or listening to instructions
- May speak without considering the consequences
- Make important decisions in the spur of the moment
  e.g. – impulsively buying
  – suddenly quitting a job
  – breaking up with a friend
Uncomfortable doing things slowly

- Being uncomfortable doing things slowly and systematically
- Often rushes through activities or tasks

Difficulty Resisting Temptation

- Finding it difficult to resist temptation or opportunities even if it means taking risks
- Commit to a relationship after only a brief acquaintance
- Take a job or enter into a business arrangement without due diligence
Number of Symptoms Required

- Most conditions require 93rd percentile or 1.5 standard deviations
- DSM-IV for adults was 99th percentile
- Adults would need 4 symptoms to get 93rd percentile or 1.5 standard deviations
- Criteria in DSM-5: 5 symptoms (thought backlash would be great for 4 symptoms)

Summary of Changes for ADHD in DSM-5

- Under neurodevelopmental disorders
- Autism spectrum not excluded
- Age of onset before age 12
- Presentations not subtypes
- Adults need 5 (not 6 symptoms)
- New symptoms added
  - Impatient
  - Act without thinking
  - Uncomfortable doing things slowly
  - Difficult to resist temptation
Differential Diagnosis

Differential Diagnosis in ADHD: Psychiatric and Medical

<table>
<thead>
<tr>
<th>Psychiatric disorders that can mimic ADHD</th>
<th>Medical disorders that can mimic ADHD</th>
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<tbody>
<tr>
<td>Anxiety disorders</td>
<td>Developmental disorders</td>
</tr>
<tr>
<td>Mood disorders</td>
<td>Use of other medications</td>
</tr>
<tr>
<td>Adjustment disorders</td>
<td>Substance use disorder</td>
</tr>
<tr>
<td>Learning and language deficits</td>
<td>Seizure disorder (petit mal)</td>
</tr>
<tr>
<td>Psychotic disorders</td>
<td>Brain lesions</td>
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<tr>
<td>Stress</td>
<td>Sleep apnea</td>
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<td></td>
<td>Hearing &amp;Vision problems</td>
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<td></td>
<td>Thyroid disorder</td>
</tr>
<tr>
<td></td>
<td>Hypoglycemia</td>
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McCracken JT, Kaplan and Sadock ‘s Comprehensive textbook of psychiatry. 2000;2679-2688.
### Psychiatric Disorders to Consider in the Differential Diagnosis of ADHD in Adults

<table>
<thead>
<tr>
<th>Psychiatric disorder</th>
<th>Features Shared With ADHD</th>
<th>Differential Features</th>
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<tbody>
<tr>
<td>Major depression</td>
<td>• Subjective report of poor concentration, attention and memory</td>
<td>• Substantial and episodic dysphoria</td>
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<tr>
<td></td>
<td>• Difficulty with task completion</td>
<td></td>
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<tr>
<td>Bipolar Disorder</td>
<td>• Increased activity, difficulty with maintaining attention and focus</td>
<td>• Enduring dysphoric or euphoric mood</td>
</tr>
<tr>
<td></td>
<td>• Irritability</td>
<td>• Insomnia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Psychotic symptoms</td>
</tr>
<tr>
<td>Generalized Anxiety</td>
<td>• Fidgetiness</td>
<td>• Exaggerated apprehension and worry</td>
</tr>
<tr>
<td></td>
<td>• Difficulty concentrating</td>
<td>• Somatic symptoms of anxiety</td>
</tr>
</tbody>
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**IMPAIEMENT**
Developmental Impact of ADHD

- Behavioural disturbance
  - Pre-school: 15-25% of children have poor academic outcome
  - School-age: 46% of ADHD pupils suspended
  - Adolescent: 25% persistently antisocial
  - College-age: Difficulty with note-taking, planning assignments, writing, efficiency, and transitioning from “homework” to self-motivated study
  - Adult: Occupational failure, self-esteem issues, relationship problems, injury/accidents, substance abuse, risky sexual behaviour

School in Adolescence

- 15-25% of children have poor academic outcome
- Almost 30% of ADHD subjects fail grades
- 46% of ADHD pupils suspended
- 25% persistently antisocial
- Difficulty with note-taking, planning assignments, writing, efficiency, and transitioning from “homework” to self-motivated study

