

What's New in the Treatment of Child and Adolescent Attention Deficit Hyperactivity Disorder?

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The past two decades have seen a dramatic increase in research into the biologic nature of mental disorders. The more we know, the more it appears that biology and environmental influences each have a great effect on behavior and personality. With the increase in our knowledge of neuroscience, the physician's armamentaria to help those suffering from many psychological disorders have expanded dramatically. The majority of the advances in medication treatment have been on disorders that are clearer to diagnosis and have been more intensively studied in the adult population than in children and adolescents. Therefore, although the overall number of choices on the psychiatrist's medication list has significantly increased, the safety and efficacy of these medications is better documented in adults than in youth.

The one area where pediatric psychopharmacology has focused extensively in the last decade has been in the treatment of Attention-deficit Hyperactivity Disorders. For these groups of disorders, there are a variety of different compounds available and the FDA has approved their use in the pediatric population. When one looks at medication options for other disorders of childhood, i.e., depression, bipolar disorder, psychosis, aggressive and disruptive behavior disorders, many of the drugs used in present practice are used in what we call "off label" use. Some are used in youth for other conditions but not approved for the psychological disorder they may be applied to in children. For example, valproic acid is used for the treatment of seizure disorders in children and adults, and also FDA approved for treatment of bipolar disorders in adults. Clinically, it is often used by clinicians in bipolar youngsters for mood control despite the absence of rigorous studies for this indication.

Those of us who work with children and adolescents agree that many of these youths seem more ill than those in the past, regardless of etiology. In addition, in children, comorbidity with other psychiatric disorders is very common. This issue of comorbidity further complicates the work of a child psychopharmacologist, since treatment of one disorder may exacerbate a coexisting disorder. For example, treatment with an antidepressant in a depressed youngster, may contribute to the precipitation of bipolar symptoms, in predisposed youth. Treating a child with a motor tic disorder for coexisting ADHD by use of a stimulant may exacerbate the movement disorder.

Another confounding variable for child psychopharmacologists is the fact that pharmacodynamically children are not just miniature adults. They metabolize and clear drugs at different rates than grownups. In addition, as they are developing organisms, and they are in a constant dynamic state of growth. The risks of negative effects on development always need to be considered before medication is prescribed.

As mental health professionals, we've all heard parents say that they would never medicate their child with "mind altering" drugs. In general, psychopharmacologic intervention should not be the first resort with children or adolescents. But, if the youngster is struggling with a clear biologic disorder, not treating the disorder appropriately would be a significant mistake. It is not uncommon to see youth who have been out of control despite the family having received excellent counseling and behavioral interventions. For many of these children the biology has to be tamed first. This can then allow them to be much more available for other therapies. These children will say things like "there's something wrong with my brain' or "my brain made me do it." They are aware of their inability to control their impulses, and very much want help. If the

disorder is better controlled, the child is more capable of incorporating what they have been told for years, and can now put into action what they have learned.

ADHD affects anywhere from 3-5 % of the school age population. Core symptoms include problems with overactivity, inattention, and impulsivity. It is much more common in boys than girls, with a 4-9:1 male: female ratio depending upon the setting, (i.e., general population or clinic). Age of onset of symptoms (by DSM-IV definition) is before age 7 and impairment has to occur in at least two settings. . The DSM-IV describes 4 different types of ADHD: Combined Type, Predominantly Inattentive Type, Predominantly Hyperactive-Impulsive Type, and ADHD-Not Otherwise Specified.

Over time, as the diagnostic nomenclature changed from an attempt at causality to more descriptive criteria, approaches to treatment advanced. Previously these children were subsumed under a variety of diagnoses with a myriad of symptoms. These included Minimal Brain Damage (indicating some form of brain damage as the etiology), Minimal Brain Dysfunction (indicating it was more a functional cerebral problem especially as a clear area of cerebral damage was not found), to the The Hyperactive Child (a more descriptive terminology without reference to causality), to eventually the more modern terminology of ADHD. This last diagnostic label recognizes that for some, the attention is the main problem, for others, the hyperactivity/impulsivity are the core features, and for many others it is all of the above.

ADHD is the most studied mental disorder in childhood. With the recognition that it affects a significant number of children, and that for many the disorder continues into adolescence and adulthood, there was a dramatic increase in research in the 1980's and 1990's into the phenomenology and treatment of this disorder. It was first observed by C. Bradley (1937) in the late 1930's that amphetamine was helpful in the treatment of behaviorally

disordered boys and since the late 1960's, dextroamphetamine and methylphenidate have been the main stimulants used.

