Update on Selecting and Prescribing ADHD medications

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**Disclosure**

- No actual or potential conflict of interest in relation to this program
- Objective: to learn the rationale for selecting and dosing stimulant and non-stimulant medications in the treatment of ADHD

**Basic assumptions**

--Correct diagnosis (and history/PE)
--Educational aspects are being addressed
--Parenting/behavior aspects are being addressed
Medication is a piece of the "therapeutic pie"

*** but it isn’t the first slice!

**The future...**

- Genetic testing to identify which stimulant will likely be the most effective and best tolerated (no more trial and error!!)
- …not there yet…
- (stay tuned for future CAPS programs)

**Really nice review:**

- State-of-the-Art Review Article:
  PEDiatrics Vol.136, number 2
  August 2015
  Pediatric Psychopharmacology for Treatment of ADHD, Depression, and Anxiety
  (Southammakosane and Schmitz)

- CYP 2D6 genotyping has been well associated with Atomoxetine metabolism, and therefore exposure and possible side effects.
- CYP 2B6 genotyping has also been identified as a primary drug metabolizing enzyme for Bupropion; however the CYP 2B6 gene is fairly inducible. The polymorphic alleles of interest can occur up to 28% in Caucasians, 23-25% Latin Americans, 16% in Japanese, 21% Chinese, and 27% of African Americans.
- COMT data is still conflicting about what variants are or aren’t associated with response/tolerability.
- ADRA2A: the C>G polymorphism (alleles 1291C>C or rs1800544) was associated with response to MPH but was not correlated to non-stimulant response in this study and remains controversial.
- What we are left with, is the art, (informed by a lot of science)
• Efficacy: how a drug works under optimal circumstances

**Effectiveness: how a drug works under usual practice circumstances

What you already know…

• AAP and AACAP clinical practice guidelines both endorse stimulants as the 1st line treatment
• Methylphenidate (+ dexamethylphenidate)
• Amphetamine (mixed salts, dextroamphetamine, lisdexamfetamine)

The synapse…

• MPD and AMP: inhibit DAT-1 and NE transporters (inhibit reuptake of dopamine and norepinephrine)
  AMP also gets into the presynaptic terminal to release the store of NTs
  Both have 2 isomers, the dextro form of which is the more effective

Medication effect sizes

<table>
<thead>
<tr>
<th>Effect Size</th>
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<td>Stimulants</td>
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<td>alpha agonists, ER</td>
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<td>atomoxetine</td>
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(* 0.4-0.8 in preschoolers)


Texas Children’s Medication Algorithm Project

--Titrate the dose to effect, and if response is unsatisfactory, switch to the other family and titrate dose to effect

--NIMH (2012) booklet…
However, a one-size-fits-all approach does not apply for all children with ADHD. What works for one child might not work for another. One child might have side effects with a certain medication, while another child may not. Sometimes several different medications or dosages must be tried before finding one that works for a particular child. Any child taking medications must be monitored closely and carefully by caregivers and doctors.

• Inadequate response: when it does not produce sufficient reduction of symptoms to produce functional improvement
• Poor adherence; severity of the ADHD; inadequate stimulant dosing; dose limiting adverse effects

Both d-AMP and IR mixed AMP salts are approved down to 3 yrs, and the others down to age 6…
• MPD selected for the medication arm of the Preschool AD/HD Treatment Study
• MTA study: combo or intensive med better (more frequent visits to titrate the dose)

Since you are treating a patient, not a diagnosis…
• Aspects to consider:
  • what the child needs currently
  • family's history with the various meds
  • lifestyle/schedule (for the formulation)
  • can the child swallow pills?
  • abuse potential …
  • cost

Cool medication guide
• Updated versions can be viewed at www.ADHDMedicationGuide.com
• www.ADDWarehouse.com for laminated copies ($10 at last check)
**Methylphenidate**

- Immediate release tablets (IR) and liquid
- Wax matrix, single pulse (SR)
- OROS technology
- Beaded, in capsules (30/70 and 50/50), and beaded (40/60, with multi-layered release)
- Skin patch
- Dexmethylphenidate (IR, beaded)
- Extended release liquid

**Amphetamine**

- Immediate release (dexamphetamine, and the mixed salts)
- Beaded capsules
- Liquid (immediate release d-AMP)
- Pro-drug (lisdexamfetamine) — d-AMP with 2 amino acids attached

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- MPD 10mg = d-MPD 5mg = AMP 5mg
- Vyvanse compared to Adderall XR
  - 30mg 10mg
  - 50mg 20mg
  - 70mg 30mg

- Start low and titrate the dose to FUNCTIONAL IMPROVEMENT, or annoying side effects
- Give “choices within limits”
- Get feedback from family, school — and the patient!!

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- --multiple informants (home, school, etc)
- --Vanderbilt, Child Behavior Checklist, Conner’s Parent and Teacher Rating Scales
- --Medication Effects Rating Scales

- Drug holidays (maybe just a day / week — or month…) to minimize tachyphylaxis
- Monitor growth (CIB, Boost, Pediasure) —
- Monitor sleep

***Aim for the lowest but still MOST EFFECTIVE dose for that particular child***
Nonstimulants

- Alpha agonists: clonidine, guanfacine; approved for > 6 yrs; monotherapy or to augment a stimulant
  --ER versions available now

atomoxetine

- ADHD with anxiety seems to respond the best
  start with 10 mg daily and work up weekly by 10mg, to 30 or 40mg (BID, taken with food for GI)
  (may take a month to work)
(TCA’s available)

What is new?

