REVIEW ARTICLE

CNS Drugs 2009; 23 Suppl.1: 21-31
1172-7047/09/0001-0021/$49.95/0

Efficacy and Safety Limitations of Attention-Deficit Hyperactivity Disorder Pharmacotherapy in Children and Adults

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Abstract

There have been major advances in the treatment and understanding of attention-deficit hyperactivity disorder (ADHD) in the last decade. Among these are the availability of newer stimulant formulations, an appreciation of the combined effects of medication and behavioural therapies, and a better understanding of the neurobiology of the disorder in children (aged 6–12 years), adolescents and adults. This article focuses on the evaluation of the efficacy and safety profiles of medications used for the management of ADHD.

In assessing the various medical treatments for ADHD, certain issues and analyses have become important to address. The diagnosis, characterization and quantification of ADHD symptoms are crucial to assessing treatment effectiveness. A standardized setting for measuring the severity of ADHD symptoms is the laboratory school protocol, which simulates a school environment with tightly controlled timing of measurements. This method has been adapted successfully to the adult workplace environment to help with the evaluation of adult ADHD symptoms.

Statistical analyses, such as effect size and number needed to treat, may aid in the comparison and interpretation of ADHD study results. Although an objective approach to evaluating the efficacy and safety profiles of the available medications provides necessary details about the medical options, typical clinical decisions are often based on trial and error and may be individualized based on a patient's daily routine, comorbidities and risk factors.

Stimulants remain the US FDA-approved medical treatment of choice for patients with ADHD and are associated with an exceptional response rate. Findings of the Multimodal Treatment of Children With ADHD study suggest that the combination of behavioural and medical therapy may benefit most patients. Nonstimulant agents, such as atomoxetine (FDA-approved), and several non-approved agents, bupropion, guanfacine and clonidine, may offer necessary alternatives to the stimulants. This is especially important for patients who have comorbidities that are contraindicated for stimulant use based on medical issues and/or risk for stimulant abuse. Typical psychiatric comorbidities in patients with ADHD include oppositional defiant disorder, conduct disorder, major depressive disorder, bipolar disorder, anxiety, substance abuse disorder, tic disorder, and Tourette's syndrome.

Although relatively safe, both stimulants and atomoxetine have class-related warnings and contraindications and are associated with adverse effects that require consideration when prescribing. Polypharmacy is a common psychiatric approach to address multiple symptoms or emergent adverse effects of necessary treatments. Future research may provide an improved understanding of polypharmacy and better characterization of the factors that influence the diagnosis and successful treatment of patients with ADHD.

Stimulants have been used to manage attention-deficit hyperactivity disorder (ADHD) in children since the 1930s.[1] Although they are considered safe and effective drugs, they have the potential for abuse and may not be appropriate for some patients with comorbidities. Before 2000, the choices among stimulants for patients with ADHD were limited to immediate-release and first-generation extended-release formulations.[2,3] Now, newer formulations of stimulants and a nonstimulant agent (atomoxetine) offer convenience, flexibility and dosing simplicity with a potentially lower risk for abuse than previously available options.[3,4]

Just as the choice of more sophisticated medications and delivery systems has expanded, so has our understanding of ADHD as a disorder. Once considered rare in adults, ADHD is now recognized as a lifelong disorder, with similar treatment to that in children. This review focuses on the evaluation and comparison of the efficacy and safety of current ADHD therapies in children and adults. Remaining needs also are highlighted.

1. Efficacy of Attention-Deficit Hyperactivity Disorder Treatments

1.1 Assessing Attention-Deficit Hyperactivity Disorder Symptoms in Clinical Trials in Children and Adults

Highly controlled settings provide key data regarding response to medication that are difficult to assess at normal clinic visits.[5] The laboratory school protocol (LSP) simulates a school environment and has been used to assess stimulant medications since the 1990s. This methodology employs a tightly controlled timing and context of measurements cycled/repeated throughout the day. In the current version of the LSP, symptoms of ADHD are assessed using attention, activity and productivity measures related to age and using the Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) rating scale.[5-7] One productivity measure is an age-adjusted maths test, the permanent product measure of performance (PERMP). The adult workplace environment is an adaptation of the LSP that assesses adult functioning in tasks related to ADHD symptom expression.[5]

