Clinical Practice Guidelines for Treatment of ADHD with Stimulant Medications

presented by
Susan M. Franer RN, CNS
Division of Child and Adolescent Psychiatry

Learning Objectives

- Describe recommended use of stimulant medication as addressed in the American Academy of Pediatrics 2011 Clinical Practice Guideline for Diagnosis, Evaluation, and Treatment of ADHD in Children and Adolescents
- Describe recommended use of stimulant medication as addressed in the American Academy of Child and Adolescent Psychiatry's 2007 Practice Parameter for the Assessment and Treatment of Children and Adolescents with ADHD

AAP Action Statement 1

- The primary care clinician should initiate an evaluation for ADHD for any child age 4-18 years of age who presents with academic or behavioral problems and symptoms of inattention, hyperactivity or impulsivity

- Quality of evidence = B/strong recommendation (RCTs or diagnostic studies with minor limitations; overwhelmingly consistent evidence from observational studies)

AAP Action Statement 2

- To make a diagnosis of ADHD, the primary care clinician (PCC) should determine that the DSM IV-TR criteria have been met (including documentation of impairment in **more than 1 major setting**), and information should be obtained primarily from reports from parents or guardians, teachers and other school and mental health clinicians involved in the child's care. PCC should also rule out any alternative cause

- Quality of evidence: B/ Strong recommendation

DSM IV-TR Diagnostic Criteria ADHD

A. Either (1) Inattention or (2) hyperactivity-impulsivity

(1) Six or more of the following symptoms of ***inattention*** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level

a. Often fails to give close attention to details or makes careless mistakes in schoolwork, work or other activities

b. Often has difficulty sustaining attention in tasks or play activities

c. Often does not seem to listen when spoken to directly

DSM IV-TR Diagnostic Criteria ADHD

d. Often does not follow through on instructions and fails to finish schoolwork, chores, or duties in the workplace (not due to oppositional behavior or failure to understand instructions)

e. Often has difficulty organizing tasks and activities

f. Often avoids, dislikes or is reluctant to engage in tasks that require sustained mental effort (such as schoolwork or homework)

g. Often loses things necessary for tasks or activities (e.g. toys, school assignments, pencils, books or tools)

DSM IV-TR Diagnostic Criteria ADHD

h. Is often easily distracted by extraneous stimuli

i. Is often forgetful in daily activities OR

(2) **Six or more** of the following symptoms of ***hyperactivity or impulsivity*** have persisted for at least 6 months to a degree that is maladaptive and inconsistent with developmental level:

a. often fidgets with hands or feet and squirms in seat

b. often runs about or climbs excessively in situations in which it is inappropriate (in adolescents or adults, may be limited to subjective feelings of restlessness)

DSM IV-TR Diagnostic Criteria ADHD

d. Often has difficulty playing or engaging in leisure activities quietly

e. Is often “on the go” or often acts as if “driven by a motor

f. Often talks excessively

Impulsivity

g. Often blurts out answers before questions have been completed

h. Often has difficulty awaiting turn

i. Often interrupts or intrudes on others (e.g. butts into conversations or games)

DSM IV-TR Diagnostic Criteria ADHD

B. Some hyperactive-impulsive or inattentive symptoms that caused impairment were present before age 7

C. Some impairment from the symptoms is present in two or more settings (e.g. school, work, or home)

D. There must be clear evidence of clinically significant impairment in social, academic , or occupational functioning

E. The symptoms do not occur exclusively during the course of a Pervasive Developmental Disorder, Schizophrenia, or other Psychotic Disorder and are not better accounted for by another mental disorder (e.g. Mood disorder, Anxiety disorder, ect.)

