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EVIDENCE-BASED BEST PRACTICES FOR THE MANAGEMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD) IN PEDIATRIC PRIMARY CARE IN SOUTH CAROLINA

Key Messages for
Management of Attention-Deficit/Hyperactivity Disorder (ADHD)

Assess input from both home and school before diagnosing ADHD in children and adolescents.

Discuss strengths/weaknesses of pharmacotherapy and behavioral therapy while considering comorbidities to individualize treatment plan.

Have functional and symptomatic improvements included in negotiated treatment goals with parents and teachers.

Do monthly follow-up in early phases of care for each new ADHD patient or new ADHD medication.

BACKGROUND

A group of physicians (including psychiatrists and primary care physicians) and clinical pharmacists was created to develop this evidence-based best practices summary for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) in pediatric primary care. A comprehensive literature review and report summarizing current evidence (Report) focusing on the management of ADHD in pediatrics was the group's primary source of information.[1] The literature review and Report utilized several clinical practice guidelines published in the United States (US) and England from 2000 through 2009.[2, 3, 4, 5, 6] This summary also provides supplemental information from additional review of primary literature and clinical consensus from the SCORxE writing group.

The information contained in this summary is intended to supplement the knowledge of clinicians regarding best practices and drug therapy to treat ADHD in children and adolescents in a pediatric primary care setting. This information is advisory only and is not intended to replace sound clinical judgment, nor should it be regarded as a substitute for individualized diagnosis and treatment. Special considerations are needed when treating some populations with certain conditions (e.g., pregnancy/breast-feeding, cardiac disease, liver and renal impairment).

ADHD MANAGEMENT AT-A-GLANCE

➢ **Initial Diagnosis**
- Functional impairment in more than one setting (e.g., home and school) with clinically significant impairment of social, academic, or occupational functioning is necessary for the diagnosis of ADHD.
- A comprehensive evaluation of ADHD usually requires 2 to 3 visits which include individual interviews with the patient and parents.
- A detailed family history is helpful in determining the nature of comorbid conditions and the presence of ADHD and other mental health disorders in family members.
- Standardized assessment instruments for parents and teachers are helpful to assess ADHD symptoms, psychiatric comorbidities and functioning.
- Response to stimulants does not confirm diagnosis – stimulants can positively impact children who do not have ADHD.

➢ **Goal of Therapy and Treatment Strategies**
- The goal of treatment is symptomatic and functional improvement.
- Discuss the benefits and limitations of medications and psychosocial interventions when used alone or in combination, and consider parent input and opinion before individualizing treatment plan.
- Stimulants are considered first-line treatment for uncomplicated ADHD ($\geq$ 6 years old) by the American Academy of Pediatrics (AAP) and American Academy of Child and Adolescent Psychiatry (AACAP).
- Initiate stimulants at low dose and titrate based on response and side effects – the optimal dose is not closely correlated with age, weight or symptom severity.
- Atomoxetine is a first-line consideration: in the presence of select comorbidities; if patients experience severe side effects to stimulants; or if parent and child preferences need to be considered.
- Psychoeducation (e.g., education about ADHD for patients and parents/guardians, tips on behavior modification techniques) is recommended along with pharmacotherapy.
- Behavior therapy alone may be recommended as initial treatment: if ADHD symptoms are mild; if the diagnosis of ADHD is uncertain; if patients are < 6 years old; or if parents oppose pharmacotherapy.
- Adding behavioral therapy to pharmacotherapy is especially beneficial for patients with comorbid conditions.

➢ **Adherence**
- Good communication with parents and patients about ADHD and the importance of medication adherence impacts effectiveness of all medication strategies.
- "Medication holidays" should be addressed so that providers are part of the decision process.
- Medications are not just to improve schoolwork but also to help with social interactions and relationships, behavioral problems, and teen driving performance.

➢ **Follow-Up**
- Rating scales (e.g., Vanderbilt Assessment Follow-Up scales) can be useful for providers, parents, and teachers to assess symptomatic and functional improvement as well as medication side effects.
- There is no evidence to support monitoring recommendations. Close monitoring with a follow-up visit within 4 weeks of a medication trial is recommended. Once patients are stable, visits may be scheduled every 3-6 months.
- ADHD commonly persists into adulthood (either as full disorder or in partial remission), but it resolves in some patients, thus the need for long-term treatment should be re-evaluated every 1-2 years.
- Re-evaluate the need for treatment if: the child is symptom free for a year; missing a stimulant dose does not cause deterioration; the child performs well on extended "medication holidays"; or no dose adjustment is needed after a large growth spurt.
- Surveillance of the mental and physical health of all family members is an important consideration.

➢ **Substance Abuse - Diversion**
- Stimulant treatment does not increase the risk of substance use disorders, it may even decrease or delay its onset.
- Consider non-stimulants or stimulant formulations with a lower abuse potential if substance abuse is a concern.
- Diversion is a growing problem, particularly among college-age students – assess potential for misuse (e.g., family members or friends) and consider non-stimulant alternatives if misuse is a concern.

ADHD

Prevalence of ADHD

ADHD is a condition now recognized to occur in both children and adults. Childhood ADHD is the most commonly referred condition to child and adolescent psychiatric services .[4] Greater than 70% of general pediatricians indicate that they are responsible for treating ADHD.[7] Boys are diagnosed with the condition approximately 4 times more frequently than girls, and the condition is said to occur in 1 of every 20 children of elementary school age in the US.[8] Using 2001 National Health Interview Survey (NHIS) data from a representative structured sample of 10,255 US children between the ages of 4 and 17, the prevalence of clinically significant ADHD symptomatology was 4.2% in males and 1.8% in females.[9] Estimates on ADHD prevalence are strongly influenced both by the actual methods used to estimate overall prevalence as well as the changes in definitional characteristics of the condition over the past forty years.[10] Prevalence rates in children and adolescents range from 1.7% to 16% depending on the source of the estimate.[5, 11] In the US there is evidence for both misdiagnosis as well as underdiagnosis of ADHD. Persuasive evidence for gender specific under- or over-diagnosis of ADHD is unavailable. To date, there appears to be little compelling evidence for systematic differences in the prevalence of ADHD among different racial groups.

Etiology

The exact etiology of ADHD is unknown. Extensive neuropsychological studies have repeatedly shown that ADHD actually results from a complex interplay between genetic and environmental factors. ADHD has been found to be the most inherited form of psychiatric disorders.[12, 13] Inadequate parenting has often been suggested as an important environmental factor. However, research suggests that the prevalent observation of greater family dysfunction[14] and environmental adversity[15] in families caring for children with ADHD may be more associated with a reaction to the condition, rather than the cause of the condition itself.

Diagnostic Criteria

The American Psychiatric Association's revised text version of the fourth edition of the Diagnostic and Statistical Manual (DSM-IV-TR)[16] has defined the condition as comprising 2 symptom groupings. The 2 groupings are termed inattention and hyperactivity-impulsivity. Each grouping consists of 9 separate symptoms.

Symptoms of inattention include: not giving attention to details or making careless mistakes; failure to listen; having difficulty sustaining attention; not following through with things; having difficulty organizing; avoidance or dislike of sustained mental effort; losing things; being easily distracted; and forgetfulness.

Symptoms of hyperactivity include: frequent fidgeting or squirming in the seat; leaving a seat when remaining seated is expected; often running about or climbing when such activity is inappropriate; having difficulty playing quietly; persistently being on-the-go; and often talking excessively; The 3 impulsivity symptoms include: having difficulty waiting in turn; often interrupting or intruding on others; and blurting out answers before questions have been completed.

