ADHD: Current Concepts & Controversies

Nathaniel M. Rickles, Pharm.D., Ph.D., BCPP
Associate Professor of Pharmacy Practice & Administration
Department of Pharmacy Practice
Northeastern University School of Pharmacy

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School of Pharmacy

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Outline

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- Clinical Presentation
- ADHD- Diagnostic Criteria
- Epidemiology of ADHD
- Costs with ADHD
- ADHD Treatments- Pharmacologic/Non-Pharmacologic
- ADHD Policy Considerations
- Conclusion

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Learning Objectives

- Distinguish between childhood and adult presentations of Attention-Deficit/ Hyperactivity Disorder (ADHD).
- Identify diagnostic tools use childhood and adult forms of ADHD.
- Describe pharmacologic and non-pharmacologic options in the treatment of childhood and adult ADHD.
- Evaluate the role of off-label medications for the treatment of childhood and adult ADHD.

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Learning Objectives (Cont.)

- Develop an optimal monitoring plan to evaluate efficacy and toxicity of ADHD treatments.
- Analyze the clinical, socioeconomic, and regulatory challenges and controversies of ADHD treatments for both children and adults.

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Clinical Presentation

- MF is a 34 y/o male who reports to his primary care doctor difficulty concentrating at work and sitting still for long (restlessness). His wife complains he is constantly forgetting appointments and often irritable. He is easily bored with activities. He reports having had difficulty concentrating in the classroom when a child and often getting in trouble.

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DSM-IV[1]

- A. Either 1 or 2 situations:
  - 1. ≥ 6 of the following symptoms of inattention persisting for 6 months or more
    - Often fails to give close attention- makes careless mistakes in schoolwork, work, or other activities
    - Often has difficulty sustaining attention in tasks/play activities
    - Often doesn't follow through on instructions, fails to finish tasks
    - Often does not listen to when spoken directly
    - Often difficulty organizing tasks/activities
    - Often avoids to engage in tasks that require sustained mental effort
    - Often loses things necessary for tasks/activities
    - Easily distracted by extraneous stimuli
    - Forgetful in daily activities

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DSM-IV[1] (Cont.)

- 2. ≥ 6 of the following symptoms of hyperactivity persisting for 6 months or more
  - Often fidgets with hands/feet or squirms in seat
  - Often leaves seat in situations in which remaining seated is expected
  - Often runs about/climbs excessively in situations that are inappropriate (feelings of restlessness)
  - Often has difficulty playing/engaging in leisure activities quietly
  - Acts as if driven by a motor
  - Talks excessively
  - Blurts out answers before questions have been completed
  - Difficulty waiting turn
  - Interrupts or intrudes on others

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DSM-IV[1] (Cont.)

- B. Some hyperactive-impulsive or inattentive sxs that caused impairment were present before 7 yr age
- C. Some impairment from sxs is present in two or more settings
- D. Must be clear evidence of clinically significant impairment in social, academic, or occupational functioning
- E. Not accounted for by any other mental disorders
- Subtypes: Only have A1 (inattentive subtype) or A2 (hyperactive subtype) or A1 and A2 (combined subtype).

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Children vs. Adults

- Hyperactivity, a common symptom in children with ADHD, is not as evident in adults.
- Adults may experience restlessness, and fidgeting, difficulty relaxing, and an ever-present feeling of being nervous or edgy.
- Adults may experience impulsivity as blurting out, rude or inappropriate comments or interrupting others during conversation.
- Adults often choose highly active jobs, avoid situations with little to no activity, work long hours or multiple jobs, easily bored or inpatient, hot tempered, make impulsive decisions.

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Children vs. Adults

- Adults are often forgetting deadlines, important appointments, deadlines, social obligations, procrastination; indecisive, poor time management, difficulty initiating and completing tasks, constantly shifting attention.

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Epidemiology of ADHD

- 7-8% of school-age children[2] and 4-5% of adults[3]
- Prevalence varies with risk factors including age, male gender, chronic health problems, family dysfunction, low socioeconomic status, presence of a developmental impairment and urban living.[4]
- ADHD more common in boys
- Genetics- Twin studies, greater concordance in monozygotic vs. dizygotic twins. Siblings of hyperactive children 2x likely to have ADHD than general pop; 1 in 2 born to parents with ADHD will develop it in their childhood.

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Epidemiology of ADHD (Cont.)

