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Psychiatry and Addictions Case Conference

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ADHD: TREATMENT OVERVIEW

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GENERAL DISCLOSURES

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DISCLOSURE OF POTENTIAL CONFLICTS

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OBJECTIVES

1. After participating in this program, learners will be able to describe common components of a comprehensive treatment plan for ADHD
2. After participating in this program, learners will be able to describe at least one recommended psychosocial intervention for pre-adolescents, adolescents, and adults with ADHD.
3. After participating in this program, learners will be able to describe commonly used medication classes for ADHD, including side effects associated with each class

ADHD TREATMENT ACROSS THE DEVELOPMENTAL CONTINUUM

MULTIMODAL TREATMENT OF ADHD

- Psychoeducation
- Medication treatment if indicated
- Behavioral interventions
 - Rewarding desirable behaviors, non-punitive consequences for negative behaviors for youth
 - cBT for adults
- Parent management training for youth
 - Maintain schedule, organize home, set small goals, limit choices, use charts/lists to maintain focus, encourage successful activities, reduce distractions, use calm discipline
 - Incredible Years Parenting Program, New Forest Parenting Program, Parent-Child Interaction Therapy, Positive Parenting Program
- Training in skills deficits
 - Organization and planning for adolescents and adults
 - cBT for adults

PSYCHOEDUCATION ON ADHD SHOULD INCLUDE DISCUSSION OF:

- Nature of disorder (causes, prevalence, clinical course)
- Establishing goals of treatment
- Importance of assessing level of impairment and response to treatment in terms of lowering impairment
- Safety issues (escalating doses, cardiac concerns, etc)
- Importance of having a multimodal approach to treatment
- Role of behavioral interventions (eg, parent management training in for children, cBT for adults)
- Importance of lifestyle modifications (eg, sleep, exercise)
- Medication selection and monitoring of response
- Possible need for referrals (eg, neuropsych testing, specialty providers, vocational services and/or disability)

ADULT PSYCHOEDUCATION EXAMPLES:

- “Adults with ADHD are often trying extremely hard and have the best of intentions, but because their brains have trouble keeping track of time, or remembering what they were in the middle of doing, the result is often failure and disappointment.”
- “A lifetime of ADHD behaviors and problems can lower self-esteem and affect your relationships. Individual counseling, medications and support groups can help.”
- “There are small, strategic changes we can help you make in your daily routine to compensate for these difficulties and help you become more successful at work and at home.”

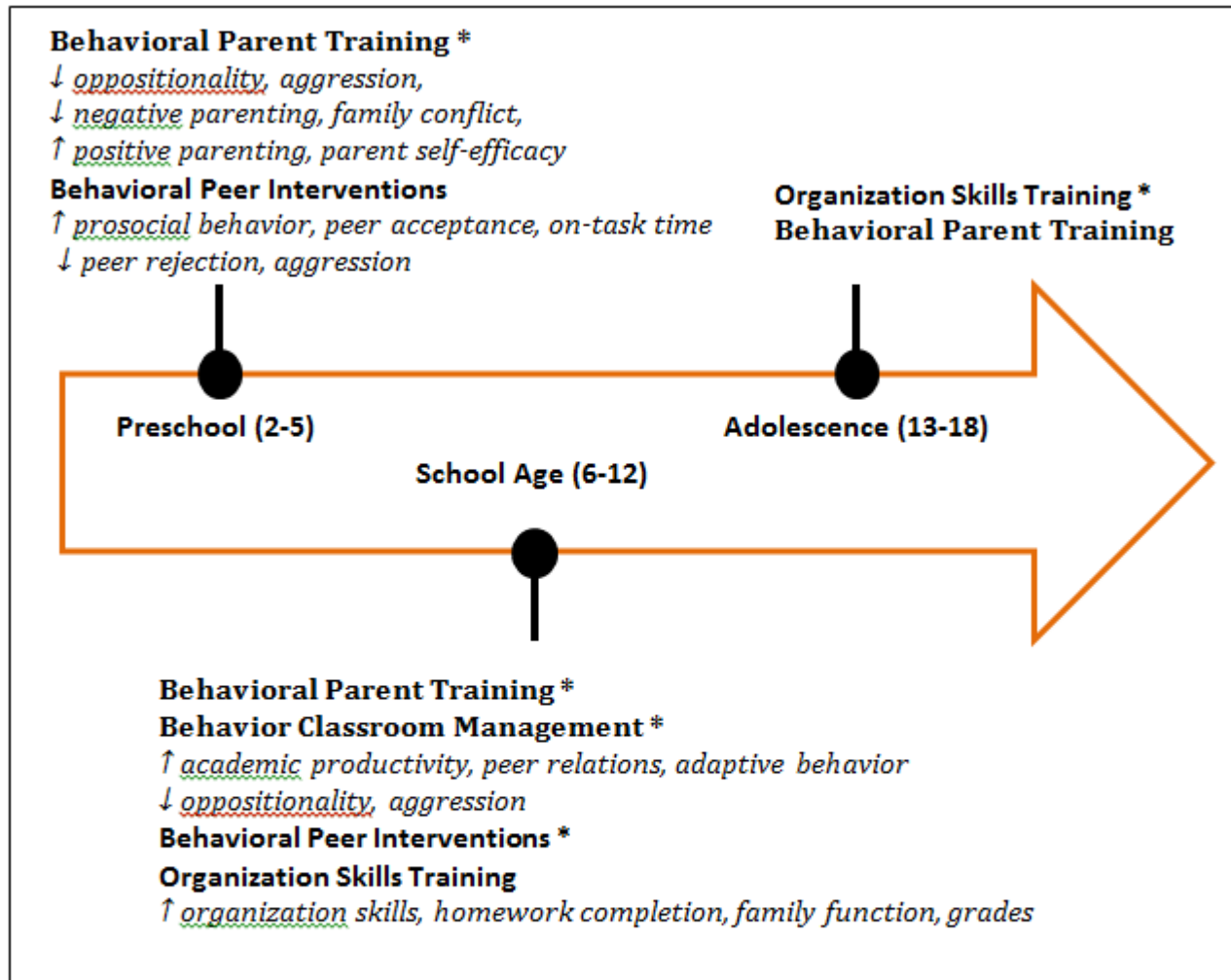


Figure 1. Functional Outcomes of “Well Established” Psychosocial Treatments for ADHD Throughout Development.