References:
Academic Performance

![Bar Chart]


Sexual Reproductive Risks

- The Milwaukee Young Adult Outcome Study (MKE) found:
  - Begin sexual activity earlier (15 years vs. 16 years)
  - More sexual partners (18.6 vs. 6.5)
  - Less likely to use contraception
  - Risk of teen pregnancy (38% vs. 4%)
  - Ratio for number of births (42:1)
    - 54% do not have custody of offspring
  - Higher risk for STDs (16% vs. 4%)

Increased Risk for Traffic Violations and Accidents

Negative Driving Outcomes From a Driving History Interview

- Drived before licensed
- 12 or more traffic citations
- 5 or more speeding citations
- License suspended or revoked
- 3 or more vehicular crashes

p=0.003
p=0.001
p=0.001
p=0.002
p=0.007

ADHD (n=105)
Control (n=64)


Misuse and Diversion

- Survey of students in grades 7-12, N=13,549
- 8.5% had used non-prescribed stimulants in the year prior
- Of those students prescribed stimulants:
  - 14.7% had given away medications
  - 7.3% had sold medication to other students

Prevalence of Smoking in Children and Adolescents

Boys aged 6 to 17 years followed prospectively for 4 years


Smoking as Risk Factor for Later Substance Abuse

Smoking and Subsequent Substance Abuse Use Outcomes in ADHD Youth

97 ADHD and 203 control youth of both genders, aged at least 12 years

Predictors of SUD Among ADHD Youth

- Followed 142 ADHD children and 100 non-ADHD controls into adolescence (mean age 16 years)
- Probands: Increased alcohol tobacco and illicit drug use symptoms but not disorders
- Predictors of abuse:
  - Severity of inattention symptoms in childhood
  - Disruptive disorders (ODD/CD)
  - Persistence of ADHD


Prevalence of SUD:
Prospective 4-Year Follow-up Study

Overall Rate of Substance Use Disorder

p<0.001 across groups

Effect of ADHD Pharmacotherapy on Later Substance Use Disorders

More likely to have SUD* | Less likely to have SUD*
---|---
Barkley | | | | | | | |
Molina | | | | | | | |
Loney | | | | | | | |
Huss | | | | | | | |
Biederman | | | | | | | |
Lambert

*Compared to unmedicated youth with ADHD


Developmental Impact of ADHD

Academic problems
Difficulty with social interactions
Self-esteem issues
Legal issues, smoking, drugs
Injury/accidents
Risky sexual behavior

Occupational failure
Self-esteem issues
Relationship problems
Injury/accidents
Substance abuse,
Risky sexual behavior

Behavioural disturbance
Pre-school
School-age
Adolescent
College-age
Adult

Behavioural disturbance
Academic problems
Difficulty with social interactions
Self-esteem issues
Academic failure
Occupational difficulties
Relationship Problems
Self-esteem issues
Substance abuse
Injury/accidents
Risky sexual behaviour
Common Associated Comorbidities

- Oppositional defiant disorder: 40%
- Anxiety disorder: 11%
- Learning disorder: 14%
- Mood disorder: 34%
- Conduct disorder: 40%
- Smoking: 11%
- Substance use disorder: 4%
- Tics: 31%

Co-occurring Disorders in Children (n=579)

MTA Cooperative Group. Arch Gen Psychiatry 1999; 56:1088–1096

Castellanos. Arch Gen Psychiatry 1999; 56: 337–338
Goldman et al. JAMA 1998; 279: 1100–1107
Patients with ADHD Frequently Have Coexisting Disorders

Children and Adolescents

- 31% ADHD only
- 11% Tics
- 14% Conduct Disorder
- 4% Mood Disorder
- 40% Oppositional Defiant Disorder
- 34% Anxiety

Adults

- 14% ADHD only
- 15% Panic Disorder
- 13% OCB
- 25% Cyclothymia
- 34% Alcohol Abuse/Dependence
- 25% Dysthymia
- 30% Drug Abuse
- 53% Generalized Anxiety Disorder

31% ADHD only
14% Conduct Disorder
11% Tics
14% Oppositional Defiant Disorder
34% Anxiety

