ADHD: MANAGEMENT, STRATEGIES AND TREATMENT

DAVID L. SHADID, D.O.
ADULT, CHILD & ADOLESCENT PSYCHIATRY
TYPES OF ADHD

- Inattentive only
- Hyperactive/Impulsive
- Combined Inattentive/Hyperactive/Impulsive (50-75%)
Estimated Prevalence of ADHD in Children Is 3% to 6%

Epidemiologic studies show prevalence of 3%-6% of children and adolescents

- United States (Shaffer et al 1996)
- Tennessee (Wolraich et al 1996)
- Mannheim, Germany (Esser et al 1990)
- Germany (Baumgaertel et al 1995)
- Iowa (Lindgren et al 1990)
- Pittsburgh, Pa (Costello et al 1988)
- US inner city (Newcorn et al 1989)
- Ontario (Szatmari et al 1989)
- New Zealand (Anderson et al 1997)

Prevalence of ADHD (%) in school-age children

ADHD: Prevalence

- Affects 8 - 10% of school-aged children\(^1,2\)
  - Diagnosed in boys 3 to 4 times more than in girls\(^3\)
- Accounts for 30 - 50% of mental health referrals for children\(^4\)
- Persists in some patients into adolescence and adulthood\(^5-7\)
  - 40 - 70% of adolescents
  - Up to 50% of adults
- White children more often diagnosed than black or Hispanic children\(^8\)

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**Lifetime Course of ADHD**

**Symptoms: Inattention Domain**

**Childhood**
- Difficulty sustaining attention
- Doesn’t listen
- No follow through
- Can’t organize
- Loses important items

**Adult**
- Difficulty sustaining attention (meetings, reading, paperwork)
- Paralyzing procrastination
- Slow, inefficient
- Poor time management
- Disorganized

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Lifetime Course of ADHD Symptoms: Hyperactivity/Impulsivity Domain

**Childhood**
- Squirming, fidgeting
- Can’t stay seated
- Can’t wait turn
- Runs/climbs excessively
- Can’t play/work quietly
- On the go/driven by motor
- Talks excessively
- Blurts out answers
- Intrudes/interrupts others

**Adult**
- Inefficiencies at work
- Can’t sit through meetings
- Can’t wait in line
- Drives too fast
- Self-selects very active job
- Can’t tolerate frustration
- Talks excessively
- Interrupts others
- Makes inappropriate comments

DIFFERENTIAL DIAGNOSIS

- ADJUSTMENT DISORDER
- PHYSICAL PROBLEMS
- MEDICATION
- ABUSE OF DRUGS
- SITUATIONAL ANXIETY
- CHILD ABUSE OR NEGLECT
- CD OR ODD
- DEPRESSION AND ANXIETY DISORDER
- MANIA OR BIPOLAR MIXED STATE
- PSYCHOSIS
- PERVASIVE DEVELOPMENTAL DISORDER
- MENTAL RETARDATION OR LEARNING DISORDER
ADHD: Comorbid Conditions

- Oppositional defiant disorder: 40%
- Language disorders: 30-35%
- Anxiety disorders: 20-25%
- Learning difficulties: 15-25%
- Mood disorders: 15-20%
- Conduct disorder: 20%
- Smoking: 19%
- Substance use disorder: 15%

ADHD: Comorbid Conditions

- General assessment guidelines
  - Be aware of the significant occurrence of comorbidities in patients with ADHD
    - Comorbidity is the rule rather than the exception
  - Consider the possible existence of comorbidities when diagnosing ADHD
    - Review of symptoms: representative questions about symptoms in multiple categories and domains of function
  - Consider the possible existence of ADHD when diagnosing other conditions
  - Treatment options: offer appropriate treatment options for both ADHD and comorbidities, including counseling / education, behavioral / cognitive / family therapy, pharmacological treatment