AAP Action Statement 3

- In the evaluation of a child for ADHD, the primary care clinician (PCC) should include assessment for other conditions that might co-exist with ADHD, including emotional or behavioral (e.g. anxiety, depressive, oppositional defiant, and conduct disorders), developmental (e.g. learning and language disorders or other neurodevelopmental disorders), and physical conditions (e.g. tics, sleep apnea)
- Quality of evidence: B/strong recommendation

Comorbidities in Children

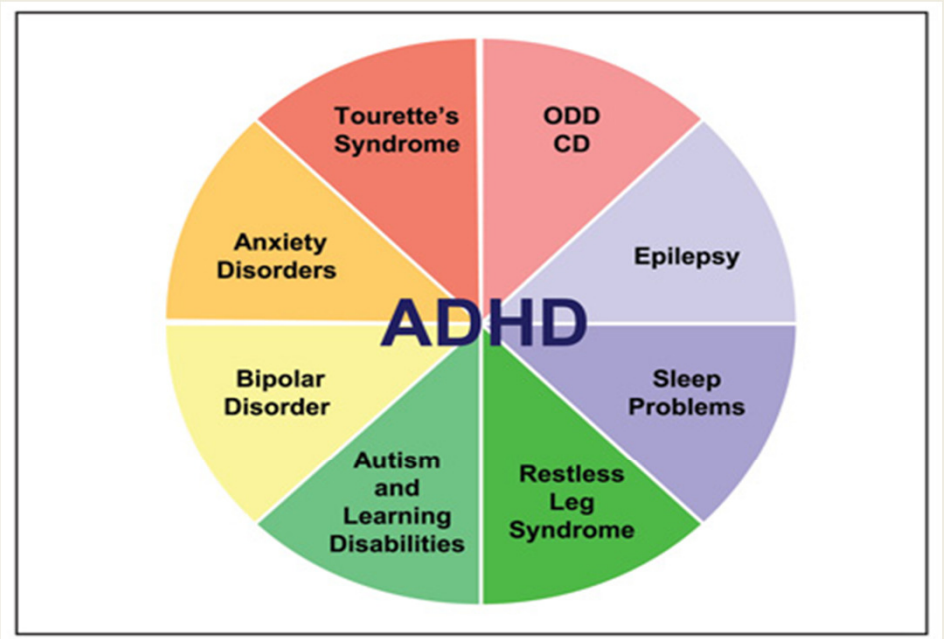

FIGURE 3.2. It has been suggested that ADHD, Tourette's syndrome, and restless leg syndrome may be comorbid in children and that iron deficiency could be one of the underlying causes. Additionally, 50% of school-aged children with ADHD also meet the DSM-IV criteria for oppositional defiant disorder (ODD) or conduct disorder (CD). It becomes clear that no matter what the comorbidity is, children with ADHD can be further burdened. It is therefore imperative to properly diagnose them and treat them appropriately.

http://stahlonline.cambridge.org/. Accessed November 11, 2011.

What Should be Treated First?