The DSM-IV-TR divides ADHD into 3 types: predominantly inattentive; predominantly hyperactive/impulsive; or combined type. Diagnosis is made depending on whether 6 or more symptoms are present in either or both of the 2 groupings. Some of the symptoms need to have been present before the age of 7; the symptoms need to persist for more than 6 months and are inconsistent with developmental level; there needs to be some impairment as a result of the symptoms in 2 or more settings (e.g., school, home or occupational settings); and there needs to be clear evidence of clinically significant impairment in social, academic, or occupational functioning. The symptoms should not occur exclusively when another pervasive disorder is being experienced (e.g., developmental disorders, psychotic disorders, schizophrenia) or when a different mental disorder better accounts for symptoms.

Initial Psychiatric and Medical Evaluation

A primary goal of clinic visits is to gain an understanding of the full range of problems and their history, in particular the child's developmental history. A full medical assessment is necessary to uncover any other undiagnosed problems. Laboratory or neurological testing is generally not indicated. There are few medical conditions that masquerade as ADHD, and the vast majority of patients with ADHD will have an unremarkable medical history.[4]

Family, general health, social, educational, and demographic information need to be documented. Understanding the way that families have coped and managed the problems that they have faced is critical. To achieve this understanding, separate interviews with different family members are often necessary. The opportunity to see the child and parent individually is valuable. AAP states that a full evaluation of ADHD usually requires more than one visit, often 2 to 3 visits.[2]

An essential step for diagnosis of ADHD in children of school age is to obtain input from their teachers or other relevant adult school/educator staff. The goal of evaluation in this particular context is to gain information on social and academic functioning. Frequently there are significant discrepancies between parent and teacher ratings. These discrepancies do not preclude the diagnosis of ADHD. The AAP suggests obtaining additional information from other informants, such as former teachers, religious leaders, or coaches, to reconcile discrepant findings and evaluate if DSM-IV criteria are met.[2]

Symptom counts for the DSM-IV-TR ADHD inattention and/or hyperactivity/impulsivity and their impact on functioning should be documented. This can be done in simple direct fashion, or through use of one of the ADHD rating scales (see Rating Scales section below).

Comorbidities

The diagnosis of ADHD is commonly associated with other comorbid conditions that may require further evaluation. Common comorbidities associated with ADHD are: language difficulties or learning disabilities (25-35%); oppositional defiant disorder (ODD) or conduct disorder (CD) (54-84%); anxiety disorder (up to 33%); depression (up to 33%); smoking or other substance use disorder (15-19%); and tic disorders (20-34%).[4, 17, 18] The prevalence of mania in patients with ADHD remains controversial and challenging. It is critical to identify any comorbid conditions and determine if they are primary or secondary to the diagnosis of ADHD. Identifying the comorbid conditions may change clinical treatment, pharmacologic decisions, and prognosis.[4] An important additional point beyond the need to identify and manage such comorbidities in children with ADHD, is the need to ensure that ADHD, depression, and anxiety, prevalently found in parents and caregivers of children with ADHD, are similarly identified and effectively managed.[6]

Rating Scales

Rating scales provide greater depth to the clinical interview and collateral information on ADHD symptomatology and functional impairment.[6, 19, 20] Global, nonspecific questionnaires and rating scales are generally not sufficiently sensitive and specific for diagnosing ADHD.[2] Multiple ADHD rating scales that have adequate reliability are available and include the Conners Rating Scales-Revised – CRS-R; ADHD Rating Scale-IV – ADHD RS-IV; Swanson, Nolan and Pelham-IV questionnaire – SNAP-IV; Vanderbilt ADHD Teacher Rating Scale and Vanderbilt ADHD Parent Rating Scale - VADTRS and VADPRS, respectively. Each rating scale has individual features which may make it particularly suitable to individual circumstances. The Vanderbilt scale (included in the AAP Toolkit for ADHD) is a widely used scale that provides a DSM-IV symptom count for the 2 sub-scales of inattention and hyperactivity/impulsivity, with symptoms being rated as occurring 'occasionally', 'often' or 'very often'. Both teacher (VADTRS) and parent (VADPRS) versions of the Vanderbilt scale assess ODD/CD, provide a screening for anxiety/depression, and include an assessment of functioning. The Vanderbilt scale has good psychometric properties in a high-risk referred sample, but it has not been validated in a low-risk sample such as in general pediatric clinic samples.

ADHD ALGORITHM

<u>Use of Algorithm</u>

The ADHD algorithm (Figure 1) provides sequenced medication recommendations for children 6 and older based on best available evidence or consensus of the SCORxE writing group where evidence is lacking. The algorithm's format and the approach of using algorithms to assist with optimal treatment decisions are based on the Texas Medication Algorithm Project and the Texas Children's Medication Algorithm Project.[21]

A thorough evaluation and detailed history from various informants (including psychosocial and developmental history, level of family functioning, detailed medical history) and comprehensive physical assessment (including a careful cardiac examination) should be performed to diagnose ADHD prior to making treatment decisions. Patients may enter the algorithm at different stages depending on prior treatment history and response, relevant psychiatric factors (e.g., comorbidity) and general medical factors (e.g., age, concomitant medications or illnesses). Each stage of the algorithm represents a trial of a different medication. Different formulations of a medication or combinations of different formulations may be tried within a given stage to optimize response. Progression to different stages should be considered in cases of insufficient symptom improvement or intolerable side effects. Psychosocial therapy is an option before starting or in combination with pharmacotherapy at any stage in the algorithm. If adequate trials of stimulants and atomoxetine monotherapy fail to produce satisfactory response, an ongoing and thorough diagnostic re-evaluation with special attention and screening for comorbid psychiatric disorders is recommended to confirm diagnosis and identify other confounding disorders.

TREATMENT OPTIONS FOR ADHD

There is evidence supporting psychosocial and pharmacologic interventions in the treatment of ADHD. The choice of first-line intervention depends on the preferences of the child and/or parent, severity of disturbances of peer relationships, school and classroom environments, comorbidities, effectiveness of interventions, side effects, cost, and availability.[6, 22, 23] Evidence generally suggests greater efficacy with stimulants than psychosocial interventions; the overall difference in efficacy is small, however, and it is unclear if the differential benefits are sustained over time.[6]

AACAP generally recommends pharmacotherapy as first-line, along with psychoeducation of parents (usually delivered in the context of medication management and involving education about ADHD and general advice to parents and children). Behavioral therapy may be recommended as an initial treatment: if ADHD symptoms are mild with minimal impairment; if the diagnosis of ADHD is uncertain; if patients are less than 6 years old; or if parents oppose pharmacotherapy.[4]

Combining psychosocial interventions with pharmacotherapy does not yield substantial additional benefits in patients with ADHD alone.[24] However, the NIMH Multisite Multimodal Treatment study (MTA) provided strong evidence that patients with ADHD and comorbid disorders (such as anxiety disorder, ODD or CD) and/or psychosocial stressors benefit from an adjunctive psychosocial intervention.[4]

Long-term functioning does not seem to be affected by the type or intensity of initial ADHD treatment. In the MTA study, early symptom patterns appeared to be more prognostic for outcomes at the 8 year follow-up. Children with behavioral or socio-demographic advantage who had had the best response to any of the treatments had the best prognosis.[25]

Parental ADHD, anxiety, depression, and substance abuse may be contributors to family dysfunction, complicating effective management of the child with ADHD.[26] The AACAP Guidelines point out that such issues of parental health need to be evaluated and addressed when needed.[4]

