BLUEPRINT FOR CHANGE:
Building a Better ADHD Treatment Regimen for
College Students

American College Health Association – Chicago – May 31, 2012

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Learning Objectives

① Discuss the neurologic pathways affected by ADHD and how the various medications which are used to treat this condition affect those pathways.

② Understand the extended-release delivery mechanisms of various ADHD medications, potential interactions with other psychotropic agents, and how these factors impact the selection of agents in designing the most effective therapeutic coverage.

③ Describe basic strategies to reduce the impact of potential adverse effects of ADHD medications and for minimizing the diversion of controlled substances including the role of newer medications and non-stimulants in the treatment of ADHD.
Disclosures

• **Charles F. Caley, Pharm.D., BCPP**
  University of Connecticut School of Pharmacy, Storrs, CT / Institute of Living, Hartford, CT
  – No potential conflicts of interest to report
  – I will be discussing some off-label applications of medications

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  – No potential conflicts of interest to report
  – I will be discussing some off-label applications of medications
Blueprint for Change:
Building a Better ADHD Tx Regimen for Students

1. ADHD NEUROBIOLOGY
   (PATHWAYS, RECEPTORS, PHARMACOLOGY, GENETICS)
Which one of the following is believed to be the “cognitive attention network” that is central to the pathophysiology of attention deficit hyperactivity disorder?

- A. Hypothalamic-pituitary-adrenal
- B. Cingulo-frontal-parietal
- C. Cortico-striatal-thalamic
- D. Raphé-nigro-striatal
By virtue of our attention deficit hyperactivity disorder treatments, which two neurotransmitters are implicated in the neurobiology of patients with ADHD?

- A. Acetylcholine
- B. Dopamine
- C. Gamma-amino butyric acid (GABA)
- D. Histamine
- E. Norepinephrine
- F. Serotonin
Cognitive Attention Network (Cingulo-Frontal-Parietal Network)

Cognitive Attention Network
(Cingulo-Frontal-Parietal Network)

CFP Network Function

- Dorsal anterior mid-cingulate cortex (daMCC)
  - Attention, cognitive processing, response inhibition, error detection, motivation…

- Dorsolateral prefrontal cortex (DLPFC) and ventrolateral prefrontal cortex (VLPFC)
  - Vigilance, selective and divided attention, planning, executive control, working memory…
  - VLPFC also associated with behavioral inhibition

- Parietal cortex…attention, spatial processing

Neurotransmitters/Receptors

- Norepinephrine
  - Alpha-2A receptors
  - Responsible for “network firing”

- Dopamine
  - D1 receptors
  - Responsible for “decreasing noise”

Norepinephrine System

Alpha 2A Receptors:
- PFC
- LC
- Amygdala
- Hippocampus
- Thalamus

Dopamine Receptors

Too Little

Optimal

Too Much

Figure 1. Maladaptive Signal-to-Noise Ratios (Deficient Signals or Excessive Noise) in ADHD May Cause “Out of Tune” Cognitive Function

ADHD Pharmacogenomics

- **Drug Target Functionality**
  - DA Transporter - 9R allele; 10R allele
  - D4 receptor - 7R allele
  - Alpha-2a receptor – G allele
  - COMT – Met allele

- **Drug Metabolism Functionality**
  - CYP2D6

GeneSightRx® ADHD Results

Patient, Sample
DOB: 11/14/1984

Reference: 546666
Clinician: Sample Clinician

Order Number: 5290
Report Date: 4/23/2012

USE AS DIRECTED
- dexmethylphenidate (Focalin®)
- methylphenidate (Ritalin®, Concerta®, Metadate®, Daytrana®)

USE WITH CAUTION
- atomoxetine (Strattera®)

USE WITH INCREASED CAUTION AND WITH MORE FREQUENT MONITORING
- amphetamine salts (Adderall®)
- dextroamphetamine (Dexedrine®)
- lisdexamfetamine (Vyvanse®)

All ADHD medications require clinical monitoring.

Drugs are reported in alphabetical order. This report is not intended to imply that the drugs listed are approved for the same indications or that they are comparable in safety or efficacy. The brand name is shown for illustrative purposes only; other brand names may be available. The prescribing physician should review the prescribing information for the drugs (please consult and make treatment decisions based on the patient's individual needs and the characteristics of the drug prescribed).

Patient Genotypes and Phenotypes

<table>
<thead>
<tr>
<th>CYPI2D6</th>
<th>Poor Metabolizer</th>
</tr>
</thead>
<tbody>
<tr>
<td>*4/*4</td>
<td></td>
</tr>
</tbody>
</table>

CYP2D6*4: This allele produces no enzyme activity.
CYP2D6*4: This allele produces no enzyme activity.

Comment: This genotype is associated with a poor metabolizer phenotype. This patient may have reduced enzyme activity as compared to individuals with the normal genotype.

<table>
<thead>
<tr>
<th>COMT</th>
<th>High Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAL/VAL</td>
<td></td>
</tr>
</tbody>
</table>

This patient does not carry the Met allele and may be expected to experience a positive response with stimulants.

<table>
<thead>
<tr>
<th>ADRA2A</th>
<th>Improved Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>C/G</td>
<td></td>
</tr>
</tbody>
</table>

This patient is heterozygous for the C allele and is more likely to experience an improved response to methylphenidate and dexmethylphenidate.
ADHD Neurobiology

• Brain Regions
  – CFP Network
    • Cingulate, Pre-frontal, Parietal
  – Basal ganglia
  – Cerebellum

• Neurotransmitters
  – Dopamine
  – Norepinephrine
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2. ADHD PHARMACOTHERAPY
(RELEASE MECHANISMS, INTERACTIONS)
Which one of the following has an extended release product available for use in the treatment of ADHD?

- A. Atomoxetine
- B. Clonidine
- C. Dextroamphetamine
- D. Guanfacine
- E. Methylphenidate
- F. All of the above
- G. All but atomoxetine
1st Line Tx Options

- **Psychostimulants**
  - Methylphenidate
    - Immediate/short: Ritalin®, Methylin®, Focalin®
    - Delayed/intermediate: Ritalin® SR, Methylin® ER, Metadate® ER
    - Delayed/long: Ritalin® LA, Metadate® CD, Concerta®, Daytrana®
  - Dextroamphetamine
    - Immediate/short: Dextrostat®
    - Delayed/intermediate: Adderall®
    - Delayed/long: Dexedrine Spansules, Adderall XR, Vyvanse
Extended Release Mechanisms
(Methylphenidate)
<table>
<thead>
<tr>
<th>Medication</th>
<th>Brand</th>
<th>Initial Titration Dose</th>
<th>Frequency</th>
<th>Time to Initial Effect</th>
<th>Duration, h</th>
<th>Maximum Dose</th>
<th>Available Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methylphenidate</td>
<td>Concerta</td>
<td>18 mg</td>
<td>QD</td>
<td>20–60 min</td>
<td>12</td>
<td>54 mg (&lt;13 y); 72 mg (≥13 y)</td>
<td>18-, 27-, 36-, and 54-mg capsules</td>
</tr>
<tr>
<td>Methyl ER</td>
<td></td>
<td>10 mg</td>
<td>QD</td>
<td>20–60 min</td>
<td>8</td>
<td>60 mg</td>
<td>5-, 10-, and 20-mg tablets</td>
</tr>
<tr>
<td>Methyltin</td>
<td></td>
<td>5 mg</td>
<td>BID–TID</td>
<td>20–60 min</td>
<td>3–5</td>
<td>60 mg</td>
<td>liquid and chewable forms</td>
</tr>
<tr>
<td>Daytrana</td>
<td></td>
<td>10 mg</td>
<td>Apply for 9 h</td>
<td>60 min</td>
<td>11–12</td>
<td>30 mg</td>
<td>10-, 15-, 20-, and 30-mg patches</td>
</tr>
<tr>
<td>Ritalin®</td>
<td></td>
<td>5 mg</td>
<td>BID–TID</td>
<td>20–60 min</td>
<td>3–5</td>
<td>60 mg</td>
<td>5-, 10-, and 20-mg tablets</td>
</tr>
<tr>
<td>Ritalin LA</td>
<td></td>
<td>20 mg</td>
<td>QD</td>
<td>20–60 min</td>
<td>6–8</td>
<td>60 mg</td>
<td>20-, 30-, and 40-mg capsules</td>
</tr>
<tr>
<td>Ritalin SR®</td>
<td></td>
<td>20 mg</td>
<td>QD–BID</td>
<td>1–3 h</td>
<td>2–6</td>
<td>60 mg</td>
<td>20-mg capsules</td>
</tr>
<tr>
<td>Metadate CD</td>
<td></td>
<td>20 mg</td>
<td>QD</td>
<td>20–60 min</td>
<td>6–8</td>
<td>60 mg</td>
<td>10-, 20-, 30-, 40-, 50-, and 60-mg capsules</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Focalin®</td>
<td>2.5 mg</td>
<td>BID</td>
<td>20–60 min</td>
<td>3–5</td>
<td>20 mg</td>
<td>2.5-, 5.0-, and 10.0-mg tablets</td>
</tr>
<tr>
<td></td>
<td>Focalin XR</td>
<td>5 mg</td>
<td>QD</td>
<td>20–60 min</td>
<td>8–12</td>
<td>30 mg</td>
<td>5-, 10-, 15-, and 20-mg capsules</td>
</tr>
</tbody>
</table>
Methylphenidate HCl (Concerta®) Extended-Release Tablets: Trilayer Capsule-Shaped Tablets

Before Operation
- Drug Compartment #1
- Drug Compartment #2
- Push Compartment

During Operation
- Orifice/Exit Port
- Rate-Controlled Membrane


Methylphenidate HCl (Metadate® CD) Extended-Release Capsules: Biphasic Release Bead-Delivery System


Methylphenidate HCl (Ritalin® LA) Extended-Release Capsules: Bimodal Release for Once-Daily Dosing

Each Ritalin® LA capsule contains 50% immediate-release beads and 50% extended-release beads.