DIAGNOSIS OF ADHD IN ADULTS

DSM-IV-TR Diagnosis of ADHD in Adults

Symptoms: Consistent with the 18-item DSM-IV-TR symptoms
Impairments: In two or more settings (e.g., home, school (work), social)
History: Consistent with childhood onset of disorder
ADHD DIAGNOSTIC EVALUATION

- BLUEPRINT FOR SUCCESS
  - A LONG-TERM MANAGEMENT PLAN WITH
    - TARGET OUTCOMES FOR BEHAVIOR
    - FOLLOW-UP FOR BEHAVIOR
    - FOLLOW-UP ACTIVITIES
    - MONITORING
BLUEPRINT FOR SUCCESS (cont.)

- EDUCATION ABOUT ADHD
- TEAMWORK AMONG DOCTORS, PARENTS, TEACHERS, CAREGIVERS, OTHER HEALTH CARE PROFESSIONALS, AND THE CHILD
- MEDICATION
- BEHAVIOR THERAPY
- PARENT TRAINING
- INDIVIDUAL AND FAMILY COUNSELING
GENETIC AND MEDICAL RISKS FOR ADHD

- GENETIC RISKS
  - HYPERACTIVITY
  - CONDUCT DISORDER
  - ALCOHOLISM & SOCIOPATHY
  - MOOD & ANXIETY DISORDERS
  - LEARNING DISORDERS
  - MINOR PHYSICAL ANOMALIES
  - ADOPTION

- MEDICAL RISKS
  - PREGNANCY/BIRTH & DELIVERY
  - TOXEMIA
  - PREMATURE LABOR
  - LOW BIRTH WEIGHT
  - C-SECTION W/COMPLICATIONS
  - MEDICAL HISTORY
  - CENTRAL NERVOUS SYSTEM INFECTION
  - CHRONIC MEDICAL ILLNESS
  - HEAD INJURY W/UNCONSCIOUSNESS
  - SEIZURES
  - SEVERE ALLERGIES/ASTHMA
TEMPERAMENT AND ENVIRONMENTAL RISK FACTORS FOR ADHD

- TEMPERAMENT RISKS
  - ACTIVITY LEVEL
  - NOVELTY SEEKING, IMPULSIVITY
  - INCONSOLABILITY
  - FEARFULNESS
  - RESPONDS WITH HIGH INTENSITY
  - IRREGULAR EATING AND SLEEPING PROBLEMS
  - RIGID, TENSE, NOT CUDDLY

- ENVIRONMENTAL RISKS
  - FAMILY STRESS
  - ECONOMIC PROBLEMS
  - EXPOSURE TO HEAVY METALS
  - DIETARY FACTORS
    - POOR DIET
    - POSSIBLE ROLE OF LINOLEIC ACID
    - ROLE OF MULTIVITAMIN SUPPLEMENTS
    - ROLE OF EXCLUSIONARY DIETS
Impact and Costs of ADHD

Academic limitations  Low self-esteem  Smoking and substance abuse  Legal problems

Childhood  Adolescence  Adulthood

Impaired family and peer relationships  Injuries  Motor vehicle accidents  Occupational/vocational difficulties

ADHD: Impact of Untreated and Undertreated ADHD

Health Care System
- 50% ↑ in bike accidents¹
- 33% ↑ in ER visits²
- 2 - 4x more motor vehicle crashes³-⁵

Patient

School and Occupation
- 46% expelled⁶
- 35% drop out⁶
- Lower occupational status⁷

Society
- Substance use disorders: 2x risk⁸
- Earlier onset⁹
- Less likely to quit in adulthood¹⁰

Family
- 3 - 5x ↑ parental divorce or separation¹¹,¹²
- 2 - 4x ↑ sibling fights¹³

Employer
- ↑ parental absenteeism and productivity¹⁴

SOCIAL IMPAIRMENT IN CHILDREN WITH ADHD

![Graph showing the comparison of ADHD and normative behaviors.](image-url)
IMPAIRMENT IN MOTOR VEHICLE DRIVING

