Clinical considerations for the management of pediatric patients with attention-deficit/hyperactivity disorder

Dustin Linn, PharmD, BCPS[1]
Andrea Murray, PharmD[1]
Thomas Smith, PharmD[1]
David Fuentes, PharmD, BCPP, CGP[2]

[1]Assistant Professor of Pharmacy Practice, Manchester University College of Pharmacy, Fort Wayne, IN
[2]Department Chair of Pharmacy Practice, Associate Professor of Pharmacy Practice, Manchester University College of Pharmacy, Fort Wayne, IN

ABSTRACT

Introduction: Attention-deficit/hyperactivity disorder (ADHD) is a chronic health condition presenting with symptoms of hyperactivity, impulsivity, and/or inattention in early childhood, adolescence and adulthood. Many patients will persist with associated symptoms throughout their life and may require long term treatment to maintain adequate control.

Objective: The purpose of this article is to review the current literature in regards to diagnosis, treatment, and management of ADHD in the pediatric and adolescent population.

Methods: A search was conducted using PubMed, Medline, Ovid, and CINHAL with a focus on studies and reviews in the English language from 2008 – 2013, featuring pediatric/adolescent patients across the ages of 4-17 years using the terms: "management", "attention-deficit", "hyperactivity", and "treatment." Literature referenced prior to the five-year time frame outlined herein provided foundational information on diagnostics and medications.

Discussion: Stimulants, in conjunction with behavioral therapy, are standard first line treatments used in ADHD. While stimulant medications have been shown to be effective in treating symptoms associated with ADHD, there are a variety of concerns that may prevent their use. These concerns are related to adverse consequences, many of which are not supported by concrete evidence. Other pharmacotherapy options such as norepinephrine reuptake inhibitors and selective alpha-2 adrenergic agonists are typically reserved as second line options. The use of novel and emerging complementary therapies will also be explored.

Conclusion: Patients diagnosed with ADHD must be thoroughly evaluated when making decisions regarding treatment. Many studies and reviews support the efficacy of pharmacotherapy in treatment of ADHD; however, there is insufficient evidence regarding long-term safety of the medications. Further research is warranted to evaluate current treatment options and associated risks and benefits to guide the clinician in optimal management of these patients.

KEYWORDS

pediatric, attention-deficit/hyperactivity disorder (ADHD), treatment, stimulant

OVERVIEW

This is an invited review of the management of attention-deficit/hyperactivity disorder (ADHD) in pediatric patients designed to present a summary of the pediatric treatment options for ADHD. A case will highlight aspects of the review and connect the literature to a scenario of an adolescent with ADHD.

INTRODUCTION/BACKGROUND

ADHD is a chronic health condition present in early childhood, adolescence, and adulthood. It has been estimated that ADHD will continue into adolescence in 70% of children diagnosed, and will continue into adulthood in 66%.[1,2] The definition of ADHD currently includes the presence of at least six inattention-related symptoms, or six hyperactivity/impulsivity-related symptoms, persisting over a period of at least 6 months to a degree that is maladaptive and inconsistent with development level. Psychiatrists currently use the criteria from the Diagnostic and Statistical Manual's fourth revision to diagnose patients with ADHD, referring to five major areas: 1) symptoms, duration, and subtype of

presentation; 2) timing of the onset of symptoms; 3) degree of impairment across two, or more, settings and environments; 4) presence of measurable evidence of impairment across the identified settings; and 5) diligent exclusion of other potential causes such as medications, or other comorbidities. Further, ADHD subtypes, predominately inattentive or predominately hyperactive-impulsive, are added if at least six symptoms can be identified in only one of these two symptom categories. The ADHD-combined type may be diagnosed if the six symptoms threshold is reached in both categories in a 6 month period.[3] In addition, some of the symptoms should appear before the age of seven, and impairment should be observed in two or more settings, usually including home and school. Evidence of impairment must exist in social, academic, or occupational areas, and all other mood disorders, medical conditions, and medication/substance usage should be explored and ruled out to ensure the most appropriate diagnosis is assigned.[3] The appropriate diagnosis of ADHD is further complicated by the presence of other conditions and the overlap of symptomatology. A systemic review focusing on evaluation and treatment of ADHD investigated the presence of other conditions, finding that symptoms defined as components of ADHD are also found in other disorders, including autism.[4] Symptoms such as hyperactivity, impulsivity, and inattention are also components of a variety of other psychiatric disorders, including bipolar disorder, depression and substance abuse.[5] We are hopeful that the upcoming revisions to the Diagnostic and Statistical Manual will provide some guidance in differentiating across commonly interwoven conditions. Future changes anticipated, but not yet confirmed, from the fifth revision of the Diagnostic and Statistical Manual will distance ADHD from oppositional defiant disorder and conduct disorder, as well as introduce specific alterations in diagnostic criteria. Such changes include an increased maximum age of onset, a shift away from specific ADHD subtypes, additional examples of behaviors to the criteria descriptor, and possibly a reduction in the number of symptoms required for diagnosis. The last two modifications may reduce the number of individuals who, under DSM-IV, no longer meet many criteria for ADHD as they age and allow for proper identification of older individuals with this disorder.[6]