Methylphenidate Transdermal System (MTS, Daytrana™): DOT MatrixTM

Evenly dispersed methylphenidate blend

# ER MPH Products

<table>
<thead>
<tr>
<th>Product*</th>
<th>ER Technology</th>
<th>%IR</th>
<th>%ER</th>
<th>Release Profile</th>
<th>Doses Available</th>
<th>Sprinkle?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concerta® OROS</td>
<td>22</td>
<td>78</td>
<td></td>
<td>Compares w/ tid</td>
<td>18,27,36,5,4</td>
<td>N</td>
</tr>
<tr>
<td>Metadate CD®</td>
<td>30</td>
<td>70</td>
<td></td>
<td>Biphasic, mimics</td>
<td>10,20,30</td>
<td>Y</td>
</tr>
<tr>
<td>Ritalin LA®</td>
<td>50</td>
<td>50</td>
<td></td>
<td>Biphasic, mimics</td>
<td>20,30,40</td>
<td>Y</td>
</tr>
<tr>
<td>Ritalin SR®</td>
<td>Wax matrix</td>
<td>0</td>
<td>100</td>
<td>Gradual</td>
<td>20</td>
<td>N</td>
</tr>
<tr>
<td>Focalin® XR</td>
<td>SODAS beads</td>
<td>50</td>
<td>50</td>
<td>Biphasic, mimics</td>
<td>5, 10, 20</td>
<td>Y</td>
</tr>
<tr>
<td>Focalin®</td>
<td>NA</td>
<td>100</td>
<td>0</td>
<td>Immediate release</td>
<td>2.5,5,10</td>
<td>N</td>
</tr>
<tr>
<td>Ritalin®</td>
<td>NA</td>
<td>100</td>
<td>0</td>
<td>Immediate release</td>
<td>5,10,20</td>
<td>N</td>
</tr>
</tbody>
</table>

*Except for Focalin, mph products exist as 50/50 mixtures of the d–and l–isomers; serum concentrations of the d–isomer are 10–40 times that of the l–isomer; the d–isomer is pharmacologically more active than the l–isomer.
ER MPH Blood Levels

- ER mph products designed to have >1 concentration “peaks”
  - Ritalin LA - 2
  - Metadate CD - 2
  - Concerta - 2-3

- Trying to take advantage of the “peak-response” phenomenon

*Data presented are intended for illustrative purposes only and are not derived from a single cross-over study. These pharmacokinetic profiles represent the superimposition of data generated in three previously published bioavailability studies of MPH dosage formulations at similar strengths administered to healthy adult volunteers. [62,107,107]*
Transdermal MPH

- Three patch strengths:
  - 10 mg
  - 20 mg
  - 30 mg
- Similar Tmax, but different Cmax and AUCs
Extended Release Mechanisms
(Dextroamphetamine)
## Dextroamphetamine Products

<table>
<thead>
<tr>
<th>Medication</th>
<th>Brand</th>
<th>Initial Titration Dose</th>
<th>Frequency</th>
<th>Time to Initial Effect</th>
<th>Duration, h</th>
<th>Maximum Dose</th>
<th>Available Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed amphetamine salts</td>
<td>Adderall&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.5–5.0 mg</td>
<td>QD–BID</td>
<td>20–60 min</td>
<td>6</td>
<td>40 mg</td>
<td>5.0-, 7.5-, 10.0-, 12.5-, 15.0-, 20.0-, and 30.0-mg tablets</td>
</tr>
<tr>
<td></td>
<td>Adderall XR&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 mg</td>
<td>QD</td>
<td>20–60 min</td>
<td>10</td>
<td>40 mg</td>
<td>5-, 10-, 15-, 20-, 25-, and 30-mg capsules</td>
</tr>
<tr>
<td>Dextroamphetamine</td>
<td>Dexteroxine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.5 mg</td>
<td>BID–TID</td>
<td>20–60 min</td>
<td>4–6</td>
<td>40 mg</td>
<td>5- and 10-mg (Dextrostat only) tablets</td>
</tr>
<tr>
<td></td>
<td>Dextrostat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dextrostat</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Dextrostat</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Dextrostat</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisdexamfetamine</td>
<td>Vyvanse</td>
<td>20 mg</td>
<td>QD</td>
<td>60 min</td>
<td>10–12</td>
<td>70 mg</td>
<td>20-, 30-, 40-, 50-, 60-, and 70-mg capsules</td>
</tr>
</tbody>
</table>
Lisdexamfetamine

- Trade name = Vyvanse®
- Prodrug for dexamphetamine
  - L-Lysine (+) d-Amphetamine
- Pharmacology same as dextroamphetamine
  - “Prolonged” release via rate limited hydrolysis of parent
  - No multiple peaks like with mph products
  - Food delays absorption
  - Still need to be aware of 2D6 inhibitors
(2S)-2,6-diamino-N-[(1S)-1-methyl-2-phenylethyl]hexanamide dimethanesulfonate; C_{15}H_{25}N_3O \cdot (CH_4O_3S)_2; M_r = 455.6
2nd/3rd Line Tx Options

- Atomoxetine
  - Straterra®
- Clonidine
  - Catapres®, Kapvay®
- Guanfacine
  - Tenex®, Intuniv®
- Bupropion (off label)
  - Wellbutrin® IR/SR/XL
Extended Release Mechanisms
(Bupropion, Clonidine, Guanfacine)
Bupropion

- **Wellbutrin® SR**
  
  Each tablet contains...inactive ingredients: carnauba wax, cysteine hydrochloride, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, polysorbate 80, and titanium dioxide, printed with edible black ink. In addition, 100-mg tablet contains FD&C Blue No. 1 Lake, 150-mg tablet contains FD&C Blue No. 2 Lake & FD&C Red No. 40 Lake, 200-mg tablet contains FD&C Red No. 40 Lake.
Wellbutrin® XL

- Each tablet contains...inactive ingredients: ethylcellulose aqueous dispersion (NF), glyceryl behenate, methacrylic acid copolymer dispersion (NF), polyvinyl alcohol, polyethylene glycol, povidone, silicon dioxide, triethyl citrate, printed with edible black ink. Insoluble shell of extended-release tablet may remain intact during GI transit and is eliminated in the feces.
Clonidine

- Catapres®-TTS
  - Patch
    - 0.1 mg/d (x 7d)
    - 0.2 mg/d (x 7d)
    - 0.3 mg/d (x 7d)
Clonidine

- Kapvay® XR tablets
  - 0.1 mg
  - 0.2 mg
Guanfacine

- Intuniv® XR tablets
  - 1 mg
  - 2 mg
  - 3 mg
  - 4 mg
Drug Interactions
Which stimulant treatment for ADHD will not interact with fluoxetine, a strong CYP2D6 inhibitor?

- A. Dextroamphetamine
- B. Methylphenidate
- C. Neither will interact
- D. Both will interact
FDA Stimulant Warnings

• Psychostimulants and concerns about:
  ✴ Psychosis/mania
  ✴ Aggression
  ✴ Cardiovascular effects
  ✴ Seizures
  ✴ Abuse
ACUTE MYOCARDIAL INFARCTION RELATED TO METHYLPHENIDATE FOR ADULT ATTENTION DEFICIT DISORDER

Jan Thompson, RN* and James R. Thompson, MD†

*Division of Cardiovascular Services and †Department of Emergency Medicine, University of Mississippi Medical Center, Jackson, Mississippi

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Abstract—Adult Attention Deficit Disorder is increasingly diagnosed and treated (1). Treatment is typically with psychostimulant drugs that are either amphetamine based, or similar in pharmacology to amphetamines. In children, the psychostimulant drugs have been used for many years and have minimal reported cardiac side effects, other than small increases in heart rate and blood pressure (2,3). These drugs are less well studied in adults, and use and abuse are increasing in adolescents and adults. We report the case of a young man who suffered an acute anterolateral myocardial infarction related to use of prescribed methylphenidate.

INTRODUCTION

Adult Attention Deficit Disorder (AADD) is increasingly diagnosed and treated (1). Treatment is typically with psychostimulant drugs that are either amphetamine based, or similar in pharmacology to amphetamines. In children, the psychostimulant drugs have been used for many years and have minimal reported cardiac side effects, other than small increases in heart rate and blood pressure (2,3). These drugs are less well studied in adults, and use and abuse are increasing in adolescents and adults. We report the case of a young man who suffered an acute anterolateral myocardial infarction related to use of prescribed methylphenidate.

CASE REPORT

A 27-year-old man presented to an outlying Emergency Department at about midnight. He complained of sharp, midsternal/epigastric chest pain since 9:00 a.m. that morning, which had become worse over the prior few hours. The patient had vomited once earlier that evening after taking an antacid for what he described as “a bad case of gas.” He denied shortness of breath, diaphoresis, or radiation of pain.