Impairment: Effects on Motor Vehicle Driving

Drivers with ADHD tended to have more severe accidents than controls*

- Hit and Run*
  - Control (n=36)
  - ADHD (n=35)

- Totaled Vehicle*

- License Suspended
Effect of Core and Broad Symptoms on Patients with ADHD

- Repeated Grade
- Teen Pregnancy
- Sexually Transmitted Diseases
- Substance Abuse
- Intentional Injury
- Fired from Job
- Attempted Suicide
Medical Costs Are Greater in Children With ADHD

Annual Costs of Healthcare for Children and Adolescents With ADHD*

- Annual costs of healthcare were 31% higher for children and adolescents with ADHD than for those without.
- ADHD care accounted for >5% of all pediatric health expenditures in the state.
- Extrapolated nationwide annual cost of caring for children and adolescents with ADHD was $2.15 billion.

*Population-based study conducted in North Dakota, case population = 7745 children and adolescents.
Untreated ADHD Is Associated With Higher Risk of Substance Abuse

Treatment Options

- Education
- Psychosocial/behavioral interventions
- Pharmacotherapeutic interventions

TREATMENT OF ADHD

- Non-Pharmacological
  - Counseling
  - Support Groups
  - Education
  - Communication
  - Behavioral Therapy
  - Parent Training
Treatment of ADHD (cont.)

- Pharmacological
  - Stimulants
  - Noradrenergic agents
  - Antidepressants
  - Antihypertensives
Medications Used in ADHD

- First-line treatments
  - Psychostimulants
    - Methylphenidate (extended-release, eg, CONCERTA®)
    - Amphetamine (extended-release, eg, Adderall XR®)
- Other treatments
  - Antidepressants / noradrenergic agents
    - TCAs (including imipramine, desipramine, nortriptyline)
    - Bupropion
    - Venlafaxine
    - Atomoxetine (Strattera®)
    - Antihypertensives clonidine guanfacine

FDA-Approved Medications Indicated for ADHD

<table>
<thead>
<tr>
<th>Stimulants</th>
<th>Brand Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>$d,l$-methylphenidate</td>
<td>Ritalin®, Ritalin SR®, Ritalin LA®, Concerta®, Metadate® CD</td>
</tr>
<tr>
<td>$d$-methylphenidate</td>
<td>Focalin™, Focalin™ XR</td>
</tr>
<tr>
<td>Mixed amphetamine salts</td>
<td>Adderall®, Adderall SR®</td>
</tr>
<tr>
<td>$d$-Amphetamine</td>
<td>Dexedrine®, Dexedrine® Spansule</td>
</tr>
<tr>
<td><strong>Nonstimulant</strong></td>
<td></td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Strattera®</td>
</tr>
</tbody>
</table>

Ritalin®, Ritalin SR®, and Ritalin LA® are trademarks of Novartis Pharmaceuticals Corporation; Concerta® is a trademark of McNeil Pharmaceuticals; Metadate® CD is a trademark of Celltech; Adderall® and Adderall SR® are trademarks of Shire US Inc.; Dexedrine® and Dexedrine® Spansule are trademarks of GlaxoSmithKline; Strattera® is a trademark of Eli Lilly and Co.
# Stimulants Used in ADHD

