

An Update on Medications Used In The Treatment Of Attention Deficit Disorder

by John Ratey, M.D.

The use of medication to treat adults with Attention Deficit Disorder is a happy intersection of neuroscience and availability of a drug to fit the supposed problem. To the best of our knowledge the major problem in the attention system in the brain of the person who has the diagnosis of ADHD, or of ADD without the H, is a difference in their dopamine system. Current research shows that there may be as many as 13 different genes that vary from the so-called normal genes that are involved in making up what we call the attention deficits. These genes, which are called alleles as they are alternatives to the most common variety of gene, are mainly involved with the dopamine system. This is reflected in the fact that there is not enough dopamine around to support the system to work in a consistent and predictable manner.

Thus the treatment for ADHD/ADD rests on the drugs we know as those which affect the dopamine system: the antidepressants, the stimulants, and precursors that may boost the effectiveness of dopamine. While most neuroscientists and neuroscience wannabes are hesitant to reduce anything to a simple equation or catch phrase we might be on fairly firm ground in saying that attention problems may be seen as a dopamine deficiency. Thus the job of medication is to correct this deficit and its associated problems like anxiety, depressed and demoralized moods, overactive startle response, and the many problems with aggression and addictions.

The use of stimulant medications is still the easiest and most accurate route and the one that has proven to be the most efficacious for the greatest number of people with the diagnosis of ADHD. Contrary to popular wisdom and media perception, they are among the safest drugs. For instance, the only longitudinal studies to date on adolescents show that rather than being a stepping stone to addiction, the one robust finding is that those ADHD adolescents who took Ritalin were *less* likely to have a substance abuse problem at the end of their teens and early twenties. For the adult population this is also true. Most of the patients who are treated with stimulants do very well and have little need to escalate the dose once the proper level has been established. In fact, given the pain that monthly prescriptions are for both physician and patient, I am keenly aware of the fact that most adult patients use less and less stimulant as time goes on rather than any creep upwards in dose which some fear may be the quick step to problems with addictions.

The stimulants are usually the first choice as I have stated because they have a positive effect almost 90% of the time and have fewer side effects than any of the antidepressants. We are still confined to using three types of stimulants: methylphenidate or Ritalin, amphetamine and its brothers and sisters known to most as Dexedrine or Adderall, and pemoline or Cylert. All these medications act by affecting the levels of dopamine at the synapse. Some release dopamine directly, Ritalin and Dexedrine act also to block the reuptake mechanism, and they also act to block some of the metabolic enzymes that hang around the synapse to gobble up loose dopamine.

Pemoline (Cylert) is a long acting medication that takes a while to get to its therapeutic action and thus it does not have an immediate effect like Ritalin or Dexedrine. It also has a saga attached to its use of reported deaths due to liver failure. While the circumstances and the real incidences of the number versus the chance effect is yet to be fully detailed, as of yet it is considered controversial as a first line treatment and recommended only as a second line treatment by the FDA. Abbot Pharmaceuticals, the

company that produces Cylert, has not been aggressive in countering the complaints and perception of the risk so that its use has dropped off and Cylert probably will continue to be a second line choice. It is unfortunate as this is truly the only all-day stimulant we have available. Clinical experience shows that the longer the drug acts, the better and the closer it is to producing a normalized attention span, a predictable state of consciousness, and a stable inner core to interact with the environment.

I quickly realized when treating patients that the longer the medication worked the better. One of the most important therapeutic actions is to try and produce consistency in our patients' brain functions. We try to help them achieve a stable mood and attention function so that they begin to realistically anticipate that each day will be like the next. The argument that the shorter acting compounds offer more control over the attention system seems ludicrous since for most patients the most troubling aspect of using stimulants is the second or third dose, which they often forget. One of the major problems in the ADDer is the ability to remember and plan - so that the need to take another pill at a certain time, and to be aware of the decreasing effectiveness of the medication as it wears off, is a huge problem. Secondly, the up and down effect of the shorter acting agents can add to the disruptive inner state that the patient has dealt with all of his or her life. The shorter acting stimulants thus present problems with not getting to what I see as an important goal and benefit of any treatment - stability and predictability of attention, mood, and behavior.

Ritalin for all the media coverage has been the most used by most physicians but I see it as the second line drug, because of its short action and because in my experience it has more side effects than Dexedrine or Adderall. It seems to affect the body more than amphetamine and gives people more muscle discomfort, tenseness and the hobbey gibbeys. Its one advantage that is certainly intangible is that for some it has more of a motivational edge, driving people to do their work with a bit more intensity. But like many other aspects of medicine this is a double-edged sword and can lead some to complain of robotic effects, lack of flexibility, workaholic tendencies and the like. Ritalin lasts from 1 ½ to 3 hours in most people, and the SR preparation is no bargain in that it only seems to last another hour or so. Furthermore the idea that people are getting 20 mg of the slow release preparation is troubling as Paul Wender M.D. long ago studied the Slow Release form and found that this 20 mg pill only gave the equivalence of 7.5 mg of the quick release preparation.