CASE STUDY

To better illustrate the clinical considerations regarding ADHD management in pediatric patients, a case of an adolescent male is presented:

"DA is a 14 year old male with a history of ADHD, combined type. His past medical history is significant only for febrile seizures as a newborn. Relevant family history includes an uncle who passed after a sudden cardiac event at age 52. Because of concerns over stimulant risks, he has been managed with guanfacine, extended-release, for a year while in middle school, but recently has had difficulty transitioning to high school. He is unable to follow tasks and lessons and has lost multiple homework assignments. Additionally, he is complaining of lethargy and not performing well in after school sports activities. His mother is concerned about switching to a stimulant medication because of his and the family's medical history, the risk of abuse, and growth issues."

METHODS

A search was conducted using PubMed, Medline, Ovid, and CINHAL with a focus on studies and reviews in the English language featuring pediatric/adolescent patients across the ages of 4-17 years using the terms: "management", "attention-deficit", "hyperactivity", and "treatment."

FINDINGS/ RESULTS

Any journal articles featuring aspects of diagnosis, treatment, and management of ADHD were included in the review to provide a general, but comprehensive and multidisciplinary, overview of the impact of ADHD. Articles focusing on medication use and safety issues, co-morbidities, side effects, and complementary and alternative medicine of pediatric patients are reviewed herein.

DISCUSSION/ REVIEW

Stimulant medications are associated with a variety of concerns which may lead parents and caregivers to withhold therapy with these medications in children with diagnosed ADHD. Concerns are raised over the unknown impact these agents may have on growth rates, cardiovascular health, concurrent tic disorders, treatment-emergent suicidality, substance abuse potential, and seizure risk. Zhang, Du, and Zhuang found the use of stimulants had no impact on height or body mass index (BMI) on school-aged children followed from 2 to 4 years. Zhang and colleagues found that changes between patients' height and mean height in the methylphenidate group was -1.86+/-0.82 cm (P<0.001); in controls it was -0.26+/-0.51 cm (P<0.05), accompanied by changes of height standard deviation score (SDS) in the methylphenidate group and controls of -0.14+/-0.23 cm SD (P<0.001) and +0.05+/-0.10 cm SD (P<0.05), respectively. While they report significant differences in

height (P<0.001) and conclude that duration of treatment contributed significantly to variances in height (P<0.001), the difference of these values translate to less than one inch, at most, and may not be seen as clinical significant. Further, Zhang and colleagues report that changes between the patients' weight and weight for height after methylphenidate was -0.14+/-1.25 kg (P>0.05), amounting to a change less than one pound. Finally, the authors concluded that use of methylphenidate had no significant influence on weight and BMI values.[7] Other data are conflicting, but any temporary delays in growth or enduring differences in growth between medicated and non-medicated children have not been significant. Our review found no solid evidence that growth is impaired long-term when using stimulant medications.

As it relates to the impact on cardiac health, stimulants are perceived to convey a risk of sudden cardiac death, possibly due to their impact on catecholamines that regulate blood pressure and heart rate. In a review of the cardiovascular risks associated with stimulant use in pediatric patients, investigators found increases in blood pressure and heart rate of $\leq$ 5 mmHg and $\leq$ 10 bpm, respectively with no pathological changes noted in electrocardiography.[8] In a another recent investigation, Leslie and colleagues found that pediatricians surveyed (n=1200) were 93% likely to complete a comprehensive history and physical examination in light of the perceived risk of sudden cardiac death, while less than half conducted in-depth cardiac examinations, and only 15% performed an electrocardiogram (ECG) prior to initiating stimulant therapy.[9] Conflicting literature exists on providers' perceptions of the risk of sudden cardiac death, and the measures pediatricians take in assessing patients for such risks prior to initiating stimulant therapy. Our review found no certainty within the literature that suggests a significant cardiac risk sufficient to warrant recommending ECG for all patients prior to initiation of a stimulant.