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Methylphenidate</strong></td>
<td>Ritalin</td>
<td>0.3-2 mg/kg</td>
<td>2 to 4 times daily</td>
</tr>
<tr>
<td></td>
<td>Metadate</td>
<td>0.6-2 mg/kg</td>
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</tr>
<tr>
<td></td>
<td>Concerta</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ritalin LA</td>
<td></td>
<td></td>
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<td></td>
<td>Ritalin SR</td>
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<td></td>
</tr>
<tr>
<td></td>
<td><strong>Dexmethylphenidate</strong></td>
<td>0.15-1 mg/kg</td>
<td>2 to 4 times daily</td>
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<tr>
<td></td>
<td>Focalin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Focalin XR</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Amphetamine</strong></td>
<td>Dexedrine</td>
<td>0.3-1.5 mg/kg</td>
<td>Once</td>
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<tr>
<td></td>
<td>Adderall</td>
<td></td>
<td>2 or 3 times</td>
</tr>
<tr>
<td></td>
<td>Adderall XR</td>
<td></td>
<td>Once</td>
</tr>
<tr>
<td><strong>Pemoline</strong></td>
<td>Cylert</td>
<td>1-3 mg/kg</td>
<td>Once or twice</td>
</tr>
</tbody>
</table>

11/23/2003
## Types of Stimulants

<table>
<thead>
<tr>
<th>Duration</th>
<th>Stimulants</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 hour Stimulants</td>
<td>Concerta, Adderall XR</td>
</tr>
<tr>
<td>8 hour Stimulants</td>
<td>Focalin XR, Metadate CD, Ritalin LA, Methylin ER</td>
</tr>
<tr>
<td>5-6 hour Stimulants</td>
<td>Adderall, Dexedrine Spansules, Focalin, Ritalin SR, Metadate ER</td>
</tr>
<tr>
<td>4 hour Stimulants</td>
<td>Ritalin (IR), Methylin, Dexedrine/Dextrostat</td>
</tr>
</tbody>
</table>
# Long-Acting ADHD Agents

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Active Compound</th>
<th>Doses</th>
<th>Corresponding Dose of Immediate Release Version</th>
<th>Length of Efficacy</th>
<th>Drug Delivery Mechanism</th>
<th>Immediate/Sustained Concentration</th>
<th>Monthly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concerta (J&amp;J)</td>
<td>Racemic methylphenidate HCL</td>
<td>18mg, 27mg, 36mg, 54mg</td>
<td>27mg, 36mg, 54mg</td>
<td>12 hours</td>
<td>Osmotic capsule</td>
<td>22% is on outer coat and absorbed immediately; 78% is released continuously</td>
<td>$74.70</td>
</tr>
<tr>
<td>Metadate CD (Celltech)</td>
<td>Racemic methylphenidate HCL</td>
<td>10mg, 20mg, 30mg</td>
<td>10mg bid, 15mg bid</td>
<td>8-9 hours</td>
<td>Beads</td>
<td>30% Immediate; 70% continuous</td>
<td>$76.80</td>
</tr>
<tr>
<td>Ritalin LA (Novartis)</td>
<td>Racemic methylphenidate HCL</td>
<td>10mg, 20mg, 30mg, 40mg</td>
<td>10mg bid, 15mg bid, 20mg bid</td>
<td>8-9 hours</td>
<td>Beads</td>
<td>50% Immediate; 50% 4 hours later</td>
<td>$68.40</td>
</tr>
<tr>
<td>Metadate ER (Celltech)</td>
<td>Racemic Methylphenidate HCL</td>
<td>10mg, 20mg</td>
<td></td>
<td></td>
<td>Wax Matrix</td>
<td></td>
<td>$60.00</td>
</tr>
<tr>
<td>Methylin ER (Mallinckrodt)</td>
<td>Racemic methylphenidate HCL</td>
<td>10mg, 20mg</td>
<td></td>
<td></td>
<td>Wax Matrix</td>
<td></td>
<td>$62.40</td>
</tr>
<tr>
<td>Ritalin SR (Novartis)</td>
<td>Racemic Methylphenidate HCL</td>
<td>20mg</td>
<td></td>
<td></td>
<td>Wax Matrix</td>
<td></td>
<td>$68.40</td>
</tr>
</tbody>
</table>
## Long-Acting ADHD Agents (cont.)