The amphetamine compounds are longer acting, usually lasting anywhere from an hour to two hours longer. The longer acting preparations like Dexedrine spansules and Adderall definitely seem to work upwards of 4-6 hours for most patients. But as with any drugs that affect the brain, there is no cookbook as the variety in absorption, distribution, and metabolism system in each individual makes it impossible to predict how each person will handle a given drug. Then you have the

fact that the target organ here is the brain, arguably the most complicated structure in the universe and vastly different from one person to another. Therefore, despite our need to reduce and control symptoms we have to accept the fact that dosage, effectiveness, and side effects will vary greatly. I have written that Dexedrine is "softer" than Ritalin and I still find that to be the case. The amphetamine preparations have less side effects, and their long acting preparations are definitely the real item. The difference between Adderall and Dexedrine spansules in most patients is minimal. However, there are some who have a much better response on Adderall than on long acting Dexedrine. The reverse is also true but to a much lesser extent.

I am a big fan of using the antidepressants with patients as they have the 24 hour action that I believe is so critical. The problem is that they work less well and in a smaller percentage of patients than the more popular stimulant medications. First there are the tricyclics - they have been around for more than 30 years and have proved to be invaluable and relatively safe as a treatment for ADD and related problems. I traditionally use low doses of desipramine (10-40 mg/day) in many adult patients as this has very low toxicity and is effective in about 30% of patients. Joseph Biederman M.D. and colleagues have written much about the use of desipramine, nortriptyline, and imipramine in adults and children and have found them to be effective about 50% of the time, though they use higher doses approaching what is recommended as treatment for depression (150-200 mg/day).

There is controversy over the use of desipramine in children as to its side effect on the heart's conduction system. There are a number of reports of sudden death from cardiac arrhythmia in children using desipramine. The irritant effect on the heart conduction pathway is reduced after adolescence. As in the case of Cylert, if one uses statistics to look at the actual numbers of untoward incidences of dire problems one would conclude that these drugs are not the cause of the problem. However the availability of decent alternatives seems to make the fears carry more weight and make the tricyclics second line treatments in children, and for Cylert second line treatment in adults as well. These drugs affect the norepinephrine and the dopamine system in the brain so again they act to counter the suspected dopamine deficit.

Wellbutrin (bupropion) came out as a hoped for wonder drug that was touted as the replacement for Ritalin. It blocks the reuptake of dopamine and should be an effective alternative to the stimulants. It is long acting, now there is a slow-release preparation, and it is was claimed to have fewer side effects than the tricyclics. Unfortunately, the effectiveness that we find in the clinical setting is not as happy as we had predicted and hoped for. It works well in about 50% of cases but has many more side effects than any of the previously mentioned choices. For use as an antidepressant, Wellbutrin typically is used in doses of 300-450 mg/day. To treat ADD the dose varies greatly and I have found that the new slow-release preparation marketed for smoking cessation (another dopamine problem) has fewer side effects and may be easier for patients to use, though effectiveness is still very variable.

Both of these antidepressants can be used with the stimulants and synergistically they may help overcome side effects and deficiencies of each of the agents if used separately. For instance, many people experience the rebound effect of Ritalin and Dexedrine whereby the person notices a huge return and worsening of their symptoms as the stimulant is wearing off and being metabolized out of the system. The addition of an antidepressant which acts throughout the day may help cushion

this rebound effect. In like manner, the targeted use of the stimulant while the person is on the antidepressant sharpens the attention and focusing when it is necessary.

The newer antidepressant Effexor which is used in low doses, ½ of a 37.5 mg pill twice daily, is useful for some patients. Higher doses often leads to unnecessary side effects, and there is a problem for some in withdrawal of the drug when the trial is finished. Remeron, the new antidepressant on the block, is again mainly a dopamine and norepinephrine acting agent. A problem with Remeron is that most people cannot wake up easily if they take the medicine. Without a doubt this is the best sleeping agent I have ever used over the years but the dose has to be low, low, low.

In summary, we have a number of medications which are proven effective in the treatment of Attention Deficit Disorders. There are newer medications being developed and undergoing clinical testing, including a long acting 10-hour formulation of methylphenidate. We should always keep in mind the huge variability between individuals as to how they respond to a particular medication, dosage, or drug interaction. We should also keep in mind that medication management of ADHD is a crucial part of a comprehensive treatment plan, but may not be enough in itself for most ADDers. Medication should be accompanied in most cases by education, behavioral therapies which address developing better coping skills, and ADD coaching.

FOCUS Archives: *A select article from FOCUS, Winter 1999, the newsletter of the ADDA.*