Management of tic disorders in patients diagnosed with ADHD may also be difficult due to the risk of stimulants causing tics. Investigators concluded that because the presence of tics may result in reduced use of stimulants in sufficient doses to treat core ADHD symptoms for fear of worsening tics, patients diagnosed with ADHD and tic disorders may require more careful medication management.[10] This suggests that patients with tic disorders prior to being diagnosed with ADHD may not be offered stimulant therapy at the doses necessary for optimal treatment, or may bypass this class of agents altogether for non-stimulant agents or other combinations not yet fully understood in pursuit of options that appear safer.

As it pertains to treatment-emergent suicidal ideation, parents and caregivers express concerns about starting pharmacotherapy due to the unknown effect of using various combinations of medications for treating ADHD with medications used to treat concomitant conditions such as seizures, sleep disorders, and other psychiatric conditions. A more recent retrospective study on patients using concomitant antiepileptic agents with methylphenidate to improve symptoms of inattention in the presence of childhood epilepsy alluded to increased suicidal ideation when methylphenidate was used with leviteracetam.[11] Of the medications used to treat ADHD, atomoxetine, a selective norepinephrine reuptake inhibitor, is thought to convey a greater risk.[12,13] Suicidality risks in patients concurrently using medications to treat ADHD with other medications, such as antidepressants, anti-manic or antiepileptic agents, and other psychotropic agents, may be more likely than when using ADHD medications alone.

In regard to substance abuse risks, investigators in a 2-year open-label, prospective clinical trial using extended release methylphenidate for smoking prevention in adolescents diagnosed with ADHD concluded that treatment of ADHD with stimulants may be a deterrent to smoking.[14] While larger sample sizes in studies, multiple-sites, and continued replication are continuously cited as necessary to validate these assertions, our review suggests that the relationship between smoking deterrence and ADHD treatment creates an exciting avenue of study and may positively promote the early diagnosis and treatment of ADHD. Further, longer-acting formulations, release forms with delayed onsets, pro-drug formulations, and transdermal dosage forms are available to reduce the potential risk of addiction and abuse.[15] While this review cannot rule out the potential for addiction from the use of ADHD medications, our review of the literature describing poor outcomes of untreated patients may suggest that untreated patients may develop other mechanisms to coping with their condition that may include inappropriate substance use and, potentially, abuse.

Pertaining to seizure risk, investigators retrospectively examined the addition of methylphenidate to patients diagnosed with epileptic disorders using the medications levetiracetam, lamotrigine, valproic acid and others, finding no increase in pathological electroencephalogram (EEG) activity. The investigators concluded that addition of methylphenidate did not increase EEG abnormalities in

patients using these antiepileptic agents.[11] Our review did not find that stimulants and non-stimulants used to manage ADHD can cause seizures to the extent that these medications should not be used to manage appropriately-diagnosed ADHD, even in higher risk populations being currently treated with antiepileptic agents.

ADVERSE EFFECTS

Adverse effects of these medications were found to be consistent with the FDA warning labels.[15] Stimulants were reported to cause insomnia, sleep disorders, appetite loss, and only transient and/or insignificant changes in blood pressure and heart rate. Other agents classified as non-stimulants also had side effects reported consistent with FDA labeling (Table 1). Side effects with these agents were similar when being used in a variety of regimens to treat other conditions and disorders. Difficulty in establishing additive or compounded side effect profiles lies in the use of various psychotropic agents with overlapping pharmacological and adverse effects. On a related note, Cortese and colleagues reviewed 11 clinical studies in patients with ADHD using stimulants and co-diagnosed with autistic spectrum disorder (ASD), finding the most common side effects across these studies to be consistent with the loss of appetite, sleep disturbances, and irritability reported in populations without ASD.[16] Still, the adverse effect profile from lisdexamfetamine, a longer-duration stimulant, was found to be of increased severity in stimulant naïve patients in a study conducted by Wigal and colleagues on stimulant-naïve and stimulant-experienced patients.[17] This may suggest that patients starting any stimulant for the first time may be eligible for more frequent follow-up and education on the side effects, or a slower titration of the medications to ensure that patients' long-term desire to adhere is not affected negatively.