NON-PHARMACOLOGIC THERAPY

Psychosocial Interventions

Parent/Child Interventions. Several interventions based on various social, learning, and behavioral principles have shown moderate beneficial effects for children with ADHD: parent training, cognitive behavioral therapy (CBT), social skills training, and self-instructional manuals. Beneficial effects of psychosocial interventions for ADHD, however, do not appear to transfer to the classroom environment. Generally, therapist-led psychosocial interventions are delivered following a pre-specified curriculum over the course of 8 to 12 sessions (either individually or in groups) lasting 1 to 2 hours each.[6] The most commonly evaluated psychosocial intervention is behavioral parent training. This is a technique that teaches parents how to apply child management strategies, improve their parenting skills, and deal better with specific problem behaviors.[27] Behavioral therapy involves use of rewards and other re-enforcers which encourage a child to implement changes in targeted motor, impulse or attentional control.[26]

For the preschool-age group, good evidence exists that individual parent training is helpful to improve core ADHD symptoms and conduct problems.[6]

In school-age children, the clinical evidence supports interventions using mixed behavioral and cognitive training, and social skills training group sessions for children along with parallel group sessions for parents.[6]

No controlled data are available for adolescents; however, it is likely that CBT/social skills therapy interventions would be applicable to young people with ADHD.[6]

School/Teacher Interventions. A recent review of studies of teacher and school interventions concluded that teacher-led interventions for children with ADHD (e.g., giving effective commands) have large beneficial effects on conduct problems; the beneficial effects on children with ADHD remain inconclusive.[6]

Psychoeducation

Psychoeducation draws on elements of psychosocial interventions described above, but is much more limited in scope and intensity; it is usually delivered by the provider in the context of medication management. Psychoeducation aims to provide information to the parent and child about the diagnosis of ADHD, help parents anticipate developmental challenges that are difficult for ADHD children, and give general advice to the parent and child to help improve the child's academic and behavioral functioning.[4] General advice may include: teaching the use of behavior modification techniques such as simple commands; rewards for positive behavior; and consequences for undesirable behavior. (Table 1)

Diet Modifications

Dietary factors have attracted much public attention as a potential cause or contributor to ADHD prevalence. As with other environmental factors and their influence on ADHD, a complex picture has emerged. There is no compelling evidence that sugar affects behavior or cognition. Despite the emergence in 2007 of more convincing information supporting the long-standing contention that food colorings and additives exacerbate hyperactivity in children,[28] there is little support in current guidelines for dietary interventions as a means of management of ADHD. The quality of evidence for dietary interventions is generally poor. The evidence that elimination or supplementation diets, when compared with placebo, may reduce ADHD symptoms has been inconclusive.[6] A new study providing support for elimination diets reported that children who showed significant improvement in ADHD symptoms on a restricted diet had significant relapse upon re-challenge with the eliminated foods.[29]

Clinical assessment should include asking about foods or drugs that appear to influence a child's hyperactive behavior. Healthcare professionals should advise parents to keep a diary of food and drink intake and ADHD behavior. If the diary supports a relationship between specific foods/drinks and behavior, then strategies such as specific dietary eliminations may be tried under professional supervision. The possibility of symptom benefit associated with removal of specific foods, artificial colorings and/or preservatives must be balanced with the additional stress placed on the family to explore and carry out dietary modifications.[30]

PHARMACOTHERAPY

First-Line Medications

Stimulants and atomoxetine are considered first-line medications in the treatment of ADHD in school-age children and adolescents. Although some amphetamine formulations are FDA-approved for use in children under 6 years of age, there is a lack of evidence of efficacy with amphetamines, and limited evidence supporting the efficacy of methylphenidate in this age group.[4, 5] After consideration and analysis of all research on use of pharmacotherapies in preschoolers, the British National Institute for Health and Clinical Excellence (NICE) Guidelines recommend against the use of ADHD medications in pre-school children.[6] In their practice parameter, AACAP summarizes the evidence with methylphenidate, and neither advises for or against its use in children under 6 years of age. They do caution about higher rates of side effects in this age group, and cite a general recommendation for more conservative dose titration and lower effective doses than school-age children.[4]

Stimulants. There are 2 stimulant medications currently available, methylphenidate (MPH) and amphetamines (AMP). The benefits of short-term stimulant therapy on ADHD symptoms are well documented. Symptomatic improvement has been observed in 65% to 75% of patients randomized to receive stimulants versus only 5% to 30% of those assigned to placebo.[4] When clinical symptom-reduction response to stimulant therapy has been quantified via rating scales relative to placebo a mean effect size of about 1.0 has been observed, representing one of the largest effect sizes for any psychotropic medication.[4] Stimulant treatment has been associated with small and moderate effect size on academic and social functioning improvement, respectively.[31] Of note, stimulant effects on human behaviors and cognition are not restricted to patients with ADHD; stimulants can positively impact children who do not have ADHD.[32]

Stimulants are available as short-acting, intermediate-acting, and long-acting formulations. Although pharmacokinetic characteristics of individual formulations impact timeline and duration of action, overall efficacy does not differ; adherence and persistence with therapy is improved, however, with long-acting formulations.[33, 34, 35, 36, 37] Different formulations of the same stimulant may be tried to optimize response and tolerability. Short-acting formulations are less expensive and offer dosing flexibility during initial treatment, especially in small children; disadvantages include higher risk of abuse/misuse and social stigmatization stemming from administration at school. Intermediate-acting formulations provide a longer duration of action (up to 8 hours), but often require a second dose administered at school. Long-acting formulations allow for once daily dosing and are less likely to be abused; disadvantages include potential adverse effects on evening appetite and sleep, and higher cost. Short- or intermediate-acting formulations can be used to augment long-acting formulations early in the day (e.g., for faster onset in the morning) or later in the day (e.g., management of late afternoon "rebound").[38]

Within the stimulant class, there are more studies of MPH than AMP. Evidence suggests that AMP may be moderately more efficacious than MPH; this should be balanced with evidence of patient preference for MPH and wider spectrum of neural bioactivity with AMP.[5, 6, 39] There are currently no methods to determine which patients or which symptoms will respond better to one or the other stimulant group.[4] If treatment with maximum tolerated doses of a stimulant fails, then after review of clinical circumstances, the option remains to switch the patient to another formulation within the same stimulant class or to another stimulant class.

Atomoxetine, a selective norepinephrine reuptake inhibitor, may be considered as first-line medication based on parent/child preferences or the presence of comorbidities such as anxiety, tics, or active substance abuse problem. Atomoxetine is an effective alternative for patients who experience severe side effects to stimulants.[4] However, evidence suggests that atomoxetine is less efficacious than stimulants[4, 5, 6] In a meta-analysis of atomoxetine and stimulant studies, the effect size for atomoxetine was 0.62 compared with 0.91 and 0.95 for immediate-release and long-acting stimulants, respectively.[4, 40] Atomoxetine has a slower onset of action than stimulants; clinical changes are gradual and maximum effect may not be reached for 6 to 8 weeks.[38]

Second-Line Medications

Alpha-2 agonists (α₂-agonists), clonidine and guanfacine, are available as immediate-release and extended-release formulations (ER). ER formulations of clonidine and guanfacine were recently FDA-approved for ADHD monotherapy or adjunctive therapy to stimulants. Clonidine and guanfacine (as immediate-release tablets) have been used off-label for ADHD for many years. In 4 out of 6 controlled studies available by 2007, clonidine was described as providing benefits in management of ADHD.[41] An early meta-analysis of mostly poor quality studies suggested that for symptoms of ADHD, clonidine has a small to moderate effect size, less than that observed with stimulants.[42] The effect size as well as side effect prevalence of guanfacine appear to be dose related. The effect size at higher dosages exceeds that observed with other non-stimulant treatments but at the cost of substantial side effect levels.[43, 44, 45]

Other Agents. Bupropion, tricyclic antidepressants (TCAs), and modafinil are sometimes used in the treatment of ADHD even though they do not have an FDA indication for ADHD. The evidence base for these medications is far weaker, and their effect sizes are considerably less than for the FDA-approved medications.[6, 46, 47] Serious adverse effects observed with modafinil have resulted in its parent company and the FDA recommending that it not be used in children.[48]