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Active Compound</th>
<th>Doses</th>
<th>Corresponding Dose of Immediate Release Version</th>
<th>Length of Efficacy</th>
<th>Drug Delivery Mechanism</th>
<th>Immediate/Sustained Concentration</th>
<th>Monthly Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate SR (Geneva)</td>
<td>Racemic Methylphenidate HCL</td>
<td>20mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dexedrine Spansules (Glaxo Smith Kline)</td>
<td>Dextroamphetamine Sulfate</td>
<td>5mg 10mg 15mg 20mg 10mg 15mg</td>
<td>8 hours</td>
<td></td>
<td></td>
<td></td>
<td>$64.80</td>
</tr>
<tr>
<td>Dextroamphetamine Sulfate Spansules (Generic)</td>
<td>Dextroamphetamine Sulfate</td>
<td>5mg 10mg 15mg 20mg 10mg 15mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$49.81</td>
</tr>
<tr>
<td>Adderall XR (Shire Inc.)</td>
<td>Neutral salts of dextroamphetamine with dextroamphetamine saccharate and d, l-amphetamine aspartate monohydrate extended release</td>
<td>5mg 10mg 15mg 20mg 25mg 30mg 2.5mg bid 5mg bid 10mg bid 15mg bid</td>
<td>12 hours</td>
<td>Beads</td>
<td>50% Immediate; 50% 4 hours later</td>
<td></td>
<td>$73.20</td>
</tr>
<tr>
<td>Strattera (Eli Lilly)</td>
<td>Selective Norepinephrine Reuptake inhibitor</td>
<td>10mg 18mg 25mg 40mg 60mg 10mg bid 15mg bid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$90.00</td>
</tr>
</tbody>
</table>
Focalin™ XR: A Once-Daily Formulation of Dexmethylphenidate

- Rapid onset, similar to immediate-release Focalin
- Uses SODAS™ extended-release technology to mimic BID dosing
  - 50% of dose released immediately upon administration
  - 50% of dose released ≈4 h later for extended duration of action
- Once-daily dose in morning eliminates need for in-school or midday dose
- Flexible, individualized dosing
- Smooth response curve over postdose interval

<table>
<thead>
<tr>
<th>Dose</th>
<th>d-MPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Immediate</td>
<td></td>
</tr>
<tr>
<td>release 2.5 mg</td>
<td>50%</td>
</tr>
<tr>
<td>5 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Second release</td>
<td></td>
</tr>
<tr>
<td>2.5 mg</td>
<td>5 mg</td>
</tr>
<tr>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>
Summary

- Dexmethylphenidate (\textit{d}-MPH, Focalin™) is the active enantiomer of racemic MPH (\textit{d},\textit{l}-MPH, Ritalin®)
- The \textit{d}-isomer differs from the \textit{l}-isomer in brain binding sites, pharmacokinetics, and pharmacodynamics
- Focalin IR remains significantly more effective than placebo at 6 hours postdose
- Focalin XR is the first and only formulation of \textit{d}-MPH that uses extended-release technology to allow rapid onset of action and once-daily dosing
ADHD Treatment With Stimulant Medication

• Initiating stimulant therapy
  – Dose titration to achieve optimal dose\(^1\)
    • Appropriate starting dose
    • Titrate to optimal effect, not just to measurable effect
• Trial of second stimulant in patients who fail to respond to maximum dose of first stimulant\(^1\)
• Regular monitoring to ensure symptoms of ADHD are optimally managed\(^2\)

ADHD Importance of Titration

• AAP Guidelines\(^1\) state
  – Begin with an appropriate starting dose and titrate upward
    • The first dose that achieves response may not be the optimal dose to improve function
  – Clinicians should continue to use higher doses to achieve better responses
  – Optimal dose: best individualized response with minimal side effects
• Dosage should be individualized according to the needs and responses of the patient\(^2\)

Common Side Effects of Stimulants
(most common)

- Decreased appetite/weight loss
- Sleep problems
- Headaches
- Jitteriness
- Social withdrawal
- Stomachaches
Common side effects of Stimulants (less common)