*Treatments to be prioritized for this developmental period

NON-MEDICATION TREATMENT RECOMMENDATIONS FOR YOUTH

- Classroom interventions
 - Homework notebook, extended time for tasks, daily report card, reduced distractions (seat away from window, doors), frequent breaks, physical movement when possible, tutoring, help with creating organizational system, signal from teacher when off task, occupational therapy tools.
 - Classroom interventions effective in improving achievement scores, but benefits sustained only as long as interventions continued
- Training in skills deficits
 - Organization and planning
 - CBT for adolescents (builds organizational and management skill, set up for success to avoid distractibility, adaptive thinking strategies)

ADHD TREATMENT IN ADOLESCENTS

Review

Treatment of Attention-Deficit/Hyperactivity Disorder in Adolescents A Systematic Review

Eugenia Chan, MD, MPH; Jason M. Fogler, PhD; Paul G. Hammerness, MD

CONCLUSIONS AND RELEVANCE Evidence supports the use of extended-release methylphenidate and amphetamine formulations, atomoxetine, and extended-release guanfacine to improve symptoms of ADHD in adolescents. Psychosocial treatments incorporating behavior contingency management, motivational enhancement, and academic, organizational, and social skills training techniques were associated with inconsistent effects on ADHD symptoms and greater benefit for academic and organizational skills. Additional treatment studies in adolescents, including combined pharmacological and psychosocial treatments, are needed.

Chan E, Fogler JM, Hammerness PG. Treatment of Attention-Deficit/Hyperactivity Disorder in Adolescents: A Systematic Review. JAMA. 2016 May 10;315(18):1997-2008.

CBT FOR ADULT ADHD

cBT emphasizes the interactive role of automatic thoughts, images and belief systems as well as behaviors in perpetuating symptoms of ADHD (small c, capital B to emphasize the behavioral component). Focus on helping the patient lay out specific functional treatment goals Help the patient improve organizational, time-management, and problem-solving skills by:

- Chunking large tasks into smaller steps
- Introducing a daily planner and emphasizing use of one planner or notebook only
- Manage to-do's using assistive devices, such as mobile phones
- Starting tasks well in advance of their deadline
- Reducing distraction (i.e. clutter-free desktop, windowless and quiet space to work, etc.)
- List-making and task prioritization
- Self-monitoring with regular completion of behavioral check-lists and logging
- Target behaviors as they come up in session, such as arriving late for appointments or losing homework

MEDICATION TREATMENT FOR ADHD

TREATMENT SEQUENCING

- Starting with behavioral therapy instead of medication therapy may improve treatment outcomes

Pelham WE Jr, Fabiano GA, Waxmonsky JG, Greiner AR, Gnagy EM, Pelham WE 3rd, Coxe S, Verley J, Bhatia I, Hart K, Karch K, Konijnendijk E, Tresco K, Nahum-Shani I, Murphy SA. Treatment Sequencing for Childhood ADHD: A Multiple-Randomization Study of Adaptive Medication and Behavioral Interventions. *J Clin Child Adolesc Psychol*. 2016 Jul-Aug;45(4):396-415.

TREATMENT SEQUENCING FOR CHILDHOOD ADHD: A MULTIPLE-RANDOMIZATION STUDY OF ADAPTIVE MEDICATION AND BEHAVIORAL INTERVENTIONS

- Behavioral and pharmacological treatments for children with attention deficit/hyperactivity disorder (ADHD) were evaluated to address whether endpoint outcomes are better depending on which treatment is initiated first and, in case of insufficient response to initial treatment, whether increasing dose of initial treatment or adding the other treatment modality is superior.
- Children with ADHD (ages 5–12, N = 146, 76% male) were treated for 1 school year. Initially randomized to parent management training or low dose methylphenidate. After 8 weeks insufficient responders were re-randomized to secondary interventions that either increased the dose/intensity of the initial treatment or added the other treatment.
- The group beginning with behavioral treatment displayed significantly lower rates of observed classroom rule violations (the primary outcome) at study endpoint and tended to have fewer out-of-class disciplinary events. Further, adding medication secondary to initial behavior modification resulted in better outcomes on the primary outcomes and parent/teacher ratings of oppositional behavior than adding behavior modification to initial medication.
- Normalization rates on teacher and parent ratings were generally high. Parents who began treatment with behavioral parent training had substantially better attendance than those assigned to receive training following medication. Beginning treatment with behavioral intervention produced better outcomes overall than beginning treatment with medication.

Pelham WE, Fabiano GA, Waxmonsky JG, Greiner AR, Gnagy EM, Pelham WE, Coxe S, Verley J, Bhatia I, Hart K, Karch K, Konijnendijk E, Tresco K, Nahum-Shani I, Murphy SA. Treatment Sequencing for Childhood ADHD: A Multiple-Randomization Study of Adaptive Medication and Behavioral Interventions. *J Clin Child Adolesc Psychol.* 2016 Feb 16:1-20.

MULTIMODAL TREATMENT OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER STUDY (MTA)

- 600 children, 7-9 yo
- Treatment modes:
 - intensive medication management (methylphenidate tid, other drugs if necessary; algorithmic adjustments; general advice and readings);
 - intensive behavioral treatment alone (parent training; structured teacher consultation; full time summer treatment program; half time classroom behavioral specialist);
 - a combination of both;
 - routine community care (the control group).