Initial Dosing

Generally, ADHD medications are initiated at low doses and titrated gradually based on response and tolerability (Tables 2 and 3). Stimulant doses can be titrated upwards every one to 3 weeks, until either symptoms remit, a maximum dose is reached, or side effects limit further upward dose adjustment.[4] Stimulant onset of effect is rapid; however, a 1 week trial or longer at adequate therapeutic dose may allow for better assessment of full effect. Of note, there does not appear to be a therapeutic window for response to stimulant therapies; effective dosage is not closely correlated with age, weight or symptom severity.[38] Atomoxetine can be increased to target therapeutic dose after a minimum of 3 days according to FDA labeling. Compared to stimulants, onset of effect is slower for atomoxetine and α₂-agonists (e.g., 2 weeks or longer), and maximum effect may not be reached for several weeks (e.g., 6 weeks or longer) at an adequate therapeutic dose.[38, 49, 50, 51]

Medication Changes or Discontinuation

Medication doses should be maximized as tolerated for an adequate period of time before changing treatment regimen due to insufficient symptomatic and functional improvement. (Tables 2 and 3) Guidelines for switching between ADHD stimulants or different stimulant formulations are provided in Table 4. Particular caution is recommended in discontinuing clonidine and guanfacine; the dose should be gradually decreased to avoid sudden increases in blood pressure.

Side Effects

Both MPH and AMP share a set of common side effects which are usually mild or temporary, and generally acceptable in light of the relief from ADHD symptoms achieved. Side effects that tend to persist in long-term treatment with all stimulants include insomnia, and decreased appetite and/or weight loss.[4] Atomoxetine may have less pronounced effects on appetite and sleep than stimulants, but it is associated with somnolence and more vomiting.[5] Long-acting formulations of clonidine and guanfacine are associated with a high prevalence of side effects including sedation, irritability, and reduction in heart rate and blood pressure. Refer to Table 5 for common and serious side effects of ADHD medications and management considerations.

Medication holidays. If a time period off stimulant medication ("medication holiday") or a reduced dose is required to minimize a side effect, consider planning it during long vacations,

summertime, or long weekends to minimize impact on school performance. Clinically, it is observed that interrupting stimulant medication every weekend may, in fact, increase side effects. Taking the medication each day will help develop a tolerance toward side effects. Except for stimulants, ADHD medications need to be taken continuously to maintain clinical effect.

Growth impairment. There is now general agreement that a height deficit of approximately 1cm per year can be expected while taking stimulant medication during the first one to 3 years of treatment.[4, 52, 53] Slower growth rates appear to apply to both boys and girls,[54] and a significant relationship exists between growth in height and weight as a result of pharmacotherapies.[55, 56] It appears that children with a higher body mass index (BMI) tend to lose more weight on stimulant medication than children with a lower BMI.[57] With prolonged childhood ADHD stimulant treatment for 2 to 3 years or more, growth rates tend towards normal for stimulant-treated children with ADHD.[56] When children stop stimulant therapies a growth catch-up phase appears to occur.[58] Adults who received stimulant medication in childhood appear to have heights which are comparable to adults who did not receive stimulant medication.[59] Among childhood ADHD-stimulant-treated patients, it remains uncertain to what extent time lapses in medication adherence affect the final adult height and weight. The AACAP recommends that patients treated with ADHD medications should have their height and weight monitored throughout treatment using growth charts labeled with lines showing major percentiles. Furthermore, AACAP states that an aberrant growth trajectory would be indicated by a change in weight or height that crosses 2 percentile lines.[4]

Cardiac events. Concerns of sudden cardiac death with stimulant therapy have been raised.[60] However, the rate of sudden death in children taking stimulants or atomoxetine does not appear to exceed the base rate of sudden death in the general population. Although a causal relationship has not been established, stimulants should generally not be used in children and adolescents with preexisting heart disease or symptoms suggesting significant cardiovascular disease. Prior to initiation, a detailed medical history of the child and family should be obtained, and a physical exam with special attention to the cardiovascular system should be performed. Additional tests and referral to a pediatric cardiologist are indicated prior to initiation of stimulant therapy if any symptoms or risk factors for cardiovascular disease are detected.[61, 62]

Psychiatric adverse events to ADHD medications have been reported to the FDA. In controlled trials, these events were slightly more common in the active drug group relative to placebo, but with the exception of suicidal thinking with atomoxetine, these differences did not reach statistical significance. The risk of suicidal thinking was 4 out of every 1,000 in the atomoxetine group versus none in the placebo group. The risk is small, however, it should be discussed with patients and family. In addition, patients should be monitored for the onset of suicidal thinking, especially in the first few months of medication use.[63] Controlled trials of stimulants do not support the widespread belief that stimulant medications induce aggression. Aggressive acts and antisocial behavior usually decrease with stimulant treatment of ADHD. Clinicians should distinguish between aggression/emotional lability that is present when the stimulant is active (which may indicate excessive dosage) and increased hyperactivity/impulsivity in the evening or at the end of any dosing interval when the medication is no longer effective (commonly referred to as "rebound"). The latter may be addressed by administering a small dose of short-acting stimulant in the late afternoon.[4] Children who experience emotional lability, irritability (e.g., feeling too 'wired') or feel too serious, tired, dull, flat, or listless when the stimulants are active, may benefit from a dose reduction or a switch to an alternate agent.[38]

Hepatotoxicity. Rare cases of hepatotoxicity, including liver failure, have been reported with the use of atomoxetine.[5, 64] Routine monitoring of hepatic function is not required during atomoxetine treatment; however, liver function tests should be checked upon the first sign or symptom of liver dysfunction. Patients who develop jaundice, dark urine, or other symptoms of hepatic disease should discontinue atomoxetine.[65]

Abuse Potential. Stimulants are controlled drugs that have the potential for abuse and diversion. Oral use carries very little risk of inducing euphoria; intravenous administration or inhalation can produce a 'high'. Extended-release formulations of MPH and AMP produce a slower rise in plasma concentrations over a longer duration, thus, they may result in less potential for abuse.[66] In the case of short- and long-acting MPH preparations, this point has been demonstrated through use of a 'likeability' index in which the long-acting form was shown to be significantly less 'likeable' than the short-acting form.[67] People diagnosed in childhood with ADHD are up to twice as likely to develop a substance abuse disorder relative to people who have never had an ADHD diagnosis.[68] The presence of ADHD comorbid with ODD or CD amplifies this risk even further.[69] Overall, stimulant treatment does not appear to increase the risk of developing substance use disorders. Stimulant treatment may even reduce the risk of developing a substance use disorder or delay its onset, but more research is needed before firm conclusions can be drawn. Non-stimulants are not considered to have a potential for euphoria or for inducing dependence.[6]

Duration of Treatment

Treatment of ADHD should continue as long as symptoms are present and cause functional impairment.[4] Limited long-term studies (up to 2 years) show that benefits are maintained during treatment with ADHD medications. However, some patients with ADHD (particularly those with comorbidities) may deteriorate while on ADHD medication, while other patients who have benefited from medication treatment may no longer need it.