CARE STRATEGIES AND TREATMENT INITIATION FOR ADHD PATIENTS

Once diagnosed with ADHD, this set of reviewers recommends that pharmacotherapeutic options should be considered after conducting a thorough medical and psychiatric evaluation of the patient. During this time, parents and caregivers should also receive information on behavioral therapy that can be incorporated into their family's daily schedule. Parents and caregivers should work closely with their pediatricians, prescribers, and health care providers to agree on the direction and goals of the treatment. The relationship between healthcare providers and patients, parents, and caregivers is very important and warrants significant effort in order to establish and maintain in light of some of the challenges that exist in successfully establishing that level of teamwork. According to Brinkman and colleagues, shared decision-making between providers and parents of children with ADHD focuses on initiation of medication. Such shared decision-making was found to be generally low, and especially low in non-white patients with lower education and with limited socioeconomic means.[18] Parents must be prepared to work with school teachers and other representatives from their children's schools. Parents may not be able to, nor should they feel they should, solely manage their children's ADHD. A group of investigators across 24 pediatric practice locations set to find out if there were differences in medication management approaches for ADHD if they used a parent scale, versus a combined parent and teacher scale, to assess the efficacy of the treatment.[19] The authors concluded that both parent and teacher reports of child behavior may be better indicators of treatment success than parent reports alone.[19] Using this information, parents should work collaboratively with teachers and other school personnel to be able to gauge the efficacy of the child's treatment in both domains. In support of behavioral interventions targeting both home and school, investigators examined the role of a family-school treatment program, implied by the authors to be less intensive than Multi-modal therapy, in children of grades 2-6 that included behavioral consultations, daily report cards, and homework interventions targeting behaviors of ADHD. They found an improvement in symptoms in only 12 weeks in groups using either the family-school treatment program, or those using the program along with medications.[20] Other strategies, such as neurofeedback and sensory behavioral therapy were concluded to be only potentially efficacious, or acceptable, but not conclusively necessary.[21,22] Other avenues that could be used with family-targeted behavioral therapy and/or pharmacotherapy include access to mental health care using telephone systems,[23] informative and supportive internet portals,[24] and computer-assisted medication management tools.[25] Such aids have been explored and may provide another source of support to complement therapy and medications.

While useful alone, behavioral therapy for families and their children with ADHD can be supplemented with stimulants. Stimulants can be effective and can help children with ADHD experience a reduction in core symptoms that could help them achieve the most out of their therapy. Zoëga and colleagues examined the earlier start of medications in patients ages 9-12, rather than later. Reasons for withholding therapy in this population

were reported to be due to availability of care, time to reach proper diagnosis, and concerns regarding long-term medication safety. The investigators concluded, based on academic decline, that starting medications sooner spared children from poorer academic outcomes.[26] This study supports the initiation of medication soon after an appropriate diagnosis of ADHD is made, suggesting there is very little to be gained, and much to lose, if pharmacotherapy is withheld.

TRANSITION FROM CHILDHOOD TO ADULTHOOD

Stigma often occurs in relationship to psychiatric disorders and poses a barrier to the continued use of mental health services and treatments. In ADHD, not only do the individuals diagnosed with ADHD confront stigma in social situations, but parents of children may also face stigma related to their child's diagnosis. Increased public health efforts and education can be utilized to improve public perceptions regarding mental illnesses such as ADHD.[27-30] Educational efforts for patients and their caregivers should be aimed at methods to continue treatment for ADHD as they transition from childhood to adulthood. There are many potential consequences of discontinuation of ADHD therapy from childhood into adolescence and adulthood. These consequences may include difficulties in school, social relationships, vocational performance, and high-risk behaviors such as dangerous driving and criminal activity.[31] Montano and colleagues identified obstacles to the continuity of care from childhood to adulthood. In their review, they found that clinicians' knowledge and ability to prescribe medication, lack of resources, obstacles with the college health care system, lack of health insurance coverage, lack of transition planning, and patient/family resistance were obstacles to care continuity. Oftentimes adult practitioners may inherit management of adult ADHD patients while co-morbid psychiatric conditions may also be present, making recognition and differentiation of ADHD difficult.[32, 33] Young and colleagues proposed a set of recommendations for transition of care in ADHD from adolescence to adulthood in the United Kingdom; however, formal guidelines do not exist in the United States.[34]

Additional research and guidance is needed to establish effective care of adolescent patients with ADHD as they transition into adulthood.

EFFECTIVE AND EMERGING TREATMENT STRATEGIES AND OPTIONS FOR ADHD

Stimulants are the most effective pharmacological agents used to manage ADHD. Within the class of stimulants, there is no literature that currently identifies the most effective stimulant to date. The use of non-stimulant medications currently reserved for ADHD symptomatology not responding to stimulants is not first-line in pediatric patients with ADHD. The concern among prescribers for comorbid addiction and substance abuse behaviors in the pediatric population may not be as great as for adults receiving pharmacotherapy to treat ADHD due to the control of the medications by parents and caregivers. Still, more research is needed to provide prescribers with more direction on the most optimal specific agents, dosage forms, dosing regimens, and combinations to manage ADHD symptoms (Table 1).

