PRACTICAL TREATMENT STRATEGIES FOR ADULTS WITH ADHD
Learning Objectives

• Understand some evolving concepts about diagnosis and treatment for adult ADHD

• Define a thoughtful process for considering ADHD medication choices

• Review treatment options for stimulant side effects

• Consider a place for alpha agonists in adult ADHD
“CLINICIANS MAKE PRUDENT DECISIONS IN THE ABSENCE OF ADEQUATE INFORMATION.”
Onset Age for ADHD

- Nine prospective studies on late-onset ADHD
  - Two studies provide information on young adults (>25yo)
  - New York ADHD cohorts comparison subjects
  - Dunedin Multidisciplinary Health and Development Study
    - Moffitt 2015

ONSET OF SYMPTOMS VS. TIME OF DIAGNOSIS

SYMPTOMS

IMPAIRMENTS

AGE 7 12 18 25 32 50 60 70 80

Child Diagnosis

Adult Diagnosis

Medical Illnesses
Polypharmacy
SUD

Pseudodementia of Depression
Age related Menopause
MC
Dementia

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Neuropsychological Studies: Inconsistent Deficits

• Neuropsychological tests alone will not make an accurate diagnosis of ADHD

• Neuropsychological tests are not a criteria for the diagnosis of ADHD

• Symptom and executive ratings correlated better with function and quality of life than neuropsychological tests
Diagnostic Prioritization for Pharmacotherapy

Alcohol and substance abuse
Mood disorders
  Bipolar and MDD
Anxiety disorders
  Obsessive-compulsive disorder,
  generalized anxiety disorder, panic
ADHD

Order of treatment also considers the severity of the concurrent disorders.

International Adult ADHD Treatment Guidelines Consensus

- ADHD International Consensus Statement (World ADHD Federation), 2020

- European Consensus by the European Network of Adult ADHD, 2019

- Canadian Attention Deficit Hyperactivity Disorder Resource Alliance (CADDRA), 2018

- National Institute for Health and Clinical Excellence (NICE) UK, 2018

- No U.S. guidelines established
What to say to the patient?

• **Diagnoses** (what’s there, what’s not)

• **Education** (what this is, what it’s not)

• **Environmental changes** (academic, occupational, social, family)

• **Psychopharm/Psychotherapies**
  - Behavior, social, individual, family, couples
  - Support associations (www.CHADD.org)
TREATMENT OPTIONS AND MEDICATION
Benefits of ADHD Medication: Functional Outcomes

- Patients with ADHD and psychiatric comorbidities had the highest risk of subsequent sexually transmitted infections (STI).

- Lichtenstein et al. reported that compared with patients with ADHD who did not use ADHD medication, those who did exhibited a significant decrease in criminality rates (men, 32%; women, 41%); furthermore, the findings of the present study suggest that ADHD medication use was related to a lower risk of subsequent STIs.

Benefits of ADHD Medication: Functional Outcomes

• Groenman et al. investigated the effects of psychostimulant treatment on the subsequent risk of substance use disorder in a prospective longitudinal ADHD case-control study and found that patients with ADHD who received psychostimulant treatment had a lower risk of substance use disorder than those who did not receive the treatment.

• Cox et al. reported that patients with ADHD who received methylphenidate treatment self-reported fewer total ADHD and inattentive symptoms, were less likely to exhibit risky driving behaviors, and had fewer collisions than those without methylphenidate treatment.

“If stimulant medication is prescribed, a positive response *does not confirm* the diagnosis of ADHD.”

Medication response does not make a diagnosis

In fact, 30% of ADD adults do not have a beneficial response to the first stimulant. They may respond to an alternative stimulant.

Number of Stimulant Preparations?