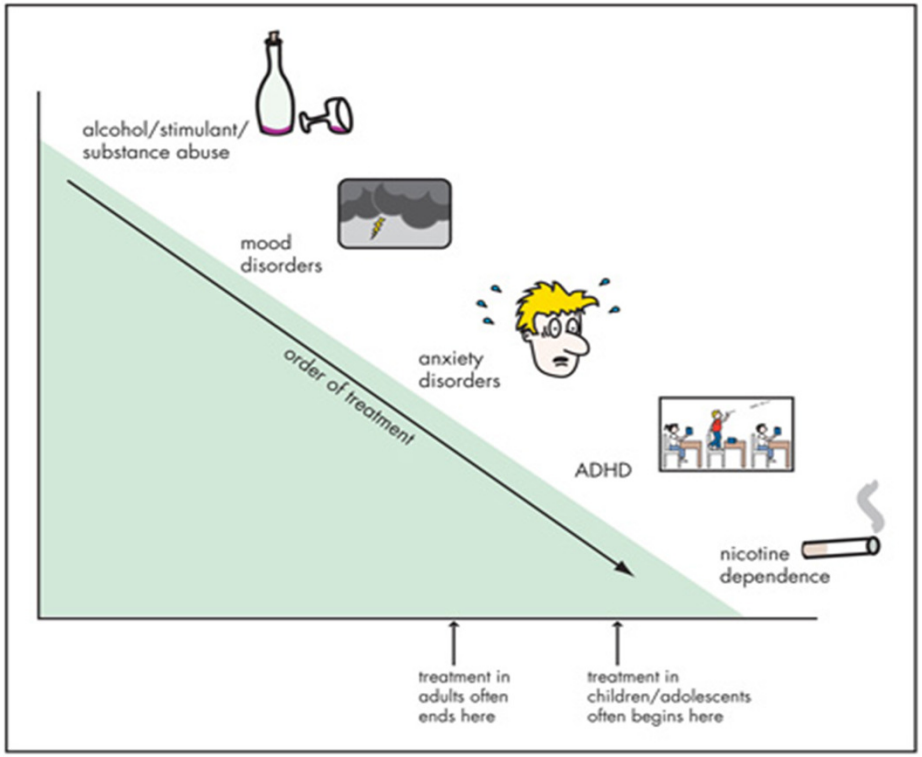

FIGURE 3.9. So what should a psychopharmacologist do with a patient with ADHD and comorbid disorders? Once the proper diagnosis has been reached, it is imperative to treat all disorders appropriately, and in terms of highest degree of impairment. This might mean that in one patient it is necessary to first stabilize the alcohol abuse, while in another patient the symptoms of ADHD might be more impairing than the underlying anxiety disorder. Additionally, some medications used to treat these disorders could exacerbate the comorbid ailment. Thus, care needs to be taken when choosing the appropriate treatment. An individualized treatment plan should therefore be established for each patient, depending on his/her symptomatic portfolio.

http://stahlonline.cambridge.org/. Accessed November 11, 2011.

AAP Action Statement 4

- The primary care clinician (PCC) should recognize ADHD as a chronic condition and, therefore, consider children and adolescents with ADHD as children and youth with special health care needs. Management of children and youth with special health care needs should follow the principles of the chronic care model and the medical home

- Quality of evidence: B/strong recommendation

AAP Action Statement 5

- Recommendations for treatment of children and youth with ADHD vary depending on patient age
- Action Statement 5A: For preschool aged children (4-5 years of age), the primary care clinician should prescribe evidence-based parent and/or teacher-administered behavior therapy as the first line of treatment (quality of evidence is A/strong recommendation/well designed RCTs or diagnostic studies on relevant population)
- And may prescribe methylphenidate if the behavior interventions do not provide significant improvement and there is moderate-to-severe continuing disturbance in the child's function.

AAP Action Statement 5
5a- Preschool (cont.)

- In areas in which evidence based behavioral treatments are not available, the clinician needs to weigh the risks of starting medication at an early age against the harm of delaying diagnosis and treatment

- Quality of evidence: B/recommendation

AAP Action Statement 5
5b: Elementary School Aged 6-11 yrs

- The primary care clinician should prescribe FDA-approved medications for ADHD (quality of evidence: A/strong recommendation) and/or evidence based parent and/or teacher administered behavior therapy as treatment for ADHD, preferably both (quality of evidence B/strong recommendation)
- The evidence is particularly strong for stimulant medications and sufficient but less strong for atomoxetine, extended release guanfacine, and extended release clonidine (in that order) (quality of evidence A/strong recommendation)
- The school environment, program or placement is a part of any treatment plan

AAP Action Statement 5
5c: Adolescents Aged 12-18 yrs

- The primary care clinician should prescribe FDA approved medications for ADHD with the assent of the adolescent (quality of evidence: A/ strong recommendation) and may prescribe behavior therapy as treatment for ADHD (quality of evidence: C/ observational studies (case control and cohort studies) preferably both

AAP Action Statement 6

- Primary care clinicians should titrate doses of medication for ADHD to achieve maximum benefit with minimum adverse effects (quality of evidence: B/strong recommendation)

Methylphenidate Products

Product	Dosage Form	Duration of Action
Ritalin, Methylin	5,10,20mg tablets	3-4 hours
Methylin Chewable	2.5,5,10mg chew tablets	3-4 hours
Methylin Oral Solution	5mg/5ml, 10mg/5ml	3-4 hours
Focalin	2.5,5,10mg tablets	4-5 hours
Focalin XR	5,10,15,20mg capsules	Up to 12 hours
Ritalin LA	10,20,30,40mg LA capsules	8-10 hours
Ritalin SR	20mg SR tablets	6-8 hours
Metadate ER, Methylin ER	10,20mg ER tablets	6-8 hours
Concerta	18,27,36, 54mg ER tablets	12 hours
Metadate CD	10,20,30,40,50,60mg ER capsules	8-9 hours
Daytrana Transdermal patch	10,15,20,30mg/9hr patch	12 hours

Pharmacist's Letter. Comparison of Drugs for ADHD. Jan 2011.