Emerging pharmacotherapy options in the form of prescribed and complementary agents may be on the horizon. One example, a norepinephrine reuptake inhibitor, evidoxetine, studied by Kielbasa and colleagues may provide an alternative to atomoxetine as an adjunctive agent with stimulants, or may be used in place of stimulants if further research confirms its safety and efficacy.[35] The order in which currently-available agents are used may also require further investigation. Researchers explored the impact of treating stimulant-naïve patients, versus experienced patients, with lisdexamfetamine dimesylate and found a superior effect on treating core symptoms when used on stimulant naïve patients, than when prescribed in those with prior use of medications such as methylphenidate or mixed amphetamines.[17] This may suggest that once-daily dosing agents, more typically prescribed after a trial of shorter-acting stimulants, may now have a place as earlier therapeutic options.

As it pertains to complementary therapy, non-prescribed agents have received some recognition in the study of options to treat ADHD symptoms. In one such example, investigators studying the use of L-theanine 400mg daily to improve sleep in boys of ages 8-12 with ADHD found that the agent may be a safe and effective option.[36] Further, an 8-week, double-blind, controlled comparison of ningdong granule and methylphenidate suggested that ningdong granule may be safe, but requires further study to better understand its place in therapy.[37] Both of these examples highlight the need to stay abreast of emerging options about which patients might inquire. We do not recommend that these agents be used simply based on these trials, but that health care providers exercise vigilance and remain aware of asking patients, parents, and caregivers, about any complementary, non-prescribed agents as they review medications regimens in this population.

Table 1. Effective drug therapy summary

Class	Specific Options	Effects	General Concerns
Stimulants	Various Dextroamphetamine Methylphenidate Lisdexamfetamine	Reduction of core symptomatology Less proposed risk of addiction with longer-acting/effect products and transdermal formulations	Growth reduction, hallucinations and labile mood and sudden cardiovascular death
Selective norepinephrine reuptake inhibition	Atomoxetine	Reduction of core symptomatology	Reduced appetite, somnolence, insomnia, less common suicidal ideation, and rare hepatitis
Selective alpha-2 adrenergic agonists	Guanfacine, extended-release Clonidine, extended-release	Reduction of core symptomatology	Somnolence, dry mouth, and expected blood pressure effects
Combination therapy: Stimulants + Selective alpha-2 adrenergic agonists	Stimulants + guanfacine, extended-release, Stimulants + clonidine, extended-release	Individual class effects	Individual class concerns
Non-approved combination therapy	Various	N/A	Anecdotal support

Other interventions found in the literature focus on dietary supplementation and avoidance of ingredients thought by scientists to contribute to ADHD. Millichap and Yee reviewed the use of dietary restriction including: reduced intake of preservatives, dyes, fat, and refined sugars.[38] The consumption of folate and fiber, iron and zinc supplementation in patients with known deficiencies, and omega-3 fatty acid use was proposed to be of benefit in patients who do not respond to ADHD medications.[38,39] In addition, Hurt and colleagues, found that supplementation with carnitine, dimethylaminoethanol, and homeopathic remedies have little support for their use in the treatment of patients with ADHD.[39] This information on dietary supplementation and avoidance of potentially harmful ingredients highlights the continued need for research related to the causes of, and contributing factors to, ADHD.

Potential research on the horizon for ADHD may also focus on other pharmacological pathways. Hammerness and colleagues studied the use of OROS extended-release methylphenidate products in otherwise healthy adolescents with ADHD and found changes to glutamatergic processes.[40,41] This may suggest a potential role and area of future scientific inquiry for medications affecting glutamatergic pathways.

CONCLUSION

A variety of issues give both prescribers and caregivers much to consider when deciding whether to initiate pharmacotherapy to treat ADHD in their loved ones. While there is a paucity of evidence in the literature regarding the certainty of the safety of medications, there are studies and reviews supporting the efficacy of pharmacotherapy. All medications used to treat this condition have side effects and risks. Current studies in pediatric patients with ADHD may benefit from more attention to duration, definition of symptomatology, consideration for additional co-morbid conditions and other medications, greater subject numbers, and accounting for different social, economic, and psychosocial differences. Across various review articles, authors consistently describe their difficulties in analyzing diverse data and some state that meta-analyses cannot routinely be produced due to the complexity of subjects' medication regimens and concomitant medical and psychiatric disorders. More research is needed that addresses the common challenges in study methodology and variability in patients' symptoms. Additionally, investigators must critically review the use, efficacy, and safety of emerging dietary, complementary alternative agents, and pharmacotherapy options to better inform health care providers on the most optimal strategies for managing pediatric patients with ADHD.