29
Number of Stimulant Compounds?

- Methylphenidate
- D-MPH
- Amphetamine
- D-Amph
- MAS
Decision Process: Medication

• Compound
• Form of administration
• Duration of action
• Delivery system/technology
• Dosing
• Patient preference
• Insurance allowances
• Copay cost
Differential Response to Stimulants

Meta-Analysis of Within-subject Comparative Trials Evaluating Response to Stimulant Medications

AMP = amphetamine
MPH = methylphenidate

Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis

Samuele Cortese, Nicoletta Adamo, Cinzia Del Giovane, Christina Mohr-Jensen, Adrian J Hayes, Sara Carucci, Lauren Z Atkinson, Luca Tessari, Tobias Banaschewski, David Coghill, Chris Hollis, Emily Simonoff, Alessandro Zuddas, Corrado Barbui, Marianna Purgato, Hans-Christoph Steinhausen, Farhad Shokранeh, Jun Xia, Andrea Cipriani

Summary

Background The benefits and safety of medications for attention-deficit hyperactivity disorder (ADHD) remain controversial, and guidelines are inconsistent on which medications are preferred across different age groups. We aimed to estimate the comparative efficacy and tolerability of oral medications for ADHD in children, adolescents, and adults.

“Taking into account both efficacy and safety, for the first time evidence supports methylphenidate in children and adolescents, and amphetamines in adults as first choice at the group level.”

Pharmacogenetic Testing in ADHD

• “In conclusion, we report moderate effects of the genes SLC6A3, DRD4, SNAP25, and ADGRL3 in the response to MPH, thereby supporting several previous studies of these genes. We also found interactions between response to treatment over 12 months and genotypes of SLC6A3 and DRD2.

• (However) When all the covariates are taken into account, the models explain around 20% of the response to MPH. Therefore, other genetic or non-genetic factors must be involved in the variability of response to MPH. More research is required to find pharmacogenetic variants that could help to establish the best treatment regimen.”

Form of Administration

The form doesn’t convey duration of action!

• Liquid
  • Procentra (d-amph) short-acting
  • Dyanavel (d-amph) long-acting

• Tablet
  • MPH (short-acting)
  • Concerta (long-acting)

• Dissolvable tablets
  • Cotempla (MPH)
  • Adzenys (d-amph)

• Sprinkles
  • Methylin (short acting MPH)
  • Jornay (delayed release MPH)

• Capsule
  • Evekeo (amph) intermediate-acting
  • Adderall XR (MAS) long-acting

• Patch
  • All are long-acting

• Chewable
  • Methylin chewable short-acting
  • Quillichew (MPH) long-acting
  • Vyvanse chew (long-acting MPH)
Decision Process: Medication

- Compound
- Form of administration
- Duration of action
- Delivery system/technology
- Dosing
- Patient preference
- Insurance allowances
- Copay cost
ADHD Medication Sequencing

Delivery System Technology
- Beaded (IR/ER ratio, double/triple beaded)
- OROS (osmotic release)
- Microparticles (liquid/dissolvable tabs, chewables)
- Patch

Efficacy

Duration/Side effects

Monotherapy
- Atomoxetine
- Methylphenidate (D-MPH)
- Amphetamine (D-Amph)
- Guanfacine
- Clonidine

Adjunctive

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Non-Stimulants

• Atomoxetine
• Approved for children/adolescents:
  • Guanfacine ER
  • Clonidine ER
• Off-label:
  • Bupropion (positive controlled adult trials)
  • Desipramine (positive adult trial)
  • Modafinil (child study positive, adult study negative)
• Memantine
DOSING OF STIMULANT MEDICATION FOR ADHD
## FDA-Approved Medications for Adults with ADHD

<table>
<thead>
<tr>
<th>Medication</th>
<th>Child dosing</th>
<th>Adolescent dosing</th>
<th>Adult dosing</th>
<th>U.S. trials (adult)</th>
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<tbody>
<tr>
<td>Atomoxetine</td>
<td>0.5 mg/kg (&lt;70 kg) max 1.2 mg/kg (max 100 mg)</td>
<td>40 mg max 100 mg</td>
<td>120 mg</td>
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<tr>
<td>Dexmethylphenidate XR</td>
<td>5 mg max 20 mg</td>
<td>10 mg max 20 mg</td>
<td>40 mg</td>
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<tr>
<td>Triple bead mixed amphetamine salts</td>
<td>No indication</td>
<td>12.5 mg Max 25 mg</td>
<td>12.5 mg Max 50 mg</td>
<td>75 mg</td>
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<tr>
<td>Mixed amphetamine salts XR</td>
<td>10 mg max 30 mg</td>
<td>20 mg max-none</td>
<td>60 mg</td>
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</tr>
<tr>
<td>OROS Methylphenidate HCL</td>
<td>18 mg max 54 mg</td>
<td>18 mg max 72 mg</td>
<td>18 or 36 mg max 72 mg</td>
<td>108 mg</td>
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<tr>
<td>Triple bead MPH</td>
<td>25 mg max 70 mg</td>
<td>25 mg max 70 mg</td>
<td>25 mg max 85 mg</td>
<td>100 mg</td>
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Stimulants may be prescribed in combination with a non-stimulant to ensure coverage into the evening.

