Therapeutic Class Overview
Attention Deficit/Hyperactivity Disorder (ADHD) Agents

Therapeutic Class Overview/Summary:
This review will focus on the agents used in the treatment of attention deficit/hyperactivity disorder (ADHD). These agents come from a variety of drug classes and are summarized in Table 1.[1-25] ADHD is a common psychiatric disorder often diagnosed during childhood; however, children with ADHD may continue to manifest symptoms into adulthood.[1] The core symptoms of ADHD utilized in the diagnosis of the disorder include hyperactivity, impulsivity and inattention. There are three subtypes of ADHD, including a predominantly inattentive subtype, a predominantly hyperactive-impulsive subtype and a combined subtype in which both symptoms are displayed.[26] Untreated, or undertreated, ADHD is associated with adverse sequelae, including delinquent behavior, antisocial personality traits, substance abuse and other comorbidities[27]. There are several central nervous system agents that are Food and Drug Administration (FDA)-approved for the treatment of ADHD, including the cerebral stimulants (amphetamines and methylphenidate derivatives), as well as atomoxetine (Strattera®), clonidine extended-release (Kapvay®) and guanfacine extended-release (Intuniv®).[1-25] Due to the potential for abuse, the cerebral stimulant agents are classified as Schedule II controlled substances.[1-22] Atomoxetine, clonidine extended-release and guanfacine extended-release are not classified as controlled substances.[23-25] Clonidine and guanfacine extended-release formulations are approved for use as both adjunctive therapy with stimulant medications and as monotherapy.[24,25]

Most ADHD agents and stimulants are currently available generically. Agents that are available only as a brand name product include: lisdexamfetamine capsules (Vyvanse®), amphetamine tablets (Evekeo®) and extended-release suspension (Dyanavel XR®), atomoxetine capsules (Strattera®), dextroamphetamine solution (ProCentra®), methylphenidate patch (Daytrana®), and extended-release suspension (Quillivant XR®). Aptensio XR (methylphenidate extended-release) is also available only as a brand name product; however, other extended-release biphasic capsules are available generically.[29]

Table 1. Current Medications Available in the Therapeutic Class[1-25]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines			
Amphetamine (Dyanavel XR®, Evekeo®)	Treatment of ADHD, narcolepsy‡, exogenous obesity‡	Extended-release suspension 2.5 mg/mL Tablet: 5 mg 10 mg	-
Amphetamine/dextroamphetamine salts (Adderall®*, Adderall XR®*)	Treatment of ADHD, narcolepsy†	Capsule: 5 mg 10 mg 15 mg 20 mg 25 mg 30 mg Tablet: 5 mg 7.5 mg 10 mg 12.5 mg	a

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
		15 mg 20 mg 30 mg	
Dextroamphetamine (ProCentra®, Dexedrine®*, Dexedrine Spansule®*, Zenzedi®*)	Treatment of ADHD, narcolepsy	Solution: 5 mg/5 mL Sustained-release capsule: 5 mg 10 mg 15 mg Tablet: 2.5 mg 5 mg 7.5 mg 10 mg	a
Lisdexamfetamine (Vyvanse®)	Treatment of ADHD	Capsule: 20 mg 30 mg 40 mg 50 mg 60 mg 70 mg	-
Methamphetamine (Desoxyn®*)	Treatment of ADHD, exogenous obesity:	Tablet: 5 mg	a
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous			
Dexmethylphenidate (Focalin®*, Focalin XR®*)	Treatment of ADHD	Extended-release capsule: 5 mg 10 mg 15 mg 20 mg 25 mg 30 mg 35 mg 40 mg Tablet: 2.5 mg 5 mg 10 mg	a
Methylphenidate (Aptensio XR®, Concerta®*, Daytrana®, Metadate CD®*, Metadate ER®*, Methylin®*, Methylin ER®*, Quillivant XR®, Ritalin®*, Ritalin LA®*, Ritalin SR®*)	Treatment of ADHD, narcolepsy§	Chewable tablet: 2.5 mg 5 mg 10 mg Extended-release capsule (Aptensio XR®)	a

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
		10 mg 15 mg 20 mg 30 mg 40 mg 50 mg 60 mg Extended-release capsule (Metadate CD®, generic): 10 mg 20 mg 30 mg 40 mg 50 mg 60 mg Extended-release capsule (Ritalin LA®, generic): 10 mg 20 mg 30 mg 40 mg Extended-release suspension: 25 mg/ 5 mL Extended-release tablet (Concerta®, generic): 18 mg 27 mg 36 mg 54 mg Extended-release tablet (Metadate ER®, generic): 20 mg Solution: 5 mg/5 mL 10 mg/5 mL Sustained-release tablet (Ritalin SR®, generic): 20 mg	

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
		Tablet: 5 mg 10 mg 20 mg Transdermal patch: 10 mg/9 hours (1.1.mg/hour) 15 mg/9 hours (1.6 mg/hour) 20 mg/9 hours (2.2 mg/hour) 30 mg/9 hours (3.3 mg/hour)	
Central α-Agonists			
Clonidine extended-release (Kapvay®*)	Treatment of ADHD	Extended-release tablet: 0.1 mg 0.2 mg	a
Guanfacine extended-release (Intuniv®*)	Treatment of ADHD	Extended-release tablet: 1 mg 2 mg 3 mg 4 mg	a
Central Nervous System Agents-Miscellaneous			
Atomoxetine (Strattera®)	Treatment of ADHD	Capsule: 10 mg 18 mg 25 mg 40 mg 60 mg 80 mg 100 mg	-