Stimulant treatment of ADHD is one of the most rewarding treatments in children. Studies by J. Rapoport, et al. (1978, 1980a) have shown that stimulants can help a normal child sit still and improve attention. These studies demonstrated that the response to stimulant medication is nonspecific and therefore not diagnostic. Put another way, giving a child a stimulant, with subsequent improvement in classroom behavior, attention, and activity level could easily happen even if the youngster does not have ADHD.

Most of the newer medications used to treat ADHD are variations of the stimulants: methylphenidate, dextroamphetamine(D) amphetamine, or a combination of dextro and levo (D and L) amphetamine salts. The more recent agents have different mechanisms of release to create varying durations of action. By comparison, dextroamphetamine is twice as potent as methylphenidate on a weight to weight basis. One other old and available, but much less frequently used stimulant medication is magnesium pemoline (Cylert). It has gone out of favor in recent years due to the increased awareness of the risk of fatal hepatotoxicity with its use. Generally, the response rate to the first short-term stimulant tried is approximately 70%. Having problems with one stimulant does not mean that the child will have difficulty with another. Also depending upon the type of difficulty, a different form of release may work better with some individual patients than others.

The stimulants can be divided into three groups in terms of duration of action: short acting, intermediate, and relatively long action. The short acting compounds, which generally last approximately 2-5 hours, and require administration 2-3 times/day include: methylphenidate (Ritalin, Methylin, and Metadate and other generic forms of methylphenidate),

dexmethylphenidate (Focalin), d-amphetamine (Dexedrine, Dextrostat), and dextroamphetamine spansule. Although time to onset of action in this group can be as quick as 20 minutes, the short duration of action results in the need for these compounds to be given a few times a day. This type of short-acting agent can be difficult for both the child and family. Clinically this can create an uneven behavioral effect for the youngster, with a resumption of uncontrolled behavior recurring prior to the next dose. These breakthrough symptoms are due to the decreasing plasma drug concentration. This "rollercoaster" effect has been often obvious to the families and teachers of ADHD youngsters, and has required fairly close monitoring of the time of the wear off of dosage. Given that many of these children struggle with ADHD symptoms after school, for homework, or sports, or for behavioral reasons, an after school medication dose is often helpful. The need for remembering frequent administration of the medication often results in inconvenience for the patient and family and affects compliance. Many children are reluctant to go to the school nurse to receive their medication for fear of being singled out as different. Therefore, more frequent dosing was not necessarily adhered to as much as the clinician might recommend.

The intermediate group of stimulant medications includes sustained release preparations of methylphenidate (Ritalin-SR, Metadate ER, and Methylin ER) and a combination of 75% dextroamphetamine and 25% levoamphetamine salts (Adderall). Generally these medications can take 30-60 minutes to onset of action, and last from 4-6 hours. Dosing often needs to be twice daily. Although good for some youngsters, the slower onset and decreased effectiveness helped make these preparations less popular than immediate release formulations. Clinicians sometimes find it necessary to supplement intermediate acting agents with a small dose of immediate release stimulant in order to help the child get to school in the morning.

The newer longer-acting compounds have the advantages of having rapid onset of action, as well as the potential for once a day dosing to get positive results. With them, single dosing can replace multiple daily dosing, with the youngster receiving medication in the morning, without interfering with school or his social life. This helps improve compliance, and clinically often appears to help with self-esteem. They also vary in their method of delivery of the stimulant compound. The long acting forms of methylphenidate that last 6-8 hours include Metadate CD and Ritalin LA. These preparations may need to be given twice a day. These compounds have a mixture of beads that allow for immediate and extended release time of action.

A longer duration of action, of 10- 12 hours, can be seen with the methylphenidate preparation Concerta and the d,l-amphetamine combination Adderall XR. There are important differences in the delivery systems of these medications. Concerta works via an osmotically released timed drug delivery system (Oros system), such that 22% of the medication is immediately released, and the rest of the medication is released between 4 and 12 hours during gastrointestinal system transport. Adderall XR is taken as a capsule which contains different beads to provide immediate release, and later delayed release of the active components 4-6 hours after oral administration.

