Evaluation and Treatment of ADHD

An Overview

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Objectives

- Describe the prevalence and characteristics of ADHD throughout the lifetime.
- Review options in the treatment of ADHD.
- Examine a case of ADHD Comorbid with Depression.

Epidemiology of ADHD

- 4-9% in children and adolescents
- 4% in adults
- More prevalent in boys
- More prevalent in the United States due to increased awareness and available treatment

Etiology: Multifactorial

Genetic: Candidate Gene Studies

- Numerous genes in catecholamine systems implicated in ADHD: DRD4, DAT1, DRD5, DBH, 5HTT, SNAP-25
- Genes of small effect likely to combine with each other and environmental factors to cause ADHD

Etiology: Multifactorial

- CNS Insults
  - Circulatory, toxic, metabolic, mechanical
  - Subtle brain damage perinatally
- Psychosocial Factors: Stressful psychic events

Etiology: Multifactorial

Neurochemical: multiple neurotransmitters involved

- Dopamine: abnormal DAT binding and DA transmission
- Norepinephrine
- Other

Neurophysiological

- PET Scan: decreased cerebral blood flow and metabolic rates to frontal lobes
- Inadequate inhibition of lower structures leading to disinhibition

Characteristics-Children

- Persistent pattern of inattention and/or hyperactive and impulsive behavior
- More severe than expected of children of similar age and level of development
- Some symptoms must be present before age 7, although often diagnosed later

Characteristic-Children

- Symptoms must be present in 2 settings: academic, extracurricular, social
- Preschool:
  - disruptive behavior
- School-age:
  - academic failure
  - poor socialization
  - injuries

Characteristics-Adolescents

- Academic Failure:
  - Disorganized
  - Poor work follow through
  - Difficulty with independent work
- Low self esteem, poor peer relationships
- Risky behavior:
  - Substance abuse
  - Car accidents
  - Crimes

Characteristics-Adults

- Until 1980's ADHD thought to be outgrown
- Hyperactivity diminishes (but restlessness)
- Academic/occupational failure
- Relationship failures
- Substance abuse and legal problems
- Diagnostic key: symptoms present before age 7

DSM-IV TR Criteria: ADHD

A. Either 1 or 2

1. Six or more of the following symptoms of inattention have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level.

a.) often fails to give close attention to details or makes careless mistakes in schoolwork, work, or other activities.

b.) often has difficulty sustaining attention in tasks or play activities.

c.) often does not seem to listen when spoken to directly

d.) often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the work place (not due to oppositional behavior or failure to understand instructions.

e.) often has difficulty organizing tasks and activities

f.) often avoids, dislikes, or is reluctant to engage in tasks that require sustained mental effort

g.) often loses things necessary for tasks or activities

h.) is often easily distracted by extraneous stimuli

i.) is often forgetful in daily activities

DSM IV – TR continued

2.Six or more or the following symptoms of hyperactivity-impulsivity have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level.

-Hyperactivity

a.) often fidgets with hands or feet or squirms in seat.

b.) often leaves seat in classroom or in other situations in which remaining seated is expected.

c.) often runs about or climbs excessively in situations in which it is inappropriate

d.) often has difficulty playing or engaging in leisure activities quietly.

e.) is often “on the go” or often acts as if “driven by motor”

f.) talks excessively

- Impulsivity

g.) often blurts out answers before questions have been completed

h.) often has difficulty awaiting turn

i.) often interrupts or intrudes on others.

Evaluation

- Usually first noticed by teacher
- Hyperactive type diagnosed earlier
- Must occur in at least 2 settings

Evaluation

- History: prenatal, early development, current
- Family History
- Physical: include blood pressure, pulse, weight and height
- Lab Testing
- Direct Observation

Evaluation – Screening Tests

- Children and Adolescents
  - Connors Parent's Rating Scale
  - Connors Teacher's Rating Scale
- Adolescents
  - Connors
  - Adolescent self report
- Adults
  - Adult self report scale (screener and checklist)
- Continuous Performance Tests
  - Connors
  - TOVA
  - Useful as part of a battery

Differential Diagnosis vs. Comorbitities

- Behavioral Disorders: ODD, CD
- Learning Disorders, MRDD, PDD
- Tic Disorders
- Mood/Anxiety Disorders (Bipolar Disorder)
- Psychotic Disorders
- Substance Abuse Disorders

Treatment: Multimodal

- Multimodal Treatment Study of Children with ADHD
  - 14 month clinical trial, 579 children
  - 4 treatment groups: percent improvement at 14 months
    a. medication management 56%
    b. behavioral treatment 45%
    c. combination (a & b) 70% plus
    d. community based
- combination therapy did best

Treatment: Non Pharmacologic Therapy

- Behavioral Therapy
  - Most effective
  - Rewards/consequences
  - Daily report card monitoring target symptoms
- Educating those involved
- Environmental modification/management
  - Work
  - School
  - Home
- Cognitive Therapy