Methylphenidate Doses

Product	Starting Dosage	FDA Max Dose	Off-Label QDAY MAX dose
Ritalin, Methylin	≥6yrs: 5mg BID	60mg	> 50kg: 100mg
Methylin Chewable	≥6yrs: 5mg BID	60mg	> 50kg: 100mg
Methylin Oral Solution	≥6yrs: 5mg BID	60mg	> 50kg: 100mg
Focalin	≥6yrs: 2.5mg BID	20mg	50mg
Focalin XR	5mg QDAY	30mg	50mg
Ritalin LA	20mg QDAY	60mg	>50kg: 100mg
Ritalin SR	10mg QDAY	60mg	>50kg: 100mg
Metadate ER, Methylin ER	10mg QDAY	60mg	>50kg: 100mg
Concerta	18mg QDAY	72mg	108mg
Metadate CD	20mg QDAY	60mg	>50kg: 100mg
Daytrana Transdermal patch	10mg QDAY	30mg	Unknown

Pharmacotherapy 2009;29(6):656-679.

Transdermal Methylphenidate

- 10,15,20,30mg patches available
- Apply to clean, dry area on hip, rotate site
- 21% greater drug delivery and 31% higher bioavailability of methylphenidate when the patch is applied to the **hip** versus when applied to the scapular area of the back.
- Onset within 2 hours after applying patch
- Avoids 1st pass effect, 20mg patch = 20mg TID PO
- 9 hours of wear time recommended
- Absorption continues 3 hours after patch removal

Daytrana® package insert.

Child & Adolescent Psychopharmacology Update September 2009

Transdermal Methylphenidate

- Advantages: good for kids who cannot swallow, optimal for long duration of action
- Disadvantages: oppositional child can remove patch, toddler or pet may ingest it
- Adverse effects: similar to QDAY oral products
- Irritation at patch site: 10-40%

Anderson VR, Scott LJ. *Drugs*. 2006;66(8):1117-1126.
Prince JB. *Child Adolesc Psych Clin N Am.* 2006;15:13-50.

Amphetamine Products

Product	Dosage Form	Duration of Action
Adderall	5,7.5,10,12.5,15,20,30mg tablets	4-6 hours
Adderall XR	5,10,15,20,25,30mg ER capsules	10-12 hours
Dexedrine	5,10mg tablets	4-6 hours
Dexedrine Spansule	5,10,15mg SR capsules	6-10 hours
ProCentra	1mg/ml oral solution	4-6 hours
Vyvanse	20,30,40,50,60,70mg capsules	13-14 hours

Pharmacist's Letter. Comparison of Drugs for ADHD. Dec 2011.

Amphetamine Dosing

Products	Starting Dosage	FDA Max Dose	Off-Label QDAY MAX Dose
Adderall	3-5 yrs:2.5mg QDAY ≥ 6yrs:5mg QDAY-BID	40mg	>50kg: 60mg
Adderall XR	≥ 6yrs:10mg QDAY	30mg	>50kg: 60mg
Dexedrine	3-5 yrs:2.5mg QDAY	40mg	
Dexedrine Spansule	≥ 6yrs:5-10mg QDAY-BID	40mg	> 50kg: 60mg
ProCentra	3-5 yrs: 2.5mg QDAY ≥ 6yrs:5mg QDAY-BID	40mg	> 50kg: 60mg
Vyvanse	≥ 6yrs:20-30mg QDAY	70mg	unknown

Pharmacotherapy 2009;29(6):656-679.

Pharmacist's Letter. Comparison of Drugs for ADHD. Dec 2011.