In addition to adapting the setting of assessment for adults compared with children, the diagnostic criteria and symptoms in adults may require adjustment. These adaptations for the diagnosis and assessment of ADHD symptoms generally require the translation of childhood symptoms to the adult setting in terms of workplace and relationship functioning as well as factoring in coping mechanisms.[8] For example, hyperactivity in adults often does not manifest the same way as it does in children, since adults may have learned social constraint or simply avoid situations that require sitting still.[8] The QUEST method (Query about current debilitating problems, Uncover history, Evaluate symptom by symptom, Setting pervasiveness is judged, and Test for comorbidities) allows clinicians to probe for adult ADHD symptoms while addressing common diagnostic problems. The QUEST methodology refines the age-appropriateness of symptom development, allows for inquiries about symptoms in a specific order, and uses probes that are appropriate for adults.[8]

Interpreting how these types of measured effects in controlled research studies are clinically relevant may be difficult for medical practitioners. Two statistical analyses may be helpful in

evaluating and comparing the efficacy of pharmaceutical treatments in patients with ADHD: effect size (ES) and number needed to treat (NNT). The ES is an index that provides a quantitative assessment of clinical response and allows a rough comparison between study results. Although statistical significance is a key factor in interpreting clinical results, it does not indicate the degree of response. A typical calculation of ES (Cohen's *d*) is the difference between the means divided by the standard deviation. This value is compared on a generalized scale, on which 0.2 indicates a small effect, 0.5 indicates a medium effect and 0.8 indicates a large effect.[9] Because the ES is a generalized value it allows for a comparison of different efficacy measures (i.e. improvement in different rating scale scores). As such, it is often used in meta-analyses.

The NNT is another measure that provides clinicians with practical guidance to the effectiveness of a treatment. This measure is based on the study definitions of response but may allow comparison of treatments from different studies. It can be interpreted as the number of patients one must treat to achieve one response. It is calculated by taking the reciprocal of the difference between the proportions of patients who responded to treatment and those who responded to placebo.[10] It can also be thought of as the inverse of the absolute risk reduction.

ADHD treatment response remains difficult to predict. However, several factors have been shown to be predictive of response, including inherited and environmental factors.[11-13] Depressive symptoms in the parent and higher initial ADHD severity in the child exert a negative influence on therapy,[11] whereas a higher IQ score and comorbid anxiety in the child have been shown to positively influence response to therapy.[13]

1.2 Stimulants

Stimulants include amphetamines and methylphenidate (table I).[14-21] Seventy percent of patients respond to the first stimulant and response rates of more than 90% have been reported by switching nonresponders to a second stimulant.[22-24] Given their proclivity to yield high rates of response, stimulants continue to be the mainstay of ADHD medical treatment.

Newer formulations address maximizing ADHD symptom control throughout the day.[4] Different formulations offer plasma level peaks at various postdose times and unique onset times that allow symptom control catered to a patient's specific needs (figure 1).[4,19,25,26]

Based on one analysis of NNT, 2.5 patients would need to be treated for a response to be seen in one patient. This is calculated based on data from a study of an extended-release formulation of mixed amphetamine salts (MAS XR), in which there was about a 70% response to the 30 mg/day dosage compared with a 30% response to placebo.[27] An NNT of 2.5 represents a good response, since approved psychiatric medications are associated with NNTs ranging from 9 to 20, and stimulants are associated with NNTs of 4 or 5.[28]