ADHD=attention deficit hyperactivity disorder
*Generic available in at least one dosage form or strength.
† Adderall
‡ Evekeo
§Metadate ER®, Methylin®, Ritalin® and Ritalin SR®

Evidence-based Medicine

- Clinical trials demonstrating the safety and efficacy of the attention deficit/hyperactivity disorder (ADHD) agents and stimulants in Food and Drug Administration (FDA)-approved indications are outlined in Table 5.[37-124]
- The efficacy of amphetamine extended-release suspension (Dyanavel XR®) was evaluated in a laboratory classroom study conducted in 108 pediatric patients (aged 6 to 12 years) with ADHD. The primary efficacy endpoint was change from pre-dose Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale combined score at four hours post-dosing at the end of the week. SKAMP-combined change scores from pre-dose demonstrated a statistically significant improvement at all time points (1, 2, 4, 6, 8, 10, 12, 13 hours) post-dosing with amphetamine extended-release compared to placebo. At hour four, the placebo-subtracted difference in SKAMP-combined score was -14.8 (95% CI, -17.9 to -11.6, P value not reported).[2]

- Overall, there is insufficient evidence to suggest that one ADHD agent and stimulant is more efficacious than another for the treatment of ADHD.[37-125]
- Limited data exists to demonstrate the efficacy of a variety of cerebral stimulants and atomoxetine in the adult population.[42,50,68,93,94,109]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Current consensus clinical guidelines for the treatment of children and adolescents with ADHD recommend that stimulants are highly effective for reducing core symptoms of ADHD in children.[27,28,30]
  - Although initial therapy with atomoxetine or extended-release formulations of clonidine and guanfacine may reduce core symptoms of ADHD, there is less evidence to support their use compared to stimulants. The selection of therapy should be based on comorbid conditions, adverse event profiles, compliance issues, risk of drug diversion and patient/parent preference.[31]
  - Stimulants, particularly methylphenidate, are recommended as first-line therapy in adult patients with ADHD.[28,32]

- Other Key Facts:
  - At least one short-, intermediate-, and long-acting stimulant is available generically.[29]

References

1. Evekeo® [prescribing information]. Atlanta (GA): Arbor Pharmaceuticals, LLC; 2015 Feb.
2. Dyanavel XR® [prescribing information]. Monmouth Junction (NJ): Tris Pharma; 2015 Oct.
3. Adderall® [prescribing information]. Wayne (PA): Shire US Inc.; 2014 Apr.
4. Adderall XR® [prescribing information]. Wayne (PA): Shire US Inc.; 2013 Dec.
5. Dexedrine® Spansule® [prescribing information]. Research Triangle Park (NC): GlaxoSmithKline; 2013 Oct.
6. Dexedrine® [prescribing information]. Horsham (PA): Amedra Pharmaceuticals LLC; 2014 May.
7. Zenzedi® [prescribing information]. Atlanta (GA): Arbor Pharmaceuticals, Inc.; 2014 Jan
8. ProCentra® [prescribing information]. Newport (KY): Independence Pharmaceuticals, LLC; 2014 Apr.
9. Vyvanse® [prescribing information]. Wayne (PA): Shire US Inc.; 2014 Nov.
10. Desoxyn® [prescribing information]. Deerfield (IL): Ovation Pharmaceuticals, Inc.; 2013 Dec.
11. Focalin® [prescribing information]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2013 Dec.
12. Focalin XR® [prescribing information]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2013 Dec.
13. Daytrana® [prescribing information]. Miami (FL): Noven Therapeutics, LLC; 2013 Dec.
14. Aptensio XR® [prescribing information]. Coventry (RI): Rhodes Pharmaceuticals L.P.; 2015 May.
15. Concerta® [prescribing information]. Titusville (NJ): McNeil Pediatrics, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.; 2014 Jul.
16. Metadate CD® [prescribing information]. Smyrna (GA): UCB, Inc.; 2013 Dec.
17. Metadate ER® [prescribing information]. Smyrna (GA): UCB Manufacturing, Inc.; 2014 Jan.
18. Methylin® solution [prescribing information]. Atlanta (GA): Shionogi Pharma, Inc.; 2013 Dec.
19. Methylin® chewable tablets [prescribing information]. Atlanta (GA): Shionogi Pharma, Inc.; 2013 Dec
20. Quillivant XR® [prescribing information]. New York (NY): NextWave Pharmaceuticals Inc.; 2014 Oct.
21. Ritalin®, Ritalin-SR® [prescribing information]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2013 Dec.
22. Ritalin LA® [prescribing information]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2013 Dec.
23. Strattera® [prescribing information]. Indianapolis (IN): Lilly USA, LCC; 2014 Feb.
24. Intuniv® [prescribing information]. Wayne (PA): Shire US Inc.; 2014 Nov.
25. Kapvay® [prescribing information]. Atlanta (GA): Shionogi Pharma Inc.; 2014 Nov.
26. Krull KR. Attention deficit hyperactivity disorder in children and adolescents: treatment with medications. In: Torchia MM (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2014 [cited 2014 Dec 18]. Available from: .
27. American Academy of Child and Adolescent Psychiatry. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2007;46:894-921.
28. American Academy of Pediatrics. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics. 2011;128:1-16.
29. DRUGS@FDA.com [database on the internet]. Rockville (MD): U.S. Food and Drug Administration [cited 2014 Dec 18]. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.
30. Institute for Clinical Systems Improvement. ADHD, Attention Deficit Hyperactivity Disorder in Primary Care for School-Age Children and Adolescents [guideline on the Internet]. 9th ed. Bloomington (MN): Institute for Clinical Systems Improvement; 2014 Apr [cited 2014 Dec 18] Available at: https://www.icsi.org/guidelines__more/catalog_guidelines_and_more/catalog_guidelines/catalog_behavioral_health_guidelines/adhd/.