The patient was a smoker, with a 5 pack-year history. He reported current medications to be only cefdinir and a combination extended-release tablet of fexofenadine/pseudoephedrine for a sinus infection. At this time, the patient forgot to report that he also had recently been started on methylphenidate 5 mg twice daily for AADD. He denied a family history of cardiac disease.

Vital signs revealed a pulse of 69 beats/min, respiratory rate 20 breaths/min, blood pressure 112/71 mm Hg, and temperature 36.2°C (97.1°F). He appeared moderately uncomfortable. The lungs were clear, pulses were strong and equal. The cardiac examination revealed a regular rate and rhythm with no murmurs or gallops. The remainder of the physical examination was unremarkable.

The initial electrocardiogram was read as non-diagnostic, but showed some concerning ST elevation in leads I, AVL, V5, and V6. The patient was treated with 30 cc of a gastrointestinal cocktail (viscous lidocaine and...
Pharmacodynamic

• Concurrent medications which increase NE / DA activity (e.g., Stimulant plus…)
  – Wellbutrin®, Effexor®, Straterra®
  – Caffeine, Decongestants, Cocaine derivatives

• Concurrent medications which block NE / DA activity
  – Beta blockers (e.g., propranolol)
  – Antipsychotics (e.g., Risperdal®, Haldol®)
Pharmacokinetic

• Metabolism
  – Methylphenidate – carboxyesterase-1
  – Dextroamphetamine – CYP2D6/renal
  – Atomoxetine – CYP2D6
  – Clonidine – CYP2D6/renal
  – Guanfacine – CYP3A4/renal
  – Bupropion – CYP2B6
Clinically Important Inhibitors

- Inhibitors slow down metabolism of other meds
  - CYP2B6 – none known
  - CYP3A4 – Nefazodone (Serzone®)
  - CYP2D6
    - Fluoxetine (Prozac®)
    - Paroxetine (Paxil®)
    - Bupropion (Wellbutrin®)
    - Duloxetine (Cymbalta®)
Clinically Important Inducers

- CYP2B6 – none known
- CYP2D6 – non known
- CYP3A4
  - St. John’s Wort
  - Carbamazepine (Tegretol®)
## Potential Pk Interactions

<table>
<thead>
<tr>
<th></th>
<th>FLUO</th>
<th>PARO</th>
<th>DULO</th>
<th>BUPR (2D6)</th>
<th>NEFA Z</th>
<th>SJW (3A4)</th>
<th>CBZ (3A4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPH (CES-1)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>DXM (2D6)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ATMX (2D6)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>GUAN (3A4)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

*Inhibitors*  

*Inducers*

C. Caley, PharmD, BCPP
Mph Drug Interactions

- TCAs - mph may incr. TCA levels; incr. BP
- MAOI + mph can result in BP incr.
- AEDs
  - Mph may incr. phenytoin (Dilantin) levels
  - Carbamazepine (Tegretol) may decrease mph levels and effects
Amph Drug Interactions

- TCAs + amph may result in BP incr.
- MAOIs + amph may result in BP incr.
- CYP2D6 inh. + amph may incr. amph levels
- Venlafaxine (Effexor) + amph (case report) – 32 yo developing agitation, tremor, sinus tach.
- Urinary alkalinization may incr. amph levels – Topiramate (Topamax)
Atomoxetine/MAS Interaxn

- 9 yr old male patient with ADHD, developmental delay, mild chronic hypertension presented with insomnia and involuntary hand/mouth movements
- Atmx 25 mg/d had been added to MAS 60 mg qam, clonidine 0.3 mg bid 2 wks prior
- 3d after beginning atmx tx – insomnia, compulsive lip licking, visual hallucinations

Atomoxetine/MAS Interaxn

- All symptoms incr. in severity over next 5d
- ER: HR = 89 bpm, BP = 145/93, continuous involuntary twitching movements (peri-oral, fingers); restless leg movements too
- Meds stopped; pt up all night
- Next morning all movements stopped
- Sent home on meds previous to atmx, no problems as much as 5 mos later

Meds Concurrent to ADHD Tx

- Consider the mechanism of action
- Consider whether there is an impact on drug metabolism
HOW IT AFFECTS
YOUNG ADULTS
MYTH: Children usually grow out of ADHD

By self report
Of adults diagnosed with AD/HD as a child…
• 44% still fully have AD/HD
• 20% symptomatic but not fully AD/HD
• 36% fully recovered

By report of other persons
Of adults diagnosed with AD/HD as a child…
• 41% still fully have AD/HD
• 24% symptomatic but not fully AD/HD
• 35% fully recovered

Presentation in College age

- Primarily inattentive
- Mental restlessness rather than physical restlessness
- Higher IQ but lower GPA
- Higher prevalence of females than at younger ages
- Often difficult to establish onset before 7yo
- Often presents to MD at time of transition
- History of changing majors, dropping in and out of school
Presentation in College age - 2

- Failure to complete assignments
- Poor test preparation and test-taking skills
- Poor organization skills
- Poor understanding of material
- Failure to ask teachers for needed help
- Disruptive behavior in the classroom
- Skipping classes
- Discouraged / demoralized
Executive Functions

Activation

Focus

Effort

Emotional Regulation

Internalizing Language

Monitoring

Complex Problem Solving

Working Memory
## Executive Functions

<table>
<thead>
<tr>
<th>Category</th>
<th>Functions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activation</td>
<td>Organizing, Setting and maintaining priorities, Initiating tasks</td>
</tr>
<tr>
<td>Focus</td>
<td>Maintaining attentiveness, Shifting attention between tasks successfully</td>
</tr>
<tr>
<td>Effort</td>
<td>Regulating alertness, Sustaining effort until the completion of a task, Processing speed</td>
</tr>
<tr>
<td>Emotional Regulation</td>
<td>Awareness of one’s own mood, Being able to modulate emotions to appropriately fit the situation, Frustration tolerance, Ability to think before acting/speaking in reaction to emotional stimuli</td>
</tr>
<tr>
<td>Internalizing Language</td>
<td>Utilizing “self-talk” to control one’s behavior and direct future actions.</td>
</tr>
<tr>
<td>Monitoring</td>
<td>Monitoring one’s own efforts, Self-regulation</td>
</tr>
<tr>
<td>Working Memory</td>
<td>Ability to hold in the conscious areas of the brain information needed to perform one task while performing a different task</td>
</tr>
<tr>
<td>Complex Problem Solving</td>
<td>Taking an issue or problem apart, analyzing its pieces, and reconstituting and organizing it into new ideas</td>
</tr>
</tbody>
</table>
CONSEQUENCES OF UNTREATED ADHD

BLUEPRINT FOR CHANGE: Building a Better ADHD Tx Regimen for Students
Self medication

- Students with untreated AD/HD often self-medicate with
  - Caffeine (non-specific stimulant)
  - Nicotine (non-specific stimulant)
  - ADHD medication Rx’d to others
  - Alcohol (relief of stress, improve socialization)
  - Marijuana (relief of anxiety / stress)
Consequences of untreated ADHD

- Greater risk for certain types of accidents and injuries.
- School failure and drop out
- Higher incidence of depression and anxiety
- Increased amount of legal troubles
- Interference with peer and family relationships
- Job failures and frequent job changes
Adults with ADHD

- 2x more likely to rarely or never use birth control
- 4x more likely to have contracted a sexually transmitted disease
- 3x more likely to be currently unemployed
- 2x more likely to have problems keeping friends
- 47% more likely to have trouble paying bills

ADHD and driving

• AD/HD in adolescents and young adults associated with
  – Worse driving habits
  – 3x more likely to be involved in a MVC
  – More accidents at fault
  – More accidents with injury
  – Greater $$$ damage in accidents
  – More speeding tickets
  – Greater likelihood of license revoked / suspended

Barkley, Psychiatric Clin North Am, 2004
ADHD and sexual risk behaviors

- Adolescents and young adults with AD/HD
  - Earlier age of first intercourse
  - More sexual partners
  - Less use of birth control
  - More sexually transmitted infections
  - Greater frequency of HIV testing
  - More unintended pregnancies

Adolescents and young adults with a childhood diagnosis of ADHD

- ~3x more likely to smoke QD (30.4% vs. 12%)
- consumed more cigarettes in past 6 mo
- ~2x as likely intoxicated >1x in last 6 mo (23.2% vs. 12%)
- higher rates of EtOH problems overall (15.5% vs. 8.5)
- 3x more likely to use one illicit drug beside MJ (20.4% vs. 7%)

The Good News

• Studies suggest that adequate treatment (usually with stimulant medication) can lessen the frequency of
  – Substance abuse problems
  – Sexual risk behaviors
  – Adverse driving outcomes

• Re-enforces the importance of adequate treatment QD, covering as much of day as feasible
ACHIEVING OPTIMAL CARE

Blueprint for Change: Building a Better ADHD Tx Regimen for Students
Shifting the paradigm

Old school paradigm
- Minimal effective dose
- Covering only “events” – e.g. class & studying
- Frequent Drug holidays

New paradigm
- Covering all waking hours
- Titrate to optimal dose – Greatest effectiveness, Longest duration, With minimal / tolerable adverse effects
- Drug holidays – rare or none
• Inadequate effectiveness
• More frequent Adverse Effects
• Love / hate relationship with medication
  – Medication seen as inherently “bad” and to be avoided
  – Adolescents often quit taking meds at crucial times
• Long-periods uncovered
  – Greater risk of consequences from untreated ADHD
Lack of optimal dosing

- In the community treatment of ADHD, stimulant dosing for children seems to fall well below dose ranges reported to be optimally effective in clinical trials.

