A Clinician Views Treatment of ADHD in Youth

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Pre-Lecture Exam

A 12-year-old boy presents with symptoms of aggression since the age of 4 years in association with behavioral problems in school. A Teacher Conners and Parent Conners are "off the scale" in the Hyperactivity-Impulsivity subscale. Prior to the age of 11 years, he was extremely hyperactive, but lately is less so. He continues to be inattentive in school.

Question 1

1. **Which one of the following statements is true:**

A. He cannot have Attention-Deficit Hyperactivity Disorder (ADHD) since he is not hyperactive.

B. He is not a candidate for psychostimulants since they do not work in teenagers.

C. He is not a candidate for psychostimulants since all of his symptoms will disappear in his teens.

D. He is a candidate for psychostimulants.

E. He should be started on risperidone.

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2. A discussion of possible side effects of psychostimulants with parents should include one of the following:

A. He will likely develop Bipolar Affective Disorder.

B. He has a chance 50% chance of developing Major Depression.

C. If he develops hallucinations, they will be visual in type.

D. If he has side effects of nausea, his growth may be affected.

E. If he develops mild tics, then he will be immediately discontinued from the medication.

Question 3

3. Pemoline is not used as a first line drug for the treatment of ADHD because of one of the following:

A. Its onset of efficacy is delayed.

B. Its efficacy is not dose-related.

C. It has the most abuse potential of all of the psychostimulants.

D. Acute hepatic failure is common.

E. Acute hepatic failure is uncommon.

Question 4

4. **Bupropion treatment of ADHD has one characteristic of the following:**

A. Efficacy starts at the 6th week of treatment.

B. Efficacy is robust and begins about the 4th week of treatment.

C. Efficacy may be mild and begins after the 4th week of treatment.

D. Efficacy may be mild and may start as early as day 3.

E. Efficacy may be mild and always starts at the first day of treatment.

Question 5

5. When clonidine is used to treat ADHD, one of the following statements are true:

A. It should be dosed once at night only.

B. It has a short elimination half-life and needs to be dosed frequently.

C. It has a short behavioral half-life and needs to be dosed frequently.

D. The dosing range is 5-8 mg/kg/day.

E. It is contraindicated with co-existent tic disorders.

Question 6

6. If clonidine is used consistently for several months to treat ADHD, the following side effect may appear:

A. Hypertension
B. Hypomania
C. Behavioral activation
D. Nighttime awakenings
E. Drooling

Question 7

7. **A 5-year-old boy has chronic motor tics and ADHD. He is currently on clonidine, but he is having significant side effects. You want to shift him to guanfacine. Which statement is true?**

A. Because both drugs are alpha adrenergic agonists, clonidine can be stopped and guanfacine started the same day.

B. If a child is taking a total daily dose of 0,2 mgs, he will require an identical dose of guanfacine.

C. His parents should be told that his motor tics are very likely to worsen after guanfacine is begun.

D. His parents should expect more sedation when he is on guanfacine.

E. Because guanfacine is more “neurotransmitter selective” than clonidine, a cross taper is necessary.

Question 8

8. A 9-year-old boy has failed trials of methylphenidate, bupropion, and Dexedrine SR. You want to consider treatment with imipramine. What question is it important to ask his parents as you consider this possibility?

A. Is there a family history of Pervasive Developmental Disorder?

B. Is there a family history of Panic Disorder?

C. Is there a family history of Fragile X Syndrome?

D. Is there a family history of sudden death or cardiac symptoms in family members?

E. Is there a family history of trimethyluria?

ADHD

- Triad: Inattention, Hyperactivity (H), Impulsive (I)
- 3 forms of ADHD: Inattentive, HI, Combined
- Diagnosed from history and rating scales
- CPT/TOVA not foolproof
- Exclude other conditions which may mimic ADHD
- 3-6%: 3-6/1: boys/girls
- Medications used with multimodal treatment

ADHD-Combined Form

- More commonly have behavioral component (co-morbid with ODD, CD)
- More commonly seen in the tertiary centers
- Less girls in the sample

Predominantly inattentive

- Most common form in community samples
- Present with academic and social problems
- Older, more girls in samples
- Less impaired
- More commonly overlooked

How is Diagnosis Made

- From typical history
- No neuropsychological testing, CPT or TOVA makes the diagnosis
- Supported by Parent/Teacher Scales

(Conners, ACTeRs, SNAP)

- Biases in all reports are possible (e.g., girls less identified because less obstreperous

ADHD is frequently comorbid

- Pure ADHD **only** 25%
- ADHD + anxiety disorders 20-25%
- ADHD +MDD or dysthymia 15-40%
- ADHD +tics or TS 5%
- ADHD + LD 20%
- ADHD + ODD or Conduct Disorder 20-50%
- ADHD + MDI is controversial (Biederman v Klein 1998)