31. National Institute for Health and Clinical Excellence. Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people, and adults [guideline on the Internet]. London (UK). 2008 Sep [cited 2014 Dec 18]. Available at: http://guidance.nice.org.uk/CG72.
32. Bolea-Alamañac B, Nutt DJ, Adamou M, Asherson P, Bazire S, Coghill D, Heal D, et al. Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: Update on recommendations from the British Association for Psychopharmacology. J Psychopharmacol. March 2014;28:179-203.
33. Morgenthaler TI, Kapur VK, Brown T, Swick TJ, Alessi C, Aurora RN, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep. 2007;30:1705-11.
34. European Federation of Neurological Societies (EFNS). Management of narcolepsy in adults [guideline on the internet]. Vienna, Austria: European Federation of Neurological Societies; 2011 [cited 2014 Dec 18].Available from: http://www.efns.org/fileadmin/user_upload/guidline_papers/EFNS_guideline_2011_Management_of_narcolepsy_in_adults.pdf.
35. American Academy of Sleep Medicine. Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders. Sleep. 2007;30:1445-59.
36. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2014 Dec 18]. Available from: http://online.factsandcomparisons.com.
37. McCracken JT, Biederman J, Greenhill LL, Swanson JM, McGough JJ, Spencer TJ, et al. Analog classroom assessment of a once-daily mixed amphetamine formulation, SLL381 (Adderall XR) in children with ADHD. J Am Acad Child Adolesc Psychology. 2003;426(6):673-83.
38. Pliszka SR, Browne RG, Olvera RL, Wynne SK. A double-blind, placebo controlled study of Adderall and methylphenidate in the treatment of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2000;39(5):619-26.
39. Pelham WE, Aronof HR, Midlam JL, Shapiro CJ, Gnagy EM, Chronis AM, et al. A comparison of Ritalin and Adderall; efficacy and time course in children with attention hyperactivity deficit disorder. Pediatrics. 1999;103:e43.
40. Faraone SV, Biederman J, Roe C. Comparative efficacy of Adderall and methylphenidate in attention-deficit/hyperactivity disorder: a meta-analysis. J Clin Psychopharmacol. 2002;22(5):468-73.
41. Biederman J, Lopez FA, Boellner SW, Chandler MC. A randomized, double blind, placebo controlled parallel group study of SLI381 (Adderall XR) in children with attention-deficit/hyperactivity disorder. Pediatrics. 2002;110:258-66.
42. Goodman DW, Ginsberg L, Weisler, RH, Cutler AJ, Hodgkins P. An Interim Analysis of the Quality of Life, Effectiveness, Safety, and Tolerability (QU.E.S.T.) Evaluation of Mixed Amphetamine Salts Extended Release in Adults With ADHD. CNS Spectr. 2005;10(Suppl 20):26-34.
43. Biederman J, Heiligenstein JH, Faries DE, Galil N, Dittmann R, Emslie GJ, et al. Atomoxetine ADHD Study Group. Efficacy of atomoxetine vs placebo in school-age girls with attention-deficit/hyperactivity disorder. Pediatrics. 2002;110(6):e75.
44. Durell TM, Adler LA, Williams DW, Deldar A, McGough JJ, Glaser PE, et al. Atomoxetine treatment of attention-deficit/hyperactivity disorder in young adults with assessment of functional outcomes: a randomized, double-blind, placebo-controlled clinical trial. J Clin Psychopharmacol. 2013 Feb;33(1):45-54.
45. Michelson D, Faries D, Wernicke J, Kelsey D, Kendrick K, Sallee FR, et al. Atomoxetine in the treatment of children and adolescents with attention deficit, hyperactivity disorder: A randomized, placebo controlled, dose response study. Pediatrics. 2001;108(5):e83.
46. Kratochvil CJ, Vaughan BS, Stoner JA, Daughton JM, Lubberstedt BD, Murray DW, et al. A double-blind, placebo-controlled study of atomoxetine in young children with ADHD. Pediatrics. 2011;127:e862-8.
47. Spencer T, Heiligenstein JH, Biederman J, Faries DE, Kratochvil CJ, Conners CK, et al. Results from two proof-of-concept, placebo-controlled studies of atomoxetine in children with attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2002;63:1140-7.
48. Dittmann RW, Schacht A, Helsberg K, Schneider-Fresenius C, Lehmann M, Lehmkuhl G, et al. Atomoxetine vs placebo in children and adolescents with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder: a double-blind, randomized, multicenter trial in Germany. J Child Adolesc Psychopharmacol. 2011;21:97-110.
49. Hammerness P, Doyle R, Kotarski M, Georgiopoulos A, Joshi G, Zeitlin S, et al. Atomoxetine in children with attention-deficit hyperactivity disorder with prior stimulant therapy: a prospective open-label study. Eur Child Adolesc Psychiatry. 2009;18:493-8.
50. Adler LA, Spencer TJ, Williams DW, Moore RJ, Michelson D. Long-term, open-label safety and efficacy of atomoxetine in adults with ADHD: final report of a four-year study. J Atten Disord. 2008;12:248-53.
51. Wietecha L, Young J, Ruff D, Dunn D, Findling RL, Saylor K. Atomoxetine once daily for 24 weeks in adults with attention-deficit/hyperactivity disorder (ADHD): impact of treatment on family functioning. Clin Neuropharmacol. 2012 Juen;35(3):125-33.
52. Biederman J, Wigal SB, Spencer TJ, McGough JJ, Mays DA. A post hoc subgroup analysis of an 18-day randomized controlled trial comparing the tolerability and efficacy of mixed amphetamine salts extended release and atomoxetine in school-age girls with attention-deficit/hyperactivity disorder. Clin Ther. 2006;28(2):280–93.
53. Kemner JE, Starr HL, Ciccone PE, Hooper-Wood CG, Crockett RS. Outcomes of OROS methylphenidate compared to atomoxetine in children with ADHD: a multicenter, randomized prospective study. Adv Ther. 2005 Sep-Oct;22(5):498-512.
54. Newcorn JH, Kratochvil CJ, Allen AJ, Casat CD, Ruff DD, Moore RJ, et al. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response. Am J Psychiatry. 2008;165:721-30.
55. Starr HL, Kemner J. Multicenter, randomized, open-label study of OROS methylphenidate vs atomoxetine: treatment outcomes in African-American children with ADHD. J Natl Med Assoc. 2005 Oct;97(10 Suppl):11S-16S.
56. Wang Y, Zheng Y, Du Y, Song DH, Shin YJ, Cho SC, et al. Atomoxetine vs methylphenidate in pediatric outpatients with attention deficit hyperactivity disorder: a randomized, double-blind comparison trial. Aust N Z J Psychiatry. 2007 Mar;41(3):222-30.