- 50-75% will be diagnosed with ADHD combined type, 20-30% will be diagnosed with inattentive type, 15% with hyperactive-impulsive type.
- Child and adult ADHD commonly co-occurs with multiple psychiatric disorders including mood, anxiety, disruptive behavioral disorders, and substance-use disorders.[5,6]
- About 20-25% of those with ADHD do not have comorbidities.[7]

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Costs of ADHD

- Multiple studies showing that ADHD costs 2-3 times more than those without ADHD.[8]
- ADHD children had higher mean costs than those with asthma and those with neither disorder. Costs associated with greater use of ER, inpatient, and outpatient services.

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Pathophysiology

- Dysfunction of NE, DA.
- Multi-factorial- genetic, neurochemical, neurophysiological, and psychosocial issues.
- Neuroimaging studies have found lower cerebral blood flow and metabolic rates in the frontal lobe of children with ADHD.

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Clinical Course

- ADHD is chronic- begins early in life and continues into adulthood, symptoms change over time
- Early childhood- sxs of hyperactivity dominate, temper tantrums, rough play, aggression
- Beginning with school, sxs of inattention are more apparent, and impulsive behaviors and problems following rules. Poor social interaction and self-esteem may develop.

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Clinical Course (Cont.)

- Adolescence- motor hyperactivity begins to decrease but patients may complain of inner restlessness. Disorganization continues, arguing with authority & engage in risky behaviors

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Rating Scales: Children & Adolescents[9]

- ADHD Rating Scale IV: 18 items on a 4-point scale, ages 5-17, Assesses ADHD sxs based on DSM-IV criteria. Recommended as a quick screening tool, not a diagnostic tool. Available in different versions for parents, teachers, or adolescent self-report.
- Connors Parents and Teaching Rating Scale (CPRS and CTRS): 27/28 items on a 4-point scale, ages 3-17, Assesses ADHD sxs, emotional lability, and oppositional behaviors. Used in majority of clinical trials as a main outcome measure.

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Rating Scales: Children & Adolescents (Cont)[9]

- Inattention-Overactivity with Aggression (IOWA) Conners Teachers Rating Scale:10 items derived from original CTRS, ages 5-11, 4-point scale. 4 clusters of sxs.
- SKAMP Scale: 10 items, 7-point scale; Assesses ADHD and Oppositional Defiant Disorder (ODD) behaviors in the classroom setting.
- SNAP-IV: 90 items, ages 5-17, 4 point scale. Assesses ADHD sxs, ODD behaviors, and other psychopathology. Used frequently in clinical trials.

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Rating Scales: Adults[9]

- Brown ADD Scale:40 items, 5 clusters-frequency scale (4-point)
- Conners' Adult ADHD Rating Scale: Self-report and Observer Ratings- long, short, and screening versions
- Wender-Reimherr Adult ADHD Scale: measures the severity of target symptoms & assessing current symptoms; 7 categories, 5-point
- Adult Self-Report Scale:18 item self-screening questionnaire; validated and takes 5 minutes.

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Treatments- Stimulants

- Methylphenidate, Dextroamphetamine, Mixed-salts Amphetamine
  - 1st line treatment since show superior efficacy over non-stimulants[9 -11]
  - Various delivery mechanisms exist- liquid, sprinkle, tablet, capsule, or patch; active and less active isomers, or pro-drug; immediate, intermediate-release, and extended-release formulations

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Methylphenidate

Methylphenidate	Initial Dose	Max Dose/day	Duration (hrs)	SEs
Immediate Release/ Short Acting (Ritalin, Methylin, Desoxyn)	5-18 mg, BID/TID	60 mg	3-6	Appetite suppression, delay of sleep onset, anxiety Abdominal pain, HA, rebound irritability, tics, jitteriness
Intermediate-acting (Metadate ER, Metadate CD, Methylin ER, Ritalin LA, Ritalin SR)	20 mg QD or BID	60 mg	3 - 8	
Extended release/ long-acting (Concerta, Daytrana Patch)	27 mg QD 10 mg patch	54 mg 30 mg patch	12	

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Dexmethylphenidate

Dexmethylphenidate	Initial Dose	Max Dose/day	Duration (hrs)	SEs
Short-acting (Focalin)	2.5 mg BID	20 mg	5	Appetite suppression, delay of sleep onset, anxiety Abdominal pain, HA, rebound irritability, tics, jitteriness
Extended-release/long-acting (Focalin XR)	5 mg QD		12	

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Pharmacokinetic Considerations (Cont.)