The MTA Cooperative Group. A 14-month Randomized Clinical Trial of Treatment Strategies for Attention-Deficit/Hyperactivity Disorder. Arch Gen Psychiatry 1999; 56: 1073-1086.

MTA AT 14 MONTHS

- Combination treatment and medication management are superior to behavior management and community care.
- Combination treatment is better for certain areas of functioning:
 - oppositional/aggressive symptoms, anxiety symptoms, reading achievement, parent-child relations, and social skills.
- 4% of patients stopped medications due to adverse effects.

The MTA Cooperative Group. A 14-month Randomized Clinical Trial of Treatment Strategies for Attention-Deficit/Hyperactivity Disorder. *Arch Gen Psychiatry* 1999; 56: 1073-1086.

MTA AT 14 MONTHS

- About 1 mg/kg optimal
- Those in combination treatment ended up on lower doses of medication than medication treatment alone group.
 - Medication management 32.3 mg/day
 - Combined care 28.7 mg/day

Greenhill et al. Impairment and Dependent Responses to Different Methylphenidate Doses in Children with ADHD: The MTA Titration Trial. *J. Am. Acad. Child & Adol. Psychiatry* 2001 40 (2): 180-187.

MTA AT 8 YEARS

- After initial 14 months of treatment, patients returned to community care.
- No outcome differences between original treatment groups at 8 years
- Despite **overall maintenance of improvement** in functioning relative to pretreatment, the MTA group as a whole was functioning significantly less well than the non-ADHD classmate sample. Sustained improvement is achievable, but not normalization.
- Children with behavioral, socio-economic, or intellect advantage or best response to treatment have the best prognosis.

Molina et al. The MTA at 8 Years. J. Am. Acad. Child Adolesc. Psychiatry 2009; 48(5): 484-500.

PRESCHOOL ADHD TREATMENT STUDY (PATS)

- NIMH funded multi-center randomized efficacy trial
- 3-5.5 yo with severe ADHD unresponsive to 10 week psychosocial intervention
- 37/279 patient parents said behavioral treatment resulted in satisfactory improvement.

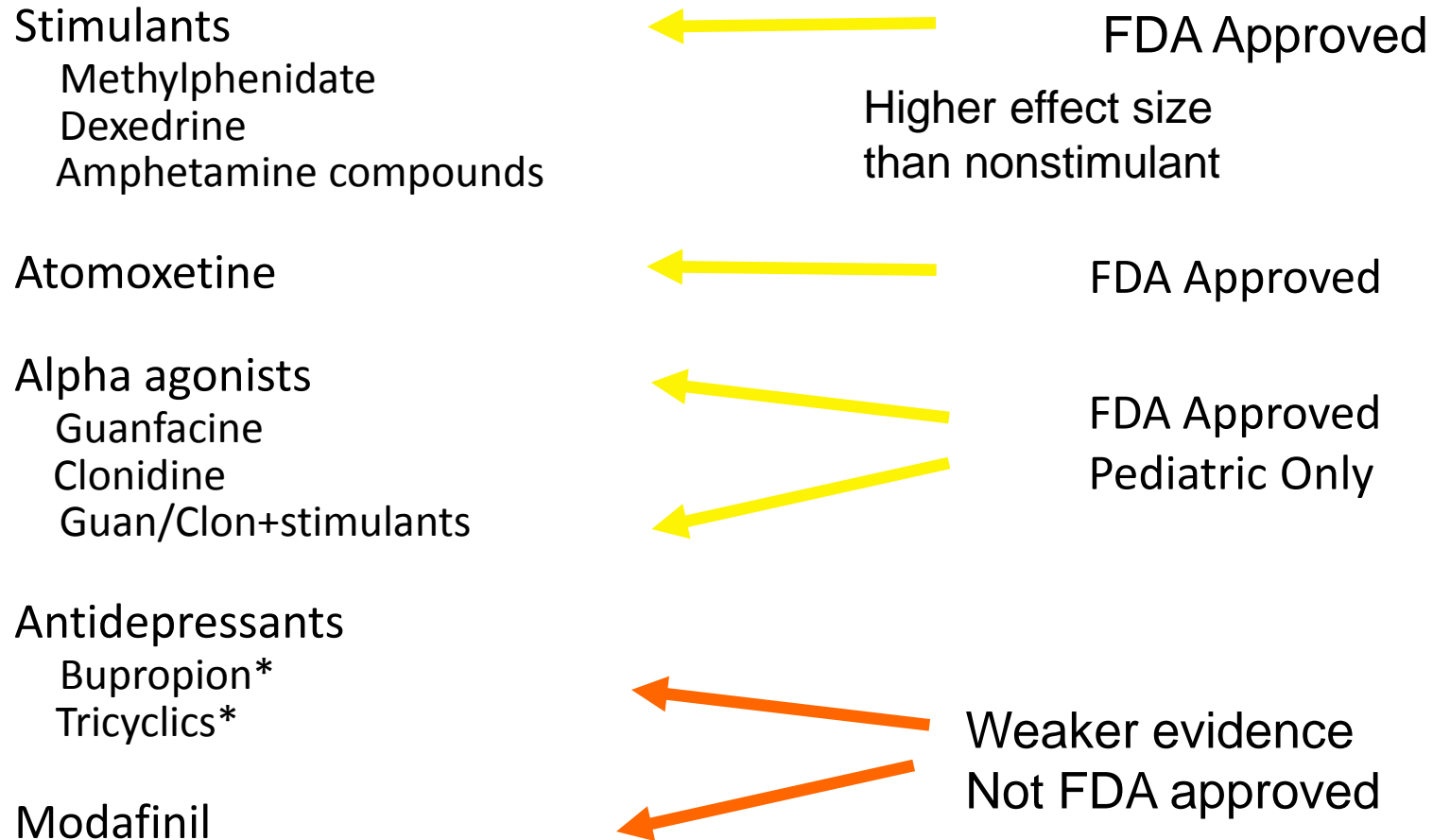
Greenhill et al. Efficacy and Safety of Immediate Release Methylphenidate Treatment for Preschoolers with ADHD. *J. Am. Acad. Child Adolesc. Psychiatry* 2006; 45(11): 1284-1293.

