Advances in understanding and treating ADHD

Kevin M. Antshel, Ph.D., Teresa M. Hargrave, MD,
Mihai Simonescu, MD, Prashant Kaul, MD and Stephen V. Faraone, Ph.D.

State University of New York - Upstate Medical University
Department of Psychiatry and Behavioral Sciences

Contact Information
Kevin Antshel, Ph.D.
SUNY – Upstate Medical University
Department of Psychiatry and Behavioral Sciences
750 East Adams Street
Syracuse, NY 13210
(315) 464-3117
(315) 464-3163 (fax)
AntshelK@upstate.edu
Abstract

Relative to even 10 years ago, there are presently far more treatment options for youth and adults with ADHD. New stimulant formulations have made it possible to tailor treatment to the duration of efficacy required by patients and to help mitigate the potential for abuse, misuse and diversion. Several new non-stimulant options have also emerged in the past few years. Cognitive behavioral interventions have been tested and are more popular in the treatment of adult ADHD, especially for those adults who cannot or will not use medications and for the many medication treated patients who continue to show residual disability.
ADVANCES IN UNDERSTANDING AND TREATING ADHD

Research on attention deficit / hyperactivity disorder (ADHD) has been published at an exponential rate during the past 30 years \(^1\). Within the past three years (2008 – current), theories regarding etiology and therapeutics have evolved concurrently \(^2\)-\(^5\). Psychopharmacological agents affecting catecholaminergic and alpha-2-adrenergic transmission continue to figure prominently in ADHD treatment \(^6\), \(^7\). Over the past three years, however, more attention is being paid to prescribing patterns \(^8\)-\(^10\), matching medication with patient characteristics \(^11\) and factors which promote treatment adherence in pediatric \(^12\)-\(^17\) and young adult populations \(^18\).

**Stimulants**

For most patients stimulants remain the first choice for medication management because meta-analysis shows they are more efficacious than non-stimulant medications \(^19\). Various delivery mechanisms exist. Physicians may choose from liquid, sprinkle, tablet, capsule, or patch; from active isomer, mixtures of active/less active isomers, or prodrug; from immediate release, intermediate release or extended release formulations \(^20\). For both the methylphenidate and amphetamine families there are arrays of choices which enable practitioners to better tailor the duration of medication efficacy throughout the day to the needs of the individual.

Research has continued to suggest that OROS-methylphenidate lessens ADHD symptoms throughout the day with greater adherence, thought to be associated with the convenience of once-a-day dosing \(^21\)-\(^23\). Dexmethylphenidate XR and transdermal methylphenidate also offer this benefit. Dexmethylphenidate comes in capsules which can be opened and mixed with food and has the earliest onset of efficacy of the long-acting preparations \(^24\), \(^25\). Transdermal methylphenidate bypasses the oral route entirely and in short-term studies is associated with
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efficacy throughout the day with improved family quality of life, and when carefully titrated, little effect on sleep\textsuperscript{26-28}. Greater absorption of medication occurs when the patch is applied to the buttocks rather than the subscapular area\textsuperscript{29}. Comorbid anxiety did not affect stimulant efficacy in one study\textsuperscript{30} and some studies suggest that treatment with stimulants can help to lessen the likelihood of other psychiatric comorbidities during adolescence\textsuperscript{31} including cigarette use and substance abuse\textsuperscript{32}. However, meta-analyses of stimulants and other ADHD medications in the treatment of ADHD comorbid with tic disorders concluded that supratherapeutic doses of dextroamphetamine should be avoided in this population, that methylphenidate best controlled ADHD, and that alpha-2-agonists best improved both tics and ADHD\textsuperscript{33, 34}. The most common side effects of stimulants (decreased appetite, trouble with sleep onset) have also continued to receive recent research interest. Some research suggests that it is difficult to predict which children with ADHD will have adverse effects based upon demographic and clinical characteristics\textsuperscript{35}. Although rare, serious cardiovascular side effects have been identified with stimulant use\textsuperscript{36}, common effects on blood pressure, heart rate and exercise parameters are usually of no clinical significance\textsuperscript{37-39}. Consensus has been reached in the United States, Canada and Europe that routine EKG screening and/or cardiology consult are needed prior to stimulant use only in those with positive family or personal cardiac history\textsuperscript{40, 41}. Likewise, no cytogenetic side effects from stimulant use have been demonstrated\textsuperscript{42, 43}. A review article showed that treatment with stimulants in childhood modestly reduced expected height and weight\textsuperscript{44}. These effects were dose dependent and attenuated over time. Within the past three years, concerns have continued to rise regarding abuse of stimulants and/or drug diversion\textsuperscript{45-47}. Some have suggested that in those with comorbid substance abuse
and ADHD, psychostimulants should be used with caution. The new stimulant prodrug, lisdexamfetamine dimesylate (LDX) offers some protection from these problems. LDX requires gut metabolism to reach its active form and hence lessens the likelihood of abuse and overdose. Its efficacy and side effects are similar to the other long-acting stimulant preparations.