- Dry mouth
- Dizziness
- Rebound effect (increased activity or a bad mood as the medication wears off)
- Transient tics
Common side effects of Stimulants (rare)

- Stuttering
- Increased in blood pressure or heart rate
- Growth delay
Noradrenergic Agents

<table>
<thead>
<tr>
<th>Atomoxetine</th>
<th>Strattera</th>
<th>&lt;1.2 mg/kg</th>
<th>Once or twice</th>
</tr>
</thead>
</table>


## Common Adverse Effects

| Atomoxetine     | - Nausea  
|                 | - Dizziness  
|                 | - Insomnia  
|                 | - Immunosuppression  

## Antidepressants

<table>
<thead>
<tr>
<th></th>
<th></th>
<th>mg/kg</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tricyclics</strong></td>
<td><strong>Imipramine</strong></td>
<td>2.5</td>
<td>Once or twice</td>
</tr>
<tr>
<td></td>
<td><strong>Desipramine</strong></td>
<td>1-3</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Nortriptyline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Bupropion</strong></td>
<td><strong>Wellbutrin</strong></td>
<td>3-6</td>
<td>3 times</td>
</tr>
<tr>
<td></td>
<td><strong>Wellbutrin SR</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Venlafaxine</strong></td>
<td><strong>Effexor</strong></td>
<td>0.5-3</td>
<td>Twice</td>
</tr>
<tr>
<td></td>
<td><strong>Effexor XR</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## Common Adverse Effects

| Tricyclics                  | - Dry mouth  
|                            | - Constipation  
|                            | - Weight loss  
|                            | - Vital signs and ECG changes  
| Bupropion                  | - Irritability  
|                            | - Insomnia  
|                            | - Risk of seizures (in doses >6mg/kg)  
|                            | - Contraindicated in bulimics  
| Venlafaxine                | - Nausea  
|                            | - Sedation  
|                            | - Gastrointestinal distress  

11/23/2003
Wellbutrin

Advantages
- Efficacy in ADHD
- May decrease hyperactivity and aggression
- Efficacy in depression
- May improve cognitive performance
- Less likely to precipitate mania

Disadvantages
- Few studies in ADHD
- May decrease seizure threshold
- May exacerbate tics
## Antihypertensives

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine</td>
<td>3-10 pg/kg</td>
<td>2 or 3 times</td>
</tr>
<tr>
<td>Guanfacine</td>
<td>30-100 pg/kg</td>
<td>twice</td>
</tr>
</tbody>
</table>
# Common Adverse Effects

<table>
<thead>
<tr>
<th></th>
<th>Clonidine</th>
<th>Guanfacine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>- Sedation</td>
<td>- Similar to clonidine but less sedation</td>
</tr>
<tr>
<td></td>
<td>- Dry mouth</td>
<td>- Insomnia</td>
</tr>
<tr>
<td></td>
<td>- Confusion (with high doses)</td>
<td>- Irritability reported</td>
</tr>
<tr>
<td></td>
<td>- Rebound hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Localized irritation with patch</td>
<td></td>
</tr>
</tbody>
</table>


Strattera™: Effects on Dopamine

- Downstream increase in dopamine levels in the prefrontal cortex
- No increase in dopamine in the nucleus accumbens
  - Not associated with abuse liability
- No increase in dopamine in the striatum
  - Not associated with motor activity (tics)

Once-Daily Efficacy (cont.)