34% Oppression only
14% Conduct Disorder
11% Tics
40% Oppositional Defiant Disorder
34% Anxiety


ADHD Subtypes, Co-morbidities, and Age

<table>
<thead>
<tr>
<th>Co-morbidity</th>
<th>n=3559</th>
<th>&lt;6 years</th>
<th>Children</th>
<th>Adolescent</th>
<th>Adults</th>
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<tbody>
<tr>
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<td>ADHD/&gt;ADD</td>
<td>ADHD/&gt;ADD</td>
<td>ADHD/&gt;ADD</td>
<td>ADHD/&gt;ADD</td>
<td>ADHD/&gt;ADD</td>
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<td>Oppositional defiant disorder (ODD)</td>
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<td>Communication disorders</td>
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<td>+</td>
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<td>Conduct disorder (CD)</td>
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<td>+</td>
<td>+</td>
<td>Anti-social</td>
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<tr>
<td>Anxiety disorders</td>
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<td>+</td>
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<td>Mood disorders</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>Depressive disorders</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Substance use</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Treatment for children with ADHD: Psychosocial Treatment

- Parent training
- Individual Educational Plan
- Organization & time management skills
- Remediation
- Social skills
- Anger management
- Relaxation techniques (anger, anxiety)
- Individual psychotherapy (low self-esteem)
- Family therapy (prevent “scape-goating”)

Managing ADHD in Adolescents

<table>
<thead>
<tr>
<th>Academic Deficits</th>
<th>Vocational Guidance</th>
<th>Socialization Deficits</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Need measure of I.Q. (learning disability?)</td>
<td>• Vocational testing – find aptitude and interest</td>
<td>• Social skills training</td>
</tr>
<tr>
<td>• Need achievement levels in key subjects</td>
<td>• Work-study program</td>
<td>• Anger management</td>
</tr>
<tr>
<td>• Individual educational plan</td>
<td>• Vocational training</td>
<td>• Conflict resolution, e.g., with parents</td>
</tr>
<tr>
<td>• Organization, time management, study skills</td>
<td>• Organizational, time management skills</td>
<td>• Parent guidance – training</td>
</tr>
<tr>
<td>• Remediation, tutoring</td>
<td></td>
<td>• Family therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Individual therapy, ↑ self-esteem</td>
</tr>
</tbody>
</table>
Prescribing Medication for Adolescents With ADHD

- See adolescent alone – avoid parental power struggle
- Form alliance with adolescent
  - Adolescent may wish treatment to be kept private
- Tailor treatment to fit the adolescents’ schedule
- Have adolescent control his medication use
- Discuss medication and use of alcohol and marijuana
  - Watch for signs of abuse/diversion
- Discuss side effects
- Discuss signs of over- and under-medication
- Some use medication intermittently
  - Projects
  - Exams

ADHD Pharmacotherapy Responsiveness

- Methylphenidate
- Amphetamine
- Atomoxetine
- Bupropion
- MAOI
- Clonidine
- Guanfacine

Meta Analysis of Controlled Crossover Comparing Stimulants

7 Studies
174 subjects

% Patients With Preferential Response

1. Arnold L.E. J Am Disorders, 2000

Stimulants Found to Improve ADHD

Core Symptoms
- Inattention
- Impulsivity
- Hyperactivity

AND
- Compliance
- Impulsive aggression
- Social interactions
- Academic efficiency
- Academic accuracy

Effects increase with dose

### Mechanism of Action of Stimulants

**Presynaptic Neurone**
- Amphetamine blocks
- Cytoplasmic DA
- Storage vesicle
- Amphetamine blocks reuptake
- DA Transporter
- Synapse
- Methylphenidate blocks reuptake