AACAP recommends reevaluation of treatment if a patient with ADHD has been symptom free for at least one year. Furthermore, they suggest that "signs that the ADHD has remitted include lack of any need to adjust dose despite robust growth, lack of deterioration when a dose of stimulant medication is missed, or new-found abilities to concentrate during drug holidays. Low-stress times such as vacations are a good time to attempt a withdrawal from medication, but parents should assign some cognitively demanding tasks (reading a book, practicing mathematics problems) to be sure that remission has occurred."[4]

Special Considerations for Treatment

ADHD subtypes (inattentive, hyperactive/impulsive, or combined) may impact response or dose-response to pharmacotherapy, although this has not been studied systematically. Many of the studies carried out over the decades have either used earlier DSM classification systems, or alternatively not clearly differentiated ADHD subtypes in their study populations.[5] Limited evidence suggests greater symptomatic improvement at higher doses of MPH (≥ 30 mg daily) in children with combined subtype of ADHD, whereas greater symptomatic improvement may occur at lower doses (≤ 18 mg daily) in ADHD inattentive subtype or in attention deficit disorder without hyperactivity.[5]

Comorbidities. The presence and severity of comorbidities may influence the choice of ADHD medications. (Table 6)

Tics. The FDA currently stipulates that most stimulant medications are contraindicated in patients who have a tic disorder or a family history of Tourette's syndrome.[70] The contraindication was a result of early reports that were likely confounded, since many children with ADHD suffer from tics irrespective of their stimulant therapy. It is now recognized that symptoms of ADHD typically precede the emergence of tics by 2 to 3 years.[71] Recent double-blind clinical trials of both immediate-release and long-acting stimulants have not found that stimulants increase the rate of tics relative to placebo. Children with comorbid ADHD and tic disorders, on average, show a decline in tics when treated with a stimulant. Stimulants offer the most immediate improvement of ADHD symptoms; α2-agonists (clonidine or guanfacine) offer the best combined improvement in both tic and ADHD symptoms. AACAP recommends trying an alternative stimulant or non-stimulant if a patient has treatment-emergent tics during a trial of a given stimulant. Combination of a stimulant and α2-agonist (clonidine or guanfacine) may be considered if the patient's ADHD symptoms respond adequately only to a stimulant medication that induces tics.[4]

Substance Abuse. The use of stimulants in people who have an active substance abuse disorder is not an absolute contraindication. In patients with ADHD and comorbid substance abuse, evidence shows that stimulant treatment leads to improvement in ADHD symptoms and no worsening of substance abuse. While the presence of alcohol or cannabis consumption may not be a contraindication to stimulant prescribing, the presence of a stimulant use disorder (e.g., cocaine) may pose a significant risk.[6] Generally, patients with significant active substance use disorders should only be prescribed a stimulant by a mental health specialist.[38]

Special Considerations for Management

Diversion of prescribed stimulants for non-therapeutic purposes (e.g., recreational, academic performance enhancement) has become a significant contemporary issue. Over half of college students prescribed a stimulant have been approached to sell, trade, or give away their medication.[72] In a large US population survey, the past year prevalence of non-medical use of ADHD medications has been estimated at approximately 2%. For respondents between the ages of 18 and 25 years, this prevalence was found to be 4.3%. Most users for recreational purposes had never had a prescription themselves but reported use on multiple occasions throughout the previous year. Two-thirds of respondents had received medications from family or friends who gave away some of their prescribed supplies. One-third had taken or stolen from friends and family. One-fifth had obtained ADHD medications through fraudulent prescriptions obtained by fabrication of symptoms, or through other means via their physician. Five percent had used the internet for supplies.[73] Initially assess for potential misuse/diversion by gathering a detailed social and family history; continue to assess on a regular basis. Educate parents and children, especially adolescents and college-age students, about diversion and its consequences. Carefully monitor use of stimulant medication and consider non-stimulant alternatives if misuse becomes a concern.

Adherence. Starting and stopping ADHD medications is common; the child's refusal to take medication is often a significant challenge.[34, 74, 75] In the MTA study, for example, approximately half of the parent-reported adherence to the medication regimen was not borne out by same-day salivary MPH sampling.[76] It has been suggested that it is natural for parents to wish to contrast time on and off stimulant therapy to help them make decisions about the necessity for ongoing medication.[77] The widely discussed concerns for children while taking ADHD medications about growth compromise, addiction, sudden cardiac death, and suicide linked to ADHD medications greatly influence parents' indecision on all matters related to adherence to prescribed ADHD medication.

The availability of effective once- or twice-a-day dosed medications has been shown to improve adherence, continuity, and persistence.[33, 34, 78] To some degree, this may be due to reduced need for emergency contact with school teachers during the working day, as well as reduced stigma associated with the need to consume medications while at school.[77, 79] Encourage parents and children (especially older) to discuss any ambivalence they may have regarding the use of stimulant medication. Inform the family that there is very limited evidence supporting the efficacy of using "medication holidays" to control side effects. If non-adherence is an issue, attempt to understand the reason for non-adherence and work with the family to find a solution. If ease of administration is important, then once-daily or twice-daily formulations may be beneficial.

Less information is available about adherence to psychosocial interventions for ADHD. In the MTA study, more than a third of the participants allocated to either the 'behavior' or 'combined behavior/medication management' groups did not achieve the 75% adherence to the behavioral training regime prescribed by the study protocol.[24] The extent, depth, and regularity with which a caring physician has been able to empathically communicate with family members about the condition and its management is a key factor which modulates all subsequent outcomes from either behavioral or medication strategies.[77, 80]

EVALUATION OF PATIENT RESPONSE

Use of Measurement-Based Care
Measurement-based care (MBC) promotes the use of rating scales or questionnaires at every visit to measure symptoms, functioning, side effects, and patient adherence as well as guide tactics to modify dosage and treatment duration. Some scales only evaluate symptoms of ADHD without assessing functional impairment, thereby shifting the focus away from the core functional problems being experienced by the child and their family. Several rating scales may be suitable for use in clinical practice. The Vanderbilt rating scale, both teacher (VADTRS) and parent (VADPRS) versions, which can be used for initial screening assessment, is also available in a follow-up assessment version. These follow-up versions assess symptoms, functioning, and side effects, making them useful tools to evaluate overall response to treatment in 2 different settings. They are relatively new, so despite strong psychometric properties, their utility has not been fully evaluated, particularly with regard to sensitivity to change in response to treatment. Another potential disadvantage is that there is not a self-report version, which could be useful for use with older children and adolescents.

Goals of Therapy
Goals of therapy should include both symptomatic as well as functional improvement across all settings (home, social, academic). Academic performance (e.g., reading, writing, mathematics) is an important goal of therapy, but ADHD affects more than grades in school. It affects self-esteem, substance abuse risk, other risk-taking behaviors/safety (e.g., crossing streets, riding bicycle, driving), and relationships with peers, parents, and teachers. Good communication with parents and patients about the importance of medication adherence and the need to take medications consistently to optimize response is crucial.

Visit Frequency
There is no evidence to support recommendations on monitoring frequency. Guidelines recommend close monitoring of efficacy and side effects upon initiation of medication trial; weekly follow-up (by phone or visit) may be necessary until medication is optimized. A follow-up visit is recommended within 4 to 6 weeks of initial medication trial to review the care plan. Once stable, visits may be scheduled every 3 to 6 months depending on the degree of dysfunction, comorbidities, and apparent adherence to care plans.[18, 38] The Children's Health Insurance Program Reauthorization Act (CHIPRA) quality indicator on follow-up care for children on newly prescribed ADHD medications measures follow-up visit within 30 days of starting the medication and 2 additional follow-up visits during the next 9 months, one of which may be by telephone.[81]

REFERRAL TO A PSYCHIATRIST

Patients with the following characteristics should be considered for referral to a mental health specialist:
- Children under 6 years of age.
- Clear adverse behavioral response to stimulants (e.g. psychosis, mania, severe dysphoria), particularly prior to puberty.
- Comorbid substance use disorder, conduct disorder, or bipolar disorder.
- Failure to respond to adequate trials of MPH, AMP, and atomoxetine.