Side Effects

Not infrequent side effects of the stimulant group, whether the older immediate-acting, or newer medium or long-acting, include problems falling asleep, decreased appetite, stomachache, headache and jitteriness or nervousness. Psychostimulants may also induce changes in blood pressure and pulse, increase in irritability, anxiety, mood instability, dysphoria, and rarely hallucinations. Caution should be used in prescribing stimulants to a bipolar child as this may cause exacerbation of mood swings, or enhance irritability and aggression.

Generally, the most common side effect is decreased appetite, especially at lunchtime when children are in school. For some, this side effect will decrease over time. It is important for the clinician to reinforce with the child and the family the importance of a good breakfast so that the youngster goes through the school day with at least one good meal. In addition to the medication's anorexic effects, medication can also cause stomachaches and headaches, so the child doesn't feel like eating. Taking the medication with food in the morning can help decrease or avoid these symptoms. Depending on the type of medication, and its time of release, one needs to look for times when the child becomes hungrier. For some it may be after school, for others at dinnertime, and for others near bedtime. Parents often will describe the child as seeming famished at 9PM and somewhat insatiable. As it is important that the child maintain a good caloric and healthy dietary intake, for some this means having a lot to eat in the evening when the medicine has worn off. This may be contrary to the individual's household rules, wherein no one should eat after a certain time. Explanation to the parent that if the child loses weight the medicine may need to be discontinued usually results in cooperation with flexibility in the eating schedule. For some, a simple decrease in dose may be enough to improve appetite and not cause significant loss of symptom control. Changing the time of medication release or changing to a different preparation can also be considered.

Insomnia is another bothersome side effect of these medications, and there are different approaches to the initial symptoms. Again, for some the side effect will go away on its own within a short while. For others it may mean giving the last dose or the all day dose earlier in the day or lowering the last dosage of the day. A change in the type of stimulant or a different preparation of the same stimulant might be helpful. One's preference is not to treat the side effect of a medication with another medication. With ADHD youth this can be challenging,

because they often have problems falling asleep even before any medication has been tried, and, stimulants can worsen the insomnia. Eliminating caffeine from the diet can be helpful. Some ADHD youngsters are so wound up in the evening that a low dose of a short acting stimulant in the evening can help them calm down enough so that they are then able to fall asleep. The addition of the alpha adrenergic agonists, especially clonidine have been effective in overcoming insomnia. These medications have the additional benefit of helping to control the ADHD symptomatology.

Another potential side effect of concern is that stimulants may induce abnormal motor movements. These include motor or vocal tics (involuntary motor movements or sounds), picking at the skin, hair pulling or twirling, biting fingernails, cuticles, and even toenails. For a long time it was believed that it was contraindicated to treat a youngster with Tourette's syndrome with a stimulant, for fear of exacerbating or bring out Tourette's Syndrome. Evidence indicates that stimulants do not cause Tourette's Syndrome, but in some youth it can worsen the tics, and in some, it can help decrease the tics, and in others it may have no effect. The fact that for some youth stimulants can be used is important because the majority of those children with Tourette's disorder suffer from ADHD (while the converse is not true). Stimulants can be very helpful in treating the ADHD in these youngsters, but must be approached with caution. If tics begin or increase, the medication may need to be discontinued.

There is a concern that stimulants may have a negative effect on growth in height and weight and there is conflicting evidence in this regard. Even if growth slowing occurs only in a small group of patients, clinical follow-up with routine checking of growth in height and weight is very important to ascertain the effects of the medication on the individual.

For most youngsters, stimulants do not appear to lower the seizure threshold and using a stimulant in a child whose seizures are well controlled with their anticonvulsant medication is not contraindicated.

One common objection to the use of stimulants in youth is the fear that taking medication early on, will lead to a substance abuse problem in later life. Recent studies indicate that most youngsters with ADHD who take stimulants do not develop substance abuse. One study found that ADHD children who received stimulants were at an 85% lower risk of substance abuse, compared to an unmedicated group. The longer acting preparations are considered less likely to be abused, in part because they are handled less frequently throughout the day.

Stimulant use is contraindicated in patients with severe anxiety, tension and agitation, those with glaucoma, or those hypersensitive to the drug or its components. Amphetamine use may cause an exacerbation of symptoms in psychotic youngsters and should be approached with caution in this diagnostic group.