Adapted from Hazell. CNS Drugs 2007;21:37-46.

<table>
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<tr>
<th>Time (h)</th>
<th>0800</th>
<th>1200</th>
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<td>Morning</td>
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<tr>
<td>Evening</td>
<td></td>
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</tr>
<tr>
<td>Long-acting stimulant</td>
<td>Immediate-release stimulant</td>
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<tr>
<td>Extended-release stimulants, lisdexamfetamine, MPH transdermal system</td>
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<tr>
<td>Atomoxetine, bupropion, tricyclic antidepressant</td>
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<td>Combination treatment: long-acting stimulant and nonstimulant</td>
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<tr>
<td>Long-acting stimulant (1/2 AM dose)</td>
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CHEMICAL EQUIVALENCE VS. CLINICAL EQUIVALENCE
<table>
<thead>
<tr>
<th>Drug</th>
<th>Conversion</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adzenys XR-ODT</td>
<td>3.1 mg -&gt; 5mg MAS XR or 2.5 mg MAS IR BID</td>
<td>Adzenys XR-ODT 18.8 mg tablet is equivalent to 30 mg of Adderall XR (MAS ER) or 15 mg MAS IR BID</td>
</tr>
<tr>
<td></td>
<td>18.8 mg -&gt; 30 mg MAS XR or 15 mg MAS IR BID</td>
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</tr>
<tr>
<td>Vyvanse Capsule</td>
<td>30 mg -&gt; 10 mg MAS XR or 5 mg MAS IR BID</td>
<td>Studies indicate the AUC and $C_{\text{max}}$ for d-amphetamine from LDX 75 mg were comparable to (d,l-amphetamine Adderall XR 35 mg</td>
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<tr>
<td></td>
<td>50 mg -&gt; 20 mg MAS XR or 10 mg MAS IR BID</td>
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</tr>
<tr>
<td></td>
<td>70 mg -&gt; 30 mg MAS XR or 15 mg MAS IR BID</td>
<td></td>
</tr>
<tr>
<td>Mydayis</td>
<td>37.5 mg -&gt; 25 MAS XR +12.5 MAS IR 8 hours later</td>
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</table>
### Methylphenidate Chemical Equivalence

<table>
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<th>Drug</th>
<th>Conversion</th>
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<tr>
<td>Cotempla XR</td>
<td>8.6 mg -&gt; 10 MPH ER or 5 mg MHP IR BID</td>
<td>8.6, 17.3, and 25.9 mg tablets contain the same amount of MPH (base equivalent) found in other 10, 20, and 30 mg ER MPH formulations</td>
</tr>
<tr>
<td></td>
<td>17.3 mg -&gt; 20 MPH ER or 10 mg MHP IR BID</td>
<td>17.3 mg exhibits a significantly higher initial peak (C_{max} 22% higher)</td>
</tr>
<tr>
<td></td>
<td>25.9 mg -&gt; 30 MPH ER or 15 mg MHP IR BID</td>
<td>When Adhansia 100 mg qam is compared to MPH IR 20 mg TID, Adhansia XR exhibits a significantly higher initial peak (C_{max} 22% higher)</td>
</tr>
<tr>
<td>Adhansia XR</td>
<td>25 mg -&gt; 5 mg MPH IR TID</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 mg -&gt; 20 mg MPH IR TID</td>
<td></td>
</tr>
<tr>
<td>Jornay PM</td>
<td>20 mg -&gt; 4 mg MPH IR TID given in the am</td>
<td></td>
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<tr>
<td></td>
<td>40 mg -&gt; 8 mg MPH IR TID given in the am</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60 mg -&gt; 12 mg MPH IR PO TID given in the am</td>
<td>After a delayed onset of action, 100 mg comparable to 20 mg TID</td>
</tr>
<tr>
<td></td>
<td>80 mg -&gt; 16 mg MPH IR PO TID given in the am</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100 mg -&gt; 20 mg MPH IR PO TID given in the am</td>
<td></td>
</tr>
</tbody>
</table>
“LET’S MANAGE THE SIDE-EFFECTS.”
Side Effects With Stimulant Medication