REFERENCES

1. Langley K, Fowler T, Ford T, Thapar AK, van den Bree M, Harold G, et al. Adolescent clinical outcomes for young people with attention-deficit hyperactivity disorder. Br J Psychiatry. 2010;196(3):235-40. DOI: 10.1192/bjp.bp.109.066274. PubMed PMID: 20194547.
2. Barkley RA, Fischer M, Smallish L, Fletcher K. The persistence of attention-deficit/hyperactivity disorder into young adulthood as a function of reporting source and definition of disorder. J Abnorm Psychol. 2002;111(2):279-89. PubMed PMID: 12003449.

3. American Psychiatric Association. (2000). Diagnostic and statistical manual of mental disorders (Revised 4th ed.). Washington, DC: APAP, 2000.
4. Mahajan R, Bernal MP, Panzer R, Whitaker A, Roberts W, Handen B, et al. Clinical practice pathways for evaluation and medication choice for attention-deficit/hyperactivity disorder symptoms in autism spectrum disorders. Pediatrics. 2012;130 Suppl 2:S125-38. doi: 10.1542/peds.2012-0900J.
5. Wilens TE, Morrison NR. The intersection of attention-deficit/hyperactivity disorder and substance abuse. Curr Opin Psychiatry. 2011;24(4):280-5. DOI: 10.1097/YCO.0b013e328345c956. PubMed PMID: 21483267; PubMed Central PMCID: PMC3435098.
6. Tannock R. Rethinking ADHD and LD in DSM-5: proposed changes in diagnostic criteria. J Learn Disabil. 2013;46(1):5-25. DOI: 10.1177/0022219412464341. PubMed PMID: 23144062.
7. Zhang H, Du M, Zhuang S. Impact of long-term treatment of methylphenidate on height and weight of school age children with ADHD. Neuropediatrics. 2010;41(2):55-9. DOI: 10.1055/s-0030-1261893. PubMed PMID: 20799150.
8. Hammerness PG, Perrin JM, Shelley-Abrahamson R, Wilens TE. Cardiovascular risk of stimulant treatment in pediatric attention-deficit/hyperactivity disorder: update and clinical recommendations. J Am Acad Child Adolesc Psychiatry. 2011;50(10):978-90. DOI: 10.1016/j.jaac.2011.07.018. PubMed PMID: 21961773.
9. Leslie LK, Rodday AM, Saunders TS, Cohen JT, Wong JB, Parsons SK. Cardiac screening prior to stimulant treatment of ADHD: a survey of US-based pediatricians. Pediatrics. 2012;129(2):222-30. DOI: 10.1542/peds.2011-1574. PubMed PMID: 22250023; PubMed Central PMCID: PMC3269113.
10. Simpson HA, Jung L, Murphy TK. Update on attention-deficit/hyperactivity disorder and tic disorders: a review of the current literature. Curr Psychiatry Rep. 2011;13(5):351-6. DOI: 10.1007/s11920-011-0223-1. PubMed PMID: 21792581.
11. Schneebaum-Sender N, Goldberg-Stern H, Fattal-Valevski A, Kramer U. Does a normalizing electroencephalogram in benign childhood epilepsy with centrotemporal spikes abort attention deficit hyperactivity disorder? Pediatr Neurol. 2012;47(4):279-83. DOI: 10.1016/j.pediatrneurol.2012.06.009. PubMed PMID: 22964442.
12. Cheng JY, Chen RY, Ko JS, Ng EM. Efficacy and safety of atomoxetine for attention-deficit/hyperactivity disorder in children and adolescents-meta-analysis and meta-regression analysis. Psychopharmacology (Berl). 2007;194(2):197-209. DOI: 10.1007/s00213-007-0840-x. PubMed PMID: 17572882.
13. Michelson D, Allen AJ, Busner J, Casat C, Dunn D, Kratochvil C, et al. Once-daily atomoxetine treatment for children and adolescents with attention deficit hyperactivity disorder: a randomized, placebo-controlled study. Am J Psychiatry. 2002;159(11):1896-901. PubMed PMID: 12411225.
14. Hammerness P, Joshi G, Doyle R, Georgiopoulos A, Geller D, Spencer T, et al. Do stimulants reduce the risk for cigarette smoking in youth with attention-deficit hyperactivity disorder? A prospective, long-term, open-label study of extended-release methylphenidate. J Pediatr. 2013;162(1):22-7.e2. DOI: 10.1016/j.jpeds.2012.06.046. PubMed PMID: 22878114.
15. Subcommittee on Attention-Deficit/Hyperactivity Disorder, Steering Committee on Quality Improvement and Management, Wolraich M, Brown L, Brown RT, DuPaul G, et al. ADHD: Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. Pediatrics. 2011;128(5):1007- 22. DOI: 10.1542/peds.2011-2654. PubMed PMID: 22003063.
16. Cortese S, Castelnau P, Morcillo C, Roux S, Bonnet-Brilhault F. Psychostimulants for ADHD-like symptoms in individuals with autism spectrum disorders. Expert Rev Neurother. 2012;12(4):461-73. DOI: 10.1586/ern.12.23. PubMed PMID: 22449217.
17. Wigal SB, Wong AA, Jun A, Stehli A, Steinberg-Epstein R, Lerner MA. Adverse events in medication treatment-naïve children with attention-deficit/hyperactivity disorder: results from a small, controlled trial of lisdexamfetamine dimesylate. J Child Adolesc Psychopharmacol. 2012;22(2):149-56. DOI: 10.1089/cap.2010.0095. PubMed PMID: 22372513.