Special Problems: pharmacotherapy of youth

- Clinician must have working alliance with parents
- Children may be reluctant consumers
- Children should be told that they may not recognize changes in themselves before first med trial
- Each school may have different requirements for medicating children (and some wont do it)

Medications commonly used to Rx ADHD

- Psychostimulants
- Noradrenergic alpha 2 agonists
- Bupropion
- Tricyclic antidepressants (TCAs)
- Atomoxetine

PSYCHOSTIMULANTS

- **Best studied of all psychotropics (since 1937- benzadrine)**
- **70% kids respond to either MPH or DAS and 90% will respond to one or the other**
- **If side effects intolerable or no efficacy, try another class**
- **May be slightly reduced efficacy in adults**
- **Array of drugs with different pharmacokinetics**

Contraindications to PS

- Previous sensitivity, glaucoma, CVD; hyperthyroidism, hypertension, active psychosis, MAOIs
- Great care with hx of child or family drug abuse
- Package insert warnings:not use in motor tics or family hx TS, marked anxiety or seizures,MPHs under 6 yrs ;AMPs under 3

Pemoline (Cylert)

- Least abuse potential, but can cause insomnia, choreiform movements and tics: start low, go slow: may need bid dosing
- Onset of efficacy is rapid and dose related
- Labeling change; 13 cases of acute hepatic failure since 1975 (4-17 times the expected rate). Pre-check LFTs, educate parents on signs and symptoms of hepatitis:FDA requires biweekly LFTs- impractical requirement
- Chewable form

Many formulations of MPH

- ***immediate release: 3-4 hrs***

  MPH (Ritalin)

  d-methylphenidate (Focalin)

  SR-Ritalin 3-4 hrs (wax-matrix)

  Methylin (wax-matrix)

- ***long acting:***

  Metadate CD (particles, can use out of capsule) 6-8 hrs

  Concerta 10-12 hrs (OROS)

Many formulations of AMPs

- Dextroamphetamine sulfate (4-5 hrs)
- Dexedrine spansules (5-9 hrs) (particles)
- Adderall (4 mixed salts), generic (4-5 hrs)
- Adderall XR (8 hrs)

Psychostimulants

	AVAILABLE FORM		TYPICAL DRUG MAXIMUM (day)
MPH-IR	5, 10, 20 mg tabs Ritalin-SR (?4 hrs)		60 mg
MPH-long acting Metadate-CD (6-8 hrs), Concerta (10-12 hrs)			
DAS	5, 10, 15 mg span	begin 2.5 mg bid	40 mg
DAS-SR	5 mg tab		
Adderall*	5,10,20 mg tabs	begin 5 mg am	40 mg
+Adderall-XR*			
Pemoline	18.75, 37.5, 75m Chewable	begin 18.75mg	112.5 mg

+May be removed from cap and used as sprinkle

* Take before meal

Don't assume that all children will respond equally to extended release preparations

Pharmacokinetics/dynamics

- Used to be thought “ramp effect” necessary, absorbed quickly with large peak of plasma concentration->MA pulse from cleft
- Do just as well with gradual ascending increase in MPH over the day

Short v long-acting formulations

- MPH-IR, Focalin, DAS, Adderall- use 2-4 times a day dosing-"bactrian camel effect"
- Long-acting forms ***may*** last a school day,
- Longer acting forms may cause side effects later in day--- especially sleep and eating
- Generics may differ slightly (MPH absorbed faster and peaks sooner)
- Behavioral effects may appear before

Match the formulation with needs of the youth

- Have to know when youth “needs” the psychostimulant (e.g., school only or homework, peer activities , week-ends,)
- Parents sometimes have definite preferences for one or another
- Train parents to observe efficacy and side effects through the day and into the evening)

How to initiate dosing

- Not by weight , including teens (Findling 2001) (pediatricians use 0.3-0.6 mg/kg)
- Titrate to efficacy or intolerable side effects: start at 5 mg MPHs or 2.5 mg for Focalin, AMP, DEX- can get weekly reports and adjust upward, checking for side effects and efficacy

The Art of Fine-tuning

- Must have accurate info about kid's performance "over the day"; use scales and talk to teachers: titrate as needed
- Can mix and match PSs (e.g., if dysphoric at days end, add MPH to Concerta at the end of the day; DAS to DAS-spansule at the start of the day because of delayed effect of spansule, bunch or stretch dosing of immediate release)

The Art of Fine-tuning -II

- If only partial efficacy with PSs, can “mix and match”PSs and other anti-ADHD drugs (e.g., clonidine or bupropion or TCAs or atomoxetine)