Difference Between Amphetamine and Methylphenidate

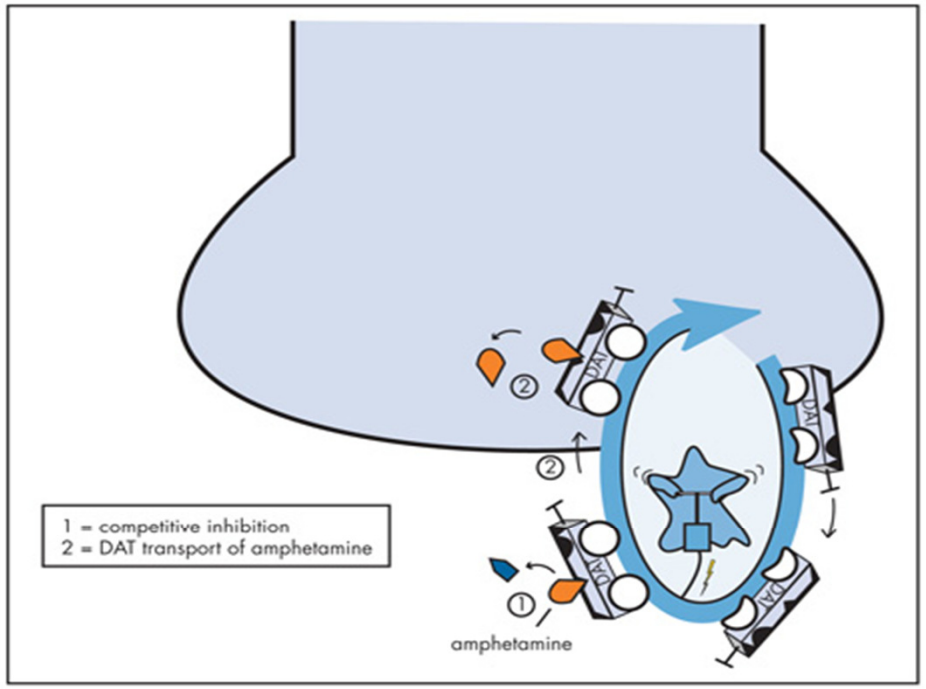

FIGURE 4.8. Stimulants such as amphetamine and methylphenidate both increase synaptic DA and NE levels, but only amphetamine enhances release as well as blocks reuptake of the neurotransmitters NE and DA, especially at high doses. Specifically, unlike methylphenidate, amphetamine is a competitive inhibitor at DAT, thus competing with DA for a seat on the transporter. By hijacking the DAT, amphetamine itself is transported into the DA terminal. This is one way by which amphetamine increases synaptic DA levels. As will be seen in Figure 4.9, amphetamine, unlike methylphenidate, has an additional pharmacological property to lead to high levels of DA release. This additional pharmacological property is most relevant to high dose pulsatile delivery of amphetamine. At therapeutic doses of amphetamine, the net effects of its actions are very similar to those of methylphenidate.

http://stahlonline.cambridge.org/. Accessed November 11, 2011.

Prescribing Pearls

- Start with short acting methylphenidate and use an incremental approach to increasing dose (2.5-5 mg/week depending on age)
- Generally speaking methylphenidate is about half the strength of amphetamine therefore amphetamines make a better second line choice
- Take advantage of the multiple products and duration of actions available
- Don’t be afraid to recycle from time to time
- Consider adding Strattera as a secondary agent rather than prescribe higher and higher doses of stimulants

FDA Safety Communication on Medications used to treat ADHD

- Stimulant products and atomoxetine should generally not be used in patients with serious heart problems, or for whom an increase in blood pressure or heart rate would be problematic
- Patients should be periodically monitored for changes in heart rate or blood pressure

http://www.fda.gov/Drugs/DrugSafety/ucm277770.htm. Accessed November 14, 2011.

Ongoing Safety Review on Cardiovascular effects of Stimulants

- A retrospective cohort study > 1 million children and young adults found no significant differences in serious cardiac events among those who did not use ADHD medications, current users, and former users.
- Only 3.1 serious cardiovascular event/100,000 person-years.

http://www.nejm.org/doi/full/10.1056/NEJMoa1110212. Accessed November 17, 2011.

Stimulant Side Effects/Management

- Common (10-50%):
  - Upset Stomach – give on a full stomach, lower dose, titrate slowly
  - Insomnia – dose earlier, add med for sleep
  - Headache – short-term analgesic, should abate
  - Rebound symptoms – adjust dosing/change drug
- Uncommon (1-10%) to rare (<1%):
  - Tics – lower dose, change drugs
  - Dysphoria, irritability – reassess diagnosis, ↓ dose, change drugs
  - Hallucinations – d/c drug (rare)
  - Over-focused, zombie-like, lower dose

López FA. *J Dev Behav Pediatrics.* 2006:27(5):410-416.