ADHD-RS Total Score

- Placebo (n=83)
- Strattera™ (n=84)

Mean Dose (mg/kg/day)
0.8
1.0
1.4
1.4

*p<.05 vs placebo.
# Tolerability Relative to Placebo and Methylphenidate

<table>
<thead>
<tr>
<th>Event</th>
<th>Stratterta™ (n=129)</th>
<th>Placebo (n=124)</th>
<th>Methylphenidate (n=37)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>30.2</td>
<td>28.2</td>
<td>45.9*</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>31.0</td>
<td>21.8</td>
<td>29.7</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>25.6</td>
<td>32.3</td>
<td>13.5*</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>21.7*</td>
<td>7.3</td>
<td>32.4*</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>16.3</td>
<td>15.3</td>
<td>10.8</td>
</tr>
<tr>
<td>Vomiting</td>
<td>14.7</td>
<td>12.1</td>
<td>13.5</td>
</tr>
<tr>
<td>Cough increased</td>
<td>13.2</td>
<td>11.3</td>
<td>16.2</td>
</tr>
<tr>
<td>Nervousness</td>
<td>13.2</td>
<td>6.5</td>
<td>16.2</td>
</tr>
<tr>
<td>Somnolence</td>
<td>9.3</td>
<td>8.1</td>
<td>10.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>10.1</td>
<td>10.5</td>
<td>16.2</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7.0</td>
<td>8.9</td>
<td>27.0***</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6.2</td>
<td>6.5</td>
<td>16.2</td>
</tr>
<tr>
<td>Fever</td>
<td>6.2</td>
<td>9.7</td>
<td>18.9**</td>
</tr>
<tr>
<td>Dizziness</td>
<td>3.9</td>
<td>4.0</td>
<td>13.5**</td>
</tr>
</tbody>
</table>

*p<.05 vs placebo. **p<.05 vs Strattera. Spencer, T et al. Manuscript in preparation.
Drug Interactions

- No clinically significant inhibition or induction of cytochrome P450 enzymes (3A, 2D6, 2C9, and 1A2)
- Dosage adjustment may be needed when coadministered with strong CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, and quinidine)
- Coadministration with I.V. albuterol (600 µg over 2 hours) induced modest increases in heart rate and blood pressure
- Use with MAOIs is contraindicated

Data on file, Eli Lilly and Company.
Drug Interactions (cont.)

- Co-administration of methylphenidate (MPH) did not increase cardiovascular effects beyond those seen with MPH alone
- Consumption of ethanol with Strattera™ did not change the intoxicating effects of ethanol

Data on file, Eli Lilly and Company.
Convenience for Patient/Parent/Physician

- Non-stimulant, non-controlled substance
- In an abuse potential study, Strattera™ was not associated with stimulant or euphoriant properties
- Availability of samples
- Ability to refill
- Ability to "call in" prescriptions to pharmacy
- No triplicate forms

**Strattera™: Ease of Dosing**

- Choose starting dose and maintain for minimum of 3 days
- Proceed to target dose thereafter

<table>
<thead>
<tr>
<th>Patient Weight Range</th>
<th>Starting Dose (Minimum of 3 days)</th>
<th>Target Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-62 lbs</td>
<td>18 mg</td>
<td>25 mg</td>
</tr>
<tr>
<td>63-93 lbs</td>
<td>25 mg</td>
<td>40 mg</td>
</tr>
<tr>
<td>94-126 lbs</td>
<td>40 mg</td>
<td>60 mg</td>
</tr>
<tr>
<td>127+ lbs</td>
<td>40 mg</td>
<td>80 mg</td>
</tr>
</tbody>
</table>

- Starter packs contain
  - 4 day supply of starting dose**
  - 14 day supply of target dose

*Combination of (2) 40 mg capsules. **Minimum of 3 days on starting dose is recommended.
Data on file, Eli Lilly and Company.
Strattera™: Conclusions

- Provides continuous symptom relief dosed once-daily
- Demonstrates long-term sustained effect (up to 76 weeks)
- Improves functional outcomes
- Incidence of insomnia comparable to placebo in children/adolescents
- Not contraindicated in patients with tics or anxiety
- Convenient for the patient/parent/physician
  - Nonstimulant, noncontrolled
  - Ease of dosing
Strattera

- **Advantages**
  - FDA approval for ADHD
  - ? Exacerbation of tics
  - Non-stimulant

