#CHAIR2017

10TH ANNUAL CHAIR SUMMIT

neuroscience CME

Master Class for Neuroscience Professional Development

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ADHD Targets and Treatments

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Disclosures

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- ***Consultant:*** Akili Interactive Labs.; Alcobra Pharma; Jazz Pharmaceuticals Inc.; KemPharm, Inc.; Medgenics, Inc.; Otsuka America Pharmaceutical, Inc.; Rhodes Pharmaceuticals L.P.; Shire; Sunovion Pharmaceuticals Inc.

Learning Objective 1

Recognize the early presentation of ADHD to accurately diagnose patients with ADHD.

Learning Objective 2

Utilize evidence-based treatment in patients with ADHD.

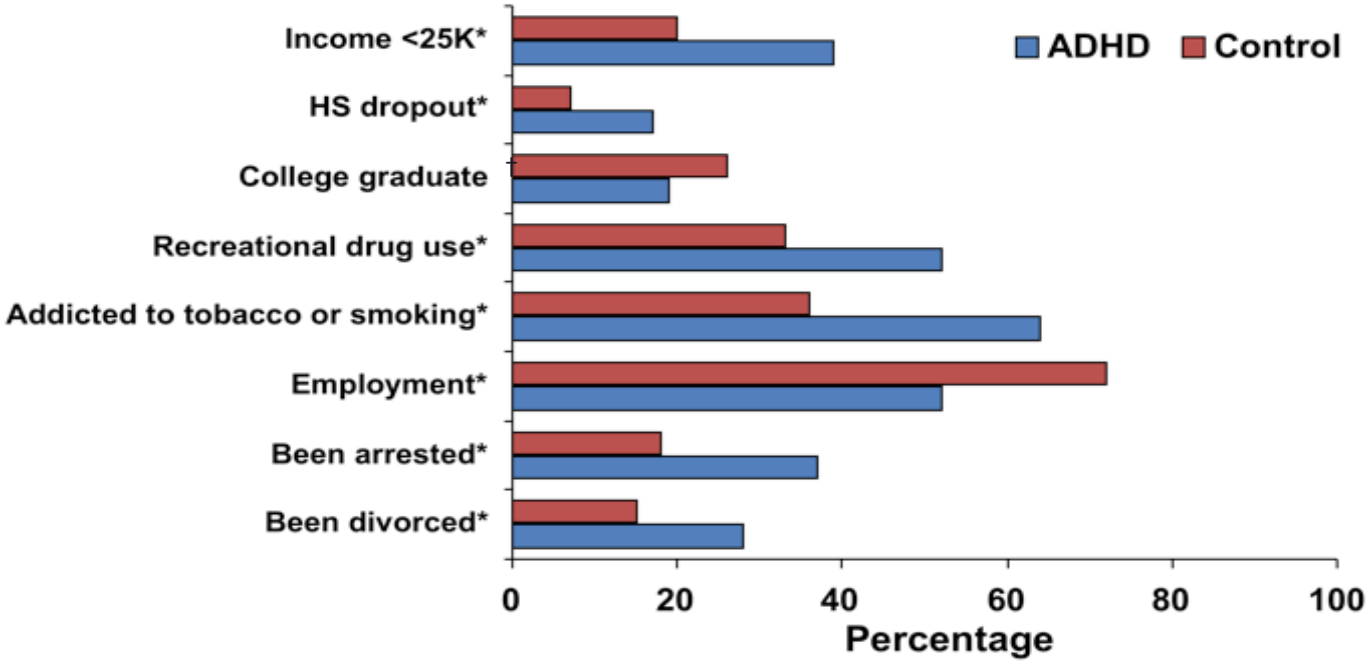
Learning Objective 3

Use shared decision-making with patients and family members to develop strategies to help manage the impact of ADHD on daily and long-term functioning.

Overview

- Introduction
- Diagnosis of ADHD
- Current & Emerging Therapies
- Addressing Treatment Adherence
- Q & A

Real-Life Consequences of ADHD



Survey of 500 community adults with ADHD compared with 501 age- and gender-matched controls; 36% of ADHD patients reported medication use

*$p \leq .001$; †$p < .01$

Biederman J, et al. *J Clin Psychiatry*. 2006;67(4):524-540; Biederman J, et al. *MedGenMed.* 2006;8(3):12.