Three main questions

• Is medication STRONG ENOUGH?
• Does medication last LONG ENOUGH?
• Are the ADVERSE EFFECTS TOO ROUGH?
### Is medication STRONG ENOUGH?

*(How well does it cover the basic ADHD Symptoms?)*

<table>
<thead>
<tr>
<th>Area</th>
<th>Very Helpful</th>
<th>Helpful</th>
<th>Not Effective</th>
<th>Makes Problem Worse</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sustaining my Attention in Class</td>
<td>very helpful</td>
<td>helpful</td>
<td>not effective</td>
<td>makes problem worse</td>
<td>N/A</td>
</tr>
<tr>
<td>Being Able to Concentrate While Studying Outside of Class</td>
<td>very helpful</td>
<td>helpful</td>
<td>not effective</td>
<td>makes problem worse</td>
<td>N/A</td>
</tr>
<tr>
<td>Paying More Attention to Details</td>
<td>very helpful</td>
<td>helpful</td>
<td>not effective</td>
<td>makes problem worse</td>
<td>N/A</td>
</tr>
<tr>
<td>Being Less Easily Distracted by Things around Me</td>
<td>very helpful</td>
<td>helpful</td>
<td>not effective</td>
<td>makes problem worse</td>
<td>N/A</td>
</tr>
<tr>
<td>Finishing Assignments without Taking Too Long</td>
<td>very helpful</td>
<td>helpful</td>
<td>not effective</td>
<td>makes problem worse</td>
<td>N/A</td>
</tr>
<tr>
<td>Avoiding Trouble from Impulsively Acting before Thinking</td>
<td>very helpful</td>
<td>helpful</td>
<td>not effective</td>
<td>makes problem worse</td>
<td>N/A</td>
</tr>
<tr>
<td>Refraining from Interrupting Others While Talking</td>
<td>very helpful</td>
<td>helpful</td>
<td>not effective</td>
<td>makes problem worse</td>
<td>N/A</td>
</tr>
<tr>
<td>Keeping My Mind on the Road While Driving</td>
<td>very helpful</td>
<td>helpful</td>
<td>not effective</td>
<td>makes problem worse</td>
<td>N/A</td>
</tr>
<tr>
<td>Remembering Appointments</td>
<td>very helpful</td>
<td>helpful</td>
<td>not effective</td>
<td>makes problem worse</td>
<td>N/A</td>
</tr>
<tr>
<td>Having Better Organizational Skills</td>
<td>very helpful</td>
<td>helpful</td>
<td>not effective</td>
<td>makes problem worse</td>
<td>N/A</td>
</tr>
<tr>
<td>Managing My Daily Activities More Effectively</td>
<td>very helpful</td>
<td>helpful</td>
<td>not effective</td>
<td>makes problem worse</td>
<td>N/A</td>
</tr>
<tr>
<td>Regulating My Emotional Responses</td>
<td>very helpful</td>
<td>helpful</td>
<td>not effective</td>
<td>makes problem worse</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Does medication last **LONG ENOUGH**?
*(Does medication work well during each segment of the day?)*

<table>
<thead>
<tr>
<th></th>
<th>8-10:30am</th>
<th>10:30am-1pm</th>
<th>1-3:30pm</th>
<th>3:30-6pm</th>
<th>6-9pm</th>
<th>After 9pm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfect</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Great</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Good</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Fair</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Poor</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td></td>
<td>If present, how severe?</td>
<td>How frequent?</td>
<td>Is this related to medication?</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------</td>
<td>------------------------</td>
<td>---------------</td>
<td>-------------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appetite decrease</td>
<td>none</td>
<td>mild</td>
<td>occasional</td>
<td>related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep disturbance</td>
<td>none</td>
<td>mild</td>
<td>frequent</td>
<td>not related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daytime drowsiness</td>
<td>none</td>
<td>mild</td>
<td>frequent</td>
<td>related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headaches</td>
<td>none</td>
<td>mild</td>
<td>occasional</td>
<td>not related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach upset</td>
<td>none</td>
<td>mild</td>
<td>occasional</td>
<td>related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability/Mood swings</td>
<td>none</td>
<td>mild</td>
<td>occasional</td>
<td>not related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harder to have fun</td>
<td>none</td>
<td>mild</td>
<td>occasional</td>
<td>related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tics</td>
<td>none</td>
<td>mild</td>
<td>occasional</td>
<td>not related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blunted personality</td>
<td>none</td>
<td>mild</td>
<td>occasional</td>
<td>related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Suicidal thoughts</td>
<td>none</td>
<td>mild</td>
<td>occasional</td>
<td>not related</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others:</td>
<td>none</td>
<td>mild</td>
<td>occasional</td>
<td>related</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>moderate</td>
<td>frequent</td>
<td>not related</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>severe</td>
<td>frequent</td>
<td>not related</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Are the **ADVERSE EFFECTS TOO ROUGH?**
Secondary questions

- During which hours of the day is the student in class?
- During which hours of the day is the student studying?
- During which hours of the day is the student working?
- During which hours of the day is the student sleeping?
Secondary questions

• Is the patient complying with the medication prescription?
• Is the medication being diverted to others?
Ultimate questions

• **How satisfied** is the student with the medication?
• **What changes** would the student make to the medication if she or he could?
Optimizing ADHD Treatment in a College population

PHARMACOLOGIC TREATMENT OPTIONS
Choice of medications in adolescents & college students

• Stimulants remain first line tx
  – Methylphenidate
  – Dexmethylphenidate
  – Dextroamphetamine
  – Mixed amphetamine salts

• If one does not work, try another (then another)

• Second line medications
  – Atomoxetine
  – Buproprion
  – Tri-cyclic anti-depressants
  – Clonidine
  – Guafancine
Principles of pharmacologic tx of AD/HD in adolescents & college students

- Start with low dose and gradually taper up to minimize adverse effects
- Aggressively titrate to most effective dose with minimal or no adverse effects
- Most effective dose based on individual response rather than standard mg/kg dose
- Administer meds frequently enough to cover all AD/HD symptoms & homework
- Consider co-morbid symptoms
Principles of pharmacologic tx of AD/HD in adolescents -2

• Longer acting forms preferred
  – Increase satisfaction
  – Improve compliance
  – Lessen risk of abuse

• Reassess dose frequently
  – Assess for effectiveness
  – Assess for duration of effect
  – Assess for changing needs

• Most adverse effects diminished or extinguished with consistent QD dosing
  – Most AEs greatly reduced within 2-3 weeks
  – Appetite suppression takes longer to diminish

• Frequent monitoring needed for adverse effects, compliance, abuse, diversion
Drug Holidays

Valid Reasons FOR Drugs Holidays
- Weight loss to below acceptable BMI
- Significant AEs on all effective medications
- Risk of abuse or diversion of medication

Valid Reasons AGAINST Drug Holidays
- AD/HD affects all areas of life
- One doesn’t stop learning after class
- Important tasks to complete in other places
- Extinguishing AEs
- Reducing risk of risky behaviors due to impulsivity
- Consistency
- Driving safety
- Avoid re-titration of meds
Keys to compliance

- Spending time to educate patient about AD/HD
- Dispel myths about medication
- Discuss possible adverse effects and ways to minimize
- Enlist patient as part of treatment team
- Empower patient with feeling of control
- Negotiate trials on or off medication
- Start with low dose and titrate to effective dose
STIMULANTS
Immediate release

- ADDERALL (mixed amphetamine salts)
- DEXEDRINE (dextro-amphetamine)
- RITALIN (methylphenidate)
- FOCALIN (dexamphetamine)

Extended release

- ADDERALL XR
- DEXEDRINE SPANSULES
- VYVANSE
- RITALIN LA
- METADATE CD
- CONCERTA
- FOCALIN XR

STIMULANTS

AMPHETAMINES

METHYLPHENIDATES
**Methylphenidate s vs. Amphetamines**

- In a trial of both amphetamine and MPH:
  - approximately 41% of subjects with ADHD responded equally to both MPH and AMPH
  - 44% responded preferentially to one of the classes of stimulants.

- A meta-analysis of the 5 studies in children that compared MPH to AMPH in blinded crossover conditions found:
  - about 37% of patients had a clearly better outcome on an AMPH preparation
  - 26% had a clearly better response to MPH
  - The other 37% of stimulant responders responded equally well to either molecule

Arnold LE (2000), J Atten Disord 3:200-211
Comparing atomoxetine to stimulants

- Meta-analysis of atomoxetine and stimulant studies comparing effect sizes
  - atomoxetine = 0.62
  - immediate-release stimulants = 0.91
  - long-acting stimulants = 0.95

Optimizing dosage of ADHD medications
Dosing Of Stimulants

- In clinical practice, the dosage is determined by individual subject response.
- No identified parameter predicts the molecule, dose, timing of dose, and frequency of dose at which a unique individual will derive optimal benefit from medication.
- FDA guidelines tend to be cautious and vague about the methods and expected outcomes of dosages of the first-line agents.
- There is a dose that is unique to each patient that provides optimal performance with a low level of side effects. This is usually found through a trial and error fine-tuning of the molecule and dose.
- In clinical practice, stimulant class medications are adjusted to the needs and responses of the individual patient in at least five ways:
  - molecule
  - delivery system
  - dose,
  - duration
  - frequency

Dosing Of Stimulants

- Many adults [& college students] have very long days and need medication in multiple settings other than work [and school].
- Total # doses/day taken by a particular patient determined by number of factors
  - tasks to be performed
  - duration of medication action
  - use of XR vs. IR formulations
  - extent of side effects
- [considerations of protective effects vs. risky behaviors including driving safety]
- Subsequent doses are commonly overlapped by 30 minutes [1 hr] so that 2nd dose can be absorbed while 1st dose is wearing off in order to minimize rebound effects.