18. Brinkman WB, Hartl J, Rawe LM, Sucharew H, Britto MT, Epstein JN. Physicians' shared decision-making behaviors in attention-deficit/hyperactivity disorder care. Arch Pediatr Adolesc Med. 2011;165(11):1013-9. DOI: 10.1001/archpediatrics.2011.154. PubMed PMID: 22065181.
19. Lavigne JV, Dulcan MK, LeBailly SA, Binns HJ. Can parent reports serve as a proxy for teacher ratings in medication management of attention-deficit hyperactivity disorder? J Dev Behav Pediatr. 2012;33(4):336-42. doi: 10.1097/DBP.0b013e31824afea1.
20. Power TJ, Mautone JA, Soffer SL, Clarke AT, Marshall SA, Sharman J, et al. A family-school intervention for children with ADHD: results of a randomized clinical trial. J Consult Clin Psychol. 2012;80(4):611-23. DOI: 10.1037/a0028188. PubMed PMID: 22506793; PubMed Central PMCID: PMC3404236.
21. Lofthouse N, Arnold LE, Hersch S, Hurt E, DeBeus R. A review of neurofeedback treatment for pediatric ADHD. J Atten Disord. 2012;16(5):351-72. doi: 10.1177/1087054711427530.
22. Section On Complementary And Integrative Medicine, Council on Children with Disabilities, American Academy of Pediatrics, Zimmer M, Desch L. Sensory integration therapies for children with developmental and behavioral disorders. Pediatrics. 2012;129(6):1186-9. DOI: 10.1542/peds.2012-0876. PubMed PMID: 22641765.
23. McGrath PJ, Lingley-Pottie P, Thurston C, MacLean C, Cunningham C, Waschbusch DA, et al. Telephone-based mental health interventions for child disruptive behavior or anxiety disorders: randomized trials and overall analysis. J Am Acad Child Adolesc Psychiatry. 2011;50(11):1162-72. DOI: 10.1016/j.jaac.2011.07.013. PubMed PMID: 22024004.
24. Epstein JN, Langberg JM, Lichtenstein PK, Kolb R, Altaye M, Simon JO. Use of an Internet portal to improve community-based pediatric ADHD care: a cluster randomized trial. Pediatrics. 2011;128(5):e1201-8. DOI: 10.1542/peds.2011-0872. PubMed PMID: 22007005; PubMed Central PMCID: PMC3208964.
25. Lavigne JV, Dulcan MK, LeBailly SA, Binns HJ, Cummins TK, Jha P. Computer-assisted management of attention-deficit/hyperactivity disorder. Pediatrics. 2011;128(1):e46-53. DOI: 10.1542/peds.2010-2684. PubMed PMID: 21669891; PubMed Central PMCID: PMC3124100.
26. Zoëga H, Rothman KJ, Huybrechts KF, Ólafsson Ö, Baldursson G, Almarsdóttir AB, et al. A population-based study of stimulant drug treatment of ADHD and academic progress in children. Pediatrics. 2012;130(1):e53-62. DOI: 10.1542/peds.2011-3493. PubMed PMID: 22732167.
27. Lebowitz MS. Stigmatization of ADHD: A Developmental Review. J Atten Disord. 2013 [Epub ahead of print]. DOI: 10.1177/1087054712475211. PubMed PMID: 23407279.
28. Mueller AK, Fuermaier AB, Koerts J, Tucha L. Stigma in attention deficit hyperactivity disorder. Atten Defic Hyperact Disord. 2012;4(3):101-14. DOI: 10.1007/s12402-012-0085-3. PubMed PMID: 22773377; PubMed Central PMCID: PMC3430836.
29. DosReis S, Barksdale CL, Sherman A, Maloney K, Charach A. Stigmatizing experiences of parents of children with a new diagnosis of ADHD. Psychiatr Serv. 2010;61(8):811-6. DOI: 10.1176/appi.ps.61.8.811. PubMed PMID: 20675840.
30. Kellison I, Bussing R, Bell L, Garvan C. Assessment of stigma associated with attention-deficit hyperactivity disorder: psychometric evaluation of the ADHD stigma questionnaire. Psychiatry Res. 2010;178(2):363-9. DOI: 10.1016/j.psychres.2009.04.022. PubMed PMID: 20580842; PubMed Central PMCID: PMC2902633.
31. Montano CB, Young J. Discontinuity in the transition from pediatric to adult health care for patients with attention-deficit/hyperactivity disorder. Postgrad Med. 2012;124(5):23-32. DOI: 10.3810/pgm.2012.09.2591. PubMed PMID: 23095423.
32. Barkley RA, Murphy KR, Fischer M. ADHD in Adults: What the science says. New York: Guilford Press; 2008.
33. Barbaresi WJ, Colligan RC, Weaver AL, Voigt RG, Killian JM, Katusic SK. Mortality, ADHD, and psychosocial adversity in adults with childhood ADHD: a prospective study. Pediatrics. 2013;131(4):637-44. DOI: 10.1542/peds.2012-2354. PubMed PMID: 23460687.
34. Young S, Murphy CM, Coghill D. Avoiding the 'twilight zone': recommendations for the transition of services from adolescence to adulthood for young people with ADHD. BMC Psychiatry. 2011;11:174. DOI: 10.1186/1471-244X-11-174. PubMed PMID: 22051192.