**Non-Stimulants**

While modafinil and reboxetine have both shown some promise in the treatment of ADHD, the selective norepinephrine reuptake inhibitor, atomoxetine, and guanfacine (both FDA approved) continue to be the most commonly prescribed non-stimulant medications used to treat ADHD. Also, a long-acting FDA approved version of clonidine is now available.

Several reviews on the use of atomoxetine have been recently published and studies in populations around the world have continued to confirmed its efficacy, including those children with psychiatric comorbidity or previous stimulant therapy. When atomoxetine is administered once daily, some evidence suggests that morning dosing may be more efficacious yet evening dosing more tolerable. In adolescents, doses in the higher ranges have been associated with greater long term efficacy. Since atomoxetine has been rarely associated with acute suicidality, it has been given a black box warning. As with stimulant treatment, atomoxetine rarely completely normalizes behavior, but symptom improvement is often reflected in gains in social and behavioral function.

The alpha-2-adrenergic agonists clonidine and guanfacine have long been known to be of some assistance in treating ADHD. Recently, once-daily extended release guanfacine has proven effective in both short-term and long-term studies. Sedation is a common side effect which diminishes over time.
Response to single agent treatment for ADHD frequently falls short of full remission. Recent studies have shown that adding clonidine to methylphenidate, guanfacine extended release to stimulants or OROS methylphenidate to atomoxetine improve residual ADHD symptoms and were well tolerated. The FDA recently approved a long-acting form of clonidine to be used in monotherapy or as an adjunctive therapy to stimulant medications.

ADHD is frequently comorbid with other psychiatric conditions. Treatment of ADHD can result in alleviation of comorbid depression, anxiety, oppositional defiant disorder and/or aggression. However, when this is not the case, polypharmacy targeting each condition may have added benefit without unacceptable side effects. Examples include use of atomoxetine or methylphenidate in children being treated for bipolar spectrum disorders or borderline personality disorder and atypical antipsychotics or valproic acid preparations for children with ADHD and aggression or bipolar disorder. For patients with autistic spectrum disorder, optimal results may require stimulants, SNRI’s, antipsychotics and alpha-2-agonists.

A number of reports have been published regarding the use of alternative and complementary medicines in the treatment of ADHD. In a small study, traditional Chinese medicine compared favorably with methylphenidate. Positive results were claimed for gingko biloba yet gingko biloba failed in head-to-head comparison with methylphenidate. Short-chain fatty acids and omega 3/omega 6 fatty acids have not been demonstrated to be efficacious. A meta-analysis of neurofeedback treatment studies reported encouraging results that suggested the approach would be more effective for inattention and impulsivity than for hyperactivity.

**Adult ADHD**
The need for treatment in adults with ADHD has been debated in the past with reports of suboptimal response, diversion and abuse. There is a growing body of research on the treatment and recent years have seen the creation of evidence based guidelines. As in pediatric ADHD, pharmacological agents for managing adult ADHD, meta-analysis shows stimulant medications to be more effective than non-stimulant medications. Also similar to pediatric ADHD, the stimulants are generally considered the front-line approach for managing adult ADHD. Unlike pediatric ADHD, all the agents FDA approved for treating adult are long-acting. Interestingly, some research suggests that only 49% of adults are prescribed long-acting agents.

Non-stimulant options are also similar to pediatric ADHD options, although bupropion and modafinil are used more often in adults with ADHD than children with ADHD. The only non-Stimulant with FDA approval for adults with ADHD, however, is atomoxetine.

The potential for diversion and abuse may be greater in adults than in children where parents might control the medications. Stimulant misuse seems to be more common in those with comorbid alcohol, drug and cigarette use as well as those with higher levels of ADHD symptoms. Also, long-acting stimulants are less likely to be misused or diverted than short acting stimulants.

In pediatric ADHD, a combined treatment approach generally consists of pharmacotherapy therapy and some form of psychosocial intervention, generally consisting of parent training in behavioral management, consultation with teachers/school personnel and individual work with the child. In adults, a combined treatment approach also typically consists of pharmacotherapy and psychosocial intervention. However, unlike pediatric ADHD, there is some evidence that cognitive behavioral therapy (CBT) interventions are efficacious.
Safren and colleagues developed a CBT program for adults with ADHD as a supplement to their medication treatment\(^97\). A recently published study suggests that when compared to adults with ADHD who received relaxation training and educational support, those adults with ADHD who received 12 sessions of CBT had lower self-reported ADHD symptoms as well as functional improvements rated by a blinded assessor\(^{97}\). There were more treatment responders in the CBT group (53%) relative to the relaxation training and educational support group (23%) and gains were maintained over 6- and 12-month periods \(^{97}\).

Bramham and colleagues also developed a group CBT workshop program \(^{98}\). Using three 1-day workshops held monthly, six sessions were included in the program. The results suggested that relative to the controls, adults with ADHD who participated in the workshop increased their knowledge of ADHD. However, less optimistically, one-third of participants dropped out during the course of the CBT workshop. Furthermore, both groups reported less depression and anxiety as well as improved self-esteem at the end of the study, although the intervention group reported a greater improvement in self-esteem \(^{98}\). Others have also recently developed group interventions relying on CBT strategies \(^{99}\).