ADHD and Sleep Problems

- 19% ADHD(non med) vs. 6% controls
- Stimulant use long-term 29%, acute 65%
- Difficulty falling asleep, awakenings, periodic limb movement disorder, restless sleep
- Treatments: behavioral/adjust med
  - Melatonin 1-5mg
  - Trazodone 25-50mg, Mirtazapine 7.5mg
  - Diphenhydramine 12.5-50mg
  - Alpha-2 agonists (clonidine, guanfacine)
  - Cyproheptadine 2-4mg

Smits MG, et al. *J Am Acad Child Adolesc Psych. 2003:42(11):1286-93.*

Stimulants and Growth

(32 Studies Reviewed, Including MTA)

- Height deficit: ~1cm/year over 1-3 yrs continuous (cont.) use
- Weight deficit 1st year: ↓ 3kg in weight
- Weight deficit 2nd year: ↓ 1.2kg in weight
- MTA: inconsistent use less ↓ grow vs. cont. use
- Possible alterations in growth hormone or growth factor secretion, appetite loss leading to ↓ calorie intake
- Amphetamine > than methylphenidate
- 2 studies: no detrimental effects on growth*

Poulton A. *Arch Dis Child.*2005;90:801-6. *Pliszka SR, et al. *J Am Acad Child Adolesc Psych.*2006;45:520-7. Spencer T, et al. *J Am Acad Child Adolesc Psych.*2006;45:527-537. Swanson JM, et al. *J Am Acad Child Adolesc Psych.*2007;46:1015-47.

Psychiatric Adverse Effects of ADHD Medication

- Hundreds of cases reported to the FDA
- 4 Broad categories reported to MedWatch
  - Psychosis/mania: (ATOM 292, MPH 148, AMP 77)
  - Aggression or violent behavior: (ATOM 566, MPH 110, AMP 28)
  - Severe anxiety or panic attacks
  - Increased suicidal behavior – atomoxetine significant
- Pre-screening recommended
- Counseling

Mosholder AD. Available at: http://www.fda.gov/ohrms/dockets/ac/06/slides/2006-4210s-index.htm. Accessed Nov 11, 20011.

Factors Predicting Adherence to ADHD Medications

Poor Adherence

- Multiple daily dosing
- More severe symptoms
- Higher dosage
- Later onset of diagnosis
- Family Hx of ADHD
- Higher paternal education

Good Adherence

- Once daily dosing
- Less severe symptoms
- Younger age
- Mentally retarded in treatment centers

Gau S, et al. *J Clin Psych.*2008;69:131-140. Kemner JE, Lage MJ. *Am J Health Syst Pharm.* 2006;63:317-322. Charach A, et al. *J Am Acad Child Adolesc Psychiatry.*2004;43:559-567. Correll CU, Carlson HE. *J Am Acad Child Adolesc Psychiatry.*2006;45:771-791.

Stimulant Use:
The Relationship to Future Substance Abuse

- Barkley et al in a 13 year prospective study of 147 subjects found no compelling evidence that stimulant treatment of children with ADHD leads to an increased risk for substance experimentation, use, dependence or abuse by adulthood

- This study concurred with 11 previous studies which reached the same conclusion.

Source: Pediatrics vol.111 No. 1 January 2003

Neuro-Protective Effects of Stimulants

- Beiderman et al in a 10 year follow up study found evidence that stimulant treatment decreases the risk for subsequent co-morbid psychiatric disorders and academic failure in youth with ADHD

Source: Pediatrics Vol:124 No:1 July 2009

AACAP Practice Parameter for ADHD

- Addresses treatment for:
- Preschoolers (3-5 yrs)
- Children (6-12 yrs)
- Adolescents (13-17 yrs)
- Outlines recommendations for screening, evaluation and treatment

Source: Journal of American Academy of Child and Adolescent Psychiatry, 46:7, July 2007, www.aacap.org