- Insomnia
- GI upset
- Decreased appetite
- Weight loss
- Headaches
- Dry mouth
- Constipation
- Hand tremors
- Jittery

- Research on individual stimulants has generally shown no dose relationship with side effects in group data\(^1,\,\,2\)

- Some research has shown side effects may be more likely in stimulant naïve patients\(^3\)

Side Effects With Stimulant Medication

- Insomnia
  - ADHD or medication effect?
  - Medication timing
  - Consider alpha agent at bedtime for sedation and supplement ADHD effect

- GI upset
  - Usually with dosing
  - Take with food
  - Try ginger pills (OTC)
  - Usually transient
Side Effects With Stimulant Medication

• Decreased appetite
  • Usually not an issue for adults
  • Appetite increases when stimulant wearing off
  • Monitor in diabetic patients
• Weight loss
  • Issue with eating disorders (anorexia) or low BMI
• Headaches
  • Timing:
    • After dosing: maybe a Cmax issue? Decrease dose
    • Wearing off effect: rate of descent? Change delivery system
Side Effects With Stimulant Medication

- Dry mouth
  - Sugarless gum/lounges
  - OTC products
  - Pilocarpine 5–7.5 mg tid prn
  - Cevimeline 10 mg bid prn
- Hand tremors/jittery (distinguished from hyperactivity)
  - Caffeine-induced? Reduce/stop caffeine
  - Drug interaction: lithium, bupropion, decongestant
  - Propranolol LA 60–80 mg bid prn
  - Pemoline (also liver damage, and long onset to action) 50 mg qd or bid
Side Effects With Stimulant Medication

• Irritability/anxiety

  • Timing:
    • After dose: reduce dose or change delivery system—both effectively decreases Cmax
    • Wearing off effect: change delivery system for slower wear-off effect
  • Mood disorder symptom—assess quality to past mood experiences
Side Effects With Stimulant Medication

- Constipation
  - OTC agents (Miralax, stool softener, etc.)

- Erectile Dysfunction
  - PDE5 agent

- Urinary hesitancy in males
  - Exacerbation of BPH

- Not clear if differential effect between MPH vs. AMPH
ALPHA AGONISTS FOR ADULT ADHD
Guanfacine (ER) and Clonidine (ER)

• Guanfacine
  • Metabolized by 3A4
  • 3A4 inhibitors or inducers change metabolism
  • “Immediate-release guanfacine and guanfacine ER have different pharmacokinetic characteristics; dose substitution on a milligram for milligram basis will result in differences in exposure. “
  • “A comparison across studies suggests that the C. is 60% lower and AUC 43% lower, respectively, for guanfacine ER compared to immediate-release guanfacine. Therefore, the relative bioavailability of guanfacine XR to immediate-release guanfacine is 58%.”

• Clonidine
  • 50% excreted unmetabolized
  • Metabolized by 2D6, 1A2, 3A4, 1A1, 3A5
  • Similar elimination half-lives were observed and total systemic bioavailability following clonidine ER was approximately 89% of that following clonidine.
  • Elimination half-life is 6–24 hours, mean range is 12 hours

Guanficine XR-MPH in Adults

35 Healthy Adult

MPH-Guanfacine XR in Adults

35 Healthy Adult

GUANFACINE IN ADULT ADHD
Guanfacine XR in Adult ADHD

- Phase 3, double-blind, placebo-controlled study
- Japanese patients aged ≥ 18 years with ADHD (DSM-5)
- GXR (n = 101) or placebo (n = 100) titrated
  - Dose optimization: 5 weeks, Dose 2 mg/d to 4–6 mg/d
  - Dose-maintenance: 5 weeks, Dose 4–6 mg/d
  - Then tapered doses to 2 mg/d (2 weeks).
- Primary endpoint was change from baseline in total score on the Japanese version of the ADHD-Rating Scale IV with adult prompts (ADHD-RS-IV) at week 10

