Identification & Management of ADHD in Pediatric Primary Care

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Objectives

- Understand how to best diagnose ADHD in primary care settings
- Discuss the Multimodal Treatment Study of ADHD
- Describe the mechanism of action of ADHD Meds
- Identify current and new pharmacotherapy technology for ADHD
- Recognize other ADHD interventions and their evidence base

Epidemiology of ADHD in Children

- Prevalence 7.1% in children and adolescents
- 2/3 treated
- Males > Female by 4:1
- Life course
  - Hyperactivity ↓, Inattention persists
  - High comorbidity (2/3)
  - ODD, learning disorder, smoking, etc.

CDC National Survey Children’s Health 2007-2008 – 70,000 parents
Practice Parameter for the Assessment & Treatment of Children and Adolescents with Attention-Deficit/Hyperactivity Disorder. JAACAP 2007;46(7): 894-921
Epidemiology of ADHD in Adults

- Prevalence ~4-5% in Adults
- Historically ADHD was thought not to continue beyond adolescents
- Studies suggest persistent of prominent symptoms and impairment in 50% of young adults diagnosed with ADHD in childhood

Prevalence

- Longitudinally data in ADHD youth symptoms of hyperactivity and impulsivity decay over time, the symptoms of inattention persist
- Data derived from a large group of adults with ADHD indicate
  - that whereas approximately 50% of adults display clinically significant levels of hyperactive/impulsive symptomatology
  - 90% display prominent attentional symptomatology

E. Wilcutt, Neurotherapeutics, July 2012
Kessler RC, Chiu WT, Demler O, Walters EE. Archives of General Psychiatry, 2005
ADHD Presentation in Adults

- More conflicts in social and marital relations
- Underachievement in their careers, economic status and academics despite adequate intellectual abilities
- Manifest higher rates of anxiety, mood and substance abuse disorders than non-ADHD adults
- Conversely, adults with depression, bipolar and substance abuse disorders have been characterized as maintaining high rates of ADHD

ADHD is a Complex Disorder having multiple causes including genetics as impacted by ones environment.

Blum, K et al, Neuropsychiatric Dis Treat, 2008
Symptomatic Rating of ADHD Treatment

Value of systematic rating
- Establishment of diagnosis (along with symptomatology)
- Multi-informant (parent, teacher, youth)

Conner’ Rating Scale
PSC-35
- Has Attention and Externalizing sub-scales

SNAP-IV-18

Vanderbilt Scales

Adult ADHD Rating Scale (for older teens)

DSM 5 Diagnosis of ADHD

In chapter on neurodevelopmental disorders
Criteria:
- A persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development, as characterized by 6 or more symptoms of either area
- Persist for 6 months
- Present before age 12
- 2 or more settings
ADHD and Co-Occuring Diseases

![Diagram showing the relationship between ADHD and co-occurring diseases: Behavior Problems, Anxiety & Depression, Learning Disorder, Increased Injuries, Peer Problems.]

Real Psychiatry 2015.

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**Treatment Benefit by Outcome Group**

- Compared with untreated ADHD
- Outcomes in each outcome group

![Bar chart showing treatment benefit by outcome group.]

Real Psychiatry 2015.
Treatments

- Psychoeducation
- **Stimulant medications**
- **Alternative non-stimulant medications**
- Behavioral interventions
- School interventions
- Community support
- Other interventions?

General Treatment Guidelines, The American Academy of Pediatrics

**For preschool-aged children (4 to 5 years old):** Evidence-based behavior therapy is recommended. However, medication may be added if there is no improvement. Methylphenidate is recommended over amphetamines or non-stimulants.

**For school-aged children (6 to 11 years old):** FDA-approved ADHD medications and/or behavior therapy are recommended. A stimulant is recommended over atomoxetine, guanfacine, and clonidine.

**For adolescents (12 to 18 years of age):** FDA-approved ADHD medications and behavior therapy are recommended, preferably together.
Other Interventions: Neurofeedback

“Cognitive training, neurofeedback, dietary therapy (such as restricted elimination diet), polyunsaturated fatty acids, amino acids, minerals, herbal therapy, homeopathy, and physical activity cannot be recommended as evidence-based interventions for global functioning and core ADHD symptoms until better evidence of their comparative efficacy is reported in well-designed and conducted clinical trials.”