Common errors in dosing psychostimulants

- Fail to increase dosing slowly to maximum if no side effects
- Not assessing the duration of action; (may need to “bunch up “ dosing)
- Fail to use another psychostimulant if the first or second trial fails

SIDE EFFECTS OF PS

What parents wants to know: addiction, will the youth need it forever , tics. depression

Common side effects

- **insomnia**
- **decreased appetite**
- **irritability**
- **abdominal pain**
- **Headaches**

Use Barkley Side Effect Questionaire (BSEQ)

Side effects-II

- Insomnia- probably dose related-tolerance may develop, change timing, Rx CND, IMI, others
- Decreased appetite—dose related, dose after meals, add calorie supplements and monitor
- Irritability--check timing; reduce dosage: change to long acting formulation
- Abdominal pain—dose with meals, change to long acting formulations
- Headaches--not dose related, ? tolerance

Serious side effects of psychostimulants

- 30+ cases of psychosis or formic hallucinations: discontinue the medication
- Growth: effects made up in late teens or by drug holidays; especially. those with nausea and vomiting
- Tics: may be minor or substantial or they may improve while psychostimulants active; discontinue only if serious

Psychostimulants Over Time

- In MTA study, better outcomes with monthly visits; community docs saw kids only 1-2 /year
- May need changes in dosing over time
- By year 3, 50% of children stop using PS; Moderators (specific to child) no ODD, more severe sxs, younger age of Rx initiation (Thiruchelvam 2001)
- Since pre-teen boys hate PSs, start having conversation about time off years ahead

Beware advertising!

- Prior to Concerta, Adderall had gained market shares by aggressive marketing
- Concerta is marketing directly to the consumer
- Adderall received an admonishing letter from FDA for advertising superiority to MPH
- No demonstrated differences in efficacy between equivilently dosed formulations of MPHs or amphetamine

When to add parent training

MTA Study:

- ADHD+ Anxiety = efficacy to PS
- ADHD or ADHD+ ODD/CD best outcome is with both PS and parent training

Comparable Cost #30

- 20 mg Ritalin 36.99
- 20 mg methylphenidate 23.28
- 10 mg Focalin 36.99
- 20 mg Ritalin-SR 54.99
- 18 mg Concerta 86.59, 54mg 94.99
- 10 mg DAS 24.39
- 10 mg DAS spansule 44.29
- 10 mg Adderall 56.59
- 10 mg Adderall XR 89.99

Atomoxetine (Straterra)

- Recently introduced as treatment for ADHD
- Selective inhibitor of NA
- Less abuse potential than PS, not classified as a controlled drug
- Metabolized by CYP2D6, therefore increased concentration (up to 5-fold) in slow metabolizers and in combo with 2D6 inhibitors (e.g., paroxetine,

Atomoxetine-2

- Should not be taken with MAOIs, narrow angle glaucoma
- Side effects: may increase BP and pulse with less than 2% orthostatic hypotension
- Other side effects: GI, fatigue, dizziness, mydriasis, mood swings
- Can be stopped “ on a dime”

Atomoxetine-3

- Dosed according to weight
- Less than 70 kg, start at 0.5 mg/kg and gradually increase up to 1.2mg/kg
- More than 70kg, start with 40 mg and gradually increase up to 100 mg/day
- Clinical effects may take up to 4 weeks
- Dosage available in 10, 18, 25, 40 and 60 mg capsules.

Atomoxetine-4

- Early experience suggests a slow titration will reduce side effects
- Some Docs are mixing PSs and Atomoxetine -> “smoother” day and reduced PS dose
- Good choice in families with drug abuse and prior history in child of “bad” PS side effects

Bupropion (Wellbutrin), (Zyban)

- Phenylethylamine, withdrawn in 1986 and reintroduced
- In kids,half-life of regular form 14+/- hours
- Dosing range 3 mg-6 mg/kg/dy: tid: XR bid
- Single dose below 150 mg: (maximum for children 300 mg and 450 mg for teens)
- Efficacy for ADHD may start by day 3
- Some clinicians find only mild effects

Side effects of bupropion

- Most common: rash, increased appetite, nausea, stomach discomfort, minimal weight loss, blood pressure changes, agitation, tics (Spencer 1993)
- Serious: seizures, 4/1000 (adults, Johnston 1991); lower incidence with XR

Bupropion (BP): Drug interactions

- BP- substrate of CYP2B6
- Principal metabolite is OHBP-substrate of CYP2D6
- CBZ induces CYP2B6 and decreases parent compound
- VPA and CYP2D6 inhibitors (e.g., paroxetine, fluoxetine) increase metabolite levels (Ketter 1995)
- Guanfacine addition can cause seizures (Tilton 1998, Nemerow 1999)
- Bupropion may increase VPA levels (Popli 1995)

Clonidine (Catapres)