• No studies have examined effects of doses of MPH or amphetamine in adolescents of more than 60 mg/day or 72 mg of Concerta.

• Doses in this range should be used only with caution, with frequent monitoring of side effects.

• On average, there is a linear relationship between dose and clinical response: that is, in any group of ADHD subjects, more subjects will be classified as responders and there is a greater reduction in symptoms at the higher doses of stimulant.

• There is no evidence of a global therapeutic window in ADHD patients. Each patient, however, has a unique dose-response curve.
Treating Adolescents / Young Adults With Doses Above The Standard “Recommended Daily Doses”

- 2-fold rationale:
  - (1) the recommended daily dose is simply inadequate for a sizable number of adolescent / young adult patients & larger doses can be used safely with proper monitoring
  - (2) the recommended daily dose assumes a treatment time of ~ 8 hrs
  - most adolescents and especially college students are involved in activities requiring attentiveness for many more hours of the day
  - impossible to treat for 12 - 16 hrs with the same total amount of medication as recommended for 8 hours.
# Maximum Medication Doses

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>FDA Max / day</th>
<th>Off-label Max / day</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADDERALL</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>ADDERALL XR</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td>DEXEDRINE SPANSULE</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>VYVANSE</td>
<td>70</td>
<td>Not yet known</td>
</tr>
<tr>
<td>RITALIN (IR)</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>METADATE CD</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>RITALIN LA</td>
<td>60</td>
<td>100</td>
</tr>
<tr>
<td>CONCERTA</td>
<td>72</td>
<td>108</td>
</tr>
<tr>
<td>DAYTRANA (patch)</td>
<td>30</td>
<td>Not yet known</td>
</tr>
<tr>
<td>FOCALIN XR</td>
<td>30</td>
<td>50</td>
</tr>
<tr>
<td>STRATTERA</td>
<td>Lesser of 1.4mg /kg or 100mg</td>
<td>Lesser of 1.8mg/kg or 100mg</td>
</tr>
</tbody>
</table>

Aspects of pharmacotherapy management specific to adolescents & college students

- Treating adolescents [& college students] who have ADHD
  - Potential benefit
  - Potential for negative sequelae without intervention
- Important to partner with the teens [& college students] in their treatment planning.
  - By working together, the likelihood of treatment adherence and optimal outcomes is increased.
- Dosing adjustments required to manage symptoms over longer periods of time
- Evening activities
  - extracurricular programs
  - studying
  - work
  - driving at night
- Participation in activities in which supervision is limited
  - impulsive behaviors may have significant consequences
- Goal: to provide coverage throughout the waking hours.
  - may require a long-acting stimulant alone
  - LA stimulant + a short-acting stimulant at the end of the day
  - nonstimulant
- Growing rates of substance abuse
- Need to alter treatment strategies to limit availability of agents with greater substance abuse potential, (e.g. immediate-release stimulants)
  - Sustained-release preparations or nonstimulants may help to mitigate some of the abuse potential.

## Options For Extending Coverage

<table>
<thead>
<tr>
<th>Time</th>
<th>School Activities</th>
<th>Extracurricular, studying, driving, part-time work</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:00am</td>
<td>IR stimulant</td>
<td></td>
</tr>
<tr>
<td>10:00am</td>
<td>SR stimulant</td>
<td></td>
</tr>
<tr>
<td>Noon</td>
<td>OROS methylphenidate (Concerta)</td>
<td>4:00pm - 6:00pm</td>
</tr>
<tr>
<td>2:00pm</td>
<td></td>
<td>8:00pm - 10:00pm</td>
</tr>
<tr>
<td>4:00pm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6:00pm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8:00pm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10:00pm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Midnight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lisdextroamfetamine (VYVANSE)</td>
<td>SR stimulant</td>
<td></td>
</tr>
<tr>
<td>SR stimulant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atomoxetine (Strattera), bupropion or TCA</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Useful strategies for managing common stimulant-induced adverse effects

• **Rebound phenomenon**
  - Overlap stimulant dosing.
  - Change to long-acting preparation or combine long- and short-acting preparations.
  - Switch stimulant molecules
  - Consider adjunctive or alternative treatment (e.g., clonidine, antidepressants).

• **Irritability**
  - Assess timing of phenomena (during peak or withdrawal phase).
  - Evaluate comorbid symptoms.
  - Reduce dose.
  - Consider adjunctive or alternative treatment (e.g., lithium, antidepressants, anticonvulsants).

• **Dysphoria, moodiness, and agitation**
  - Consider comorbid diagnosis (e.g., mood disorder)
  - Reduce dose or change to long-acting preparation
  - Consider adjunctive or alternative treatment (e.g., lithium, anticonvulsants, antidepressants).
Useful strategies for managing common stimulant-induced adverse effects (cont.)

• Anorexia, nausea, weight loss
  - Administer stimulant after meals.
  - Encourage breakfast.
  - Use caloric-enhanced supplements.
  - Discourage forcing meals.
  - Prescribe cyproheptadine to increase appetite (off-label usage)

• Insomnia
  - Administer stimulants earlier in day.
  - Change to short-acting preparations.
  - Discontinue or lessen late afternoon or evening dosing.
  - Consider adjunctive treatment (e.g., antihistamines, antidepressants, other sleep aids).

• Poor or variable absorption
  - Avoid citric and ascorbic acid for 1 hour prior to the stimulant dose.
New Treatment Forms Under Study

- Recent small study \((n=10)\) showed effectiveness of Agomelatine, a relatively new antidepressant, with affinities to MT1 and MT2 (responsible for the circadian rhythm) as well as to 5-HT2C receptors. (Niederhofer, Journal of Attention Disorders 2012 16: 346)
- Longer acting amphetamine (ADDERALL XR2)
- More non-stimulants
- Amphetamine patch
- Buspirone (BuSpar) patch
- Ampakines (enhanced attention, freedom from distractibility, memory and cognition)
- Others in preliminary study
  - Adrenergic receptor agonists
  - Glutamanergic agents
  - GABA receptor antagonists
  - Nicotine receptor agonists
Blueprint for Change: Building a Better ADHD Tx Regimen for Students

THE PROBLEM OF DIVERSION
Diversion of ADHD medications

- Systematic literature reviewed showed range of 5% to 35% in college-age individuals

Diversion of ADHD medications

Sample of 9161 undergraduate college students.

- 8.1% = lifetime rates of illicit use of prescription stimulants
- 5.4% within the past year rates
- Overall greater rates of illicit use than medical use of ADHD medications.
- Most common source of medication was from peers

McCabe S, et al, J Psychoactive Drugs. 2006
Diversion of ADHD medications

Sample of 334 college students
- 25% of those with ADHD reported having ever used their medication “to get high”
- 29% reported having ever given or sold ADHD medication to someone else

Sample of 50 college students who misused methylphenidate
- 30% used it only to study better
- 70% used it recreationally
  - Those who used MPH recreationally were more likely to use it intra-nasally and to use it with other substances

Diversion of ADHD medications

Sample of 1025 college students
• 16% had abused or misused prescription stimulants
• Reasons cited for misuse
  – improve attention
  – to "party"
  – to reduce hyperactivity,
  – to improve grades.
• Most abusers and misusers in that study preferred methylphenidate.
• The majority swallowed the medication, while 40% snorted it.

Are students w/ undiagnosed ADHD self medicating?

- ADHD symptoms compared among 3 groups of college students enrolled in a longitudinal study over 4 years:
  - (1) persistent nonmedical users of Rx stimulants
  - (2) persistent marijuana users not using Rx stimulants nonmedically
  - (3) consistent nonusers of drugs.

- ADHD symptoms measured with Adult ADHD Self-Report Scale

- ADHD symptoms associated with persistent nonmedical use of Rx stimulants after adjustment demographic factors

- No associations between ADHD symptoms and -
  - persistent marijuana use
  - Nonuse of MJ or stimulants w/o Rx

The science behind diversion

- Stimulants used to treat ADHD raise the levels of extracellular dopamine in the brain.
- Both the therapeutic and reinforcing effects of stimulants appear to be related to elevations in extracellular dopamine.
- Abrupt and rapid increases in dopamine are associated with reinforcing effects,
- Steady-state and slower dopamine increases are associated with therapeutic effects.

Volkow ND, et al. Arch Gen Psychiatry. 1995
Volkow ND, Swanson JM. Am J Psychiatry. 2003
The science behind diversion - 2

- Inhaling, smoking, or injecting stimulants done more easily with immediate-release than with extended-release preparations enhance the reinforcing (addictive) effects.

- Oral administration may improve therapeutic effects, with lower reinforcing (addictive) properties as compared with inhaling, smoking, or injection routes of administration.