Treatment:Accommodations

- Small, self contained classroom (less distractibility)
- More test time
- Organization skills
  - planner/schedule
  - limit choices/reduce procrastination

A Wide Array of Pharmacotherapy Options

Agents

- Stimulants
  - -Methylphenidate (MPH)
  - -Amphetamines (AMPH)
- Selective norepinephrine reuptake inhibitor
- Others

Preparations

- Immediate-release
- First-generation sustained-release
- Second-generation sustained-release

Biederman J. *Today's Therapeutic Trends* 2002

Dosing:Distinguishing Efficacy from Potency

- D,L-amphetamines and methylphenidate
  - Comparable ADHD symptom improvement (efficacy)
  - Unequal potency
    - ~ 1:2 ratio between amphetamines and MPH
    - 1 mg of amphetamine = ~ 2 mg of MPH
- Clinical benefit seen at dosages of 0.5-1 mg/kg/d of amphetamines and 1-2 mg/kg/d of MPH
- Aggressive approach often required in older adolescents, adults because of their weight
  - Underdosing is a concern in this patient population

Bieferman J. *Today's Trends* 2002
Therapeutic

Key Treatment Points

- ADHD is a “real” disorder that has genetic and neurobiologic bases
- Suboptimal dosing = suboptimal outcomes
- Titrate upward before switching or “settling”
- Emergence of side effects can serve as a guide

Stimulant Overview

- Methylphenidate (MPH)
  - DAT antagonist
- Amphetamine (AMPH)
  - increases catecholamine release
  - DAT antagonist

Immediate-Release MPH

- Methylphenidate (Ritalin, Methylin)
  - 4-hour activity→ bid or tid dosing
  - 2.5, 5, 10, 20 mg tablets
  - 5mg/mL, 10mg/mL, (elixir)

- Dexmethylphenidate (Focalin)
  - Single enantiomer MPH
  - 4-hour activity
  - 2.5, 5, 10 mg tablets
  - May have improved tolerability in some patients

Sustained-Release MPH

- Ritalin SR
  - Wax-matrix delivery
  - Flat concentration profile
  - 4-8 hours efficacy
  - 20 mg Tablet
- Metadate ER
  - Equivalent to Ritalin SR
  - 10 mg, 20 mg tablets

Extended-Release MPH

- Metadate CD
  - Dual-phase with 30% immediate release (IR) and 70% extended release (ER)
  - 10, 20, 30 mg capsule
- Ritalin LA
  - Dual-phase with 50% IR and 50% ER at 4 hours
  - 20, 30, 40 mg capsule
  - Effective for school day as single daily dose

Extended-Release MPH (cont.)

- Concerta
  - OROS (oral release delivery system)
  - Comparable to tid MPH
  - 10-12 hours efficacy
  - 18, 22, 36, 54 mg caplets
  - Dose range up to 72 mg/day in adolescent study

Extended-Release MPH (cont)

- Dexmethylphenidate extended release (Focalin-XR)
  - Once daily dosing
  - 8-12 hour efficacy
  - 5, 10, 20 mg capsules
  - Higher doses might be required

Transdermal Methylphenidate

- Dosages
  - 10 mg/12.5 cm^2
  - 15 mg/18.75 cm^2
  - 20 mg/25 cm^2
  - 30 mg/37.5 cm^2
- Dot matrix technology
- Similar efficacy to OROS-MPH

*Based on 9-hour wear time

Pierce (2005)

Dot Matrix Technology: How Does It Work?

- Drug solubilized in acrylic in very high concentrations
- Drug-in-acrylic blend is then mixed with a silicone-based adhesive
- Forms evenly dispersed, concentrated drug cells within uncompromised adhesive layer
- Concentration gradient between drug and skin allows highly efficient diffusion

Immediate-Release AMPH

- Dextroamphetamine (Dexedrine, DextroStat) 5mg tablets

- Mixed amphetamine salts (Adderall) 5, 7.5, 10, 12.5, 15, 20, 30 mg tablets
  - 6-8 hours efficacy
  - 2x potency of MPH
  - Often require bid dosing
  - Less preferable than MPH for tic disorders

Sustained-Release AMPH

- Dexadrine Spansules 5, 10, 15 mg
  - 8-12 hours efficacy
  - Useful for qd or bid dosing

Extended-Release AMPH

- MAS-XR (Adderall XR) 5, 10, 15, 20, 25, 30 mg capsules
  - Efficacy to 12 hours
  - Biphasic, pulsed, beaded delivery system provides dose at 0 and 4 hours
  - Capsule contents can be sprinkled

Comparing Stimulants

- Equal efficacy across methylphenidate and dextroamphetamine
- Approximately 70% respond in short term
- Response rate may be as high as 96%
- Some individuals have stimulant-specific responses

Greenhill LL et al. (2002)