PLOS One 2017.
Psychotherapy for ADHD & Comorbid Disorders

- Parent behavioral training
- Management of ODD & prevention of conduct disorder
- Treatment co-morbid disorders
  - CBT, etc. for mood disorder, anxiety
- May reduce needed dose of stimulant medications
- Prevent child abuse/traumatization

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Multimodal Treatment Study of ADHD

I. ADHD
No Comorbidity

Medication alone proved effective


"Outcomes of a full standard deviation improvement. 8 or greater"

Dawn Browning Wright. Behavior Discipline Trainings, 2002
MTA Study: Results

- Combination treatment and medication management alone were both significantly superior to intensive behavioral treatment alone and to routine community care in reducing ADHD symptoms.

- The study also showed that these benefits last for as long as 14 months.

MTA Study: Results

- In other areas of functioning:
  - anxiety symptoms
  - academic performance
  - parent-child relations
  - social skills
- Combination treatment was consistently superior to routine community care, whereas medication alone or behavioral treatment alone were not
- Children in the combination treatment also ended up taking lower doses of medication than the children in the medication-alone group
MTA Study: Social Skills

- Previously, it was thought that children with ADHD could only learn new social skills if they were explicitly taught.
- MTA suggest that many children can acquire these skills on their own when given the opportunity.
- Children treated with medication management (either alone or in combination with intensive behavioral therapy) showed more improved social skills and peer relations than children in the community comparison group after 14 months.

Why do stimulants work for ADHD?

Meta-analysis of functional fMRI studies in ADHD

Hurt et al., Arch Gen Psychiatry 2013; 70: 186-96

- Reduced / increased activation in attentional networks
- Reduced activation in inhibitory networks

13 data sets (171 patients with ADHD / 172 controls)
21 data sets (287 patients with ADHD / 320 controls)
Role of Cathecholamines

Dopamine

- ability to attach attention and to relate attention to working memory and problem solving
- enable active suppression of distractions
- inhibit inappropriate behavioral expressions of tangential thoughts, ideas, or behaviors
- the ability to hold an idea in conscious awareness and analyze it thoroughly before making decisions
- capacity for executive function involved in reasoning, planning, and problem solving
- engaged in attention to detail and increase perseveration of thinking -- the ability to sustain working memory

Role of Cathecholamines

Norepinephrine

- maintaining and increasing overall arousal
- contributing to affect regulation related to excitability and response to danger or opportunity
- contributing to memory storage and retrieval, especially affect-related or emotionally intense events.
- assists in maintaining basal or tonic alertness.
  - At a quieter moment, reading a book, studying at night, the effort to remain alert and stay on task partially mediated by NE


PFC and optimal levels of NE and DA

Pharmacotherapy

US FDA approved for the treatment of ADHD

School Age

- Stimulants
- Non Stimulants
  - Alpha 2 Agonists
  - Atomoxetine

Adults

- Atomoxetine
- Amphetamine (AMP)
- Methylphenidate (MPH)
Stimulant Medications: Efficacy

- One of the most robust treatments in psychiatry
- 70% of children with ADHD will respond to any one of the stimulants, all generally equal efficacy
- An additional 20% will respond to the next one attempted
- If the 1st and 2nd choices fail, check for wrong diagnosis and/or comorbidity

Stimulants: Mechanism of Action

- Increase intrasynaptic concentrations of dopamine (DA) and norepinephrine (NE)
- MPH primarily acts by blocking the reuptake of DA by binding to the DA transporter protein on the presynaptic membrane
- (AMP > MPH) increase levels of NE and 5-hydroxy-tryptamine (5-HT) in the interneuronal space
Pharmacological Treatment of ADHD: Stimulants

- Types of preparations

  - Short-acting:
    - Ritalin (methylphenidate MPH)
  
  - Intermediate-action:
    - Dextedrine
    - Adderall (mixed amphetamine salts)
    - Ritalin SR
  
  - Long acting:
    - Adderall XR (mixed amphetamine preparation)
    - Cylert (pemoline; some association with liver damage)
    - Metadate and Concerta (MPH preparations)
    - Vyvanse (unconjugated molecule; metabolized by intestinal lining enzymes); used with suspicion of abuse/diversion
    - Quillivant (liquid long acting MPH)
    - Daytrana patch (long acting MPH)
Stimulants – Immediate Release