57. Kratochvil CJ, Heiligenstein JH, Dittmann R, Spencer TJ, Biederman J, Wernicke J, et al. Atomoxetine and methylphenidate treatment in children with ADHD: a prospective, randomized, open-label trial. J Am Acad Child Adolesc Psychiatry. 2002;41(7):776-84.
58. Sutherland SM, Adler LA, Chen C, Smith MD, Feltner DE. An 8-week, randomized controlled trial of atomoxetine, atomoxetine plus buspirone, or placebo in adults with ADHD. J Clin Psychiatry 2012 Jan 10.
59. Ni HC, Lin YJ, Gau SS M D Ph D, Huang HC, Yang LK. An Open-Label, Randomized Trial of Methylphenidate and Atomoxetine Treatment in Adults With ADHD. J Atten Disord. 2013 Mar 8. [Epub ahead of print].
60. Sutherland SM, Adler LA, Chen C, Smith MD, Feltner DE. An eight-week, randomized controlled trial of atomoxetine, atomoxetine plus buspirone, or placebo in adults with ADHD. J Clin Psychiatry. 2012 Apr;73(4):445-50.
61. Prasad S, Harpin V, Poole L, Zeitlin H, Jamdar S, Puvanendran K; The SUNBEAM Study Group. A multi-centre, randomized, open-label study of atomoxetine compared to standard current therapy in UK children and adolescents with attention-deficit/hyperactivity disorder (ADHD). Curr Med Res Opin. 2007 Feb;23(2):379-94.
62. Cheng JYW, Chen RYL, Ko JSN, Ng EML. Efficacy and safety of atomoxetine for attention-deficit/hyperactivity disorder in children and adolescents-meta-analysis and meta-regression analysis. Psychopharmacology. 2007;194:197-209.
63. Hazell PL, Stuart JE. A randomized controlled trial of clonidine added to psychostimulant medication for hyperactive and aggressive children. J Am Acad Child Adolesc Psychiatry. 2003;42:886-94.
64. Jain R, Segal S, Kollins SH, Khayrallah M. Clonidine extended-release tablets for pediatric patients with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2011;50:171-9.
65. Kollins SH, Jain R, Brams M, Segal S, Findling RL, Wigal SB, et al. Clonidine extended-release tablets as add-on therapy to psychostimulants in children and adolescents with ADHD. Pediatrics. 2011;127:e1406-13.
66. Wigal S, Swanson JM, Feifel D, Sangal RB, Elia J, et al. A double-blind, placebo-controlled trial of dexmethylphenidate hydrochloride and d,l-threo-methylphenidate hydrochloride in children with attention-deficit/hyperactivity disorder. J Am Acad Adolesc Psychiatry. 2004;43(11):1406-14.
67. Greenhill LL, Muniz R, Ball RR, Levine A, Pestreich L, et al. Efficacy and safety of dexmethylphenidate extended-release capsules in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2006;45(7):817-23.
68. Spencer TJ, Adler LA, McGough JJ, Muniz R, Jiang H, et al. Efficacy and safety of dexmethylphenidate extended-release capsules in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry. 2007;61:1380-7.
69. Adler LA, Spencer T, McGough JJ, Jiang H, Muniz R. Long-term effectiveness and safety of dexmethylphenidate extended-release capsules in adult ADHD. J Atten Disord. 2009;12:449-59.
70. Brams M, Turnbow J, Pestreich L, Giblin J, Childress A, McCague K, et al. A randomized, double-blind study of 30 vs 20 mg dexmethylphenidate extended-release in children with attention-deficit/hyperactivity disorder. J Clin Psychopharmacol. 2012 Oct;32(5):637-44.
71. Stein MA, Waldman ID, Charney E, Aryal S, Sable C, Gruber R, et al. Dose effects and comparative effectiveness of extended release dexmethylphenidate and mixed amphetamine salts. J Child Adolesc Psychopharmacol. 2011;21:581-8.
72. Muniz R, Brams M, Mao A, McCague K, Pestreich L, Silva R. Efficacy and safety of extended-release dexmethylphenidate compared to d,l-methylphenidate and placebo in the treatment of children with attention-deficit/hyperactivity disorder: a 12-hour laboratory classroom study. J Child Adolesc Psychopharmacol. 2008;18:248-56.
73. Scahill L, Chappell PB, Kim YS, Schultz RT, Katsovich L, Shepherd E, et al. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. Am J Psychiatry. 2001;158:1067-74.
74. Kollins SH, López FA, Vince BD, Turnbow JM, Farrand K, Lyne A, et al. Psychomotor functioning and alertness with guanfacine extended release in subjects with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2011;21:111-20.
75. Sallee FR, McGough J, Wigal T, Donahue J, Lyne A, Biederman J, et al. Guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder: a placebo-controlled trial. J Am Acad Child Adolesc Psychiatry. 2009;48:155-65.
76. Sallee FR, Lyne A, Wigal T, McGough JJ. Long-term safety and efficacy of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2009;19:215-26.
77. Sallee FR, Kollins SH, Wigal TL. Efficacy of guanfacine extended-release in the treatment of combined and inattentive only subtypes of attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2012 June;22(3):206-14.
78. Connor DF, Findling RL, Kollins SH, et al. Effects of guanfacine extended release on oppositional symptoms in children aged six-12 years with attention-deficit hyperactivity disorder and oppositional symptoms: a randomized, double-blind, placebo-controlled trial. CNS Drugs. 2010;24:755-68.
79. Biederman J, Melmed RD, Patel A, McBurnett K, Konow J, Lyne A, et al. A randomized, double-blind, placebo-controlled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. Pediatrics. 2008;121:e73-84.
80. Biederman J, Melmed RD, Patel A, McBurnett K, Donahue J, Lyne A. Long-term, open-label extension study of guanfacine extended release in children and adolescents with ADHD. CNS Spectr. 2008;13:1047-55.
81. Spencer TJ, Greenbaum M, Ginsberg LD, Murphy WR. Safety and effectiveness of coadministration of guanfacine extended release and psychostimulants in children and adolescents with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2009;19:501-10.
82. Wilens TE, Bukstein O, Brams M, Cutler AJ, Childress A, Rugino T, et al. A controlled trial of extended-release guanfacine and psychostimulants for attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2012;51:74-85.
83. Faraone SV, Glatt SJ. Effects of extended-release guanfacine on ADHD symptoms and sedation-related adverse events in children with ADHD. J Atten Disord. 2010;13:532-8.
84. Adler LA, Dirks B, Deas PF, Raychaudhuri A, Dauphin MR, Lasser RA, et al. Lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder who report clinically significant impairment in executive function: results from a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2013;74(7):694-702.