**Amphetamine blocks**

**Methylphenidate blocks reuptake**


### 2011 CADDRA Recommendations for Dosing Psychostimulants

**Starting dose**

<table>
<thead>
<tr>
<th></th>
<th>Child</th>
<th>Adolescent</th>
<th>Adult</th>
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<tbody>
<tr>
<td><strong>First-line agents – long-acting preparations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed amphetamine salts XR</td>
<td>10 mg</td>
<td>10 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>MLR methylphenidate</td>
<td>10 mg</td>
<td>10 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>OROS methylphenidate</td>
<td>18 mg</td>
<td>18 mg</td>
<td>18 mg</td>
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<tr>
<td>Lisdexamfetamine</td>
<td>20 mg</td>
<td>20 mg</td>
<td>20 mg</td>
</tr>
<tr>
<td><strong>Second-line/adjunctive agents – short-acting or intermediate-acting preparations</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Dextroamphetamine</td>
<td>2.5 mg BID</td>
<td>2.5 mg BID</td>
<td>5 mg BID</td>
</tr>
<tr>
<td>Methylphenidate IR*</td>
<td>5 mg BID</td>
<td>5 mg BID</td>
<td>5 mg BID</td>
</tr>
</tbody>
</table>

*Many papers and clinicians may recommend TID dosing for methylphenidate IR.

### 2011 CADDRA Recommendations for Dosing Psychostimulants

#### Maximum dose

<table>
<thead>
<tr>
<th></th>
<th>Child</th>
<th>Adolescent</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line agents – long-acting preparations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mixed amphetamine salts XR</td>
<td>30 mg</td>
<td>30 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>MLR methylphenidate</td>
<td>60 mg</td>
<td>60 mg</td>
<td>80 mg</td>
</tr>
<tr>
<td>OROS methylphenidate</td>
<td>72 mg</td>
<td>108 mg</td>
<td>108 mg</td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td>60 mg</td>
<td>60 mg</td>
<td>70 mg</td>
</tr>
<tr>
<td><strong>Second-line/adjunctive agents – short-acting or intermediate-acting preparations</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>30 mg</td>
<td>30 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>Methylphenidate IR*</td>
<td>60 mg</td>
<td>60 mg</td>
<td>100 mg</td>
</tr>
</tbody>
</table>

*Many papers and clinicians may recommend TID dosing for methylphenidate IR.

**Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (CADDRA): Canadian ADHD Practice Guidelines. 2011.**

### Benefits of Long-Acting Stimulant Formulations

- Core impairments continue all day long
- Use of a long-acting stimulant formulation may improve medication compliance
  
  1Swanson J., CNS Drugs, 2003; 17:117-131.
- May decrease abuse potential
- Smother, more consistent coverage
### Comparison of New Long-acting Stimulants

<table>
<thead>
<tr>
<th>Drug</th>
<th>Release mechanism</th>
<th>% of dose immediately released</th>
<th>Duration</th>
<th>Available doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLR methylphenidate(^1)</td>
<td>Multilayer beads(^*), Bi-modal</td>
<td>40%</td>
<td>10-12 hours</td>
<td>8</td>
</tr>
<tr>
<td>OROS methylphenidate(^1,2)</td>
<td>Water absorption, push mechanism, TID delivery</td>
<td>22%</td>
<td>10-12 hours</td>
<td>4</td>
</tr>
<tr>
<td>Mixed amphetamine salts XR(^1)</td>
<td>Two beads(^*), BID delivery</td>
<td>50%</td>
<td>10-12 hours</td>
<td>6</td>
</tr>
<tr>
<td>Lisdexamfetamine(^1,3)</td>
<td>Prodrug, lysine is cleaved in bloodstream(^**)</td>
<td>Continuous</td>
<td>13-14 hours</td>
<td>5</td>
</tr>
</tbody>
</table>

\(^*\)Capsules may be opened and beads inside the capsule can be sprinkled (e.g., on apple sauce) with no loss in efficacy.

\(^**\)Capsules may be opened and diluted in water with no loss in efficacy.