35. Kielbasa W, Quinlan T, Jin L, Xu W, Lachno DR, Dean RA, et al. Pharmacokinetics and pharmacodynamics of edivoxetine (LY2216684), a norepinephrine reuptake inhibitor, in pediatric patients with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2012;22(4):269-76. DOI: 10.1089/cap.2011.0151. PubMed PMID: 22849510.
36. Lyon MR, Kapoor MP, Juneja LR. The effects of L-theanine (Suntheanine®) on objective sleep quality in boys with attention deficit hyperactivity disorder (ADHD): a randomized, double-blind, placebo-controlled clinical trial. Altern Med Rev. 2011;16(4):348-54. PubMed PMID: 22214254.
37. Li JJ, Li ZW, Wang SZ, Qi FH, Zhao L, Lv H, et al. Ningdong granule: a complementary and alternative therapy in the treatment of attention deficit/hyperactivity disorder. Psychopharmacology (Berl). 2011;216(4):501-9. DOI: 10.1007/s00213-011-2238-z. PubMed PMID: 21416235.
38. Millichap JG, Yee MM. The diet factor in attention-deficit/hyperactivity disorder. Pediatrics. 2012;129(2):330-7. DOI: 10.1542/peds.2011-2199. PubMed PMID: 22232312.
39. Hurt EA, Arnold LE, Lofthouse N. Dietary and nutritional treatments for attention-deficit/hyperactivity disorder: current research support and recommendations for practitioners. Curr Psychiatry Rep. 2011;13(5):323-32. DOI: 10.1007/s11920-011-0217-z. PubMed PMID: 21779824.
40. Hammerness P, Biederman J, Petty C, Henin A, Moore CM. Brain biochemical effects of methylphenidate treatment using proton magnetic spectroscopy in youth with attention-deficit hyperactivity disorder: a controlled pilot study. CNS Neurosci Ther. 2012;18(1):34-40. DOI: 10.1111/j.1755-5949.2010.00226.x. PubMed PMID: 21143432.
41. Zheng Y, Wang YF, Qin J, Wang LW, Zou LP, Jin XM, et al. Prospective, naturalistic study of open-label OROS methylphenidate treatment in Chinese school-aged children with attention-deficit/hyperactivity disorder. Chin Med J (Engl). 2011;124(20):3269-74. PubMed PMID: 22088519.

How to cite this article
Linn D, Murray A, Smith T, Fuentes D. Clinical considerations for the management of pediatric patients with attention-deficit/hyperactivity disorder. Ment Health Clin [Internet]. 2013;2(11):362-9. Available from: http://dx.doi.org/10.9740/mhc.n145467