The Multimodal Treatment of Children With ADHD (MTA) study provides an excellent example of the evaluation of stimulant medications. In this study children were randomly assigned to one of four treatment groups: intense medical management, intense behavioural treatment, combination medical and behavioural treatment, and routine community care.[29] The medications used were primarily stimulants. The assessment of response was based on the Swanson, Nolan, Atkins and Pelham IV Parent and Teacher ($SNAP\text{-}IV_{PT}$) rating scale score, a calculation of the mean of the inattention, hyperactivity/impulsivity and oppositional defiant disorder (ODD) data subsets that are further averaged for both parent and teacher assessments.[30,31] The mean baseline score for the two groups receiving medical management was 1.8 on the $SNAP\text{-}IV_{PT}$ scale.[29] Scores of <1 on this scale, which assigns values from 0 (not at all) to 3 (very much), represent a lack of ADHD symptoms.[30,31] Patients with reductions in scores to <1 are considered normalized.[30]

At the end of 14 months of treatment in the MTA study, medical management and combination treatment was found to yield significantly greater improvement in ADHD symptoms than behavioural or community care.[32] Interestingly,

Table I. Currently approved longer-acting medications for patients with attention-deficit hyperactivity disorder

Generic	Brand	Delivery	Year approved	Pharmacokinetic parameters	Duration of behavioural action/expected efficacy	Pivotal clinical trials
Nonstimulants						
Atomoxetine	Strattera®	Capsule	2002	EM: half-life 5 h PM: half-life 24 h	Up to 24 h	Michelson et al.[20]
Stimulants						
Amphetamine-based stimulants						
Mixed amphetamine salts	Adderall® XR	Double-pulsed delivery capsules	2001	Mean elimination half-life 9–11 h and 11–14 h depending on patient age and weight	8–12 h	McCracken et al.[18]
Lisdexamfetamine	Vyvanse™	Capsule	2007	t_{max} of dextroamphetamine 3.5 h	12–14 h	Biederman et al.[14]
Methylphenidate-based stimulants						
OROS® methylphenidate	Concerta®	Coated/osmotic tablet	2000	Initial concentration peak reached in 1 h, followed by reduction then gradual increase to maximum level over 5–9 h	10–12 h	Wolraich et al.[21]
Methylphenidate	Daytrana™	Transdermal system	2006	Consistent delivery as long as patch is worn	10–12 h Activity continues 3 h after patch is removed	McGough et al.[19]
	Metadate® CD	IR (30%)/ER (70%) capsules	2001	Median early peak at 1.5 h; median second peak at 4.5 h	4–8 h	Greenhill et al.[15]
	Ritalin® LA	Bimodal-release capsule with SODAS®	2002	t_{max} at 1–4 and 5–8 h	6–8 h	Markowitz et al.[17]
Dexmethylphenidate	Focalin® XR	ER capsules	2005	t_{max} at 1.5 and 6.5 h	3–4 h	Greenhill et al.[16]

CD, ER, LA, XR = extended release; **EM** = extensive metabolizers; **IR** = immediate release; **OROS** = osmotic release oral system; **PM** = poor metabolizers; **SODAS** = spheroidal oral drug absorption system; **t_{max}** = time to maximum concentration.

medical treatment (medical management and combination therapy groups) provided superior results to community care despite the fact that 66% of community care patients received similar medication during the study.[32] Based on an analysis of ES, the combination group had a small advantage (0.26) over the medical management group.[31] Together the medical management and combination groups had a 0.59 ES advantage compared with the behavioural management and community care groups.[31]

Following the treatment phase in the MTA study, the benefits to the medical management group subsided such that by 24 months there was no apparent advantage to receiving medication.[33] Possible explanations for these results included an age-related decline in ADHD symptoms, changes in medication management intensity, and starting or stopping medications altogether.[33] Analyses of the response rates to stimulant therapy may provide another plausible explanation. For instance, at the end of the treatment phase in the MTA study, the proportion of patients who had normalized was statistically significantly different among the treatment groups: 68% of patients receiving combination treatment, 56% receiving medical management, 34% receiving behavioural management and 25% receiving community care.[30] So a greater proportion of patients were able to achieve a complete response when given intense behavioural treatment in addition to medical management.