- MPH- OROS uses an osmotic-release delivery system to simulate TID dosing. First peak in 2 hrs, second peak in next 3-4 hrs, followed by a gradual decline.
- Transdermal has slower onset of action with onset often not seen for 3 hrs. Peak at 8 hrs after placement. Patch removed after 9 hrs.
- Dex-MPH IR faster to peak (1-1.5 hrs) than MPH. Dex-MPH-XR delivers 50% doses immediately with peak in 1.5 hrs, second peak in 6.5 hrs.

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Pharmacokinetic Considerations (Cont.)

- IR products reach peak plasma in 1-3 hrs, clinical effects in 30 - 60 min; often given am and noon (later dose can help with homework)
- SR products reach peak plasma in 4 -5 hrs
- LA uses an extended-release beaded technology to simulate twice a day dosing; 50% of dose like IR, 50% second peak occurs 5-6 hrs after ingestion.
- CD uses same technology as LA but 30% release initially, 70% released later with second peak 5-6 hrs after ingestion.

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Amphetamines

Amphetamines	Initial Dose	Max Dose/day	Duration (hrs)	SEs
Dextroamphetamine (Dexedrine,Dextrostat)	2.5 mg QD-BID: 3-5 y/o	40 mg	4 – 5	Appetite suppression, delay of sleep onset, anxiety Abdominal pain, HA, rebound irritability, tics, jitteriness
(Dexedrine Spansules)	5 mg BID: >6 y/o	40 mg	8	
Dextroamphetamine Liquid (Liquadd)	2.5 mg BID-TID	40 mg	4 -5	
Mixed Amphetamine Salts (Adderall)	2.5 mg QD-BID: 3-5 y/o 5 mg BID: >6 y/o	40 mg	4-6	
Mixed Amphetamine Salts XR (Adderall XR)	10 mg QD	30 mg	10-12 hrs	

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Amphetamines (Cont.)

Amphetamines	Initial Dose	Max Dose/day	Duration (hrs)	SEs
Lisdexamfetamine (Vyvanse)	30 mg QD: 6-12 y/o 50 mg QD: >13	70 mg	12	Appetite suppression, delay of sleep onset, anxiety Abdominal pain, HA, rebound irritability, tics, jitteriness

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Pharmacokinetic Considerations

- Younger children eliminate amphetamines faster than adolescents and adults
- Dextroamphetamine IR reaches peak in 2 hrs while extended-release achieves peak in 8 hrs. Clinical effects seen within 30-60 min.
- Mixed amphetamine salts IR reach peak in about 3 hrs, XR uses beaded technology with 2 peaks.
- Lisdexamfetamine- prodrug converted to dextroamphetamine and L-lysine in gut.
- High fat meal may delay time to peak by 2 hrs.

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Monitoring/Counseling Notes

- Monitor weight and blood pressure periodically
- Stimulants taken in am unless instructed otherwise. Last dose not too late in the day to reduce insomnia.
- All extended-release products should not be crushed or chewed
- MPH-LA, MPH-CD, Dex-MPH-XR, and mixed amphetamine salts XR can be opened up and sprinkled on applesauce for immediate consumption and not heated.

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Monitoring/Counseling Notes (Cont.)

- Lisdexamfetamine can be opened & dissolved in a glass of water for immediate use.
- MPH and dextroamphetamine are available as liquids.
- Apply MPH transdermal patch 2 hrs before needed effect.
- Stimulant effects of medications can be additive with other stimulants.
- MAOIs should not be given with 14 day of stimulant therapy.
- TCA concentrations may increase when taken with MPH

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Atomoxetine

- Atomoxetine is first-line for non-stimulant options and FDA approved for ADHD.
- Inhibits reuptake of NE in CNS
- Dosing:
  - <70 kg: 0.5 mg/kg/day, after 3 days increase to target 1.2 mg/kg/day; Max dose: 1.8 mg/kg/day
  - > 70 kg: 40 mg daily, increase to 80 mg after 3 days. Max dose: 100 mg daily.