- New formulations, mainly:
  - Quillivant 25 mg/5 ml
    --12 hr liquid, allowing for micro-dose changes
    ---specific size bottles (order the next larger amount)

This and that...

- Daytrana patch: site actually does matter-on hip: 31% more higher bioavailability and 21% greater drug delivery than on the scapula (leukoderma has been described)
- Aptensio: new, beaded capsules which should be 12 hr

Gonzalez, Campbell; J of Child and Adolescent Psychopharmacology 2009
New rules authorize electronic prescribing of controlled substances

- Missouri’s Bureau of Narcotics and Dangerous Drugs (BNDD) promulgated regulations effective July 30 that formally authorize electronic prescribing of controlled substances in Missouri. The state’s rules now match federal DEA rules, which will eliminate some of the confusion that has plagued the e-prescribing process here. Now, electronic prescribing may be performed in accordance with the DEA rules (21 CFR 1306.08, and 1311.100 - 1311.305). The BNDD offers additional information about the rules:
  - 1. Previous forms of transmission (writing, telephoning and faxing) are still permitted where applicable;
  - 2. The option of electronic prescribing is voluntary and is not mandatory;
  - 3. The new federal rules were effective June 1, 2010. Missouri registrants may begin when they have met all the federal guidelines. Missouri will not implement additional requirements;
  - 4. Prescriptions may be transmitted electronically in Schedules II, III, IV, and V;
  - 5. Prescriptions may be transmitted electronically in Schedules II, III, IV, and V;
  - 6. Not all providers may be ready at the same time. A physician may be ready to transmit, but a local pharmacy may not be ready yet to receive. It will take some time for all parties to become authorized;
  - 7. There are medical software companies that may have an approved system in place. These companies are called “application providers.” They will have their new systems audited and reviewed by a third-party independent company. Once they have received clearance from the auditing company, these application providers will receive authorization and a certificate to begin implementing their systems and hardware systems. There are similar software companies for pharmacies. These software providers and application providers cannot implement their systems until they receive approval;
  - 8. Once the application provider has received a certificate and is authorized to begin, these providers may begin providing their systems to individual practitioners and pharmacies. The doctors should receive a certificate from the software provider that shows they are an approved provider. These software providers may also provide the practitioners with a certificate that shows the practitioners are authorized to electronically prescribe using their system.
  - 9. What starts electronic must stay electronic. If a practitioner transmits an electronic prescription, it shall arrive at a pharmacy and then be stored and archived electronically. The practitioner cannot transmit a prescription and then have it printed to a pharmacy fax machine. A faxed prescription arrives on paper and those require a physical and manual signature before the document is faxed.
  - 10. Participating prescribers must undergo “identity proofing” before hitting the send/transmit button each time. Verification is required to ensure the transmission of the prescription is from the proper registrant. There are three ways to verify identity and prescribers will be required to provide any method of identity proofing;
  - 11. A prescription gets filled out with all of the information required. The prescriber with proper identity may transmit it. The completion of the two identity checks above before transmitting. An assistant or employee may hold an electronic device and prepare it; however, only the registered practitioner with proper identity may transmit it. The completion of the two-factor identity code is considered part of the signature;
  - 12. A digitally scanned in signature or a follow-up is not considered an acceptable method of identity proofing;
  - 13. Prescriptions can only be transmitted for one patient at a time;
  - 14. Prescriptions must be transmitted as soon as possible after identity proofing/signature;
  - 15. If any prescription data/record is printed after transmission, the document must be labeled “COPY ONLY—NOT VALID FOR DISPENSING”; and
  - 16. If the transmission fails, the prescriber must be notified the transmission failed, then the prescription may be printed out for manual signature. The prescription must be signed that the initial prescription was electronic, name of pharmacy, date and time;
  - 17. Controlled drug records must be maintained for two (2) years;
  - 18. Pharmacies have controls on who is allowed to access and retrieve data. Any changes or annotations must also be electronic. Receipt of a prescription is documented electronically; and
  - 19. Pharmacy records must be backed up daily and retained electronically.

New rules authorize electronic prescribing of controlled substances

- Kessler’s article in Southern Medical Journal 1996
- 292 patients (210 males)
- 272 (93%) responded well to SR D-Amp and 21 (7%) to SR MPD
- D-amp dose 0.2-3.6 mg/ kg/d
- MPD dose 1.4 – 7.7 mg/kg/d
• Age ranged from 2 to 22 yr at diagnosis
• Convenience sample of a private practice
• **D-amp** started at 0.2mg/kg/d (SR form) and increased by 5 mg/ day/ week
  Mean dose was 56 ± 35 mg !!!
  86% had <= 1.6 mg/ kg/day; **10% up to 3.6mg/kg/day**

• **21 patients switched to SR MPD due to side effects, failure to respond, family’s request, hallucinations , Tourette Syn.**
  MPD: average dose 168 +/- 64mg/day (!)
  range of **40-260 mg/day.**
  On meds mean of 78 +/- 61 months (2-279)

• **Anorexia, wt loss in 90% for first 3-6 mo.**
• Insomnia (up to 3 hr) in all during 1st 3 wks then was down to 1 hr, for 3-6 mo
  On therapeutic doses, 90% had mild depr’n and weeping; along with hostility, verbal aggressiveness, argumentativeness in

• **ANY QUESTIONS? 😊**