PATS

- Outcomes: Stimulants were effective, but
 - lower end doses (mean optimal methylphenidate dose 14.2 mg/day or 0.7 mg/kg)
 - lower effect sizes
 - higher rates of side effects (crabbiness, proneness to crying, irritability)
- PATS at 6 years:
 - Persistent ADHD diagnoses—89.9% still meeting diagnostic criteria for ADHD.
 - Patients with comorbid ODD or conduct disorder had higher rates of ADHD.
 - Girls experienced a steeper symptom decline (but girls' baseline symptoms more severe).
 - Hint of positive long-term benefit on parent ratings for those who completed the study.

Greenhill et al. Efficacy and Safety of Immediate Release Methylphenidate Treatment for Preschoolers with ADHD. *J. Am. Acad. Child Adolesc. Psychiatry* 2006; 45(11): 1284-1293. Riddle et al. Preschool ADHD (PATS) 6-Year Follow-up. *J. Am. Acad. Child Adolesc. Psychiatry* 2013; 52(3): 263-278.

ADHD: PHARMACOLOGICAL TREATMENT



*Off-label use.
Adapted from Wilens TE, Spencer TJ. *Postgrad Med.* 2010;122:97-109.

STIMULANTS

- Medications for ADHD are dopaminergic or noradrenergic.
- Evidence exists for the protective effect of stimulants on comorbid disorders.
 - Depressive and anxiety disorders
 - Disruptive behavior
 - Family quality of life
 - Repeating a grade

Biederman et al. Do stimulants protect against psychiatric disorders in youth with adhd? *Pediatrics*. 2009 Jul;124(1):71-8. Pliszka S. AACAP Work Group on Quality Issues. Practice Parameter. *J. Am. Acad. Child Adolesc. Psychiatry* 2007; 46(7):894-921.

STIMULANTS

- Can start with either a methylphenidate or an amphetamine product
 - Amphetamines FDA approved $>$ or $=$ 3 yo
 - Methylphenidates FDA approved $>$ or $=$ 6 yo
- Similar efficacy
- Side effects may be more pronounced with amphetamine products.
- Push a stimulant dose before moving on to next trial.
 - Avoid unsafe doses.

Efron et al. Side effects of methylphenidate and dexamphetamine in children with attention deficit hyperactivity disorder. *Pediatrics* 1997; Oct 100(4): 662-6.

IMMEDIATE RELEASE STIMULANTS

Name	Duration of Action	Notes
Methylphenidate (Ritalin, Methylin)	4-6 h	
D-methylphenidate (Focalin)	4-6 h	*2x potency of methylphenidate
Mixed amphetamine salts (Adderall)	4-6 h	
D-amphetamine (Zenzedi, ProCentra)	4-6 h	Liquid 5 mg/5 ml Approved ages 3-5
Methamphetamine Desoxyn	4-6 h	FDA-indicated for ADHD and obesity
Amphetamine (Evekeo)	4-6 h	Approved ages 3-5 FDA-indicated for ADHD, obesity, and narcolepsy

LONG ACTING STIMULANTS

Name	Mode of Delivery	Duration of Action
Ritalin SR, Metadate ER, Methylin ER	Gradual release	4-8 h
Metadate CD	30% IR, 70% 3 h later	7-9 h
Ritalin LA	50% IR, 50% 4 h later	7-9 h
Quillivant XR	20% IR, 80% gradual release	8-10h
Focalin XR	50% IR, 50% 4 h later	Up to 12 h
Concerta	22% IR, pump	Up to 12 h
Daytrana patch	Gradual release	3-5 h after removal
Adderall XR	50% IR, 50% 4 h later	8-12 h
Dexedrine spansule (dextroamphetamine)	50% IR, 50% gradual	10 h
Vyvanse	Activated in GI tract	10 h
Aptensio XR (methylphenidate)	40% IR, 60% ER (may be sprinkled)	12 h

TREATMENT HIERARCHY

- If IR is not tolerated or ineffective, try XR and vice versa.
- If first stimulant class is unsuccessful, try the other class.
- If stimulants are ineffective, revisit diagnosis before proceeding to non-stimulants.
- Use a single medication when possible.
- Consider adding alpha agonists if response is suboptimal but increasing stimulant not possible due to side effects.
- Adding Strattera to stimulant generally not advised but may be useful in certain cases.

VARIABILITY IN ADHD CARE IN COMMUNITY-BASED PEDIATRICS

- 93% received medication, 13% received psychosocial treatment
- Half using rating scales during assessment
- Variability at patient but also practice level
- “Almost no ADHD care follows ADHD consensus guideline recommendations for treatment”
- “the proportion of children receiving psychosocial treatment was miniscule”

Epstein et al. *Pediatrics*. 2014;134:1-8.