### Drug-drug Interactions of Stimulants

**Drug-drug interactions (methylphenidate)**
- Caution with monoamine oxidase inhibitors (MAOIs) antidepressants, e.g., phenelzine
- Inhibits metabolism of warfarin, anticonvulsants, tricyclic antidepressants – need to adjust dose

---

Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (CADDRA): Canadian ADHD Practice Guidelines
2011
Adverse Effects of Stimulants

Adverse effects

• Methylphenidate and dextroamphetamine have similar side effect profiles
  – Decreased appetite
  – Insomnia
  – Upset stomach
  – Headache
  – Irritability

• Side effects decrease with time


Areas of Concern and Controversy with Stimulant Use

• Growth suppression
• Development of tics
• Medication abuse
• Medico-legal concerns
• Use in adolescents
• Rebound
• Cognitive toxicity
• Cardiovascular effects

Next Analyses of the MTA Follow-up

Z-height of Naturalistic subgroups at the 72-month assessment

Long-term Effects of Extended Exposure to Stimulant Medication for ADHD on Mature Adult Stature
Figure 2
Cumulative Stimulant Exposure and Prevalence of Blood Pressure Equal or Above the 90th Percentile at the 10-Year Assessment

Summary of Results

No serious cardiovascular adverse effects over 10 years.

Blood Pressure
- Stimulant Medication (7-9 yrs. for 10 years)
- Intensive, sustained, continuous
- No increase in BP
- No increase in prehypertension
- No increase in hypertension

*NBP or and dBP ≥90th percentile for age, gender, and height. Based on one measurement only (see text for discussion)
*Cumulative stimulant medication exposure over 10 years, in methylphenidate-equivalent mg.
Summary of Results

Heart Rate (all within normal range)
- 14 months ↑ stimulants → ↑ HR
- Current use ↔ ↑ HR
  - No accommodation
- 8 year  some evidence of cumulative effect regardless of current use
- 10 year no evidence of cumulative effective

Dose Response of Mixed Amphetamine Salts XR
Study: Summary of CGI-I (Responders) at Week 4

CGI-I values presented include "very much improved" and "much improved"
*p<0.001 (non-zero correlation CMH statistic with adjustment for centre)
Adverse Events Reported Over Time

<table>
<thead>
<tr>
<th>Week</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>191</td>
</tr>
<tr>
<td>2</td>
<td>184</td>
</tr>
<tr>
<td>3</td>
<td>168</td>
</tr>
<tr>
<td>4</td>
<td>151</td>
</tr>
</tbody>
</table>

Total treatment-emergent AEs, %


CONCERTA*: OROS Technology to Clinical Efficacy

- Mean methylphenidate plasma concentration (ng/ml)
- Time (hours)
- 0 4 8 12 16 20 24 28 32
- CONCERTA* methylphenidate TID
- An initial dose dissolves within an hour
- Specially engineered capsule releases a steadily rising concentration of methylphenidate
- Design ensures that physiological activity lasts no longer than that seen with an immediate-release TID methylphenidate preparation
OROS MPH Demonstrated Lower Impaired Driving Scores (FIX)

Participants performed significantly better when receiving OROS MPH q.d. compared with MPH t.i.d. ($F = 9.3$, $df = 1$, $p = .004$).

N=6, mean age 17.2, 15.8 months driving experience
IDS 0= average driving, IDS>0 worse than average driving

Cox et al. JAACAP, 2004
Biphentin®
(CR Methylphenidate MLRTM)

Clinical Global Impressions
(Last 2 weeks average)

Adverse Effects
- None
- Mild
- Moderate
- Severe-Extreme

Therapeutic Effect
- Marked
- Moderate
- Minimal
- Unchanged or Worse

Efficacy Index
- Very much improved
- Much improved
- Minimally improved
- No change
- Minimal
- Unchanged or Worse

Global Improvement
- Very much worse
- Much worse
- Minimally worse
- No change
- Minimal
- Unchanged or Worse
- Not assessed

* p=0.0066; ** p=0.0033; *** p=0.0015 vs. placebo
**Adderall XR ®**

**Pulse Delivery System**

**Immediate-release Bead**
- Bead Core
- Drug Layer
- Overcoating

**Extended-release Bead**
- Bead Core
- Drug Layer
- Release-delaying polymer
- Overcoating

**ADDERALL XR ® Capsule**

Available in 5 mg, 10mg, 15mg, 20mg, and 30 mg capsules

---

**Mixed Amphetamine Salts XR**

**Effect on Driving**

![Graph showing effect on driving](image)

Sustained Symptom Control During Long-term Treatment with Mixed Amphetamine Salts XR

*p < 0.001 by 1-sample t test of mean change from baseline of long-term study

The approved dose of Adderall XR for adults is 20 mg/day.