Figure 1. ALGORITHM FOR THE TREATMENT OF ADHD[1,2]

Stage 0
Diagnostic Assessment[3] &
Family Consultation
Regarding Treatment
Alternatives

→ Non-Medication Treatment Alternatives[4]

Stage 1
MPH, AMP, Atomoxetine[5]

Partial Response or Non-response

Stage 2
MPH, AMP, Atomoxetine[5]
(Choose medication not used in Stage 1)

Partial Response or Non-response

Stage 3
MPH, AMP, Atomoxetine[5]
(Choose medication not used in Stages 1 or 2)

Partial Response

Stage 4
MPH/AMP + α$_2$-agonist
MPH/AMP + atomoxetine[6]

Non-response

Referral to mental health specialist[2] or
α$_2$-agonist

**For further management of a non-responsive
patient, refer to a mental health specialist[2]**

Important Treatment Considerations

Selection and Initiation
Include psychoeducation (e.g., general advice and education about ADHD) along with pharmacotherapy.

Start stimulants at low dose and titrate based on response and side effects.

Stimulant onset of effect is rapid; however, a 1 week trial or longer at adequate therapeutic dose may allow for better assessment of full effect.

Compared to stimulants, onset of effect is slower with atomoxetine and α$_2$-agonists (e.g., 2 weeks or longer), and maximum effect may not be reached for several weeks (e.g., 6 weeks or longer) at an adequate therapeutic dose.

For Partial Response or Non-Response
Rule out non-adherence as reason for treatment failure at every stage.

Different formulations of the same stimulant may be tried within a given stage to optimize response and tolerability.

If treatment with maximum tolerated dose for an adequate period of time fails, switch to alternate medication.

If adequate trials of stimulants and atomoxetine monotherapy fail to produce satisfactory response, evaluate accuracy of original diagnosis and possibility of undiagnosed comorbid conditions.

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1. This algorithm is for the management of children 6 years of age or older and does not address the management of ADHD with comorbidities (*see* Table 6).
2. Consider referral to mental health specialist at any stage if: 1) clear adverse behavioral response to medications (e.g., psychosis, mania, severe dysphoria), particularly prior to puberty; 2) comorbid substance use disorder, conduct disorder or bipolar disorder.
3. Parent and teacher rating scales (e.g., Vanderbilt Assessment scales) are helpful to assess ADHD symptoms, psychiatric comorbidities and functioning.
4. Behavioral therapy is an option: 1) before starting medication, especially if ADHD symptoms are mild, the diagnosis is uncertain, or parents oppose pharmacotherapy; 2) in combination with pharmacotherapy, especially with comorbid conditions.
5. Consider atomoxetine as an alternative to stimulants: 1) in the presence of comorbidities such as anxiety, active substance abuse problem, or tics; 2) if patients experience severe side effects to stimulants; 3) based on parent and child preferences.
6. Stimulant in combination with atomoxetine is based on clinical consensus of the SCORxE Writing Group.

Key

AMP (amphetamines)
dextroamphetamine
lisdexamfetamine
mixed amphetamine salts

MPH
methylphenidate
dexmethylphenidate

α$_2$-agonists (alpha-2 agonists)
clonidine
guanfacine

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Table 1. SURVIVAL STRATEGIES AND BEHAVIOR MODIFICATION TECHNIQUES FOR MANAGEMENT OF ADHD

➢ **BE REALISTIC** *by setting achievable goals; unreachable goals set up failure.*
➢ **BE CONSISTENT** *from moment to moment with daily routines, rules and discipline.*
➢ **MAINTAIN THAT CONSISTENCY** *caregiver to caregiver and setting to setting as much as possible.*
➢ **BE PATIENT** *when teaching new behaviors since learning takes time. Progress will be gradual.*
➢ **GIVE PRAISE** *for positive behaviors MUCH more than criticizing negative behaviors.*

EVERYDAY SURVIVAL STRATEGIES FOR MANAGING ADHD	
Modify Your Expectations	**Be realistic about situations your child handles well and adjust accordingly.** √ If you cannot go to the store without your child asking for things constantly, explore ways to shop without your child such as trading favors with a friend.
Identify Success	**In situations/circumstances where your child does well, let him/her do more of it.** √ If your child does homework best lying on his/her belly with work spread out, allow it and figure out how to make that happen.
Get Moving	**Physical activity gets the energy out to calm an anxious brain or stimulates to arouse a bored brain.** √ Aim for 20 minutes of physical activity (actually moving) every couple hours, outdoors when possible. Use small bursts (e.g., 30 jumping jacks, walk to the mailbox) for quick breaks.
Fidget to Focus	**Allow your child/teen to fidget or squirm when working.** √ Allow child to doodle, sit on feet, or use gel-filled squeeze ball if it helps child pay attention.
Apply the Breaks	**Schedule and/or allow your child to take breaks during homework or chores – chunking time can actually save time and improve quality of time and interactions.** √ *"Finish your math, then you can shoot basketball for 10 minutes."* Continue with similar "chunks" of work/breaks *(e.g., "Spend 20 minutes on vocabulary, then you can call a friend").*

BEHAVIOR MODIFICATION TECHNIQUES	
Simple, Specific Commands	**Set a specific, one-step command. Be firm. Do <u>not</u> state as a question.** √ <u>Child</u>: *"It's time to brush your teeth, now,"* **NOT** *"Get ready for bed, okay?"* √ <u>Teen</u>: *"Study class notes for the test tomorrow,"* **NOT** *"Go study for your test."*
Positive Reinforcement	**Praise specific behavior and give rewards/privileges immediately afterwards.** √ <u>Child</u>: *"I'm happy you listened the <u>first time</u> I asked you to pick up your clothes. You can play 15 minutes on your Xbox."* √ <u>Teen</u>: *"I like that you came home on time. Next Saturday you can extend your curfew 30 minutes."* (May delay rewards/privileges with teen)
Token Economy	**Award privileges/prizes/money for positive behavior or tasks based on net total of earned tokens/stars/points. Earned rewards are never lost.** √ <u>Child/Teen</u>: Set the total number of stars per day (child) or per week/month (teen) to receive privilege or prize. At first, set easily achievable goals to get "buy-in." Teens can earn incremental rewards (e.g., extend curfew gradually). [Daily prize: TV show, choose car radio station. Longer: new privilege, mall outing, new toy]
Consequences for Negative Behavior	**Take away reward or privilege for unwanted or problem behavior.** **Tell child/teen what to expect in advance and be consistent and fair.** √ <u>Child</u>: *"Play time was over 5 minutes ago. Time to put your toys away. If toys are not put away when the timer goes off, you'll lose 30 minutes of TV.* √ <u>Teen</u>: *"Be home by 10:30 tonight. If you miss curfew, you can't use the car tomorrow night."*
Time-Out	**Give one minute per age of child (2-12 years old) in a quiet, non-distracting, set area.** √ Useful for disruptive behaviors (e.g., spitting, hitting, kicking, screaming).
Tick-Tock to Time on Task	**Use visual/auditory aids to help child stay on task or help with transitions.** **Also useful for time-out.** √ <u>Child</u>: Set egg timer for 15 minutes of play*; say, "When the timer rings, put your toys away."* √ <u>Child/Teen</u>: *"In 10 minutes, we are going home."* LATER*: "In 5 minutes, we leave."* FINALLY: "*Time to go.*" (Useful to help transition to different activity/task)