ARTICLE

Variability in ADHD Care in Community-Based Pediatrics

AUTHORS: Jeffrey N. Epstein, PhD,^a Kelly J. Kelleher, MD,^b Rebecca Baum, MD,^c William B. Brinkman, MD, MEd, MSc,^d James Peugh, PhD,^e William Gardner, PhD,^{f,g} Phil Lichtenstein, MD,^h and Joshua Langberg, PhDⁱ

^aDepartment of Pediatrics, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio; ^bDepartment of Pediatrics, Nationwide Children's Hospital, Columbus, Ohio; ^cDepartment of Psychiatry, Dalhousie University, Halifax, Nova Scotia, Canada; ^dThe Children's Home of Cincinnati, Cincinnati, Ohio; ^eDepartment of Psychology, Virginia Commonwealth University, Richmond, Virginia

KEY WORDS

attention deficit and disruptive behavior disorders, pediatrics, behavioral medicine, guidelines, quality

ABBREVIATIONS

AAP—American Academy of Pediatrics
ADHD—attention deficit/hyperactivity disorder
DSM-IV—*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*
EHR—electronic health record

Dr Epstein contributed to the conceptualization and the design of the study, and drafted the initial manuscript; Drs Kelleher, Baum, Brinkman, Lichtenstein, and Langberg contributed to the conceptualization and the design of the study, and reviewed and revised the manuscript; Drs Peugh and Gardner carried out the initial analysis, and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

www.pediatrics.org/cgi/doi/10.1542/peds.2014-1500

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WHAT'S KNOWN ON THIS SUBJECT: In 2000/2001, the American Academy of Pediatrics published recommendations for attention-deficit/hyperactivity disorder (ADHD) care. According to pediatricians' self-report of adoption of these guidelines, community-based ADHD care appears to be marginally adequate.

WHAT THIS STUDY ADDS: Using reviews of >1500 patient charts, this study demonstrates that community-based ADHD care is not consistent with evidence-based practice. Furthermore, variability in much of community-based ADHD care is unrelated to the provider, suggesting that innovative, system-wide interventions are needed to improve ADHD care.

abstract

NIH

BACKGROUND: Although many efforts have been made to improve the quality of care delivered to children with attention-deficit/hyperactivity disorder (ADHD) in community-based pediatric settings, little is known about typical ADHD care in these settings other than rates garnered through pediatrician self-report.

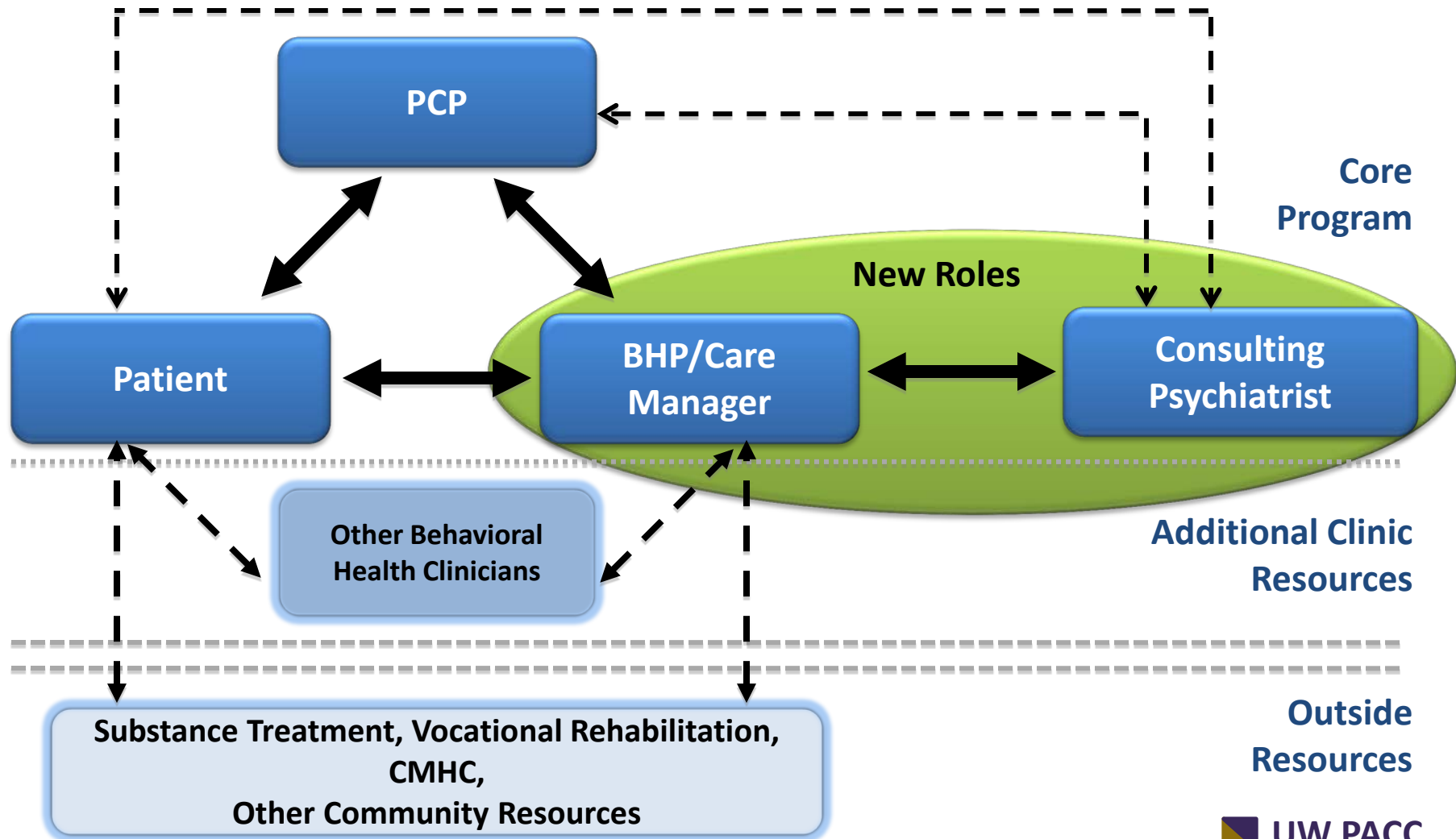
METHODS: Rates of evidence-based ADHD care and sources of variability (practice-level, pediatrician-level, patient-level) were determined by chart reviews of a random sample of 1594 patient charts across 188 pediatricians at 50 different practices. In addition, the associations of Medicaid-status and practice setting (ie, urban, suburban, and rural) with the quality of ADHD care were examined.