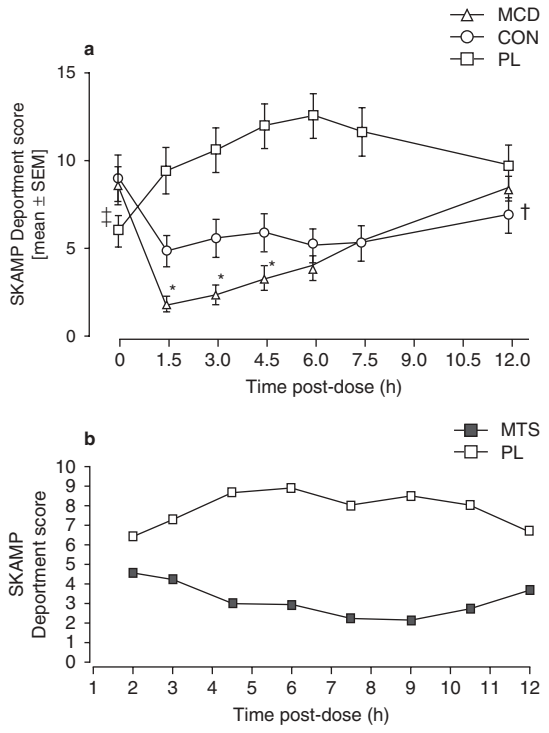

Fig. 1. Mean SKAMP Deportment Subscale scores by timepoint, intention-to-treat population. (**a**) SKAMP score for OROS methylphenidate (Concerta®; CON) and methylphenidate extended release (MCD). Reprinted with permission from Swanson et al.[25] *, times at which MCD was statistically significantly better than CON; †, times at which CON was statistically significantly better than PL; ‡, times at which PL was statistically significantly better than both MCD and CON. (**b**) SKAMP score for the methylphenidate transdermal system (MTS). $p < 0.01$ at all timepoints for MTS vs PL using ANOVA. Reprinted with permission from McGough et al.[19] **OROS** = osmotic release oral system; **PL** = placebo; **SKAMP** = Swanson, Kotkin, Agler, M-Flynn and Pelham rating scale.

1.3 Nonstimulants

Approximately 10–30% of patients either do not respond to or must avoid stimulant therapy.[34] Several nonstimulants (the α_2-agonists clonidine and guanfacine, tricyclic antidepressants, bupropion, modafinil and atomoxetine) are available options in these patients.[28] Atomoxetine is the only nonstimulant approved by the US FDA for the treatment of patients with ADHD (table I). No studies provide direct comparative response rates for these therapeutic options, although one meta-analysis comparing stimulants and nonstimulants demonstrated a large overlap in efficacy among placebo-controlled trials.[35] This analysis suggested that nonstimulants as a group may be less effective than stimulants.[28]

Atomoxetine is a selective norepinephrine reuptake inhibitor that is used as a second-line agent after stimulants in patients with ADHD.[34,36] It has been compared with MAS XR in a randomized, double-blind trial in children (n = 203) using the LSP.[37] In this study atomoxetine was associated with significantly less improvement in SKAMP-Deportment (D) scores compared with MAS XR (–0.13 vs –0.56; $p < 0.0001$). It is interesting to note that although the MAS XR group had stable SKAMP-D scores over the 3 weeks of the study, the atomoxetine group had inconsistent SKAMP-D scores.[37] This may indicate that the atomoxetine group had not yet stabilized on treatment (figure 2).[37] Atomoxetine has been shown to take 1–2 months to stabilize ADHD.[34,37] Moreover, unlike the long-acting stimulants, the beneficial effects of atomoxetine were shown to wane 9 hours after administration in this study.[37] Administering atomoxetine once daily in the evening would be likely to leave children without effective