- Among oral preparations, extended-release formulations may enhance therapeutic effects while further reducing reinforcing effects

Volkow ND. Am J Psychiatry. 2006
Ways to reduce diversion

- Preferentially use medications less likely to be diverted
  - Extended-release medications
  - Pro-drugs (e.g. VYVANSE)
  - Alternative delivery forms (e.g. DAYTRANA patches)
  - Non-stimulants (e.g. STRATTERA)
- Only prescribe stimulants to patients after a careful evaluation confirming AD/HD
- Have clearly defined policies on prescribing controlled-substances
  - Limit the amount of pills given on each prescription
  - Discourage “PRN” usage of medication
  - Do not give early renewal of prescriptions
  - Limit “replacement Rx’s” for lost of stolen Rx’s
- Educate patients about possible dangers and legal consequences of “sharing” medication
- Be wary of non-compliant students
  - show up infrequently
  - need last minute Rx before finals (prime time for “study pill” sharing)
Case Study 1

18yo freshman presents requesting Rx for his ADDERALL XR. He has been on same dose (15mg qAM) since 9th grade. He reports medication works for about 4-5 hours after he takes it but has worn off by the time his afternoon classes begin. He only takes medication when he feels that he needs it. He sometimes takes extra to study.

What treatment options would you recommend?
Case Study 2

- 19yo junior who has been on medication for ADHD since 1st grade. She is currently taking CONCERTA 56mg qAM but medication not lasting long enough to cover late afternoon or evening studies. She denies co-morbid conditions or substance abuse. Previous trials of DEXEDRINE & ADDERALL XR were ineffective.

- What treatment options would you recommend?
Case study 3

You are seeing a 1st year law student with stable dosing of ADDERALL XR 20mg qAM for a routine medication recheck. She is getting behind in her classes & feeling overwhelmed. Today her BP is 158/94 whereas previous measurements have been normal.

- What would you want to do first?
- What questions would you want to ask her?
Case study 4

- You are seeing a sophomore for initiation of medication for recently diagnosed ADHD. He also appears rather tense when discussing starting a new medication but agrees. He comes back a week later saying that his roommates are complaining that he is making them wash their dishes. He reports not being able to get school assignments completed because he is constantly reorganizing his closet.

- What would you want to do with his prescription?
- What other questions would you want to ask him?
Case study 5

• A senior you have seen for 3 ½ years has been well controlled on Atomoxetine but now complains of moderately severe depression. You start her on Fluoxetine and have her follow-up in 2 weeks. Next week you receive a call from the patient saying she cannot sleep at night and her hands are shaking. While on the phone with you she breaks down crying and becomes agitated.

• What do you think is going on?
• What would you do with her prescriptions?
For copies of presentation slides

• See ACHA.org after July 1
• Or e-mail: mthomas@cchs.ua.edu
ADHD masqueraders

- Anemia
- Bipolar disorder
- Congenital brain anomalies
- Depression
- *Enterobius vermicularis* (pinworm) infestation
- Epilepsy
- Fetal alcohol syndrome/effects
- Fragile X syndrome
- Hearing loss
- Lead poisoning
- Learning disabilities
- Medication effects
- Mental retardation
- Metabolic disorders (e.g., adrenoleukodystrophy)

- Narcolepsy
- Neurofibromatosis I
- PANDAS*
- Pervasive developmental disorder
- Posttraumatic stress disorder
- Sex chromosome abnormalities
- Sleep apnea
- Sleep deprivation
- Static encephalopathy
- Sydenham chorea
- Thyroid disorders
- Tourette syndrome
- Vision loss

*Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections*
## Comorbidities often seen with ADHD

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Prevalence among adolescents with ADHD</th>
<th>Prevalence in general adolescent population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning disabilities and disorders</td>
<td>20%–60%</td>
<td>5%–15%</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>~6%–10%</td>
<td>3%–4%</td>
</tr>
<tr>
<td>Major depression</td>
<td>9%–32% (average, 25%)</td>
<td>3%–5%</td>
</tr>
<tr>
<td>Anxiety disorders</td>
<td>10%–40% (average, 25%)</td>
<td>3%–10%</td>
</tr>
<tr>
<td>Conduct disorder</td>
<td>20%–56%</td>
<td>Unknown</td>
</tr>
<tr>
<td>Oppositional-defiant disorder</td>
<td>20%–67% (average, 35%)</td>
<td>2%–16% (average, 7%–8%)</td>
</tr>
</tbody>
</table>

**REFERENCES**
5 “P’s” of Sustained-release stimulants

**Pulse** - Single-pulse sustained-release medication
- Include **RITALIN SR, METADATE ER, & METHYLIN ER**
- Use wax-matrix, an older technology
- Less reliable and less consistent release
- Must be swallowed whole to retain sustained effect
Pearls - capsules filled with immediate-release and delayed-release beads

- Enteric coating dependent on acid in proximal gut to release active agent. Acidic drinks of PPIs may affect absorption.
- **DEXEDRINE SPANSULE, RITALIN LA, FOCALIN XR, ADDERALL XR** 50% immediate-release / 50% delayed-release
- **METADATE CD** 30% immediate released / 70% released 3 hours later.
- Capsules may be opened and sprinkled into soft foods. Beads should not be chewed.
5 “P’s” of Sustained-release stimulants (cont’d)

Pump - osmotic-release oral system (OROS) technology

• Methylphenidate tablet (CONCERTA) tablet coated with a 22% immediate-release initial dosing.
• Long-duration component delivered by an osmotic pump gradually releases methylphenidate producing an ascending serum concentration curve to approximate a three-times-daily dosing schedule (but smoother).
• Should not be opened or chewed.
• Tablet passed into the stool intact.
• Reduced GI absorption or intestinal resections may decrease amount release into circulation
5 “P’s” of Sustained-release stimulants (cont’d)

**Patch** - transdermal delivery system

- **DAYTRANA** contains methylphenidate mixed with a multipolymeric adhesive layer attached to transparent backing

- Controlled duration of effect ending approximately 2 to 3 hours after the patch is removed.

- Medication steadily released for up to 16 hours then gradual decline

- Flexible dosing - FDA indication for only 9 hours - may be worn longer or apply at varying times of day as schedule changes

- Mild skin reactions to the patch are common

- No first-pass metabolism so more medication bioavailable
5 “P’s” of Sustained-release stimulants (cont’d)

**Prodrug** - inactive prodrug pharmacologically activated after oral ingestion

- Lisdexamfetamine dimesylate (VYVANSE) = d-amphetamine bound to lysine (an essential amino acid)
- Requires cleavage by Lyase (rate-limiting step) to release active d-amphetamine
- Duration ≤13-14 hrs w/ smoother more consistent delivery than other long-acting amphetamines
- ↓ risk for abuse because of its delayed release after IV or intranasal administration and delayed blood level spike after oral ingestion, ↓-ing immediate effects.
- More subtle onset and waning of effectiveness
23yo fifth year junior requesting Rx for “ADDERALL.” He reports problems focusing in classes and while studying. He has changed majors several times and an overall GPA is 2.1. He admits to regular MJ use. He has taken his roommate’s ADDERALL several times and reports that it helps his concentrate and studying a great deal.

How would you manage this case?
Typically developing controls

Figure 1b: right lateral view of the cortical regions where peak thickness was attained at each age (shown age 7 through 13). Again, the delay in ADHD group in attaining peak cortical thickness is apparent.
## Meditations

**Mechanism of Action**

- **Methylphenidate (Ritalin, Ritalin SR, Concerta, Metadate, Methylin, Focalin, Daytrana)**
  - Release and/or inhibit reuptake of catecholamines (eg, DA & NE) ↑level of these NT at the synapse

- **Amphetamine (Dextroamphetamine, Dextrostat, Adderall, Vyvanse)**
  - Release &/or inhibit reuptake of catecholamines (eg, D & NE) ↑level of NT at the synapse

- **Atomoxetine (Strattera)**
  - Selective norepinephrine reuptake inhibitor

**Cardiac Effects and Comments**

- **Methylphenidate (Ritalin, Ritalin SR, Concerta, Metadate, Methylin, Focalin, Daytrana)**
  - ↑d HR & BP, no ECG changes

- **Amphetamine (Dextroamphetamine, Dextrostat, Adderall, Vyvanse)**
  - ↑d HR & BP, no ECG changes

- **Atomoxetine (Strattera)**
  - ↑d HR & BP in adults & children, palpitations in adults, no ECG changes

**Recommendations for Cardiovascular Monitoring**

<table>
<thead>
<tr>
<th>Class I, Level of Evidence C</th>
<th>Class IIa, Level of Evidence C</th>
</tr>
</thead>
<tbody>
<tr>
<td>BP, HR</td>
<td>ECG on first visit</td>
</tr>
<tr>
<td>BP, HR</td>
<td>ECG on first visit</td>
</tr>
<tr>
<td>BP, HR</td>
<td>ECG on first visit</td>
</tr>
</tbody>
</table>

**Notes:**

- DA = dopamine; NE = norepinephrine; BP = blood pressure; and S = serotonin
- ↑d = ↑dose
- NT = neurotransmitter; HR, = heart rate; ECG = electrocardiogram
- Recommendations for cardiovascular monitoring may vary based on individual patient factors and should be guided by healthcare providers.
# Cardiovascular effects of ADHD medications

<table>
<thead>
<tr>
<th>Medications</th>
<th>Mechanism of Action</th>
<th>Cardiac Effects and Comments</th>
<th>Recommendations for Cardiovascular Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonidine (Catapres)</td>
<td>α₂-Adrenergic agonist</td>
<td>↓d HR &amp; BP, no ECG changes, rebound hypertension w/ abrupt discontinuation</td>
<td>BP, HR; additional BP when medication is started &amp; weaned</td>
</tr>
<tr>
<td>Guanfacine (Tenex)</td>
<td>α₂-Adrenergic agonist</td>
<td>↓d HR &amp; BP, no ECG changes</td>
<td>BP, HR</td>
</tr>
<tr>
<td>Desipramine, imipramine</td>
<td>Block the reuptake of D and NE</td>
<td>Prolongation of QTc, PR, QRS, tachycardia; rare reports of sudden death</td>
<td>BP, HR</td>
</tr>
<tr>
<td>Bupropion (Wellbutrin)</td>
<td>↓d firing rate of NE- &amp; S-releasing neurons</td>
<td>↑d BP in adults (not in children) cardiac toxicity w/ overdose</td>
<td>BP, HR</td>
</tr>
</tbody>
</table>

DA = dopamine; NE, = norepinephrine; NT = neurotransmitter; HR, = heart rate; BP = blood pressure; and S = serotonin
Growth curves show that ADHD patients' brain development trajectories, although lower in volume, parallel those of normal volunteers (NV). Solid lines compare the total brain volume in milliliters (vertical axis) of normal and ADHD males (top) and females (bottom) at different ages (horizontal axis) through childhood and adolescence.