AACAP Recommendations Ratings

- MS= minimal standard applied to recommendations that are based on rigorous empirical evidence
- CG=clinical guideline is applied to recommendations that are based on strong empirical evidence and/or strong clinical consensus and apply approximately 75% of the time
- OP=opinion is applied to recommendations that are acceptable based on emerging empirical evidence or clinical opinion but lack strong empirical evidence and/or strong clinical consensus
- NE=not endorsed is applied to practices that are known to be ineffective or contraindicated

AACAP Practice Parameter: Screening

- Recommendation #1: Screening for ADHD should be a part of every patient's mental health assessment

- Rating=MS/Minimal Standard

AACAP Practice Parameter: Evaluation

- Recommendation #2: Evaluation of the preschooler, child or adolescent for ADHD should consist of clinical interviews with the parent and patient, obtaining information about the patient's school or day care functioning, evaluation of co-morbid psychiatric disorders, and review of the patient's medical, social and family histories

- Rating= MS/Minimal Standard

AACAP Practice Parameter: Evaluation

- Recommendation #3: If the patient's medical history is unremarkable, laboratory or neurological testing is not indicated
- Rating=NE/Not Endorsed

- Recommendation #4: Psychological and neuropsychological tests are not mandatory for the diagnosis of ADHD, but should be performed if the patient's history suggests low general cognitive ability or low achievement in language or mathematics relative to the the patient's intellectual ability
- Rating=OP/Opinion based on emerging empirical evidence

AACAP Practice Parameter: Evaluation

- Recommendation # 5:the clinician must evaluate the patient with ADHD for the presence of co-morbid psychiatric disorders
- Rating=MS/Minimal Standard

AACAP Practice Parameter: Treatment

- Recommendation #6: Well thought out and comprehensive treatment plan should be developed for the patient with ADHD.
- This recommendation includes use of stimulant medication (MHP or amphetamine)
- Atomoxetine may be considered as the first line medication for ADHD in individuals with and active substance abuse problem, co-morbid anxiety or tics
- Atomoxetine is also preferred if the patient experiences severe side effects to stimulants such as mood liability or tics
- Rating: MS/ Minimal Standard

AACAP Practice Parameter: Treatment

- Recommendation #8: If none of the above agents result in satisfactory treatment of the patient with ADHD, the clinician should undertake a careful review of the diagnosis and then consider behavior therapy and/or the use the medications not approved by the FDA for the treatment to ADHD (SNRI,TCA, alpha agonists)
- Rating=CG/Clinical Guideline, recommendations based on strong empirical evidence which apply approximately 75% of the time

AACAP Practice Parameter: Treatment

- Recommendation#9: During a pharmacological intervention for ADHD, the patient should be monitored for treatment emergent side effects
- Rating=MS/Minimal Standard
- Recommendation #10: If a patient with ADHD has a robust response to psychopharmacological treatment and subsequently shows normative functioning in academic, family and social functioning then psychopharmacological treatment of ADHD alone is satisfactory
- Rating=OP/recommendations acceptable based on emerging empirical evidence

AACAP Practice Parameter: Treatment

- Recommendation #11: If a patient with ADHD has a less than optimal response to medication has a co-morbid disorder, or experiences stressors in family life then psychosocial treatment in conjunction with with medication treatment is often beneficial
- Rating=CG/Clinical guideline recommendations based on strong empirical evidence which apply approximately 75% of the time

AACAP Practice Parameter: Treatment

- Recommendation #12:Patients should be assessed periodically to determine where there is continued need for treatment if symptoms have remitted. Treatment of ADHD should continue as long as symptoms remain present and cause impairment
- Rating=MS/Minimal Standard
- Recommendation #13: Patients treated with medication for ADHD should have their height and weight monitored throughout treatment
- Rating= MS/Minimal Standard

Other Resources

- OBN Formulary Revisions for Schedule II Medications (updated October 22, 2012)
- Pediatric Grand Rounds 9-11-12 regarding AAP Guidelines for treatment of ADHD
- AAP Supplemental Information with algorithm and explanation for process of care for evaluation, diagnosis, treatment and monitoring of ADHD in children and adolescents
- NIMH Multimodal Treatment of ADHD (MTA Study)-nimh.gov
- American Academy of Child and Adolescent Psychiatry Website-www.aacap.org

Thank You