MEDICATION ADHERENCE AND CONTINUITY

- ½ of the children experienced their first 30-day gap in medication supply within the first 3 months of treatment
- Fewer than ½ of the parents had contact with their physicians within the first month of medication initiation with the average time being greater than 2 months
- The average time to the first medication change was over 3 months.
- Results indicated that early physician contact and titration were related to greater continuity and medication supply over a period of 1 year

Brinkman WB, Baum R, Kelleher KJ, Peugh J, Gardner W, Lichtenstein P, Langberg J, Epstein JN. Relationship Between Attention-Deficit/Hyperactivity Disorder Care and Medication Continuity. *J Am Acad Child Adolesc Psychiatry*. 2016 Apr;55(4):289-94.

ADHD TREATMENT IN INTEGRATIVE SETTINGS: THE UW INTEGRATED CARE MODEL



ADVERSE EFFECTS OF ADHD MEDICATIONS

Adverse Effect	MPH ¹⁻⁵	Amph. ⁵⁻⁷	ATX ⁸⁻¹¹	Alpha-2 Agonists ¹²⁻¹⁵
↓ Appetite/anorexia	+++	+++	+	-
Abdominal pain	+	+	++	-
Nausea/vomiting	-	-	++	-
Irritability	++	++	+/-	+/-
Somnolence/asthenia	-	-	+++	+++
Sleep problems/Insomnia	++	++	-	-
Emotional lability	++	++	+	+
Depressed mood	+	+	-	-
Tics	+	+	-	-
Light-headed/Dizzy	-	-	+	++
Increased heart rate	++	++	+++	-
Increased blood pressure	++	++	++	-

1. Pelham *Pediatr* 2001; 2. Stein *Pediatr* 2003; 3. Swanson *Pediatr* 2004; 4. Wolraich *Pediatr* 2001; 5. Pelham *Pediatr* 1999; 6. Biederman *Pediatr* 2002; 7. McCracken *JAACAP* 2003; 8. Michelson *Am J Psych* 2002; 9. Spencer *J Clin Psych* 2002; 10. Michelson *Pediatr* 2001; 11. Kelsey *Pediatr* 2004 .

SIDE EFFECTS OF STIMULANTS

- Appetite decrease, insomnia, headaches, stomachache, dry mouth, emotional lability/aggression, priapism
- Can cause a slowing in growth velocity for weight and height
- Adrenergic effect on heart rate (5bpm in MTA)
- Obtain baseline levels.
- Options: decrease dose, switch, augment (eg, add clonidine or melatonin for sleep)

Biederman J. Spencer TJ. Monuteaux MC. Faraone SV. A naturalistic 10-year prospective study of height and weight in children with attention deficit hyperactivity disorder grown up. *Journal of Pediatrics* 2010; 157 (4): 635-40. Pliszka S. AACAP Work Group on Quality Issues. Practice Parameter. *J. Am. Acad. Child Adolesc. Psychiatry* 2007; 46(7):894-921.

SIDE EFFECTS: CARDIAC CONCERNS

- AHA says obtaining ECG reasonable.
- AAP does not recommend routine ECG.
 - Consider ECG when on high dose, combining medications, BP/pulse change from a medication, or any cardiac symptoms.
- ADHD medications do not appear to increase the risk of serious cardiovascular events.
 - 1,200,438 patients with ADHD prescription matched with 2 nonusers; 2,579,104 person years: hazard ratio 0.7.

Cooper et al. ADHD Drugs and Serious Cardiovascular Events in Children and Young Adults. NEJM 2011; 365 (20): 1896-904.

SIDE EFFECTS: CARDIAC CONCERNS

- Physical exam before initiating stimulant treatment
- Ask about palpitations, syncope, chest pain, exercise intolerance, family history of sudden death under age 35 (including drowning and motor vehicle accidents).
- Patients with known cardiac issues should be referred to cardiology before a stimulant trial.
- During treatment, monitor blood pressure and heart rate and ask about development of cardiac symptoms.

Perrin et al. Cardiovascular Monitoring and Stimulant Drugs for Attention-Deficit/Hyperactivity Disorder. *Pediatrics* 2008; 122(2): 451-453.

SIDE EFFECTS: TICS AND ADHD

- High comorbidity
 - Multi-site international database of 3500 tic disorder patients: 60% also have ADHD
- Stimulants and Tics
 - “Although stimulants have not been shown to worsen tics in most people with tic disorders, they may nonetheless exacerbate tics in individual cases. In these instances, treatment with alpha agonists or atomoxetine may be an alternative.”

--Cochrane Review, 2011

Freeman RD, Fast DK, Burd L, Kerbeshian J, Robertson MM, Sandor P. An international perspective on Tourette syndrome: selected findings from 3500 individuals in 22 countries. *Developmental Medicine and Child Neurology* 2000; 42(7): 436-47. Pringsheim T, Steeves T. Pharmacologic Treatment for ADHD in Children with Comorbid Tic Disorders. *Cochrane Database of Systemic Reviews* 2011: (4):CD007990.