Source: NIMH Child Psychiatry Branch
• Children with ADHD who had the 7-repeat version of the dopamine D4 receptor gene had thinner-than-normal areas in their brain's **out?** mantle, the cerebral cortex, which normalized during the teen years.
• This thickening in areas that control attention paralleled clinical improvement.
• Composite 3-D MRI scan data for youth, ages 8-16. Colored areas are those in which cortex thickness varied between ADHD patients and healthy controls, with brighter colors indicating greater differences.

*Source: Philip Shaw, M.D., NIMH Child Psychiatry Branch*
Molecular Structures of Sympathomimetic Amines

Epinephrine

Norepinephrine

Ephedrine

Pseudoephedrine

Phenylpropanolamine (norephedrine)

Methylphenidate

Amphetamine

Methamphetamine
Persistence into Adulthood

- follow-up studies of ADHD-diagnosed children report anywhere from 35% to 80% of cases will persist into adolescence with eventually 49% to 66% of these adults still meeting diagnostic criteria.

- (Spencer, Biederman, & Mick, 2007; Wilens, 2003).
In light of the potential benefit of treating adolescents who have ADHD, and the potential for negative sequelae without intervention, it is important to partner with the teens in their treatment planning. Several aspects of pharmacotherapy management may be specific to adolescents. Their schedules often include evening activities, such as extracurricular programs, studying, and work, so dosing adjustments may be required to manage symptoms over longer periods of time. Driving at night and participation in activities in which supervision is limited and impulsive behaviors may have significant consequences all support the need for extended coverage. This coverage may require a long-acting stimulant alone or in combination with a short-acting stimulant at the end of the day, or perhaps treatment with a nonstimulant to provide coverage throughout the waking hours. Growing rates of substance use concerns may also lead to alterations in treatment strategies to limit availability of agents with greater substance abuse potential, such as the immediate-release stimulants. Sustained-release preparations or nonstimulants may help to mitigate some of the abuse potential. By working together, the likelihood of treatment adherence and optimal outcomes is increased.
Validity of ADHD

- American Medical Association’s Council on Scientific Affairs:
  
  “Overall, ADHD is one of the best-researched disorders in medicine, and the overall data on its validity are far more compelling than for many medical conditions.”

*Goldman et al., JAMA 279:1100-1107, 1998*

Old slides
**ADDERALL ® (immediate release)** *(aka mixed amphetamine salts – “MAS”)*

- **FORM** tablets 5, 7.5, 10, 12.5, 15, 20, 25, 30 mg (scored)
- **DOSING** 5-30 mg QD-TID (↑ by 2.5-5 mg / dose)
- **DURATION OF BEHAVIORAL EFFECTS** 4-6+ hrs

**PROS** — effective in >80%
- Can significantly ↑ duration with ↑ dose
- Scoring & multiple strengths means ultimate dose flexibility
- Rebound symptoms “coming-off medication” often less frequent than MPH
- Generic available and generally reliable

**CONS** — multiple doses often required
- potential for abuse
• FORM capsules: 5mg, 10mg, 15mg, 20mg, 25mg, 30mg
  - Dual-bead system - 50% short-acting / 50% long-acting
• DOSING 10-40mg qAM (or 5-30 mg BID) (↑ q 3-7 days by 10mg QD)
• DURATION OF BEHAVIORAL EFFECTS 8-12 hrs
• PROS – QD dosing for some students
  - May be sprinkled
  - Less risk of abuse than immediate release
  - Numerous strengths means flexibility in dosing
  - Generic recently became available
• CONS – Some potential for abuse
  - Variability in individual response
VYVANSE®
(lisdexamfetamine dimesylate)

FORM  Capsule: 20 mg, 30mg, 40 mg, 50mg, 60 mg, 70mg

DOSING  20-70mg QD

DURATION OF BEHAVIORAL EFFECTS  ~12 hrs

PROS
- QD dosing
- Consistent response out to 12-13 hours for many patients
- Minimal risk of abuse *theoretically*
- ”Smother” for some / less abrupt onset & offset
- Perhaps better tolerated than other stimulants
- Can be swallowed whole or broken up and mixed with water, ice cream, applesauce, or yogurt

CONS
- New and expensive
- Some miss the abrupt onset
- Difficult to insurance approval for doses >70mg.
VYVANSE®
(lisdexamfetamine dimesylate)

• Pro-drug made from dextroamphetamine molecule with extra amino acid (l-lysine) attached

• Upon ingesting into the body, the drug has the extra amino acid removed by an enzyme (lyase) to form active drug (dextroamphetamine)

• Released at a constant rate through the day

• Difficult to abuse
  – Very complex and difficult to remove the extra amino acid except in the body so it is not a good source of free dextroamphetamine
  – Only a certain amount of the cleaving enzyme present in the body so that it becomes saturated in an overdose limiting the amount of active circulating drug

• Touted to be more consistently long-acting and to have smoother onset and offset than ADDERALL XR
DEXEDRINE®
(dextroamphetamine)

• **FORM** Tablet: 5 mg, 10 mg, 20 mg
• **DOSING** 5-20mg QD-BID (↑ by 5 mg / dose)
• **DURATION OF BEHAVIORAL EFFECTS** 3-5 hr
• **PROS** - Works quickly (30-60 minutes)
  - Good safety record
  - Generic available – relatively cheap
  - Sometimes effective when nothing else has worked
• **CONS** – Multiple doses often required
  - High abuse potential
  - Precaution in tic disorders
  - May cause rebound agitation
**DEXEDRINE SPANSULES®**  
* (dextroamphetamine)  

- **FORM**  
  *Capsules*: 5 mg, 10 mg, 15 mg  
  – 40% immediate release/ 60% sustained release coated pillete

- **DOSING**  
  5-30 mg QD (5-15mg BID)

- **DURATION OF BEHAVIORAL EFFECTS**  5-10 hrs

- **PROS**  
  - quick onset (30-60 minutes)  
  - good safety record  
  - generic available  
  - less potential for abuse

- **CONS**  
  - fewer strengths available than ADDERALL  
  - Multiple pills at each dose often required  
  - Less smooth / consistent delivery system than new SRs forms
RITALIN®
(methylphenidate)

- **FORM**: Tablets: 5 mg, 10 mg, 20 mg
- **DOSING**: 5–20 mg BID-TID
- **DURATION OF BEHAVIORAL EFFECTS**: About 3-5 hours
- **PROS**:
  - Works within 30-60 minutes
  - Effective in over 70% of patients.
  - Generic available
- **CONS**:
  - Requires multiple daily dosing
  - Easily & often diverted / abused
  - Irritability / rebound hyperactivity “coming off” meds
RITALIN LA® *(methylphenidate)*

- **FORM**  *Dual beaded - capsules*: 10, mg, 20 mg, 30 mg, 40 mg
  - 50/50% immediate / sustained release

- **DOSING** 10-60 mg QD (↑ q3-7 days by 10mg QD)

- **DURATION OF BEHAVIORAL EFFECTS**
  - Labeled for up to 8 hours

- **PROS** — may be sprinkled on food
  - QD dosing
  - Lower risk of abuse

- **CONS** — Too much immediate release for some
  - may require 2nd dose to cover late afternoons & evenings
METADATE CD®
(methylphenidate)

• **FORM**  *Dual beaded - capsules*: 10mg, 20mg, 30mg, 40mg, 50mg, 60mg
  - 70% long-acting / 30% immediate release

• **DOSING** 10-60 mg QD (BID) (↑q3-7 days by 10mg QD)

• **DURATION OF BEHAVIORAL EFFECTS**
  - 6-8 hours

• **PROS**
  - QD dosing
  - may be sprinkled
  - less likely abused than short acting
  - Often less expensive than other sustained release MPH

• **CONS**
  - may require 2nd dose for late afternoons / evenings
CONCERTA® *(methylphenidate)*

- **FORM:** capsules 18mg, 27mg, 36mg, 54mg  
  - 20% immediate / 40% intermediate / 40% long-acting  
  - Sophisticated OROS delivery system
- **DOSING** 18-108 mg *(may ↑ q3-7 days by 18mg QD)*
- **DURATION OF BEHAVIORAL EFFECTS**  
  - 10-14 hours *(usually significantly <12 hours)*
- **PROS** - QD dosing  
  - Lesser likelihood of abuse.
- **CONS** - Not enough immediate action for some  
  - Frequently under-dosed  
  - Harder to fine tune dosage
DAYTRAN® (methylphenidate patch)