Other Agents Used to Treat ADHD

Antidepressants have been shown to be effective in controlling ADHD symptoms and the most common ones are the tricyclic antidepressants: desipramine (Norpramin), imipramine (Tofranil) and nortriptylene (Pamelor). Typical side effects with the tricyclic antidepressants include change in heart rate and blood pressure, dry mouth, constipation, blurry vision, change in weight, and negative effects on the heart. In general, tricyclic antidepressants have lost their popularity and are not at present a first line agent in ADHD, partly due to the risk of cardiac arrhythmias and case reports of sudden death in a few children.

The atypical antidepressant bupropion (Wellbutrin) has some pharmacologic effects similar to the stimulants and can help with the core behavioral symptoms and the cognitive

symptoms in children with ADHD. In general, it is believed to be less effective than stimulants, but bupropion can be especially helpful if there is evidence of a comorbid depressive disorder. There is a risk of drug induced seizure with this medication, and should not be used in those with a previous history of seizure disorder or bulimia. The risk of seizures is decreased by using the slow release form of bupropion and by dividing the daily dosage. It should be remembered that none of the antidepressants are approved by the FDA for use in children in the treatment of ADHD. In addition, for some of these medications, there is no indication for their use in childhood for any disorder, e.g., bupropion. Venlafaxine (Effexor) is another being explored as a possible treatment alternative in ADHD.

Although the stimulants seem to have the most powerful ability to improve attention, other agents, the alpha-adrenergic agonist medications, i.e., the antihypertensive agents clonidine (Catapres) and guanfacine (Tenex) seem to be especially helpful with impulsivity and hyperactivity and the hyperarousal seen in ADHD youth. Unfortunately, they appear limited in their ability to help attention. Side effects include lethargy, decrease in blood pressure, depressed mood, and possibly negative effects on cardiac conduction. The Physician's Desk Reference notes that serious adverse events have been reported in concomitant use of methylphenidate and clonidine and the safety of this combination has not been systematically evaluated. Although no causality for the adverse events with concomitant use has been established, prescribing physicians should be aware of this concern.

The newest medication released for the treatment of ADHD that has received much attention, as it is the first non-stimulant medication approved by the FDA for ADHD is atomoxetine, brand name Strattera. Atomoxetine became available in January 2003 and early studies suggest that the potential for abuse is low and it is thus not classified as a controlled

substance – it can be phoned into the pharmacy and written as a renewable prescription. It is the only ADHD medication FDA approved for adults. It is taken as an oral capsule once or twice a day, and does not appear to need to be taken during the school day. Strattera needs to be swallowed whole unlike some of the other preparations that can be opened up and sprinkled on food (e.g., Adderall XR).

Side effects appear somewhat similar to stimulants and include: insomnia, dry mouth, decreased appetite, weight loss, upset stomach, constipation, nausea and/or vomiting, dizziness, mood swings, irritability, fatigue, increase in heart rate and blood pressure, and possible effect on growth in height and weight. Clinically, insomnia may be less of a side effect than treatment with stimulants. There are potential sexual side effects that can be of greater concern in adults.

Although how Strattera exactly works is unclear, it is thought to be “a potent inhibitor of the presynaptic norepinephrine transporter” which results in an increased amount of available norepinephrine. Strattera is metabolized through the cytochrome P450 2D6 pathway of the liver and may interact with other medications such as fluoxetine (Prozac), paroxetine (Paxil) and quinidine. As Strattera can increase a child's blood pressure and heart rate, it should be used very carefully in youth with heart or cerebrovascular disease. In addition caution should be used when considering Strattera in an asthmatic child on albuterol.

Another medication that is being studied in the treatment of ADHD is Modafinil (Provigil). It is used as a wake-provoking agent in those who have excessive daytime sleepiness associated with narcolepsy. Side effects include headaches, nausea, nervousness, anxiety and insomnia. Initial work has been done on adults with ADHD and appears promising.

Conclusion

In summary, the last two decades have seen a dramatic increase in the number of medications

available for the treatment of ADHD in children and adolescents. Many of the agents are variations of the basic compounds of methylphenidate and dextroamphetamine, with different modes of release, and different time courses of action. In addition, some of the antidepressants and antihypertensive alpha adrenergic agonists have a role in treatment of those with this disorder. Atomoxetine is the newest addition to the physician's treatment options, with the advantage of it being a non-stimulant compound with low abuse potential and long duration of action. Given that a significant portion of the population struggles with symptoms of ADHD, the new additions to the clinician's treatment options are definitely welcome.

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