References: 82, 83, 84, 85, 86, 87, 88

Table 2. STIMULANT ADHD MEDICATION DOSING GUIDELINES

Medication* (Brand Name)	Onset (minutes)	Duration (Hours)	Initial Dose *(Titration every 7 days)*	Doses per Day	Maximum Daily Dose	Comments
Methylphenidate						
Short-Acting						
Methylphenidate (Ritalin®, Methylin™)	20 – 30	3 – 4	5 mg BID or TID *(5 – 10 mg/day)*	1 – 3	60 mg	Take 30–45 min before meals
Dexmethylphenidate (Focalin®)	30	3 – 6	2.5 mg BID *(2.5 – 5 mg/day)*	2	20 mg	High fat meal will delay absorption by ~ 1.5 hours.
Intermediate-Acting						
Methylphenidate (Ritalin SR®) (Metadate ER™) (Methylin ER™)	60 – 90 60 – 180 60 – 90	3 – 8 (highly variable)	10 – 20 mg AM *(20 mg/day)*	1 – 2	60 mg	Take 30–45 min before meals Wax matrix tablet. Wax matrix tablet. Hydrophilic polymer tablet.
Long-Acting						
Methylphenidate (Ritalin LA®)	100	7 – 9	10 – 20 mg AM *(10 mg/day)*	1	60 mg	Capsule is 50% IR & 50% DR beads. Mimics BID dosing.
Methylphenidate (Metadate CD®)	90	7 – 9	20 mg AM *(10 – 20 mg/day)*	1	60 mg	Capsule is 30% IR & 70% DR beads. Mimics BID dosing.
Methylphenidate (Concerta®)	30 – 60	10 – 12	18 mg AM *(18 mg/day)*	1	**6-12 years:** 54 mg **13-17 years:** 72 mg **NTE:** 2mg/kg/day	Nonabsorbable tablet is 22% IR & 78% CR.
Methylphenidate transdermal (Daytrana®)	120 - 240	10 – 12	10 mg AM *(next patch size)*	1	30 mg	Remove after 9 hours; absorption may continue for several hours after removal.
Dexmethylphenidate (Focalin XR®)	30	9 – 12	5 mg AM *(5 mg/day)*	1	30 mg	Capsule is 50% IR & 50% DR beads. Mimics BID dosing.
Amphetamines						
Short-Acting						
Dextroamphetamine (generic only)	20 – 60	4 – 6	**3 - 5 years:** 2.5 mg AM *(2.5 mg/day)* **≥ 6 years:** 5 mg AM or BID *(5 mg/day)*	1 – 3	40 mg	
Mixed amphetamine salts (Adderall®)	30	5 – 8	**3 - 5 years:** 2.5 mg AM *(2.5 mg/day)* **≥ 6 years:** 5 mg AM or BID *(5 mg/day)*	1 – 3	40 mg	Duration increases with higher doses.
Intermediate-Acting						
Dextroamphetamine (Dexedrine Spansules®)	60 – 90	6 – 10 (highly variable)	5 mg AM or BID *(5 mg/day)*	1 – 2	40 mg	Capsule of IR & DR beads.
Long-Acting						
Mixed amphetamine salts (Adderall XR®)	30	10 – 12	5 – 10 mg AM *(5 – 10 mg/day)*	1	30 mg	Capsule is 50% IR & 50% DR beads. Mimics BID dosing.
Lisdexamfetamine (Vyvanse®)	90 – 120	10 – 12	20 – 30 mg AM *(10 – 20 mg/day)*	1	70 mg	Continuous-release capsule. A pro-drug. High fat meal will delay absorption by ~ 1 hour.

* All medications are FDA-approved for the treatment of ADHD in children 6 years of age or older, except for short-acting dextroamphetamine and short-acting mixed amphetamine salts which are approved for use in children 3 years of age or older.

Key: CR = controlled-release; DR = delayed-release; IR = immediate-release; NTE = not to exceed
References: 3, 4, 18, 49, 89, 90, 91, 92, 93, FDA Package Inserts: references on file and available upon request.

Table 3. NONSTIMULANT ADHD MEDICATION DOSING GUIDELINES

Medication (i) (Brand Name)	Onset	Duration	Initial Dose *(Titration)*	Doses per Day	Maximum Daily Dose	Comments
Non-Stimulants						
Atomoxetine (Strattera®) (ii)	2 – 4 weeks	24 hrs	**≤ 70 kg:** 0.5 mg/kg/day QD *(↑ to 1.2 mg/kg/day)* (iii) **> 70 kg:** 40 mg QD *(↑ to 80 mg QD or divided BID)* (iii)	1 – 2	1.4 mg/kg/day **NTE:** 100 mg	
Clonidine ER (Kapvay™) (iv)	~ 2 weeks	12 hrs	0.1 mg PM *(0.1 mg/day every week)*	2	0.4 mg	Do not stop abruptly. Not 1:1 conversion to other clonidine products.
Guanfacine ER (Intuniv™) (iv)	2 – 3 weeks	8 – 14 hrs; up to 24 hrs in higher doses	1 mg QD *(1 mg/day every week)*	1	4 mg	Do not stop abruptly. Do not administer with high fat meals. Not a 1:1 conversion to other guanfacine products.
Clonidine (Catapres®, Catapres-TTS®)	2 – 8 weeks	Oral: 4 – 6 hrs Patch: 7 days	**Oral:** ≤ 45 kg: 0.05 mg PM *(0.05 mg/day every 3 –7 days)* **> 45 kg:** 0.1 mg PM *(0.1 mg/day every 3 – 7 days)* **Patch:** 0.1 mg/week *(next patch size weekly)*	**Oral:** 2 – 4 **Patch:** weekly	**27 – 40.5 kg:** 0.2 mg **40.5 – 45 kg:** 0.3 mg **> 45 kg:** 0.4 mg	Do not stop abruptly. Not 1:1 conversion to ER
Guanfacine (Tenex™)	2 – 8 weeks	6 – 8 hrs	≤ 45 kg: 0.5 mg PM *(0.5 mg/day every 3 – 7 days)* **> 45 kg:** 1 mg PM *(1 mg/day every 3 – 7 days)*	2 – 4	**27 – 40.5 kg:** 2 mg **40.5 – 45 kg:** 3 mg **> 45 kg:** 4 mg	Do not stop abruptly. Not 1:1 conversion to ER

(i) All medications are FDA indicated for ADHD in children 6 years of age or older, except for clonidine and guanfacine immediate-release tablets which do not have an FDA indication for ADHD; (ii) FDA indicated for ADHD as monotherapy; (iii) FDA package insert states that dose can be increased to target dose of 1.2mg/kg/day after a minimum of 3 days; (iv) FDA indicated for ADHD as monotherapy or adjunctive therapy to stimulants.
Key: ER = extended-release; NTE = not to exceed
References: 3, 4, 17, 18, 49, 51, 90, 91, 93, FDA Package Inserts: references on file and available upon request.