ADHD AND IRRITABILITY

NEW RESEARCH

Treatment of Children With Attention-Deficit/Hyperactivity Disorder (ADHD) and Irritability: Results From the Multimodal Treatment Study of Children With ADHD (MTA)

Lorena Fernández de la Cruz, PhD, Emily Simonoff, MD, James J. McGough, MD, Jeffrey M. Halperin, PhD, L. Eugene Arnold, MD, MEd, Argyris Stringaris, MD, PhD, MRCPsych

Objective: Clinically impairing irritability affects 25% to 45% of children with attention-deficit/hyperactivity disorder (ADHD); yet, we know little about what interventions are effective in treating children with ADHD and co-occurring irritability. We used data from the Multimodal Treatment Study of Children With ADHD (MTA) to address 3 aims: to establish whether irritability in children with ADHD can be distinguished from other symptoms of oppositional defiant disorder (ODD); to examine whether ADHD treatment is effective in treating irritability; and to examine how irritability influences ADHD treatment outcomes.

Method: Secondary analyses of data from the MTA included multivariate analyses, and intent-to-treat random-effects regression models were used.

Results: Irritability was separable from other ODD symptoms. For treating irritability, systematic stimulant treatment was superior to behavioral management but not to routine community care; a combination of stimulants

and behavioral treatment was superior to community care and to behavioral treatment alone, but not to medication alone. Irritability did not moderate the impact of treatment on parent- and teacher-reported ADHD symptoms in any of the 4 treatment groups.

Conclusion: Treatments targeting ADHD symptoms are helpful for improving irritability in children with ADHD. Moreover, irritability does not appear to influence the response to treatment of ADHD.

Clinical trial registration information—Multimodal Treatment Study of Children With Attention Deficit and Hyperactivity Disorder (MTA); <http://www.clinicaltrials.gov>; NCT00000388.

Key Words: irritability, attention-deficit/hyperactivity disorder, oppositional defiant disorder, treatment outcomes

J Am Acad Child Adolesc Psychiatry 2015;54(1):62–70.

SIDE EFFECTS: ADHD AND IRRITABILITY

- Recent publication from the MTA examined irritability (not headstrong oppositional behavior) and treatment outcomes.
 - Irritability contributed to impairment and showed longitudinal continuity.

Intervention	Effect Size
Combined treatment	0.82
Medication management	0.63
Community comparison	0.48
Behavioral treatment	0.42

Fernandez de la Cruz, et al. Treatment of Children with ADHD: Results from the MTA. *Journal of the American Academy of Child & Adolescent Psychiatry* 2015;54(1):62-70.

SIDE EFFECTS: ADHD AND SLEEP

Stimulant Medications and Sleep for Youth With ADHD: A Meta-analysis

Katherine M. Kidwell, MA, Tori R. Van Dyk, MA, Alyssa Lundahl, MA, Timothy D. Nelson, PhD

abstract

CONTEXT: Mixed findings exist on whether stimulant medications alter youth sleep.

OBJECTIVE: To determine the effect of stimulant medications on sleep.

DATA STUDIES: Studies published through March 2015 were collected via CINAHL, PsycINFO, and PubMed. References of retrieved articles were reviewed.

STUDY SELECTION: Eligibility criteria included studies with children/adolescents who had attention-deficit/hyperactivity disorder (ADHD), random assignment to stimulants, and objective sleep measurement. Studies that did not include information about key variables were excluded.

DATA EXTRACTION: Study-level, child-level, and sleep data were extracted by 2 independent coders. Effect sizes were calculated by using random effects models. Potential moderators were examined by using mixed effect models.

RESULTS: A total of 9 articles ($N = 246$) were included. For sleep latency, the adjusted effect size (0.54) was significant, indicating that stimulants produce longer sleep latencies. Frequency of dose per day was a significant moderator. For sleep efficiency, the adjusted effect size (-0.32) was significant. Significant moderators included length of time on medication, number of nights of sleep assessed, polysomnography/actigraphy, and gender. Specifically, the effect of medication was less evident when youth were taking medication longer. For total sleep time, the effect size (-0.59) was significant, such that stimulants led to shorter sleep duration.

LIMITATIONS: Limitations include few studies, limited methodologic variability, and lack of unpublished studies.

CONCLUSIONS: Stimulant medication led to longer sleep latency, worse sleep efficiency, and shorter sleep duration. Overall, youth had worse sleep on stimulant medications. It is recommended that pediatricians carefully monitor sleep problems and adjust treatment to promote optimal sleep.

Kidwell KM, Van Dyk TR, Lundahl A, Nelson TD. Stimulant Medications and Sleep for Youth With ADHD: A Meta-analysis. *Pediatrics*. 2015 Dec;136(6):1144-53. doi: 10.1542/peds.2015-1708. Review.

ATOMOXETINE

- Brand name: Strattera
- Noradrenergic reuptake inhibitor
- Once daily or twice daily dosing
- Start at 0.5 mg/kg/day for 2 weeks. Increase to 1.2 mg/kg/day.
- Maximum 100 mg or 1.4 mg/kg (whichever is less).
- Metabolized by P450 2D6 pathway
- Approved $>$ or $=$ 6 yo

Pliszka S. AACAP Work Group on Quality Issues. Practice Parameter. J. Am. Acad. Child Adolesc. Psychiatry 2007; 46(7):894-921.

ATOMOXETINE

- Can be helpful to anxiety
- Can take up to 6 weeks for benefit
 - Counsel family on delayed effect compared to stimulants.
- Effect size 0.6 (similar to guanfacine)
 - For comparison, effect size of stimulants approximately 0.9
 - For reference, effect size 0.2 is mild, 0.6 is moderate, and 0.8 is high.

Pliszka S. AACAP Work Group on Quality Issues. Practice Parameter. J. Am. Acad. Child Adolesc. Psychiatry 2007; 46(7):894-921.