Side Effects in Stimulant Studies

- Side effects for the 2 molecules are similar
  - Dry mouth
  - Insomnia
  - Appetite suppression
  - Headache
  - Edginess
  - Cardiovascular (not clinically significant)
    - BP increased 2 to 4 mm Hg
    - HR increased 2 to 4 BPM
  - No cardiovascular black box warning

Safety Considerations

- Untreated ADHD is a risk factor for substance abuse
- Most studies on the subject indicate that ADHD pharmacotherapy exercises a protective effect against late substance abuse
- The potential for abuse of ADHD medications can be minimized by
  - Choice of medication
  - Formulation
  - Dosing schedule

Substance Use Disorders and ADHD

- Overall Rate of Substance Use Disorder
  - Controls (n=137) 18%
  - Medicated (n=56) 25%
  - Unmedicated (n=19) 75%

Biederman J, et al. *Pediatrics.* 1999

Strategies for Minimizing Abuse and Diversion of ADHD Medications

- Prescribe only once-daily medications to be taken at home
- Choose formulations that are difficult to snort or grind (eg, OROS MPH) or that are not stimulants (eg, atomoxetine)
- Screen for a family history of substance abuse; others in the house may seek to divert and abuse the patients stimulants

Stimulant Effect on Growth

- Stimulants once thought to decrease growth hormone secretion
- Studies have shown essentially no long term effect on child's ultimate height
- Consensus: less need for drug holidays

Nonstimulants: Atomoxetine (Strattera)

- Blocks presynaptic norepinephrine transporter with no significant dopamine effect
- Similar improvement in ADHD symptoms to methylphenidate
- Improves social and family functioning
- Dosage: 18-100 mg once/day
- Children <70kg*: initiate at 0.5 mg/kg and titrate to 1.2 mg/kg
- Adults initiate 40mg/d, target 80mg/d, max 100mg/d

*Package insert atomoxetine; Kratochvil CJ et al. (2002)

Nonstimulants: Atomoxetine (cont)

- Adverse effects in children: decreased appetite, nausea, abdominal pain, dizziness, somnolence
- Adverse effects in adults: constipation, dry mouth, urinary retention and sexual dysfunction
- Caution with poor CYP2D6 metabolizers
- FDA warnings: liver toxicity, suicidal thoughts in children

Other Nonstimulants

- Antidepressants
  - Wellbutrin
  - SNRI's/SSRI's
  - TCA's/MAOI's
- Clonidine
- Guanfacine

Update on Modafinil for ADHD

- Unique action: histaminergic agonist?
- Preferential benefit in inattentive subtype
- Cephalon not pursuing indication in children and adolescents
- Studies for adult ADHD

Managing Adverse Effects From ADHD Treatment

- Decreased appetite
  - Affects about 6-7% of children
  - Monitor weight
  - Administer with or after meals
  - Give high calorie snacks
  - Consider drug holidays

Dulcan M (1997)

Managing Adverse Effects From ADHD Treatment (cont)

- Insomnia (sometimes a manifestation of ADHD itself)
  - If patient can nap on meds, add another dose
  - Administer dose earlier in day or a small dose at bedtime
  - Try longer-acting preparation
  - Clonidine or guanfacine at bedtime

Dulcan M. (1997)

Case Study

- 28 year old male
- Failures in school/workplace
- Depressed over failures
- Never diagnosed with ADHD in the past
- Family Psychiatric History
  - 8 year old daughter recently diagnosed with ADHD

ADHD Comorbid with Depression

- Depression often secondary to ADHD
  - failure in school
  - failure in the work place
  - low self esteem
- Start with Antidepressant
  - that may have a positive effect on ADHD
  - then add ADHD treatment

Summary

- ADHD is the most common psychiatric disorder of childhood.
- Many of these children will continue to suffer from ADHD as adults although the characteristics may differ.
- The etiology of ADHD is multifactorial and not clear cut, which has made the public feel uncertain about treatment.

Summary

- Although inattention and hyperactivity can be part of many psychiatric disorders, they are more diagnostic of ADHD when global and consistent.
- Nonetheless, these comorbid psychiatric conditions should be addressed as well.
- Untreated ADHD can substantially increase risk of comorbidity and substance abuse.

Summary

- Combination treatment (Medication plus Behavioral Therapy) is the most effective approach leading to impressive success rates.
- Identifying target symptoms can serve as a way to organize behavioral management and provide a framework for medication adjustments.
- Behavioral management should be applied realistically and consistently.

Summary

- Risk/Benefit ratio of medication is generally quite favorable.
- It is important to titrate medication to optimal effect rather than to: just response.
- A wide variety of medication allows for customizing a regimen to fit the patient's individual situation.
- Emerging treatments may add to this variety.

Summary

- Good public psychoeducation and awareness can help demystify ADHD.
- This will allow for patients to be more readily diagnosed and appropriately treated.
- Treatment of ADHD leads to a decrease in comorbidities and substance abuse, and an increase in achievement, self esteem and overall quality of life.