Real-Life Consequences of ADHD

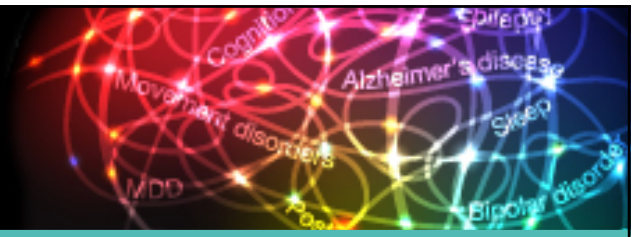
	# of deaths	Person-years	Mortality rate per 10000 person-years	Crude model MRR (95% CI)	Partly adjusted model MRR (95% CI)	Fully adjusted model MRR (95% CI)
Age at first ADHD diagnosis						
1-5	10	29944	3.34	2.23 (1.11-2.91)	1.97 (0.99-3.46)	1.86 (0.93-3.27)
6-17	59	136048	4.34	1.83 (1.40-2.35)	1.63 (1.25-2.09)	1.58(1.21-2.03)
> 17	38	17057	22.28	5.24 (3.73-7.12)	4.46 (3.18-6.07)	4.25 (3.03-5.78)
No ADHD	5473	24724510	2.21	1.00 (reference)	1.00 (reference)	1.00 (reference)
p values				$p < .0001$	$p < .0001$	$p < .0001$
Overall cohort	5580	24907560	2.24			

Based on prospective analysis of 1.92 million children born between 1981-2011

Dalsgaard S, et al. *Lancet*. 2015;385:2190-2196.

DSM-V Criteria for ADHD:

Symptoms (6/9 age <16 years; 5/9 >17 years)



Inattentive Symptoms:

- Fails to give close attention to details
- Has difficulty sustaining attention
- Does not seem to listen
- Does not follow through on instructions
- Has difficulty organizing tasks or activities
- Avoids tasks requiring sustained mental effort
- Loses things necessary for tasks
- Is easily distracted
- Is forgetful in daily activities

Hyperactive/Impulsive Symptoms:

- Fidgets with hands or feet or squirms in seat
- Leaves seat in classroom inappropriately
- Runs about or climbs excessively (or internal restlessness)
- Has difficulty playing quietly
- Is “on the go” or acts as if “driven by a motor”
- Talks excessively
- Blurts out answers before questions are completed
- Has difficulty awaiting turn
- Interrupts or intrudes on others

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* 2013.

Main Changes to ADHD DSM-V vs. DSM-IV

- Similar symptoms (e.g., 9 symptoms of inattention and/or hyperactive-impulsivity) – more prompts added
- Change in symptom requirements:
  - < 17 years: 6/9 hyperactivity-impulsivity and/or 6/9 of inattention
  - > 17 years: 5/9 hyperactivity-impulsivity and/or 5/9 of inattention
- Change in symptom onset: prior to age 12 years
- Change in "clinically significant impairment" to relative impairment
- Change in exclusion: diagnosis can be made in Autism Spectrum Disorder

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. 2013.

ADHD Diagnosis: Developmental Considerations

- Preschool Age
  - More prominent hyperactivity/impulsivity
  - May be difficult to distinguish from typical development
- School-Age
  - Emergence of school difficulties
  - Modal age for diagnosis
- Adolescents
  - Unique impairments emerge – driving, risky sexual behavior, drug use
  - Challenge – adolescents neither “old kids” nor “young adults”
- Adults
  - Might be challenging to obtain reliable history; may have long history of compensatory behaviors
  - Comorbidities and variability in vocational/family settings can confound diagnosis

Source of Clinical Data for Diagnosis Dependent on Development Level

7 12 18 25

Child	Adolescent	Adult
Teacher	Self	Self
Parent	Teacher	Spouse/Partner
Self	Parent	Sibling
Grandparent	Grandparent	Friend
Other Adult	Other Adult	Co-worker

Behavioral Observation **Self-Report**

ADHD Assessment

- Life history (with information from parents and teachers or school records, if available for adolescents)
- Self report for adults
- Mental status exam
- Rating scales – measuring core and broad features
- Medical history review; cardiac and neurologic status, blood pressure/pulse
- If medical history is unremarkable, laboratory or neurological testing is not indicated
- Assess for comorbidity (psychiatric, cognitive, psychosocial, medical)