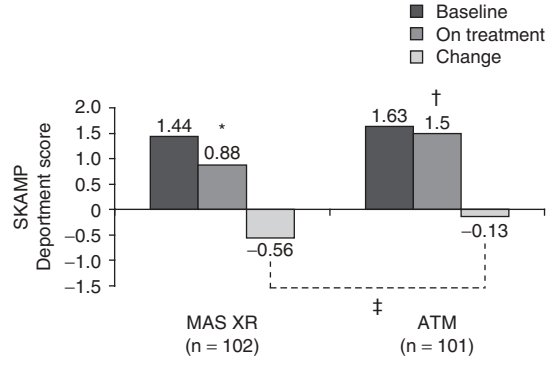

Fig. 2. Overall Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) rating scale deportment scores averaged over all timepoints and all weeks for the intent-to-treat sample (primary efficacy variable). Reprinted with permission from Wigal et al.[37] **ATM** = atomoxetine; **MAS XR** = mixed amphetamine salts extended release; * $p < 0.0001$; † $p = 0.0496$ vs baseline score, based on a 1-sample test; ‡ $p < 0.0001$ comparing treatment effect of MAS XR with ATM is based on ANCOVA; the ANCOVA model included treatment (MAS XR and ATN), site and corresponding baseline scores as the covariate.

symptom coverage for the following school day. Twice-daily administration would prevent this gap in coverage. Although not discussed in the product labelling, twice-daily administration has been shown to be a viable method for reducing the incidence of early adverse events, such as somnolence and gastrointestinal disorders.[38]

Several other nonstimulant therapies for ADHD may also be considered. Although not approved at this time, bupropion, modafinil and the α_2-agonists clonidine and guanfacine have been prescribed for the treatment of ADHD in adults and children.[35,39-44] (See also Arnsten[45] and Scahill[46]).

A meta-analysis of more than 50 ADHD studies reported the ESs for nonstimulants, immediate-release stimulants and long-acting stimulants to be 0.62, 0.91 and 0.95, respectively.[28,35] ESs for individual nonstimulants are listed in table II.[40-42,47-51] Most nonstimulants have similar ES values of approximately 0.6 to 0.7, which correspond to the upper-moderate range.

2. Efficacy in Patients with Common Comorbidities

Stimulants are generally effective for managing ADHD symptoms in patients with comorbidities such as ODD and conduct disorder.[32] Studies indicate that patients with ADHD and comorbid anxiety may generally respond well to stimulant therapy.[32] It remains unclear whether stimulants would be less effective for ADHD or exacerbate anxiety in these patients. Atomoxetine has been shown to be effective in managing the symptoms of ADHD to a similar extent in patients with and without comorbid ODD.[52]

Depression may be difficult to treat in children. In one small study, bupropion was shown to improve both ADHD and depressive symptoms in 14 (58%) of the 24 children who had both ADHD and depression, compared with 7 (29%) of the 24 children who had depression alone.[41] Michelson et al.[20] showed that Children's Depression Rating Scale–Revised scores improved with atomoxetine in children with little or no

Table II. Comparison of effect size (ES) difference in nonstimulant agents used to treat patients with attention-deficit hyperactivity disorder (ADHD)[a]

Agent	Measure	ES	Comment	Reference
Bupropion	Global improvement in ADHD, depression and functional impairment	0.70	Efficacy in question	Daviss et al.[41]
Modafinil	ADHD-RS, CGI-I	0.69, compared with other nonstimulants	Not US FDA-approved, owing to skin-related AEs	Biederman et al.[47]
Guanfacine IR	ADHD-RS, CGI-I	0.65	Possible use with comorbid tic disorder	Scahill et al.[42]
Clonidine IR	Meta-analysis using weighted variables regarding ADHD symptoms	0.58	Possible second-tier treatment for symptoms	Connor et al.[40]
Atomoxetine	ADHD-RS, CPRS-R, CGI-S, CDRS-R, CHQ	0.70	Favourable profile	Michelson et al.[20]
SSRIs	Meta-analysis including Hamilton Depression Rating Scale, Beck Depression Inventory, clinician reports and self-reported global outcome measures	0.50	For OCD or depression	Geddes and Butler[50]
Atypical antipsychotics	Meta-analysis including relapse rate	0.25	As used for schizophrenia	Pitschel-Walz et al.[51]
Antidepressants	Meta-analysis including incidence and genetic factors	0.39	As used for generalized anxiety disorders	Gale and Oakley-Browne[49]

a Different studies may reflect differences in subject selection and assessment methodology, as these were not direct comparator trials.