Pharmacologic action
- Action begin 30 to 45 minutes after ingestions
- Peaks in 1 to 2 hours
- Fades away over 3 to 5 hrs

Why isn’t the stimulant working?
- ADHD is not the actual diagnosis
- Concomitant disorders override any observable stimulant benefit
- Failure to use the proper dose (too high or low)
- Refusal of child, adolescent, and/or parent to accept medications
- ADHD type does not respond to stimulants or any medications
- Side effects of MPH and/or amphetamines are not tolerated by the patient
- Failure to start with a low dose and titrate slowly
- Use of the medication for other than amelioration of attentional dysfunction
  - (ie, use of stimulants to alter negative behavior as seen with conduct disorders)
Release Mechanisms-ER/SR

Wax Matrix
- Ritalin SR

OROS
- Concerta

Beads
- Metadate CD 30/70
- Ritalin LA 50/50
- Focalin XR 50/50
Methylphenidate HCl (Metadate® CD) Extended-Release Capsules: Biphasic Release Bead-Delivery System

OROS Technology

Rate-controlling semipermeable membrane

Water-dispersable color overcoat

2 laser-drilled delivery orifices

Drug compartment 1

Drug compartment 2

Polymer "push" compartment

CONCERTA™
(methylphenidate hydrochloride)

NOVO-METHYLPHENIDATE ER-C
(methylphenidate hydrochloride)

18 mg
27 mg
36 mg
54 mg
18 mg
27 mg
36 mg
54 mg
Mixed Salts
Adderall

- Two enantiomers of Amphetamine
  - 25% - AMP Aspartate Monohydrate
  - 25% - AMP Sulfate
  - 25% - DextroAMP Saccharate
  - 25% - DextroAMP Sulfate
Recently FDA Approved Stimulants

Contepla (Methylphenidate ODT)
- Mechanism: DAT/NET reuptake inhibitor
- Company: Neos Therapeutics
- An orally disintegrating tablet (ODT) that uses RDIM (Rapidly Disintegrating Ionic Masking) technology.
- Users will not need to worry about “swallowing” the pill with a liquid.

Adzenys
- Mechanism: TAAR1 agonist / DRI
- Company: Neos Therapeutics

Mydayis
- FDA approved in June 2017 for all-day symptom control in patients 13 years of age or older
- Long-acting, triple-bead, mixed amphetamine salts
What if they can’t swallow pills?

- **Liquid preparations:**
  - Methylin (methylphenidate oral solution)
  - ProCentra (dextroamphetamine oral solution)
  - Quillivant XR (methylphenidate extended release powder for oral suspension)

- **Patch:**
  - Daytrana Patch (methylphenidate)

- Capsules can be sprinkled for several products

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Clinical Prescribing Strategies

**Selection**
- Methylphenidate: middle potency and SE’s
- Adderall and dexedrine: higher potency and SE’s
- Atomoxetine, Bupropion, alpha agonists: Lower potency and SE’s; value with co-morbid anxiety and depression

**Dosing**
- Start low dose and gradually increase
- Use extended release preparations
- Max dose: 2 mg. per kg per day of methylphenidate daily; rarely reached (usually severe)
- If slow metabolizer: May use short acting agents alone and gradually increase
- After hepatic enzymes induced, may end up higher dose and with long acting preparations
Clinical Prescribing Strategies

School effect
- Ideal: no second dosing at school (less stigma, maximum confidentiality, less problems with school authorization)
- Extended release preparations assure this

Homework time and activities
- Should complete early PM under medication “umbrella”
- Second short-acting dose if wears off before dinner time

Sleep
- Ensure wears off after dinner
- Can use Melatonin (3 to 5 mg.), antihistamines,
- Use alpha agonists especially if ADHD itself is barrier to sleep

Drug holidays
- Weekends and summer
- Value: Catch-up growth (less appetite suppression); possibly prevent post-synaptic sensitization (increase receptors)

Stimulants: Side Effects

- Short-term
  - Insomnia, decreased appetite/weight loss, abdominal pain/nausea, headaches
- Tics
  - probably unmasks latent Tourette’s; may still need stimulant after treat tic disorder
- Drowsiness (if excess dose)
- Mood lability (can be medication effect, but may need to rule out associated mood disorder)
- Can aggravate co-morbid anxiety
- No addiction demonstrated so far shown in affected individual, but can be abused by peers
- Can lower seizure threshold
Stimulants: Medical Issues