Table 4. GUIDELINES FOR SWITCHING STIMULANT ADHD MEDICATIONS

METHYLPHENIDATE TO METHYLPHENIDATE				METHYLPHENIDATE TO AMPHETAMINES	
MPH (Ritalin®, Methylin™)	**(Ritalin SR®, Metadate ER™)**	**MPH (Ritalin®, Methylin™)**	**(Concerta®)**	**MPH (Ritalin®, Methylin™)**	**Dextro-AMP (Dexedrine Spansule®)**
IR 10 mg BID	20 mg daily	IR 5 mg BID or TID	18 mg AM	IR 5 mg BID	5 mg daily
IR 20 mg BID	40 mg daily	IR 10 mg BID or TID	36 mg AM	IR 10 mg BID	10 mg daily
		IR 15 mg BID or TID	54 mg AM	IR 20 mg BID	20 mg daily
		IR 20 BID or TID	72 mg AM		
MPH (Ritalin®, Methylin™)	**Dex-MPH (Focalin® or Focalin XR®)**	**MPH (Ritalin®, Methylin™)**	**(Ritalin LA®)**	**MPH (Ritalin®, Methylin™)**	**Mixed AMP (Adderall® or Adderall XR®)**
IR 5 mg BID	IR 2.5 mg BID or XR 5 mg AM	IR 5 mg BID	10 mg AM	IR 5 mg BID	IR 2.5 mg BID, or XR 5 mg AM
IR 10 mg BID	IR 5 mg BID or XR 10 mg AM	IR 10 mg BID	20 mg AM	IR 10 mg BID	IR 5 mg BID, or XR 10 mg AM
IR 20 mg BID	10 mg BID or XR 20 mg AM	IR 15 mg BID	30 mg AM	IR 20 mg BID	IR 10 mg BID, or XR 20 mg AM
		IR 20 mg BID	40 mg AM		
		IR 30 mg BID	60 mg AM		

AMPHETAMINE TO AMPHETAMINE					
Dextro-AMP (generic only)	**Dextro-AMP (Dexedrine Spansule®)**	**Mixed AMP (Adderall®)**	**Mixed AMP (Adderall XR®)**	**Mixed AMP (Adderall® or Adderall XR®)**	**Lisdexamfetamine (Vyvanse®)**
IR 5 mg BID	10 mg AM	IR 7.5 mg BID	XR 15 mg AM	IR 15 mg BID, or XR 30 mg AM	70 mg AM
IR 10 mg BID	20 mg AM	IR 15 mg BID	XR 30 mg AM	**Dextro-AMP (generic only)**	**Lisdexamfetamine (Vyvanse®)**
				IR 10 mg BID	50 mg AM

Key: Dextro-AMP = dextroamphetamine; Dex-MPH = dexmethylphenidate; IR = immediate-release; Mixed AMP = mixed amphetamine salts; MPH = methylphenidate; XR = extended-release
References: 49, 90, 94, FDA Package Inserts: references on file and available upon request.

Table 5: SELECT SIDE EFFECTS (SEs) OF ADHD MEDICATIONS

Side Effects		1st LINE Methylphenidate	1st LINE Amphetamines	1st LINE Atomoxetine	2nd LINE Clonidine ER	2nd LINE Guanfacine ER	Side Effect Management, Considerations/Comments
CNS	Anxiety	√	√	√*			* Reported clinically
CNS	Dizziness	√	√	√	√	√	May be temporary: use mild analgesics as needed; consider dose reduction and gradual re-titration. If persistent: monitor symptoms and blood pressure carefully; consider long-acting formulation or alternative medication.
CNS	Headache	√	√	√	√	√	
CNS	Insomnia	√	√	√	√	√	Give sleep hygiene advice; give earlier in day or discontinue afternoon/evening dose; change to short-acting formulation; consider adjunctive medication (e.g., melatonin, trazodone, clonidine); or switch to atomoxetine.
CNS	Dull/flat/listless	√	√				Consider dose reduction or switch to alternative medication.
CNS	Irritability, Dysphoria, or Agitation	√	√	√	√	√	Consider comorbid conditions. If occurs while medication is active: reduce dose; change to long-acting formulation; or consider adjunctive or alternative medication.
CNS	Rebound irritability	√	√				If occurs as stimulant wears off: overlap stimulant dosing; use step-down dosing; consider long-acting formulation alone or in combination with short-acting formulation.
CNS	Cheek chewing, nail biting, skin picking	√	√				Consider dose reduction or switch to alternative medication.
CNS	Somnolence			√	√	√	Give dose, or bulk of dose (clonidine ER), at bedtime.
CNS	Suicidality			R			Black box warning. Careful monitoring suggested.
CNS	Tics	√	√	R			Monitor for pre- and post-treatment tics. Apparent worsening or new onset may be temporary. Weigh benefit/risk if tics are mild/infrequent. If persistent or clearly problematic, consider switching to nonstimulant alternative.
CV	Blood pressure (bp)	↑bp	↑bp	↑bp	↓bp	↓bp	Monitor upon initiation; consider dose reduction or discontinuation. Discontinue α$_2$-agonists gradually.
CV	Heart rate (hr)	↑hr	↑hr	↑hr	↓hr	↓hr	
CV	Sudden cardiac death	U	U	U			Before initiation of medication, screen and refer to CV specialist if needed or if patient has pre-existing heart disease.
GI	Appetite suppression	√	√	√			Administer dose with/after meals. Give high-caloric breakfasts and snacks. Consider dose reduction.
GI	GI upset	√	√	√	√	√	
GI	Nausea/vomiting	√	√	√	√	√	
GI	Constipation or diarrhea	√	√	√	√	√	Routine management suggested.
GI	Dry mouth	√	√	√	√	√	Routine management suggested.
Growth	Height suppression	√	√	√*			Monitor on growth chart with percentiles. Consider medication holidays[1] or alternative medication. * Smaller effect than stimulants.
Growth	Weight loss	√	√	√			Monitor on growth chart with percentiles. Give high-caloric breakfasts and snacks. Consider dose reduction or medication holidays.[1]
Other	Hepatotoxicity			R			Monitor for signs and symptoms.
Other	Sexual dysfunction		√	√	√	√	
Other	Skin reactions	√	√	√	√	√	Erythema is common with transdermal systems. If contact sensitization (allergic contact dermatitis) occurs, consider alternative medication or cautious trial with oral dose form of same medication since systemic sensitization may develop.

1. There is lack of consensus among the SCORxE writing group on inclusion of medication holidays as a management strategy for growth suppression.

Key: CNS = central nervous system; CV = cardiovascular; ER = extended-release; GI = gastrointestinal; R = rare; U = unknown, causal relationship not established; √ = has been reported; ↑ = increase; ↓ = decrease

References: 18, 27, 38, FDA Package Inserts: references on file and available upon request.

Table 6. MEDICATION CONSIDERATIONS FOR ADHD WITH COMORBIDITIES

Comorbidity	Treatment
Physical Aggression - may be associated with Oppositional Defiant Disorder (ODD) or Conduct Disorder (CD)	Stimulants often beneficial for physical aggression; atomoxetine may be less beneficial. If aggression persists despite first-line ADHD medications in combination with behavioral therapy, then may consider adding an α_2-agonist or a second generation antipsychotic. Consider reassessing diagnosis or referral to mental health specialist if above suggestions are ineffective.
Anxiety	Stimulants may increase or decrease anxiety; use slow titration. Atomoxetine may be beneficial. Consider adding an SSRI if good response of ADHD symptoms to stimulants or atomoxetine but persistent anxiety despite nonpharmacologic interventions.
Bipolar Disorder (BPD)	Refer to mental health specialist for management with standard BPD treatments.
Depression	Treat the condition causing most impairment first (comorbid disorder will often improve); then reassess.
Insomnia	Stimulants unlikely beneficial and may exacerbate initial insomnia. Give stimulant dose earlier in day. Consider adjunctive insomnia treatment or switch to atomoxetine.
Substance Use Disorder[1]	Refer to mental health specialist, and consider atomoxetine or stimulant formulations with lower abuse potential (e.g., Concerta®, Vyvanse®).
Swallowing Difficulties	Can open and sprinkle: Focalin XR®, Metadate CD®, Ritalin LA®, Adderall XR®, Dexedrine® spansules. Can dissolve contents in water: Vyvanse®.
Tic Disorder	Stimulants usually do not worsen tics and may improve tics. Consider adding an α_2-agonist if good response of ADHD symptoms to stimulants but persistent tics. Consider atomoxetine if tics worsen with stimulants.

1. Stimulant medications should not be prescribed to patients with significant active substance abuse and dependence except by an expert in both disorders.

Key: SSRI = selective serotonin reuptake inhibitor

References: 21, 38, 49, 70, 93, 95   Adapted from 95

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