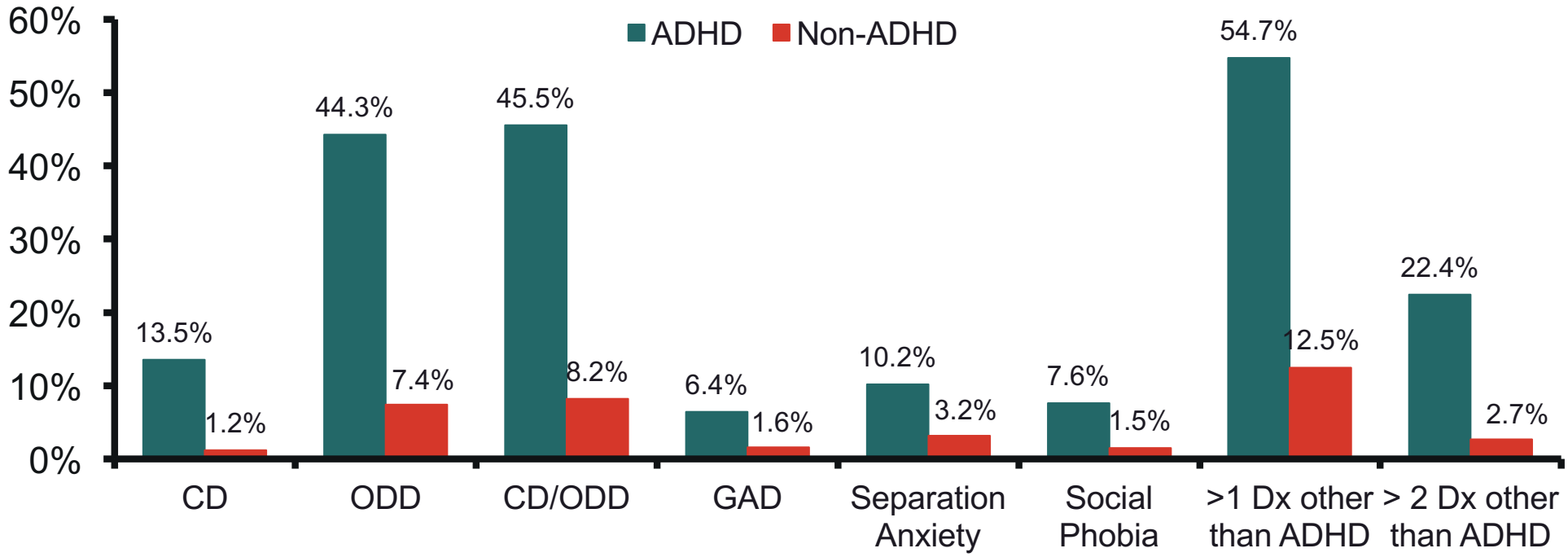
Pliszka, S. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894-921.

Representative ADHD Rating Scales

- Adult Diagnostic Scales
- Conners' Adult ADHD Diagnostic Interview for DSM-IV (CAADID)
- Barkley's Current Symptoms Scale (CSS)
- Adult ADHD Clinical Diagnostic Scale (ACDS)
- Brown ADD Rating Scales
- Symptom Assessment
- Adult ADHD Investigator Symptom Rating Scale (AISRS)
- 18-question Adult ADHD Self-Report Scale (ASRS) Symptom Checklist and 6-question Screener v1.1
- Conners' Adult ADHD Rating Scales (CAARS)

Adler LA, et al. *Attention-Deficit Hyperactivity Disorder in Adults and Children*. 2015.