ATOMOXETINE RESPONSE

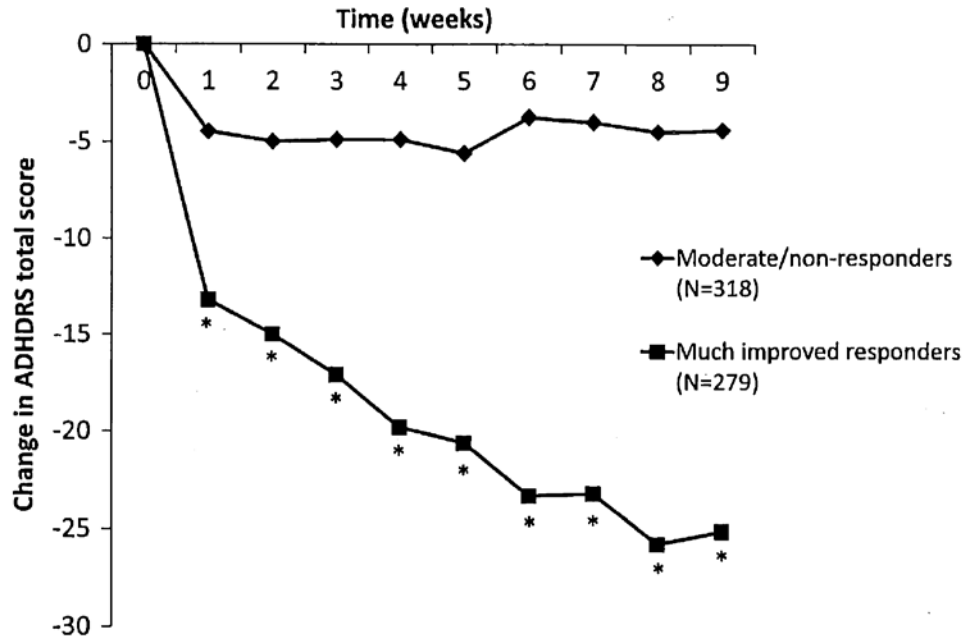


Fig. 1 Temporal course of changes in the Attention-Deficit/Hyperactivity Disorder Rating Scale–IV–Parent Version: Investigator Administered and Scored (ADHD-RS total score). Unlike moderate/nonresponders (filled diamonds), much improved responders (filled squares) experienced sharp decreases (i.e., improvements) in the ADHD-RS total score within the first 1 to 4 weeks, with continued divergence at later time points. * $p < .001$ at each time point across response groups by week.

Newcorn et al. Clinical Responses to Atomoxetine in Attention-Deficit/Hyperactivity Disorder. *J. Am. Acad. Child Adolesc. Psychiatry* 2009; 48 (5): 511-518.

ATOMOXETINE SIDE EFFECTS

- GI distress, sedation (insomnia in adults)
- Possible suppression in growth velocity
- Not recommended if structural cardiac abnormalities, cardiomyopathy, or rhythm abnormalities
- Warning for liver disease (2 reports; none in 6000 patients in clinical trial)
 - Monitoring of LFTs not recommended.
- Boxed warning for suicidal thinking (risk of 4/1000 in a large controlled study); no completed suicides

Micromedex, accessed 5/4/12.

ALPHA AGONISTS

- May be more effective for hyperactivity than inattention
- Clonidine more soporific; guanfacine may be better for inattention
- Soporific effect may wane after 2-3 weeks
- May not see full benefit for 4-6 weeks
- Sedation, dizziness, hypotension, bradycardia
- Review personal and family cardiac history
- Review risk of rebound hypertension

GUANFACINE

	Starting dose	Maximum dose	Half life	FDA
Guanfacine	<45kg, 0.5 mg qhs; >45 kg, 1 mg qhs	2 mg (27-40.5 kg); 3 mg (40.5-45 kg); 4 mg (>45 kg)	14 h	Not approved
Guanfacine extended release (Intuniv)	1 mg daily	From 3 mg (25 kg) to 7 mg (58.5 Kg and above) Alt: 0.05-0.12 mg/kg	16 h	Approved 6-17yo

Wait one week between dose increases.

Pliszka S. AACAP Work Group on Quality Issues. Practice Parameter. J. Am. Acad. Child Adolesc. Psychiatry 2007; 46(7):894-921.

CLONIDINE

	Starting dose	Maximum dose	Half life	FDA
Clonidine	<45kg, 0.05 mg qhs >45 kg, 0.1 mg qhs	0.2 mg (27-40 kg); 0.3 mg (40-45 kg); 0.4 mg (>45 kg).	12 h	Not approved
Clonidine extended release (Kapvay)	0.1 mg qhs; doses greater than 0.1 mg should be bid	0.4 mg	12-16 h	Approved 6-17yo

Wait one week between dose increases.

Pliszka S. AACAP Work Group on Quality Issues. Practice Parameter. J. Am. Acad. Child Adolesc. Psychiatry 2007; 46(7):894-921.

BUPROPION

- Brand name: Wellbutrin
- **Not FDA approved for pediatric use**
- Combined dopaminergic/noradrenergic mechanism of action
- Consider when primary treatments have failed or in patients with co-occurring mood disorders, substance abuse, or smoking.

Micromedex, accessed 5/4/12.

BUPROPION

- Side effects: insomnia, appetite decrease, less commonly tics, seizures
- Risk of drug induced seizures increases 10x at doses > 450 mg/day
- Starting dose less than 150 mg/day or 3mg/kg/day
- Maximum dose less than 300 mg/day or 6 mg/kg/day
- No single dose greater than 150 mg

Kratochvil CJ, Daughton JM. Review of ADHD Pharmacotherapies: Advantages, Disadvantages, and Clinical Pearls. *J. Am. Acad. Child Adolesc. Psychiatry* 2009; 48: 240-248.

ALTERNATIVE TREATMENTS

- Omega-3s: some evidence for benefit based upon meta-analyses (effect size: 0.31)
- Dietary: Elimination of food dye may provide small benefit in sensitive patients
- Neurofeedback and computer training: Some evidence but not well-established; remains controversial
- Physical exercise: evidence for benefit for executive functioning and behavioral disturbances