Reduction in ADHD-RS IV Total Score

Effect Size 0.52

Guanfacine XR
Placebo

*P < .0005

Guanfacine XR in Adult ADHD

• More patients in the GXR versus the placebo group reported TEAEs (81.2% vs 62.0%) and discontinued due to TEAEs (19.8% vs 3.0%)

• The main TEAEs in the GXR group were somnolence, thirst, blood pressure decrease, nasopharyngitis, postural dizziness, and constipation

• Most TEAEs were mild to moderate in severity

“They want to smoke pot.” for ADHD
Cannabinoids in Adult ADHD

• Randomized, placebo-controlled, single site, 6-week study of a cannabinoid medication, Sativex, oromucosal spray, a cannabinoid medication containing a 1:1 ratio of delta-9-tetrahydrocannabinol (Δ9-THC) to cannabidiol (CBD)

• 30 adults with ADHD; active (n =15) or placebo (n =15) group

• Outcomes at three time-points (baseline; 2-weeks; and 6-weeks)

• 2-week assessment, participants were provided with questionnaires

• Primary outcome: cognitive performance and activity level using the QbTest

• Secondary outcomes: ADHD and emotional lability (EL) symptoms

Cannabinoids in Adult ADHD

• For the primary outcome, no significant difference was found in the intent to treat (ITT) analysis

• For secondary outcomes, Sativex was associated with a nominally significant improvement in hyperactivity/impulsivity ($p = 0.03$) and a cognitive measure of inhibition ($p = 0.05$)

• Results did not meet significance following adjustment for multiple testing

Decision Process: Medication

• Compound
• Form of administration
• Duration of action
• Delivery system/technology
• Dosing
  • Patient preference
• “The Dance of the Tiers”- An Annual Performance
• Copay cost
Decision Process: Patient Factors

• Past response
  • Child vs. adult
  • Dosing adequacy
  • Dosing duration
  • Symptom changes
  • Functional changes

• Side effects
  • Child vs. adult
  • Compound vs. delivery system
  • Concurrent medication/OTC interactions
  • Concurrent medical illness that contributed
"Refractory" ADHD

Prominent Executive Function Deficits
(e.g., organization)

• Less response to stimulants.
• Organizational training
• Use of norepinephrine agent—atomoxetine, alpha agonist, tricyclic antidepressant (TCA), bupropion (alone or combined with stimulant, modafinil)
• Investigational
  • Modafinil
  • Donepezil
  • Memantine

Adapted from Findling et al. JCAP 2013.
Psychotherapies
Comprehensive Role of the Therapist

**Presentation**
- Symptom
- Impairments
- Dysfunctional Outcome
- Cognitive Distortions
- Mood Disturbance
- Behavioral Avoidance
- Lost Opportunity for Skill Development

**Treatment**
- Medication
- Organization Techniques
- Cognitive Therapy
- Behavioral Therapy
- Life Skills Building

**Outcome**
- Symptom Reduction
- Improved Productivity
- Modified Schema
- Change Behavior Frequency
- Improve Social Interactions

Psychotherapies For ADHD

• Education
  • Patients and family members
  • Books and websites

• Cognitive Behavior Therapy
  • Structure routines
  • Audio and visual cues
  • Consistent consequences for behavior

• Individual
  • Self-esteem issues
  • Social skills and relationship issues
  • Academic and occupational accommodations
WHEN TO REFER?
When to Refer?

When you are confused!
• Differential Diagnoses and Diagnostic Prioritization is critical to effective treatment

• Thoughtful sequence of medication options will help order the multiple choices available

• Combination of medications should be considered in less responsive patients

• Inquire about and treat medication side effects

• Education, behavioral changes, and cognitive therapies are effective
Posttest Question 1

Which of the following is least likely to contribute to an accurate diagnosis of ADHD in an adult?

1. History of symptoms
2. Family history of ADHD
3. Neuropsychological testing
4. Childhood symptom history
5. History of teacher interventions
Posttest Question 2

Which of the following statements is true?
FDA maximum daily dose of stimulant medication is set by…

1. safety parameters
2. weight
3. age
4. registration trials
5. abuse dosing potential
6. optimal dose response
Posttest Question 3

Given the large numbers of ADHD medications on the market, do you have a thoughtful algorithmic approach to choosing a stimulant medication after the first choice doesn’t go well?

1. Yes
2. No