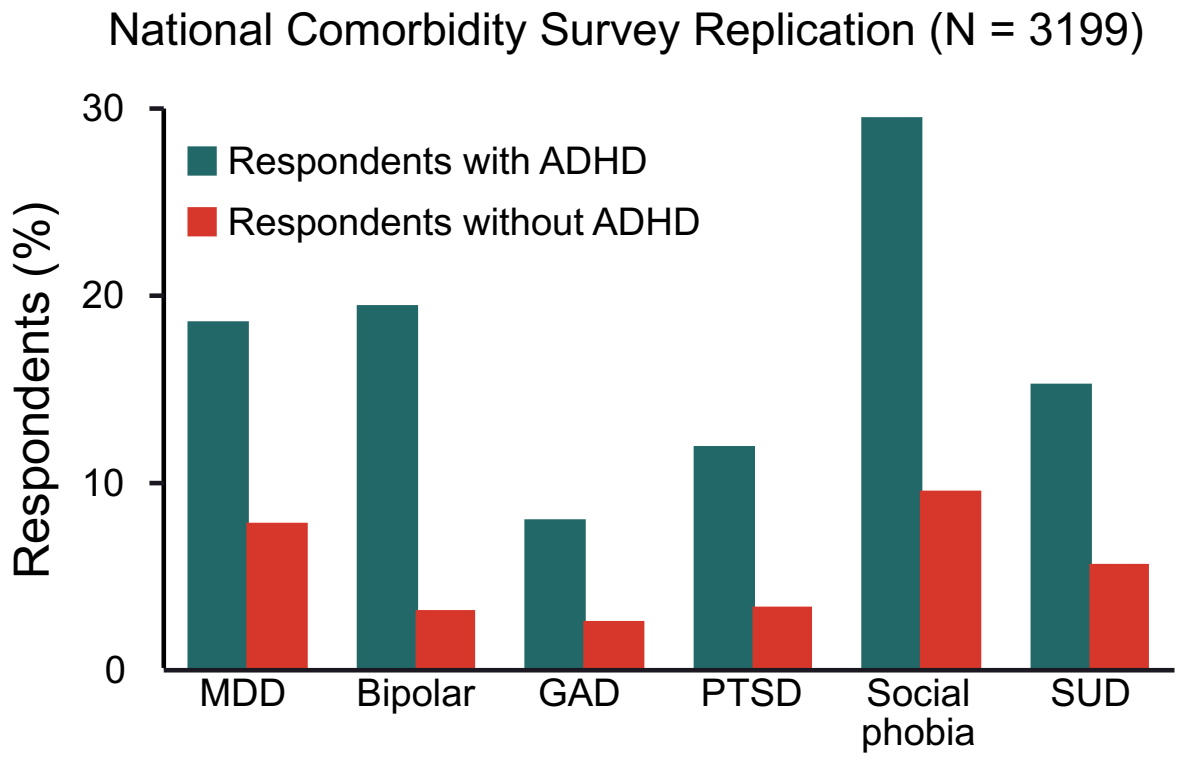
Common Comorbid Psychiatric Disorders: Children



CD = conduct disorder; ODD = oppositional defiant disorder; GAD = generalized anxiety disorder

Cuffe SP, et al. *J Atten Disord*. 2015.pii:1087054715613437.

Common Comorbid Psychiatric Disorders: Adults



Among respondents age18-44 yrs with ADHD, comorbid disorder within previous 12 months.
For all comparisons, $p < .05$
MDD = major depressive disorder; PTSD = post-traumatic stress disorder; SUD = substance use disorder
Kessler RC, et al. *Am J Psychiatry*. 2006;163(4):716-723.

Pharmacologic Treatments Approved for Children with ADHD

- Wide range of products available in a range of formulation options
- Stimulants vs. non-stimulants
- Immediate vs. extended release (time course differences)
- Route of administration (capsule/pill, tablet, liquid, transdermal)

Wilens TE, et al. *Postgrad Med*. 2010;122(5):97-109; Bhat V, et al. Available at http://www.pharmaceutical-journal.com/research/review-article/considerations-in-selecting-pharmacological-treatments-for-attention-deficit-hyperactivity-disorder/20200602.article. Accessed October 31, 2017.

Pharmacologic Treatments Approved for Adult ADHD

Amphetamine-based Formulations	Duration of Effect
Mixed Amphetamine Salts Extended Release	~12 hours
Lisdexamfetamine	~12 hours
Methylphenidate-based Formulations	
OROS Methylphenidate	~12 hours
Dexmethylphenidate XR	10-12 hours
Nonstimulants	
Atomoxetine	5-22 hours
Guanfacine XR*	10 – 30 hours

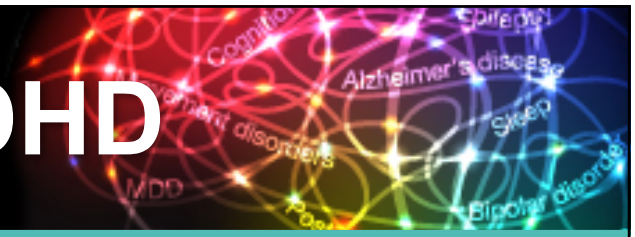
*Guanfacine XR is used in children ≥ 6 years and teenagers for the treatment of ADHD.
[Package Inserts]. Drugs@FDA Website.