There was not adequate evidence that doses greater than 20 mg/day conferred additional benefit.

Data are from all doses of Adderall XR used during the long-term study.


Greater Improvement
Mean ADHD-RS-IV Total Score

Week Month

Baseline 1 2 3 4 2 4 6 8 10 12 14 16 18 20 22 24

Transition (N=221)

Chemical Structure of Lisdexamfetamine

- Lisdexamfetamine is a prodrug that is therapeutically inactive until it is converted to active d-amphetamine in the body.

\[
\text{Lisdexamfetamine (Prodrug) \quad \rightarrow \quad \text{L-lysine} \quad \rightarrow \quad \text{d-amphetamine (active)}}
\]

Lisdexamfetamine

- Once-daily capsule for the treatment of ADHD
- Therapeutically inactive until it is converted to active d-amphetamine in the body
- Can be taken with or without food
- Dosage equivalence roughly 2 times mixed amphetamine salts XR
  - 60 mg lisdexamfetamine = 30 mg mixed amphetamine salts XR

Analog Classroom Study: Lisdexamfetamine vs. Placebo

Significantly more math problems were answered correctly with lisdexamfetamine vs. placebo, as measured on the PERMP-C scale

† p<0.001 vs. placebo
Mixed amphetamine salts XR was included as a reference arm. The study was not designed as a comparative trial between active treatments.

Indications for Atomoxetine

- Patients not responsive to stimulants
- Patients with significant side effects to stimulants (e.g., rebound, tics)
- Patients with Tourette’s Syndrome or chronic motor tic disorders
- Epilepsy
- Comorbid Anxiety
- Abuse or diversion is a concern

Problems

- 6-8 week titration
  - 0.5mg/kg 2 weeks
  - 0.8mg/kg 2 weeks
  - 1.2mg/kg 2 weeks
- Metabolized via cytochrome P450-206 system (10% slow metabolizers)
- Drug/drug interaction, e.g., paroxetine, fluoxetine, quinidine
Tolerability of Atomoxetine:  
Adult ADHD Studies

<table>
<thead>
<tr>
<th>Event*</th>
<th>Atomoxetine (n=269) %</th>
<th>Placebo (n=263) %</th>
<th>P-Value</th>
<th>Discontinuation n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dry mouth</td>
<td>21</td>
<td>6</td>
<td>&lt;.001</td>
<td>0</td>
</tr>
<tr>
<td>Insomnia</td>
<td>13</td>
<td>6</td>
<td>.013</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>12</td>
<td>5</td>
<td>.005</td>
<td>1</td>
</tr>
<tr>
<td>Constipation</td>
<td>10</td>
<td>4</td>
<td>.009</td>
<td>0</td>
</tr>
<tr>
<td>Appetite decreased</td>
<td>10</td>
<td>3</td>
<td>&lt;.001</td>
<td>0</td>
</tr>
<tr>
<td>Dizziness</td>
<td>6</td>
<td>2</td>
<td>.015</td>
<td>0</td>
</tr>
<tr>
<td>Libido decreased</td>
<td>6</td>
<td>2</td>
<td>.010</td>
<td>1</td>
</tr>
<tr>
<td>Erectile disturbance†</td>
<td>7</td>
<td>1</td>
<td>.006</td>
<td>1</td>
</tr>
<tr>
<td>Dysmenorrhea‡</td>
<td>7</td>
<td>3</td>
<td>.331</td>
<td>0</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>3</td>
<td>0</td>
<td>.015</td>
<td>2</td>
</tr>
</tbody>
</table>

*Events reported by at least 5% of atomoxetine patients  
†Based on total number of males (atomoxetine, n=174; placebo, n=172)  
‡Based on total number of females (atomoxetine, n=95; placebo, n=91)


Efficacy of Atomoxetine in Adults

* p<0.05, ** p<0.003, *** p<0.001

**Principles of Treating Comorbid Conditions**

- Treat most disabling condition with most effective treatment first
  - Psychosocial treatment
  - Medication treatment
  - Both
- Then treat other condition with most effective treatment(s)

**ADHD Treatment Algorithm**

0. Assessment/Family Consultation/Treatment Planning

1. Methylphenidate or Amphetamine
   - 1a. Amphetamine not used in Step 1
   - 2. Stimulant not used in Step 1
     - 2a. Amphetamine not used in Step 2