ADHD-RS = Attention Deficit Hyperactivity Disorder Rating Scale; **AE** = adverse event; **CDRS-R** = Children's Depression Rating Scale, Revised; **CGI-I** = Clinical Global Impressions Scale–Improvement; **CGI-S** = Clinical Global Impressions Scale–Severity; **CHQ** = Child Health Questionnaire; **CPRS-R** = Conners Parent Rating Scales-Revised; **IR** = immediate-release; **OCD** = obsessive-compulsive disorder.

depression. In a multi-site, randomized, controlled study (n = 142), atomoxetine was shown to improve ADHD symptoms, but was not helpful in treating symptoms of depression.[53] The topic of comorbid bipolarity in children with ADHD is controversial and complex, beginning with the definition of bipolar disorder in children.[54] In one study of children who had clear bipolar disorder with manic symptoms, the pretreatment of manic symptoms preceded the effective treatment of ADHD symptoms with stimulants.[55]

Stimulants may be less likely to ameliorate ADHD symptoms in patients with comorbid pervasive developmental disorder or autism and may be contraindicated.[56,57] ADHD symptoms occur in about 50% of patients with Tourette's syndrome.[58] Unfortunately, stimulants are contraindicated in patients with tics or a family history or diagnosis of Tourette's syndrome. However, patients with Tourette's syndrome or tic disorder may benefit from atomoxetine or α_2-agonists.[42,57]

Finally, it has been suggested that early treatment of ADHD with stimulants may aid in preventing future substance abuse disorders,[59,60] although recent research fails to support this.[61] Until the effects of stimulant therapy in patients with substance use disorder are better understood, the conservative approach would be to avoid stimulants in this population.

3. Safety Profiles for Attention-Deficit Hyperactivity Disorder Treatments

3.1 US FDA Guidelines and Label Warnings

Stimulant drugs provide significant benefits for and present serious risks to patients with ADHD. Recent FDA guidelines require that medication guides be given to patients when ADHD medications are dispensed. The guides are required specifically "to alert patients to possible cardiovascular risks and risks of adverse psychiatric symptoms associated with the medicines, and to advise them of precautions that can be taken".[62] The FDA also recommends that patients who take ADHD medications meet with their physician to develop a treatment plan that includes an evaluation for potential cardiovascular and psychiatric problems.[63]

An FDA review of cardiovascular and psychiatric risks has led to the addition of uniform warning language in the package inserts of all stimulants indicated for patients with ADHD. In one case, an FDA review found serious cardiovascular adverse events in patients taking standard doses of ADHD medications as well as sudden death occurring in patients with underlying serious heart problems, and stroke and myocardial infarction in adults with certain risk factors.[63] The primary concern is that increased blood pressure and heart rate, which accompany stimulant use, may pose an especially important risk in patients with underlying cardiac disease. In the second case, the FDA review of ADHD pharmacotherapeutics revealed a slightly increased risk (~1 in 1000) of drug-related psychiatric adverse events, such as delusions, hallucinations, paranoia and mania, even in patients who did not have previous psychiatric problems.[63]

Atomoxetine is not categorized as a schedule II substance. And although it does not have clear antidepressant effects, it is considered an antidepressant based on its mode of action. As such, it must include the depressant class black box warning regarding an increased risk of suicidal ideation.[64] The atomoxetine label also has warnings regarding hepatotoxicity, serious cardiovascular events and psychiatric symptoms.[64]

3.2 Contraindications

Although the language for contraindications in package inserts for stimulants varies depending on whether the stimulant is an amphetamine or methylphenidate based, the differences relate more to language than to actual clinical practice. In actuality, the contraindications are the same for the entire class of stimulants for ADHD.

3.3 Drug Discontinuations

Several adverse events have been associated with discontinuation of stimulant use. The prevalence of insomnia is doubled in patients with ADHD who are treated with stimulants, which

may be a key cause of discontinuation.[65] The initiation of tics has led to discontinuations in various controlled stimulant trials.[66] Other reasons for discontinuation may be decreased appetite and weight loss or emotional lability induced by these drugs.