• FORM: patches 10mg, 15mg, 20mg, 30mg
  — releases continuous amount transdermally for up to 16 hours

• DOSING  patch applied at start of day,
  — removed 9 hrs. later (on-label)
  — >9hrs / 2-3 hours before HS (off-label)

• DURATION OF BEHAVIORAL EFFECTS
  — As long as patch is worn + ~2-3 hours

• PROS — Ultimate flexibility in timing of dose
  — Lesser likelihood of abuse.
  — More direct route to CNS
  — Lesser likelihood of GI adverse effects
  — Attractive for patients with difficulty swallowing pills

• CONS — FDA only “approved” for use in 6-12 yo’s thus far
  — Precautions with chronic tics or anxiety disorder
  — Some skin reactions
  — Some patients uncomfortable with patch
<table>
<thead>
<tr>
<th>Nominal Dose Delivered</th>
<th>10mg</th>
<th>15 mg</th>
<th>20 mg</th>
<th>30 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dosage Rate* (mg/hr)</td>
<td>1.1</td>
<td>1.6</td>
<td>2.2</td>
<td>3.3</td>
</tr>
<tr>
<td>Patch Size (cm²)</td>
<td>12.5</td>
<td>18.75</td>
<td>25</td>
<td>37.5</td>
</tr>
<tr>
<td>Medication (mg) delivered over 9 Hrs</td>
<td>27.5</td>
<td>41.3</td>
<td>55</td>
<td>82.5</td>
</tr>
</tbody>
</table>
FOCALIN®
(dexmethylphenidate)

- R-enantiomer of racemic MPH molecule
- DOSING 2.5-10mg BID-TID (= ½ of MPH dose)
- DURATION OF BEHAVIORAL EFFECTS <6 hours
- PROS - Works quickly (within 30-60 min.)
  - Good as quick dose for late afternoons / evenings
  - May cause less sleep / appetite disturbance in some pts
- CONS – requires multiple daily dosing
  - more expensive than generic MPH
  - precautions with chronic tics or anxiety disorder
# FOCALIN XR®

*(dexmethylphenidate)*

- **FORM**: capsules: 5 mg, 10 mg, 15 mg, 20 mg
  - 50% short-acting / 50% long-acting
- **DOSING**: 5-20 mg qAM – BID (= ½ of MPH dose)
- **DURATION OF BEHAVIORAL EFFECTS**: labeled for ≤ 12 hours
- **PROS** - Works quickly (within 30-60 min.)
  - Touted to cause fewer adverse effects than racemic MPH
  - May allow higher dose titration → greater effectiveness
- **CONS**
  - More expensive than RITALIN / generics
  - Precautions with chronic tics or anxiety disorder
NON-STIMULANTS
STRATTERA® (Atomoxetine)

- **FORM**: Capsules: 10, 18, 25, 40, 60 mg

- **DOSING**: 0.5 – 1.2 mg/kg (off-label ≤1.8 mg/kg or 120 mg) QD

- **DURATION OF BEHAVIORAL EFFECTS**: ~24 hrs

- **PROS** — non-stimulant / not controlled substance
  - Useful with tic disorder
  - ? Less long-term appetite suppression
  - QD (or BID) dosing / allows 24 hr coverage (good for drivers)

- **CONS** — Takes several weeks to realize full effect
  - Response rate of only 56% and an effect size of only .35 and .40 (Michelson, 2003).
  - Daytime drowsiness not uncommon
  - Need to monitor for B/P changes and jaundice
  - Not long-term track record
  - Boxed warning re: suicidal thoughts (0.4% vs. 0% in study)
  - May need to be used with a stimulant for optimal effect
**WELLBUTRIN IR / SR / XL®** *(bupropion)*

**FORM:**  
- Tablets immediate release - 75, 100 mg  
- Sustained-release *(SR)* - 100, 150, 200 mg  
- Extended-release *(XR)* - 150, 300 mg

**DOSING:**  
- IR – TID  
- SR – BID  
- XL – QD

**DURATION OF BEHAVIORAL EFFECTS:** 14-24 hrs

**PROS:**  
- non-stimulant, non-controlled substance  
- Good for co-morbid depression / anxiety  
- 24 hour coverage – good for drivers  
- Generics available

**CONS:**  
- contra-indicated w/ seizures, bulimia, anorexia  
- May worsen some tics  
- Not as effective as stimulants  
- *Off label for treating ADHD*
CATAPRES® (clonidine)

- **FORM**
  - Tablets: 0.1 mg, 0.2 mg, 0.3 mg
  - Patches: TTS-1, TTS-2, TTS-3

- **DOSING**
  - 0.05-0.3 mg/day (patch changed qWeek)

- **DURATION OF BEHAVIORAL EFFECTS**
  - Tablets: 3-6 hrs / patch: 5-7 days

- **PROS**
  - useful with co-morbid tic disorder
  - severe hyperactivity and/or aggression

- **CONS**
  - Sleepiness, hypotension, headache, dizziness, dry mouth, depression, nightmares
  - Localized skin reactions with patch
  - Rebound hypertension if dose missed
  - Hard to keep patch on for a week
  - Off label for treating ADHD
KAPVAY® (clonidine)

• Approved for treating ADHD in ages 6-17 years (monotherapy or as adjunctive therapy)

• FORM extended-release tablet 0.1 mg

• DOSING 0.1-0.4mg qHS or BID. (increase by 0.1mg/wk)

• DURATION OF BEHAVIORAL EFFECTS:

  • PROS – maybe useful with co-morbid tic disorder
    – useful for severe hyperactivity and/or aggression
    – peak plasma concentrations 50% lower vs, IR formulations
    – less sedation than IR formulations

  • CONS - Sleepiness, hypotension, headache, dizziness, dry mouth, depression, nightmares
    – rebound hypertension if dose missed
TENEX® *(guanfacine)*

- **FORM**: tablets: 1 mg *(longer acting form soon to be approved & available)*
- **DOSING**: 0.5 - 4 mg/day ‡ BID
- **DURATION OF BEHAVIORAL EFFECTS**: 6-12 hrs
- **PROS** — useful with co-morbid tic disorder
  - severe hyperactivity and/or aggression
  - less sedation / hypotension than Clonidine
  - longer acting than Clonidine
- **CONS** - Sleepiness, hypotension, headache, dizziness, dry mouth, depression
  *Off-label for treating ADHD*
INTUNIV® (guanfacine)

• Approved for treating ADHD

**FORM** tablets: 1 mg
(longer acting form soon to be approved & available)

**DOSING**: 0.5 - 4 mg/day 😄 BID

**DURATION OF BEHAVIORAL EFFECTS**: 6-12 hrs

**PROS** — useful with co-morbid tic disorder
— severe hyperactivity and/or aggression
— less sedation / hypotension than Clonidine
— longer acting than Clonidine

**CONS** - Sleepiness, hypotension, headache, dizziness, dry mouth, depression
**ADHD has three subtypes:**

- **Predominantly hyperactive-impulsive**
  - Most symptoms (six or more) are in the hyperactivity-impulsivity categories.
  - Fewer than six symptoms of inattention are present, although inattention may still be present to some degree.

- **Predominantly inattentive**
  - The majority of symptoms (six or more) are in the inattention category and fewer than six symptoms of hyperactivity-impulsivity are present, although hyperactivity-impulsivity may still be present to some degree.
  - Children with this subtype are less likely to act out or have difficulties getting along with other children. They may sit quietly, but they are not paying attention to what they are doing. Therefore, the child may be overlooked, and parents and teachers may not notice that he or she has ADHD.

- **Combined hyperactive-impulsive and inattentive**
  - Six or more symptoms of inattention and six or more symptoms of hyperactivity-impulsivity are present.
  - Most children have the combined type of ADHD.
DSM-IV symptoms of inattention

in childhood
- Has difficulty sustaining attention
- Is easily distracted and forgetful
- Does not follow through
- Cannot organize
- Loses things
- Does not listen

in adulthood
- Has difficulty sustaining attention to reading or paperwork
- Is easily distracted and forgetful
- Has poor concentration
- Manages time poorly
- Misplaces things
- Has difficulty finishing tasks

### DSM-IV symptoms of hyperactivity

<table>
<thead>
<tr>
<th>in childhood</th>
<th>in adulthood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squirms and fidgets</td>
<td>Shows inner restlessness</td>
</tr>
<tr>
<td>Runs or climbs excessively</td>
<td>Fidgets when seated</td>
</tr>
<tr>
<td>Cannot play or work quietly</td>
<td>Self-selects active jobs</td>
</tr>
<tr>
<td>Talks excessively</td>
<td>Talks excessively</td>
</tr>
<tr>
<td>Seems &quot;on the go,&quot; driven by a motor</td>
<td>Feels overwhelmed</td>
</tr>
</tbody>
</table>

**DSM-IV symptoms of impulsivity**

**in childhood**
- Blurts out answers
- Cannot wait his or her turn
- Intrudes on or interrupts others

**in adulthood**
- Drives too fast, has traffic accidents
- Impulsively changes jobs
- Is irritable or quick to get angry

Prevalence in adults

National Co-morbidity Survey Replication (NCS-R)

- prevalence of attention deficit/hyperactivity symptoms estimated 4.4 percent of in adults ages 18-44
  - supported by National Institute for Mental Health (part of NIH)
  - conducted by researchers at Harvard Medical School