**Challenges of Treating ADHD**

There are several challenges associated with the treatment of individuals with ADHD. The first challenge is related with the clinical complexity of the cases themselves; the vast majority of individuals with ADHD, both child and adult, have a comorbid psychiatric disorder \(^{100-103}\). In this way, even relatively successful treatment of the ADHD symptoms may be associated with only modest functional improvements in the real world.

In the presence of significant comorbidity, complex, combined treatments may be required and the results may be more frustrating. Diligent attempts to clarify the co-occurring
ADHD conditions and related features (poor social skills, low academic abilities, etc.) become essential in cases resistant to treatment. While most individuals with ADHD will respond favorably to pharmacological interventions, optimal functioning is often not attained. Even in non-comorbid ADHD cases, optimal functioning occurs in only roughly 1 in 4 children with ADHD. Most patients show residual disabilities in several areas including executive functioning, deficient emotional self regulation, and “real world” functioning in school, on the job or in maintaining relationships. For this reason, establishing reasonable expectations with patients and parents may be critical for the success and continuity of the treatment.

A second challenge in treating ADHD is related to the methods of treatment and the optimization of the risk benefit ratio. Optimization of the treatment response often requires adjustments in doses and particular distributions of the doses during the day in order to maximize the effect of medications at the point of performance. Combined pharmacotherapy is frequently needed for patients having comorbid disorders and sometimes indicated when ADHD is the only presenting problem. Adjunct psychosocial treatments are frequently useful, but these should be targeted to patients based on a need assessment.

Possibly as a function of the disorder itself, non-adherence to treatment regimens is quite high in ADHD. In addition to the disorganization inherent in the disorder, other contributors to poor treatment adherence may be denial, externalization of the problem and medication side-effects. Little is known about predictors of long-term adherence so more work is needed to improve this critical component of treatment efficacy.

**Conclusions**

Recent research and drug development have provided new treatment options for youth and adults with ADHD. New stimulant formulations have made it possible to tailor treatment to
the duration of efficacy required by patients and to help mitigate the potential for abuse, misuse and diversion. Although they tend to be less efficacious than stimulants, new non-stimulant options also allow for extended duration of treatment without the adverse consequences associated with stimulant therapy. Progress in non-medical therapies now provides several options for patients who cannot or will not use medications and for the many medication treated patients who continue to show residual disability.

Looking toward the future, research will need to address several unmet needs. Many treated individuals with ADHD continue to have problems with executive functioning and deficient emotional self regulation. And symptomatic improvement frequently does not resolve functional disabilities. Future work needs to define and achieve optimal outcomes for individuals across the lifespan with ADHD.

**List of Abbreviations**

ADHD = attention deficit / hyperactivity disorder

CBT = cognitive behavioral therapy

EKG = electrocardiogram

LDX = lisdexamfetamine dimesylate

OROS = osmotic-release oral system

SNRI = Serotonin-norepinephrine reuptake inhibitor

**Competing interests**

Drs. Antshel, Hargrave, Simonescu and Kaul report no biomedical financial interests or potential conflicts of interest.

Dr. Faraone has, in the past year received consulting fees and has been on Advisory Boards for Eli Lilly, Ortho-McNeil and Shire Development and has received research support from Shire.
and the National Institutes of Health. In previous years, Dr. Faraone has received consulting fees or has been on Advisory Boards or has been a speaker for the following sources: Shire, McNeil, Janssen, Novartis, Pfizer, Ortho-McNeil and Eli Lilly. In previous years he has received research support from Eli Lilly, Shire, Pfizer and the National Institutes of Health. Dr. Faraone has a published book with Guilford Press. *Straight Talk About Your Child’s Mental Health.*

**Authors contributions**

All authors have been involved in drafting the manuscript or revising it critically for important intellectual content and have given final approval of the version to be published.

**Authors information**

Kevin M. Antshel, Ph.D., is an Associate Professor of Psychiatry and the Director of the ADHD Lifespan Treatment, Education & Research Program at the State University of New York - Upstate Medical University in Syracuse, NY.

Teresa Menke Hargrave, M.D. is an Associate Professor of Psychiatry and Clinical Associate Professor of Pediatrics at the State University of New York-Upstate Medical University in Syracuse, NY.

Mihai Simonescu, MD is an Assistant Professor of Psychiatry at the State University of New York-Upstate Medical University in Syracuse, NY.

Prashant Kaul, MD is an Assistant Professor of Psychiatry at the State University of New York- Upstate Medical University in Syracuse, NY.

Stephen V. Faraone, Ph.D. is Professor of Psychiatry and of Neuroscience & Physiology and Director, Child and Adolescent Psychiatry Research at the State University of New York - Upstate Medical University in Syracuse, NY.

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