- Alpha 1, alpha 2A (pre and post synaptic), 2B, 2C, opiate, imidazoline agonist
- 0.1 mg tablets; TTS patches deliver daily doses of 0.1 mg, 0.2 mg and 0.3 mg: use overlap of 2 days since efficacy only 5 days
- ***Behavioral half-life*** 3-6 hours; dose tid, qid
- Dosing range 5-8 micrograms/kg/day
- Start hs, maximum effect over 2-3 months, sedation is immediate
- Used for tic disorders, add-on psychostims, PTSD

Pre-treatment workup for Clonidine

- Check for history of arrythmias, relatives early sudden death
- Check for Raynaud's Disease, Diabetes Mellitus
- ECG if indicated (Biederman 1999, Kofoed 1999)
- Orthostatic blood pressure
- Pulse

Clonidine:Side effects

Common

- Sedation, dry mouth, dizziness
- Nighttime awakenings, nightmares,night terrors

Serious

- Idiosyncratic aggravation of cardiac arrhythmias
- Danger rebound hypertension if stop suddenly
- Depression in about 5%
- Hyperglycemia

Guanfacine (Tenex)

- 1 mg tablets, no patch
- Dosing range 1.5-4 mg/ day: tid
- Mainly alpha 2A agonist--> less sedation, less hypertensive rebound after sudden stop
- Used for tics/ADHD: may improve working memory
- If shifting from clonidine; must do "cross-taper”
- Drug interactions: GUA+VPA-->> inc plasma levels VPA (Ambrosini 1998); GUA+bupropion-->> seizures (Tilton 1998,Nemerow 1999)

Commonly used TCAs

Imipramine (IMI)

Generic: 10,25, 50 mg tablets

Tofranil: 10, 25, and 50mg: IM preparation

Nortriptyline (NT)

Pamelor: 10,25, 50, 75 mg and oral solution 10mg/5ml

Clomipramine (CMI) see OCD section

Anafranil: 25, 50, 75 mg tablets

Dosing 3-5mg/kg/day for kids (NT 1-3 mg/kg/day)

bid with NT (Geller 1983), tid with IMI

TCA Metabolism in kids

- Less protein binding than adults,70-95% (Ryan 1990)
- Half life shorter in kids than teens than adults (2/3)
- CYP 1st metabolism: tertiary TCAs --> deCH3 to secondary TCA AMI-> NT IMI-> DMI CMI-->deCH3CMI
- Kids more extensive demethylators (Potter 1982)
- CYP 2nd metabolism --> hydroxymetabolites (OHMs) via CYP2D6 : Kids have lowest OHM levels (Wilens 1992)
- Many genetic variations in CYP2D6 activity exist including extensive (normal), slow metabolizers, “sort of slow”, ultrafast
- Each TCA unique neurotransmitter profile

Pre-treatment workup for TCAs

- Hx of family members early or sudden death or arrthymias or cardiac sxs in child
- CBC with differential, creatinine, LFTs
- ECG
- Orthostatic blood pressure, pulse

TCA side effects

- Most common

  Dysphoria, irritability, aggression,weight loss

  increased heart rate, increased diastolic BP, central

  anticholinergic symptoms (e.g., confusion,sedation)

- Most serious

  7 deaths with DMI in kids ,? only small increased risk

  of sudden death (Werry 1994)

  Toddler siblings may accidentally overdose

  Mania induction

  Changes in cardiac status: Get ECGs at baseline, at 3 mg/kg, highest dosing , when add another drug and 6 mo-year

Cardiovascular parameters for TCAs: consult cardiologist if:

	Resting heart beats/min	Resting BP	PR	QTc
	= or <	=or<	=or<	=or<
< 10 yrs	110	140/90 or 135/85 > 1/2 time 3 wks	0.18	0.44
>10 yrs	100	150/95 or 140/85 > 1/2 time 3 wks	0.20	0.44

Adapted from Rye and Ryan: Child and Adolesc Psychiatric Clinics NA 4:275, 1995

TCAs drug interactions

- Very complicated
- TCAs demethylated by variety of CYPs and then hydroxylated via CYP2D6
- Paroxetine/ fluoxetine decrease clearance 400% of CYP2D6 substrates
- Sertraline/citalopram decrease clearance 25% of CYP2D6 substrates

CMAP-ADHD

- http://www.mhmr.state.tx.us/centraloffice/medicaldirector/adhdalgo.pdf
- 4 algorithms: ADHD, with tics, with MDD and with IED
- Tactic Tables: Dosing schedules for Stimulants,TCAs,Buproprion, Alpha Agonists and SSRIs

Post Lecture Exam

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Answers to Pre & Post Competency Exams

1. D
2. D
3. E
4. D
5. C
6. D
7. E
8. D