

30th Annual Psychopharmacology Update: Response to Unanswered Questions about ADHD

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On Saturday, Nov. 16 the MPS held its 30th Annual Psychopharmacology Update at the Mass. Medical Society. There were very many unanswered questions about ADHD and its medication treatment. I will focus on those questions for this article. Sometimes the questions touch on matters that have not been extensively researched, in which cases the answers below are guesses based on general clinical judgment knowing the basic properties of the product involved. Answers cannot be guaranteed to be correct! If you see any errors please let me know.

ADHD:

What distinguishes the deficits in attention in ADHD from that in other disorders? Answer: Not much if the focus is just on the symptom of inattention. There is a large differential diagnosis when you encounter that complaint. If you think it might be from ADHD, pull out your DSM-5 and see if the person seems to meet the criteria for the disorder, going over each of the 9 symptoms listed for the inattentive subtype, as well as the other requirements (e.g., onset before age 12). For an adult, you have to have 5 criteria, and for a child, 6 criteria and they should be present in more than one setting (such as school, home and work). These are the criteria used to screen patients for admission to studies of ADHD medications, so if you are considering medication, these criteria are a very good place to start to see if it may be reasonable to try a medication.

Maybe the inattention is a symptom of a mood disorder like depression or mania. Then, the symptoms tend to be episodic and occur during the mood episode. Again, review the criteria and see if the criteria are met for a mood disorder. Psychotic patients can be inattentive. Substance use disorder patients may have this as a symptom. Highly anxious people may not be able to focus well. This is not a complete list. But the basic principle is to make as accurate a DSM-5 criterion-based diagnosis as you can and then treat the diagnosis that best fits the situation (there may be comorbidity and more than one cause) with the evidence-based best treatments.

Have you seen hypersexuality in adults or children on stimulants? Answer: Hypersexuality is not a symptom of ADHD included in the DSM-5 criteria. So, if it develops during treatment with a stimulant, you have to wonder what happened. Is it episodic and associated with other symptoms meeting the criteria for mania or hypomania? One has to be very careful in treating ADHD and not miss a diagnosis of bipolar disorder that might be comorbid with the ADHD. This is a common comorbidity. A recent study (Viktorin and colleagues, American Journal of Psychiatry 2016) showed that if you treat ADHD with a stimulant in bipolar patients who are not on a mood stabilizer, there is a 6-fold chance of producing a mania compared with not treating with one. Another possibility is that the hypersexuality (which could come from a number of other causes) was present before the stimulant treatment but was not recognized or disclosed. Then, when it occurs after the treatment, it may be blamed on the stimulant.

Can you use a stimulant in people with both ADHD and bipolar I disorder? Answer: Yes you can but only if they are stabilized on an appropriate mood stabilizer like lithium first. The same study referred to in the last question (by Viktorin and colleagues) found that if the bipolar patient is on a mood stabilizer, the use of a stimulant (methylphenidate in this report) actually reduced the likelihood of mania (by about 40%) compared with the rate of mania in a control group whose ADHD was not treated by a stimulant. The authors proposed that treating the ADHD enabled these bipolar patients to be more adherent with their medications and otherwise lead more organized lives with fewer impulsive behaviors associated with ADHD, and this had a protective effect for their mood swings.

What can you do for affective blunting from stimulants? Answer: This is an unusual side effect. Overstimulation is more common. But, some patients are paradoxically sedated, which is perhaps an offshoot of having their hyperactivity blunted. You could try a lower dose of the initial stimulant or try a different formulation of the same medication, before moving to a different class of stimulant or a secondary medication for ADHD, like atomoxetine or bupropion, always being ready to re-examine your diagnosis and to weigh the balance of potential benefits and risks of the new medication.

Isn't it true that the FDA (as well as many pharmacy benefit managers) sets upper limits on doses for stimulants? Answer: This is true. However, one may exceed these limits with appropriate informed consent, citing the studies in the literature where doses over the FDA limits have been used in the patients with high weights, and were found safe and effective (e.g., Spencer and colleagues, *Biological Psychiatry* 2005). The potential harms may be different in the patient you are seeing compared with the patients in the studies, though, so be sure to take that into account. For example, if your patient is thought likely to abuse or divert the stimulant, you would be more reluctant to offer those higher doses. Of course, that can be hard to predict. Others may have medical safety issues to be concerned about. So, the practice should be limited to the best possible candidates – like the patients in the studies. The pharmacy benefit managers may still not let you have these higher doses. If you have a persuasive case to make of the appropriateness of the higher dose, you can appeal to the review committee of the pharmacy benefit manager.

How does lamotrigine work on symptoms of ADHD in bipolar II patients? Answer: I'm not aware of any evidence that it does.

Can you combine atomoxetine with stimulants? If you do, what happens? Answer: It seems fairly common for clinicians to try this combination. For evidence supporting it, we only have small open-label case reports so clinical experiences is pretty much all we have regarding its effectiveness and safety. I would suggest first trying standard monotherapy treatments in adequate doses, including stimulants (at least one methylphenidate-related product and one amphetamine-related product) and atomoxetine before moving to this uncharted territory.

I see a wide variation in stimulant response and side effects in the same patient depending on the manufacturer? Answer: Yes and this can be due to variations in the purity of the products, variations in the patient's pharmacokinetic and pharmacodynamic response to the particular

formulation, and variations in placebo or nocebo effects from the particular product or the timing/psychosocial circumstances when the change occurs. It's tough to sort out!

Does atomoxetine really work for ADHD in real-world adult patients in the community? And how about as a treatment for depression? Answer: Research studies say it works in adults with ADHD and it's FDA-approved. However, those real-world patients you are talking about often are disorganized, poorly adherent with medications, distracted, and impatient. In research patients, atomoxetine does not actually separate from placebo for up to 3 weeks and then the separation from placebo gradually increases and reaches a peak after about 8-10 weeks. At that peak, it is almost but not quite as effective as a stimulant. This is a very long wait and motivation to keep taking atomoxetine may flag early if the results are not obvious to the patient, especially if that patient has had a stimulant in the past and experienced the rapid effect (usually within an hour of two of each dose), or has utilized other substances that work rapidly for other kinds of symptoms, like benzodiazepines, or who has utilized illegal drugs. As for the use in depression, atomoxetine is not FDA-approved for depression but is used and can be effective.

Can ADHD start as an adult? Answer: This is a matter of recent controversy in the literature. There are some studies claiming to find that it can begin in adulthood. Critics of those studies claim that they were not able to adequately prove that it had not started in childhood or in any case before age 12. It may be that the patients in these studies had family or school experiences that were relatively easily managed by them and their ADHD did not come to clinical attention, but as adults they experienced much more challenging multitasking demands and they found themselves unable to succeed due to their ADHD symptoms. More research is needed. However, there is nothing in the literature to suggest that the treatment of putative adult-onset ADHD would be any different from youthful-onset ADHD. So, if you have a case that meets the criteria and you can't find a childhood onset, it may be reasonable to try the usual psychopharmacology.