85. Babcock T, Dirks B, Adeyi B, Scheckner B. Efficacy of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder previously treated with amphetamines: analyses from a randomized, double-blind, multicenter, placebo-controlled titration study. BMC Pharmacology and Toxicology. 2012;13:18.
86. Biederman J, Krishnan S, Zhang Y, McCough JJ, Findling RL. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: A phase III, randomized, multicenter, double-blind, parallel-group study. Clin Ther. 2007;29:450–63.
87. Biederman J, Boellner SW, Childress A, Lopez FA, Krishnan S, et al. Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: A double-blind, placebo-controlled, crossover analog classroom study. Biol Psychiatry. 2007;62(9):970-6.
88. Brams M, Weisler R, Findling RL, Gasior M, Hamdani M, Ferreira-Cornweel MC, et al. Maintenance of efficacy of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder: randomzied withdrawal design. J Clin Psychiatry. 2012;73(7):977-83.
89. Coghill D, Banaschewski T, Lecendreux M, Soutullo C, Johnson M, Zuddas A, et al. European, randomized, phase 3 study of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder. Eur Neuropsychopharmacol. 2013 Jan 14. [Epub ahead of print].
90. Findling RL, Childress AC, Cutler AJ, Gasior M, Hamdani M, Ferreira-Cornwell MC, et al. Efficacy and safety of lisdexamfetamine dimesylate in adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2011;50:395-405.
91. Findling RL, Childress AC, Krishnan S, McGough JJ. Long-term effectiveness and safety of lisdexamfetamine dimesylate in school-aged children with attention-deficit/hyperactivity disorder. CNS Spect. 2008;13:614-20.
92. Jain R, Babcock T, Burtea T, Dirks B, Adeyi B, Scheckner B, et al. Efficacy and safety of lisdexamfetamine dimesylate in children with attention deficit/hyperactivity disorder and recent methylphenidate use. Adv Ther. 2013;30:472-86.
93. Weisler R, Young J, Mattingly G, Gao J, Squires L, Adler L, et al. Long-term safety and effectiveness of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. CNS Spectr. 2009;14:573-85.
94. Mattingly G, Weisler R, Dirks B, Babcock T, Adeyi B, Scheckner B, et al. Attention deficit hyperactivity disorder subtypes and symptom response in adults treated with lisdexamfetamine dimesylate. Innov Clin Neurosci. 2012;9(5-6):22-30.
95. Wigal SB, Wigal T, Schuck S, Brams M, Williamson D, Armstrong RB, et al. Academic, behavioral, and cognitive effects of OROS® methylphenidate on older children with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2011;21:121-31.
96. Casas M, Rösler M, Sandra Kooij JJ, Ginsberg Y, Ramos-Quiroga JA, Heger S, et al. Efficacy and safety of prolonged-release OROS methylphenidate in adults with attention deficit/hyperactivity disorder: A 13-week, randomized, double-blind, placebo-controlled, fixed-dose study. World J Biol Psychiatry. 2011 Nov 22.
97. Wigal SB, Childress AC, Belden HW, Berry SA. NWP06, an extended-release oral suspension of methylphenidate, improved attention-deficit/hyperactivity disorder symptoms compared to placebo in a laboratory classroom study. J Child Adolesc Psychopharmacol. 2013 Feb;23(1):3-10.
98. Wilens TE. Biederman J. Lerner M. Concerta Study Group. Effects of once-daily osmotic-release methylphenidate on blood pressure and heart rate in children with attention-deficit/hyperactivity disorder: results from a one-year follow-up study. Journal of Clinical Psychopharmacology. 2004; 24(1):36-41.
99. Mattos P, Louzã MR, Palmini AL, et al. A Multicenter, Open-Label Trial to Evaluate the Quality of Life in Adults With ADHD Treated With Long-Acting Methylphenidate (OROS MPH): Concerta Quality of Life (CONQoL) Study. J Atten Disord. 2012 Feb 14. [Epub ahead of print].
100. Cox DJ, Merkel RL, Moore M, Thorndike F, Muller C, Kovatchev B. Relative benefits of stimulant therapy with OROS methylphenidate vs mixed amphetamine salts extended release in improving the driving performance of adolescent drivers with attention-deficit/hyperactivity disorder. Pediatrics. 2006 Sep;118(3):e704-10.
101. Yang L, Cao Q, Shuai L, Li H, Chan RC, Wang Y. Comparative study of OROS-MPH and atomoxetine on executive function improvement in ADHD: a randomized controlled trial. Int J Neuropsychopharmacol. 2011 Oct 21:1-12. [Epub ahead of print].
102. Wolraich ML, Greenhill LL, Pelham W, Swanson J, Wilens T, Palumbo D, et al. Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. Pediatrics. 2001;108:883-92.
103. Pelham WE, Gnagy EM, Burrows-Maclean L, Williams A, Fabiano GA, Morrisey SM, et al. Once-a-day Concerta - methylphenidate vs three times daily methylphenidate in laboratory and natural settings. Pediatrics. 2001;107:e105.
104. Gau SS, Shen HY, Soong WT, Gau CS. An open-label, randomized, active-controlled equivalent trial of osmotic release oral system methylphenidate in children with attention-deficit/hyperactivity disorder in Taiwan. J Child Adolesc Psychopharmacol. 2006 Aug;16(4):441-55.
105. Lopez F, Silva R, Pestreich L, Muniz R. Comparative efficacy of two once daily methylphenidate formulations (Ritalin LA and Concerta) and placebo in children with attention deficit hyperactivity disorder across the school day. Paediatr Drugs. 2003;5(8):545-55.
106. Swanson JM, Wigal SB, Wigal T, Sonuga-Barke E, Greenhill LL, Biederman J, et al. A comparison of one-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs study). Pediatrics. 2004;113:e206-16.
107. Silva R, Muniz R, Pestreich LK, Brams M, Childress A, Lopez FA. Efficacy of two long-acting methylphenidate formulations in children with attention- deficit/hyperactivity disorder in a laboratory classroom setting. J Child Adolesc Psychopharmacol. 2005 Aug;15(4):637-54.
108. Jahromi LB, Kasari CL, McCracken JT, Lee LS, Aman MG, McDougle CJ, Scahill L, Tierney E, Arnold LE, Vitiello B, Ritz L, Witwer A, Kustan E, Ghuman J, Posey DJ. Positive effects of methylphenidate on social communication and self-regulation in children with pervasive developmental disorders and hyperactivity. J Autism Dev Disord. 2009;39:395-404.