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Atomoxetine- Counseling Notes

- Commonly reported side effects:
  - GI discomfort, minimized with food
  - Insomnia & Dizziness: Dosing twice daily may lower side effects
  - Monitor for signs of heptatoxicity
- Since metabolized through CYP 450 2D6 and 2C19 to active metabolites, dosage adjustments should be made when given with a 2D6 inhibitor

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Atomoxetine- Monitoring/ Counseling Notes (Cont.)

- Atomoxetine can take 4 weeks to work.
- May have particular use in populations for which stimulants are problematic (tic disorders, anxiety disorders).
- Carries a black box warning against suicidality in pediatric populations.

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Clonidine/Guanfacine

- Alpha-2 adrenergic agonists which block inhibitory pre-synaptic receptors regulating NE.
- Clinical trials have shown efficacy in treating ADHD. May be more effective in treating hyperactive sxs than inattention.
- Guanfacine extended-release- FDA approved for ADHD. Start 0.05 to 0.08 mg/kg once daily for monotherapy. Can titrate weekly to 0.12 mg/kg/ day (Max 4 mg/day).

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Clonidine/Guanfacine

- Clonidine: Start at 0.05 mg/day. Increase by 0.05 mg/day q 3 – 7 days to a dose of 0.003 – 0.005 mg/kg/day given TID/QID. Maximum dose is 0.4 mg/day.
- Common side effects: sedation, hypotension, dizziness.
- Drug Interactions: CNS depressants and drugs that lower heart rate, Mirtazepine, Yohimbine

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Other Pharmacologic Options

- Bupropion- in a small # of clinical trials, it has been shown to be effective in ADHD.[12,13]
  - Dosing: SR, 100 mg QD x 3 days, 150 mg daily, 150 mg BID; ER. 150 mg QD, 300 mg QD.
  - Takes 4-6 wks to work
  - Irritability, agitation, diarrhea, worsen tics
  - 2nd line of therapy, useful in patients with comorbid depression or nicotine dependence.

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Other Pharmacologic Options (Cont.)

- Modafinil
- Some trials showing efficacy but safety concerns (increased risk of Steven-Johnson syndrome)[14]
  - Dosing: 100 mg daily and titrate to 300 mg daily
  - Side Effects: decreased appetite, insomnia headaches, exacerbate mania
  - Third-line option if failure to other agents

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Other Pharmacologic Options (Cont.)

- Tricyclic Antidepressants- Imipramine, Nortripytline, and Desipramine-
  - Side Effects
  - Some treatment success; considered 3rd line for ADHD- option for patients with comorbid depression, anxiety, or contraindication to other agents

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Non-Pharmacologic Options

- Family-based Interventions
- School-Focused Interventions
  - Placing child in front of classroom, small classroom sizes, well-organized class schedule
- Child-Focused Interventions
- Complementary & Alternative Medicines-
  - Mixed evidence; no clear picture. Some positive results with minerals zinc, iron, antioxidant botanical French maritime pine bark.
  - Lack of much support for Omega-3, Ginkgo Biloba, and Hypercium perforatum (St. John's wort)

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Treatment Summary[15]

- Predominant ADHD
- Step 1: MPHD or DEX/MXA
- Step 2: If inadequate response, switch to drug class not used in step 1
- Step 3: If inadequate response, try Bupropion, TCA, or Atomoxetine

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Treatment Summary[15]

- Predominant Comorbidity- Tic Disorder
- Step 1: Consider Bupropion, clonidine, guafacine
- Step 2: Partial response- add stimulant. If inadequate response, choose alternative to Step 1 choice

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Treatment Summary[15]

- Predominant Comorbidity- Bipolar or Severe Aggression
- Step 1: lithium, anticonvulsant, or atypical antipsychotic
- Step 2: Partial response- add bupropion or stimulant. If inadequate response, choose alternative to Step 1 choice

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Treatment Summary[15]

- Predominant Comorbidity- Anxiety/ Depression
- Step 1: Antidepressant
- Step 2: Partial response- add stimulant. If inadequate response, choose alternative to Step 1 choice

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Policy Thoughts/Discussion

- No guidelines for adult ADHD
- Medical management (primarily stimulants) and combo of medication and behavioral treatment yielded significantly greater improvement in ADHD sxs than behavioral alone or routine community care. Combo group had an advantage over the medical management group.[16]
- High rates of medication non-adherence.[17]
- Only 36% of adults with ADHD reported taking a prescription medication for the disorder.[18]

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Policy Thoughts/Discussion (Cont.)