Meta-analysis of Non-pharmacological Therapies for Children and Adolescents

	No. of Trials	N	Effect (OR, 95% CI)
Cognitive Training (Working Memory or Attention Training)	10	339	1.32 (0.71- 2.52)
Behavioral Therapy (Parent, Child, Teacher, or Combination Training	25	1385	0.58 (0.33 – 0.99)
Behavioral Therapy with Cognitive Training	1	26	3.39 (0.60 – 19.58)
Neurofeedback	10	271	0.59 (0.31 – 1.14)
Herbal Therapies	2	52	0.59 (0.17 – 1.99)
Polyunsaturated fatty acids	3	124	2.14 (0.83 – 5.57)

Catalá-López F, et al. *PLOS ONE*. 2017;12(7):e0180355.

Emerging Therapies for ADHD



- Wide range of both pharmacological and non-pharmacological treatments under investigation
  - Medications with novel mechanisms of action
  - Devices, including therapeutic software
  - Novel approaches to behavior therapy
- Clinicaltrials.gov lists 122 studies actively recruiting for ADHD trials

Emerging Therapies for ADHD: Methylphenidate Formulations

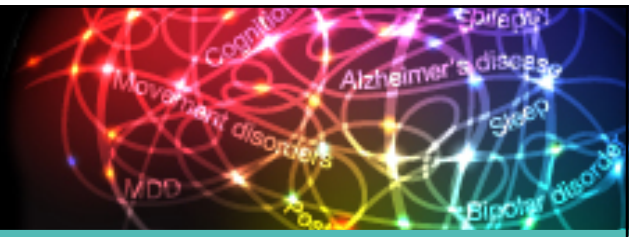
- Methylphenidate extended-release oral suspension (MEROS)
- Methylphenidate extended-release chewable capsules (NWP_{09})
- Methylphenidate hydrochloride extended-release capsules
- Methylphenidate extended-release oral disintegrating tablets (XR-ODT)
- ORADUR technology (once-daily tamper-resistant formulation) methylphenidate sustained release
- Methylphenidate modified-release (HLD-200)

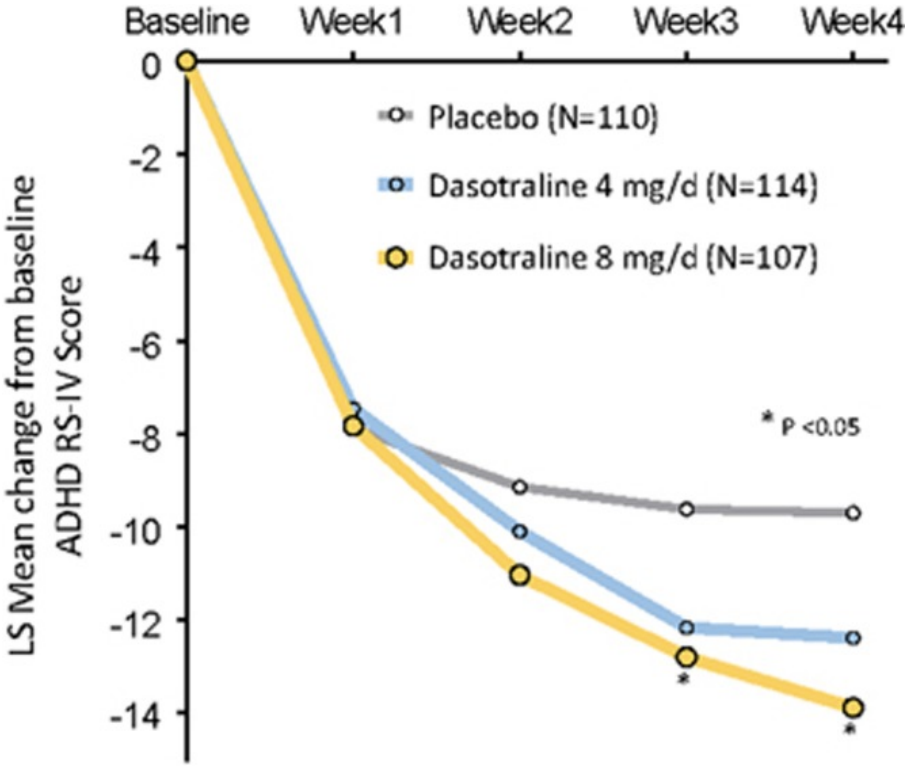
Cortese S, et al. *CNS Drugs*. 2017;31(2):149-160.