109. Spencer TJ, Mick E, Surman CB, Hammerness P, Doyle R, Aleardi M, et al. A randomized, single-blind, substitution study of OROS methylphenidate (Concerta) in ADHD adults receiving immediate release methylphenidate. J Atten Disord. 2011;15:286-94.
110. Efron D, Jarman F, Barker M. Efficacy of methylphenidate and dextroamphetamine in children with attention hyperactivity disorder: a double blind crossover trial. Pediatrics. 1997;100:662-8.
111. Pelham WE, Greenslade KE, Vodde-Hamilton M, Murphy DA, Greenstein JJ, Gnagy EM, et al. Relative efficacy of long-acting stimulants on children with attention deficit-hyperactivity disorder: a comparison of standard methylphenidate, sustained-release methylphenidate, sustained-release dextroamphetamine, and pemoline. Pediatrics. 1990;86:226-37.
112. Palumbo DR, Sallee FR, Pelham WE Jr, Bukstein OG, Daviss WB, McDermott MP. Clonidine for attention-deficit/hyperactivity disorder: 1. Efficacy and tolerability of outcomes. J Am Acad Child Adolesc Psychiatry. 2008;47:180-8.
113. Greenhill LL, Findling RL, Swanson JM; ADHD Study Group. A double-blind, placebo-controlled study of modified-release methylphenidate in children with attention-deficit/hyperactivity disorder. Pediatrics. 2002;109:e39.
114. McGough JJ, Wigal SB, Abikoff H, Turnbow JM, et al. A randomized, double-blind, placebo-controlled, laboratory classroom assessment of methylphenidate transdermal system. J of Att Dis. 2006;9(3):476-85.
115. Pelham WE, Manos MJ, Ezzell CE, Tresco KE, et al. A dose-ranging study of methylphenidate transdermal system in children with ADHD. J Am Acad Adolesc. 2005;44(6):522-9.
116. Pelham WE, Burrows-MacLean L, Gnagy EM, Fabiano GA, et al. Transdermal methylphenidate, behavioral, and combined treatment for children with ADHD. Exp Clin Psychopharmacology. 2005;13:111-26.
117. Faraone SV, Glatt SJ, Bukstein OG, Lopez FA, Arnold LE, Findline RL. Effects of once-daily oral and transdermal methylphenidate on sleep behavior of children with ADHD. J Atten Disord. 2009; 12:308-15.
118. Findling RL, Bukstein OG, Melmed RD, López FA, Sallee FR, Arnold LE, Pratt RD. A randomized, double-blind, placebo-controlled, parallel-group study of methylphenidate transdermal system in pediatric patients with attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2008;69:149-59.
119. Chou WJ, Chen SJ, Chen YS, Liang HY, Lin CC, Tang CS, et al. Remission in children and adolescents diagnosed with attention-deficit/hyperactivity disorder via an effective and tolerable titration scheme for osmotic release oral system methylphenidate. J Child Adolesc Psychopharmacol. 2012 Jun;22(3):215-25.
120. Faraone SV, Bierderman J, Spencer TJ, Aleardi M. Comparing the efficacy of medications for ADHD using meta-analysis. MedGenMed. 2006;8(4):4.
121. Schelleman H, Bilker WB, Strom BL, Kimmel SE, Newcomb C, Guevara JP, et al. Cardiovascular events and death in children exposed and unexposed to ADHD agents. Pediatrics. 2011;127:1102-10.
122. Olfson M, Huang C, Gerhard T, Winterstein AG, Crystal S, Allison PD, et al. Stimulants and cardiovascular events in youth with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2012;51:147-56.
123. Schelleman H, Bilker WB, Kimmel SE, Daniel GW, Newcomb C, Guevara JP, et al. Methylphenidate and risk of serious cardiovascular events in adults. Am J Psychiatry. 2012;169:178-85.
124. Hanwella R, Senanayake M, de Silva V. Comparative efficacy and acceptability of methylphenidate and atomoxetine in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis. BMC Psychiatry. 2011;11:176.