Atomoxetine was associated with a discontinuation rate of approximately 4% due to adverse events.[67] Typical events associated with atomoxetine include gastrointestinal disorders (abdominal pain, nausea, decreased appetite) and general complaints (fatigue, somnolence and irritability).[64]

3.4 Other Safety Issues

Growth retardation has been observed in many studies where stimulants are used to manage ADHD.[48,68,69] The MTA study showed that stimulant-treated patients were retarded in growth such that, on average, they were approximately 2 cm shorter and 2.7 kg lighter over the 3 years of follow-up compared with non-medicated patients.[69] Children typically regain the initial reduction in growth based on normalization of growth rates and long-term indirect evidence, although the literature is divided on this topic.[69-71] Drug holidays may reduce growth retardation but it is not clear how effective this planned non-usage is or what parameters (i.e. length of holiday period with duration of treatment and specific agent) need to guide such holidays compared with how the holiday interferes with the benefits of treatment. Atomoxetine was shown to have minimal effects on height.[67,72]

3.5 Effects on Special Populations

While the incidence of ADHD is higher in children with epilepsy than among the general population, physicians have been reluctant to treat such children with stimulants for fear of inducing new-onset seizures and causing interactions with antiepileptic drugs. However, chart-review and prospective studies have shown that in children whose seizures have been stabilized by antiepileptics, stimulant treatment neither exacerbates seizures nor has an adverse effect on antiepileptic drug serum levels.[73,74] Although there has been some concern raised regarding seizures related to atomoxetine use, the risk of seizures with atomoxetine was not compounded in patients with epilepsy.[74,75]

4. Combination Therapy for Attention-Deficit Hyperactivity Disorder

Rational polypharmacy has become standard treatment in patients with neuropsychiatric disorders such as bipolar disorder, schizophrenia and major depressive disorder. It is unclear whether polypharmacy may benefit the treatment of ADHD; more research is needed on the efficacy and safety of new agents for ADHD and on the role of combination therapy. Second-line agents may be necessary to address symptoms that are only partly responsive to one agent. The treatment of adverse effects, such as insomnia and sedation while maintaining ADHD symptom control may be crucial to adherence.

5. Conclusion

Over the past decade, there has been an increase in the approval and availability of new drugs and delivery systems to treat patients with ADHD. Stimulant therapy remains the first-line treatment in children, but nonstimulant agents are available and newer medications, such as the α_2-agonists, have recently demonstrated promising results. However, atomoxetine is the only nonstimulant currently approved for the treatment of children and adults with ADHD.

Some patients may not benefit from currently approved medications for ADHD because of poor response or the presence of confounding factors, such as comorbid illness, intolerance and a history of stimulant misuse. Treatment that is effective, safe and well tolerated is needed especially for patients with concomitant disorders such as Tourette's syndrome, pervasive developmental disorder, autism, anxiety disorders, major depressive disorder, bipolar disorder and substance use disorder. The gold standard for addressing efficacy and safety of new treatments, randomized, controlled trials, especially in the highly controlled laboratory school environment,

have been critical for providing research to inform clinical practice. However, the allowable concomitant medications and fixed strategies for treatment in a relatively homogeneous group of patients has limitations in reflecting how patients with comorbidities are handled in actual clinical practice.

Beyond the comparison of efficacy of the available ADHD medications, a greater focus is now given to safety concerns, and pharmaceutical manufacturers are now required to provide patients with detailed medication guides. Further research is needed to accommodate patients with comorbidities and to provide guidelines regarding the challenges of combination therapy.

Acknowledgements

Sharon B. Wigal, PhD, has received consulting fees from Abbott Laboratories, McNeil Pharmaceutical, Inc., the National Institute of Mental Health and Shire Pharmaceuticals, Inc.; has received fees for non-CME services from McNeil Pharmaceutical, Inc., Novartis AG, Shire Pharmaceuticals, Inc. and UCB Pharma, Inc.; and has contracted research with Addrenex, Cephalon, Inc., Eli Lilly & Company, McNeil Pharmaceutical, Inc., the National Institute of Mental Health, Psychogenics and Shire Pharmaceuticals, Inc.

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