Emerging Therapies for ADHD: Non-Stimulants

- Dasotraline
  - Dopamine and norepinephrine reuptake inhibitor (DNRI) for children, adolescents, and adults
  - Phase III
- Metadoxine ER
  - 5-HT2B selective agonist and GABA modulator
  - Phase III trial halted due to failure to meet endpoint
- Centanafadine
  - Norepinephrine, serotonin and dopamine reuptake inhibitor
  - Phase II

Efficacy of Dasotraline in Adults with ADHD





Koblan KS, et al. *Neuropsychopharmacology*. 2015;40(12):2745-2752.

Efficacy of Dasotraline in Children with ADHD

- Children aged 6-12 yrs old meeting *DSM-V* diagnostic criteria for ADHD; randomized 1:1:1 to 6 weeks double-blind, once-daily dasotraline (2 or 4 mg/d) or placebo
- Results:
  - ADHD Rating Scale Version IV –Home Version (ADHD RS-IV HV) significantly improved from baseline to week 6 with dasotraline 4 mg/d vs placebo (least squares mean change from baseline: -17.53 [95% CI: -20.12,-14.95] vs. -11.36 [13.89, -8.83], respectively; effect size: 0.48, $p < .001$.
  - Dasotraline 4 mg group also had significant improvements on the inattentive and hyperactivity subscale scores compared to placebo
  - Dasotraline 2mg group not statistically significantly different from placebo
  - AEs: combined insomnia, decreased appetite, weight loss, irritability, nasopharyngitis, and nausea

Goldman S, et al. The American Professional Society of ADHD and Related Disorders. 2017. Abstract S23.

Optimizing Outcomes Through Adherence and Engagement: Developing an Individualized Treatment Plan

- Pharmacotherapy is typically considered among first-line
- Cognitive / Behavior therapy may be recommended initially
- Once treatment is established, practitioner's role may also include:
  - Coordinating with team health service regarding ADHD treatment and continuity between settings
  - Therapeutic use exemptions
  - Preparing the patient (and family) for major transitions

Pliszka S. *J Am Acad Child Adolesc Psychiatry*. 2007;46(7):894-921.

Adverse Effects of ADHD Medications Leading to Non-Adherence

Frank E, et al. *J Clin Psychiatry*. 2015;76(11):e1459-1468.

Optimizing Outcomes Through Adherence and Engagement: ADHD as a Chronic Condition

TABLE

SIX "PILLARS" OF THE CHRONIC CARE MODEL FOR CHILD HEALTH

"Pillar"	*Description*	*Example (as applied to ADHD care)*
Decision support	Tools available to help clinicians make evidence-based decisions in everyday practice	AAP/NICHQ ADHD Toolkit, ADHD visit templates, EMR prescribing tools, access to psychiatrists for telephone consultations
Delivery system design	Division of labor among practice members to streamline ADHD care	Developing relationships with primary care practices that streamline the referral and follow-up process
Clinical information systems	Computerized systems that enable tracking of patients	Primary care physician and psychiatrist using the same EMR system
Family and self-management support	Helping parents and patients acquire disease management and advocacy skills	Nurse educators, frequent follow-up visits
Community resources and policies	Community organizations (e.g., schools) developing policies to accommodate children with ADHD	Special education programs/Individualized Educational Plans in schools, parent support groups (e.g., CHADD)
Health care organizations	Practice organization, insurance, and public policies regarding ADHD care	Insurance formularies, public funding for ADHD care, mental health parity, telepsychiatry

Note. AAP = American Academy of Pediatrics; ADHD = attention-deficit/hyperactivity disorder; CHADD = Children and Adults with Attention-Deficit/Hyperactivity Disorder; EMR = electronic medical record; NICHQ = National Initiative for Children's Health Care Quality.

Van Cleave J, et al. *J Psychosoc Nurs Ment Health Serv*. 2008;46:28-37.

Call to Action

- Increase your recognition and diagnosis of ADHD in children, adolescents, and adults
- Tailor treatment strategies to the developmental stage of the individual
- Incorporate the patient and parent/family members in treatment decisions to optimize adherence and treatment outcomes

Questions & Answers

Don’t forget to fill out your evaluations to collect your credit.