- Among those 18-49 whose private insurance paid costs for ADHD medications in the past 30 days, 16.6% diverted these medications. Men were more likely than women to engage in such diversion.[19]
- Estimated value of diverted prescriptions in a 30-day period is $8 million ($83 to 204 million annually).[19]
- Diversion accounted for 3.6% of the total costs that private insurers paid for ADHD medications.[19]
- Require PAs for stimulant use?
- Require PAs on FDA-approved medication, guanfacine-extended release, but no formulary restriction on guanfacine or clonidine that are not FDA approved

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References

1. American Psychiatric Association. DSM-IV-TR. Washington, DC: American Psychiatric Association;2000.
2. Barbaresi WJ, Katusic SK, Colligan RC, et al. How common is attention-deficit/ hyperactivity disorder? Incidence in a population-based birth cohort in Rochester, Minn. *Arch Pediatric Adolesc Med* 2002;156(3):217-224.
3. Kessler RC, Adler L, Barkley R, et al. The prevalence and correlates of adult ADHD in the United States: results from the National Comorbidity Survey Replication. *American Journal of Psychiatry* 2006;163(4):716-723.

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References

4. Lavigne JV, Gibbons RD, Christoffel KK, et al. Prevalence rates and correlates of psychiatric disorders among preschool children. *J Am Acad Child Adolesc Psychiatry* 1996;35(2):204-214.
5. Angold A, Costello EJ, Erkanli A. Comorbidity. J Child Psychol Psychiatry 1999;40(1):57-87.
6. Murphy K, Barkley RA. Attention deficit hyperactivity disorder adults: comorbidities and adaptive impairments. Compr Psychiatry 1996;37(6):393-401.

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References

7. Lahey BB, Appelgate B, McBurnett K, et al. DSM-IV field trials for attention deficit hyperactivity disorder in children and adolescents. *Am J Psychiatry* 1994;151(11):1673-1685.
8. Faraone SV. Using meta-analysis to compare the efficacy of medications for Attention-Deficit/ Hyperactivity Disorder in youths. P &T 2009; 34(12):678-694.
9. Minkoff NB. ADHD in managed care: An assessment of the burden of illness and proposed initiatives to improve outcomes. Am J Manage Care 2009;15;S151-S159.

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References

10. American Academy of Child and Adolescent Psychiatry. Practice parameter for the assessment of children and adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 2007; 46(7):894-921.
11. Pliszka SR, Crismon ML, Hughes CW, et al. The Texas children's medication algorithm for pharmacotherapy of Attention-Deficit/Hyperactivity Disorder. J Am Acad Child Adolesc Psychiatry 2006;45(6):642-57.

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References

12. Barrickman L, Perry P, Allen AJ et al.Bupropion versus methylphenidate in attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 1995;34(5):649-57.
13. Daviss WB, Bentivoglio P, Racusin R, et al. Bupropion sustained release in adolescents with comorbid attention-deficit/ hyperactivity disorder and depression. J am Acad Child Adolesc Psychiatry 2001;40(3):307-14.

14. Biederman J, Swanson JM, Wigal SB, et al. Efficacy and safety of modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder: results of a randomized,double-blind, plabebo-controlled, flexible dose study. Pediatrics 2005;116(6):777-84.
15. Dopheide JA, Theesen KA, Malkin M. Psychiatric disorders of childhood treatments. In DiPiro JT, et al., eds. Pharmacotherapy: A Pathophysiology Approach. 6th ed. New York, NY: McGraw-Hill;2005:1145-1154.

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References

16. The MTA Cooperative Group. A 14-month randomized clinical trial of treatment strategies for attention-deficit/hyperactivity disorder. Arch Gen Psychiatry 1999;56: 1073-86.
17. Pappadopulos E, Jensen PJ, Chait AR, et al. Medication adheren in the MTA: saliva methylphenidate samples versus parent report and mediating effect of concomitant behavioral treatment. J Am Acad Child Adolesc Psychiatry 2009;Mar 19.

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References

18. Biederman J. Breaking news: the social and economic impact of ADHD. Discussion presented at: Attention Deficit Hyperactivity Disorder (ADHD) AMA Media Briefing; September 9, 2004; New York, NY.
19. Aldridge AP, Kroutil LA, Cowell AJ, et al. Medication costs to private insurers of diversion of medications for attention-deficit hyperactivity disorder. Pharmacoeconomics 2011;29(7):621-635.

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