Therapeutic Class Review
Attention Deficit/Hyperactivity Disorder (ADHD) Agents

Overview/Summary

This review will focus on the agents used in the treatment of attention deficit/hyperactivity disorder (ADHD). These agents come from a variety of drug classes and are summarized in Table 1.[1-25] ADHD is a common psychiatric disorder often diagnosed during childhood; however, children with ADHD may continue to manifest symptoms into adulthood.[1] The core symptoms of ADHD utilized in the diagnosis of the disorder include hyperactivity, impulsivity and inattention. There are three subtypes of ADHD, including a predominantly inattentive subtype, a predominantly hyperactive-impulsive subtype and a combined subtype in which both symptoms are displayed.[26] Untreated, or undertreated, ADHD is associated with adverse sequelae, including delinquent behavior, antisocial personality traits, substance abuse and other comorbidities[27]. There are several central nervous system agents that are Food and Drug Administration (FDA)-approved for the treatment of ADHD, including the cerebral stimulants (amphetamines and methylphenidate derivatives), as well as atomoxetine (Strattera®), clonidine extended-release (Kapvay®) and guanfacine extended-release (Intuniv®).[1-25] Due to the potential for abuse, the cerebral stimulant agents are classified as Schedule II controlled substances.[1-22] Atomoxetine, clonidine extended-release and guanfacine extended-release are not classified as controlled substances.[23-25] Clonidine and guanfacine extended-release formulations are approved for use as both adjunctive therapy with stimulant medications and as monotherapy.[24,25]