- **Disadvantages**
  - 6-8 weeks until onset of action
  - 2 black box warnings
  - Hypomania/mania precipitation has been reported
  - No peer review studies for stimulants combined with Strattera (cost and hypomania concerns)
## ADHD IN ADULTS

<table>
<thead>
<tr>
<th>Medicine</th>
<th>Class</th>
<th>Dosage范围</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desipramine</td>
<td>Tricyclic</td>
<td>100 to 200 mg/d</td>
</tr>
<tr>
<td>Bupropion SR</td>
<td>Noradrenaline and dopamine reuptake inhibitor</td>
<td>150 mg bid to 200 mg bid</td>
</tr>
<tr>
<td>Venlafaxine XR</td>
<td>Serotonin and noradrenaline reuptake inhibitor</td>
<td>75 to 225 mg/d</td>
</tr>
<tr>
<td>Atomoxetine</td>
<td>Noradrenaline reuptake inhibitor</td>
<td>25 to 80 mg/d</td>
</tr>
</tbody>
</table>
ADHD PHARMACOLOGIC RESPONSE
Treatment Strategies

ADHD and Anxiety Disorders

1. Stimulant treatment may improve comorbid anxiety by around 30%. Reassess anxiety sx after ADHD sx is controlled.
2. Treat ADHD with stimulant first, then add a second agent if anxiety sx remain that cause functional impairment (ie, prioritize treatment).
3. ADHD and OCD always require both agents

Agents: SSRI, Remeron, etc.
ADHD and Depressive Disorders

- Treat ADHD first if depressive sx are mild, this will help identify those patients that are demoralized.
- Depressive sx often begin after the onset of ADHD
- Residual depression can then be treated with a variety of agents in conjunction with the tx of ADHD
- Consider SSRI (Zoloft?), Wellbutrin
ADHD with comorbid BPAD

- Girls and boys with ADHD = lifetime prevalence of BPAD approximately 11%
- Symptoms may overlap to some degree, but SEVERITY and INTENSITY of symptoms should help clarify diagnosis and resulting treatment strategies
- Treatment strategies: similar to ADHD/aggression protocols, but MUST TREAT MOOD COMPONENT FIRST!!
<table>
<thead>
<tr>
<th>BPAD</th>
<th>ADHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elated Mood</td>
<td>YES/irritable</td>
</tr>
<tr>
<td>Grandiosity</td>
<td>YES</td>
</tr>
<tr>
<td>Hyper sexuality</td>
<td>YES/cyclical</td>
</tr>
<tr>
<td>Decreased need for sleep</td>
<td>YES</td>
</tr>
<tr>
<td>Flight of ideas</td>
<td>YES</td>
</tr>
<tr>
<td>Hyperkinetic</td>
<td>YES</td>
</tr>
<tr>
<td>Distractibility</td>
<td>YES</td>
</tr>
</tbody>
</table>
Future Medication Advancements

- Adderall XXR – 18 hour duration of action
- Dexedrine/Lysine combination
- Transdermal patch systems: targeted for release early 2006 (Datrol)
- Guanfacine: once daily formulation targeted filing date in 2006/2007
- Modafilil
- NRP104
Future Medications

- **Modafinil (Provigil)**
  - Phase III Clinical trials.
  - Effective in Children and Adolescents.
  - Dosing 85 mg/day to 340 mg/day for patients weighing less than 30 kg.
  - Dosing 425 mg for patients weighing greater than 30 kg.
Future Medications (cont.)

- Modafinil (Provigil)
  - Safe
  - Effective for ADHD symptoms & behaviors
  - Well tolerated
  - No withdrawal symptoms
  - No rebound symptoms
Modafilil (Provigil)

- Side Effects
  - Insomnia 28%
  - Headaches 22%
  - Decreased appetite 18%
Future Medications

- New River Pharmaceuticals NRP 104
  - Final stages of Phase III clinical trials
  - Safer, abuse resistant
  - Potential blockbuster