Growth: Faraone meta-analysis:
- After 2-3 years on stimulants, kids were 1-2.5 cm shorter
- Growth rate increases when stimulants stopped

Cardiac Risk
- Hypertension
- Some sudden death reported but not higher than general population (ECG not required but cardiac history screen is)
- AHA: 1999 guidelines – no routine EKG
- AHA: 2008 guidelines – “...it is reasonable for a physician to consider obtaining an ECG as part of the evaluation of children being considered for stimulant drug therapy, but this should be at the physician’s judgment, and it is not mandatory to obtain one”

Pharmacological Treatment of ADHD: Alternatives

Atomoxetine (Strattera)
- Adrenergic agonist, some dopamine agonist; similar to tricyclics but with fewer SE’s/ toxicity
- Equal efficacy to stimulants in FDA stage 3 trials; clinically falls somewhat short
- Reportedly fewer side effects, though similar to stimulants
  - Cardiac
  - Hypotension
  - Sedation (minor, can shift to HS)
  - Black box warning for SI
- Value:
  - Less SE’s, less anxiety aggravation, once daily dosing, not schedule II, doesn’t aggravate tics
  - Once daily dosing recommended (25 to 80 mg. per day)
  - Long half-life in normal metabolizers (can use single dose)- takes long time to titrate
Pharmacological Treatment of ADHD: Alternatives

- Adrenergic alpha agonists Clonidine, Tenex, Kapvay (extended release clonidine), Intuniv (extended release guanfacine)
  - Original use as antihypertensive
  - Most effective with impulsivity and hyperactivity, but some with inattention
  - Mixed data on efficacy
  - Often used as adjunct to stimulants
  - Side effects:
    - Cardiac side effects (arrhythmias when combined with stimulants; best to check ECG)
    - Hypotension and rebound hypertension when discontinuing
    - Sedation

Tricyclic Antidepressants (imipramine, desipramine):
- Have some demonstrated efficacy
- Multiple side effects:
  - Anticholinergic
  - Sedation
  - Postural hypotension
  - Cardiac problems

Wellbutrin XL (bupropion):
- Adrenergic antidepressant
- Has demonstrated effectiveness in trials, though less than stimulants
- Can be used for co-morbid ADHD and depression
- Used for youth where substance abuse concern
- Side effects:
  - Seizure risk
  - Hypertension
  - Anxiety aggravation (but in some: anxiety reduction)
Collaborative Hub Procedure: ADHD

- Referring to the Hub: After screening the patient using appropriate screening tool and/or based on clinical judgment following the exam, providers can fax the PPC Hub. Providers should send a complete referral form, screening tools, and any other clinically relevant information.

- What Does the Hub Staff Need? All of the information the PPC Hub staff needs is on the referral form, including relevant background information, current clinical picture, demographic information, and reason for referral. Some providers may choose to send notes from previous visits as well, which can be very helpful, but is not required.

- Communicating with the Family: Please be sure you have discussed the PPC Hub with the patient and family prior to faxing a referral to the PPC Hub, so that the family is aware that a Hub staff psychologist/LCSW/other mental health specialist will be contacting them to discuss current concerns and suggestions for support/treatment.
Collaborative Hub Procedure: ADHD

- What will the PPC Hub Staff Do? Hub staff will call the patient’s family and complete a clinical intake. The family will discuss their main concerns. Case managers will evaluate for severity and level of care. Depending on the patient’s needs, Hub staff will:
  - Recommend an appropriate level of care - the family is sent a list of referrals for therapy services to address current mental health concerns.
  - Match the patient with a therapist based on their insurance and geographical location – the referrals are researched by staff psychologists/LCSWs, and most often accept patient insurance.
  - “Closing” the Loop: Hub staff will communicate with you, sending you notes on what occurred with the family. They will also encourage the family to call them back if they need another resource. Hub staff will also follow-up with referred families 3 and 9 months after initial referral.

Summary

- ADHD is complex disorder with multiple etiologies
- Pharmacotherapy is mainly stimulants with varying delivery methods
- Behavioral interventions and non-stimulant medications also play a role in treatment
Selected References

1. Some slides have been used from slide presentations of Dr. Pumariega and Dr. Alcera on similar topic. Thanks!