2. Non-med treatments

3. Atomoxetine

4. Bupropion or TCA

5. Agent not used in Step 4

6. Alpha agonist
   - Consultation

3a. Combine Atomoxetine & Stimulant

---

ODD Treatment

- Counseling, psychotherapy, family training and therapy, behavior management and therapy
- ODD and aggressive behavior secondary to ADHD may improve with the treatment of ADHD
- Medication: Psychostimulants, atomoxetine, antidepressants, atypical antipsychotics, clonidine

ADHD + Aggression

1. Begin ADHD algorithm
2. Add behavioral intervention
3. Add atypical antipsychotic to stimulant
4. Add lithium or divalproex sodium to stimulant
5. Use agent not used in Stage 4

Partial or non-response aggression

Consultation

### ADHD + Anxiety

- Assessment/Family Consultation/Treatment Planning
- Non-med treatments
- Atomoxetine
- Both ADHD and Anxiety improve
- Methylphenidate or Amphetamine
- No response ADHD or Anxiety
  - Methylphenidate or Amphetamine
- ADHD improves/not Anxiety
  - Atomoxetine
  - Add SSRI

---

### ADHD + Depression

- Assessment/Family Consultation/Treatment Planning
- Non-med treatments
- ADHD more severe
  - Begin ADHD algorithm Stage 1
- MDD more severe
  - Begin MDD algorithm Stage 1
- Both ADHD and MDD improve
  - Continuation
- ADHD improves/no response MDD
  - Add MDD algorithm to ADHD treatment
- ADHD and/or MDD worsens
  - Discontinue ADHD
  - Begin MDD
- MDD improves/no ADHD response
  - Begin ADHD
  - Add to MDD

---

CGI-Global, ADHD and Anxiety/Depression
OC Sample

- Global: Pax, Dex, Comb vs Placebo p=.001
- ADHD: Dex, Comb vs Pax, Placebo p=.001
- Anx/Dep: Pax, Comb vs Dex, Placebo p=.001

Adverse Events (AE)

- More severe AE in comb group (p<.05)
- More patients who discontinued in the comb group did so because they showed deterioration
Pharmacological Treatment of ADHD and Comorbidity

- Substance abuse
  - Need to treat ADHD
  - Careful with diversion
- Depression
  - If severe, treat depression prior to ADHD
  - Consider SSRI’s + stimulants, bupropion
- Bipolar I Disorder
  - Treat prior to ADHD
- Bipolar II Disorder
  - Open data with bupropion

Treatment of Bipolar Disorder and ADHD

- Treat bipolar conditions first
  a) Mood stabilizers
    - Lithium (approved down to age 12)
    - Valproate
  b) Atypical antipsychotic medication
  c) Effectiveness and safety of mood stabilizer regiments for earlier onset cases of juvenile mania had not been established (particularly in preschoolers)
  d) Patients with significant emotional behavioral dysregulation need intensive behavioral and parenting intervention
Treatment of Bipolar Disorder and ADHD

- Once bipolar condition is stabilized, e.g., on mood stabilizers, can add stimulants carefully
  a) Patients with ADHD and manic-like symptoms (broad) given stimulants improved (did not develop mania)
  b) SSRI or other mood elevators more likely to trigger mania

Pharmacological Treatment of ADHD and Comorbidity

- Tics and Tourette’s + ADHD
  – Can try stimulants may not make it worse
  – If stimulants make tics worse, try atomoxetine
  – If still problematic, add risperidone or clonidine
Pharmacological Treatment of ADHD and Comorbidity

- Pervasive Developmental Disorder + ADHD Symptoms
  - Try Risperidone
  - Can try stimulants may not be that effective
  - Then can try atomoxetine

Summary

- ADHD is very prevalent
  - 6-8% of child population
  - 4% of adult population
- Hyperactivity & impulsivity decrease with age
- Genetics & brain development implicated in etiology
- ADHD is highly comorbid
  - 70% in childhood
  - 85% in adulthood
- Nature of comorbidity changes with time
- Need to treat all impairment
  - Psychosocial treatments
  - Medication treatments