Most ADHD agents and stimulants are currently available generically. Agents that are available only as a brand name product include: lisdexamfetamine capsules (Vyvanse®), amphetamine tablets (Evekeo®) and extended-release suspension (Dyanavel XR®), atomoxetine capsules (Strattera®), dextroamphetamine solution (ProCentra®), methylphenidate patch (Daytrana®), and extended-release suspension (Quillivant XR®). Aptensio XR (methylphenidate extended-release) is also available only as a brand name product; however, other extended-release biphasic capsules are available generically.[29]

Current consensus clinical guidelines for the treatment of children and adolescents with ADHD recommend that stimulants are highly effective for reducing core symptoms of ADHD in children.[27,28,30] Although initial therapy with atomoxetine or extended-release formulations of clonidine and guanfacine may reduce core symptoms of ADHD, there is less evidence to support their use compared to stimulants. The selection of therapy should be based on comorbid conditions, adverse event profiles, compliance issues, risk of drug diversion and patient/parent preference.[31] Stimulants, particularly methylphenidate, are recommended as first-line therapy in adult patients with ADHD.[28,32]

Medications

Table 1. Medications Included Within Class Review[1-25]

Generic Name (Trade name)	Medication Class	Generic Availability
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines		
Amphetamine (Dyanavel XR®, Evekeo®)	Central nervous system stimulant	-
Amphetamine/dextroamphetamine salts (Adderall®*, Adderall XR®*)	Central nervous system stimulant	a
Dextroamphetamine (ProCentra®, Dexedrine®*, Dexedrine Spansule®*, Zenzedi®*)	Central nervous system stimulant	a
Lisdexamfetamine (Vyvanse®)	Central nervous system stimulant	-
Methamphetamine (Desoxyn®*)	Central nervous system stimulant	a
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous		
Dexmethylphenidate (Focalin®*, Focalin XR®*)	Central nervous system stimulant	a
Methylphenidate (Aptensio XR®, Concerta®*, Daytrana®, Metadate CD®*, Metadate ER®*, Methylin®*, Methylin ER®*, Quillivant XR®, Ritalin®*, Ritalin LA®*, Ritalin SR®*)	Central nervous system stimulant	a

Generic Name (Trade name)	Medication Class	Generic Availability
Central α-Agonists		
Clonidine extended-release (Kapvay®*)	α-2 adrenergic agonist	a
Guanfacine extended-release (Intuniv®*)	α-2 adrenergic agonist	a
Central Nervous System Agents-Miscellaneous		
Atomoxetine (Strattera®)	Norepinephrine reuptake inhibitor	-

*Available generically in one dosage form or strength.

Table 2. Cerebral Stimulants/Agents Used for Attention Deficit/Hyperactivity Disorder Classified by Duration of Action[1-25]

Generic Name(s)	Short-Acting	Intermediate-Acting	Long-Acting
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines			
Amphetamine	Evekeo		Dyanavel XR®
Amphetamine/ dextroamphetamine salts	Adderall®		Adderall XR®
Dextroamphetamine	ProCentra®, Zenzedi®	Dexedrine®	
Lisdexamfetamine			Vyvanse®
Methamphetamine		Desoxyn®	
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous			
Dexmethylphenidate	Focalin®		Focalin XR®
Methylphenidate	Methylin®, Ritalin®	Metadate ER®, Ritalin SR®	Aptensio XR®, Concerta®, Daytrana®, Metadate CD®, Quillivant XR®, Ritalin LA®
Central α-Agonists			
Clonidine			Kapvay®
Guanfacine			Intuniv®
Central Nervous System Agents-Miscellaneous			
Atomoxetine			Strattera®

Indications

Table 3a. Food and Drug Administration-Approved Indication-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines[1-10]

Indication(s)	Amphetamine	Amphetamine/ Dextroamphet-amine Salts	Dextroamphet-amine	Lisdex-amfetamine	Methamphet-amine
ADHD	a	a	a	a	a
Exogenous obesity	a ‡				a *
Narcolepsy	a ‡	a †	a		

ADHD: Attention Deficit/Hyperactivity Disorder
*As a short-term adjunct in a regimen of weight reduction based on caloric restriction, for patients in whom obesity is refractory to alternative therapy (e.g., repeated diets, group programs, and other drugs).
†Adderall®
‡Evekeo

In addition the Food and Drug Administration-approved indications listed above, dextroamphetamine has been used off-label in the treatment of traumatic brain injury, cocaine dependence and autism.[37]

Table 3b Food and Drug Administration-Approved Indication-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous[11-22]

Indication(s)	Dexmethyl-phenidate	Methyl-phenidate

Indication(s)	Dexmethyl-phenidate	Methyl-phenidate
ADHD	a	a
Narcolepsy		a *

ADHD: Attention Defficit/Hyperactivity Disorder
*Metadate ER®, Methylin®, Ritalin® and Ritalin SR®.

In addition the Food and Drug Administration-approved indications listed above, methylphenidate has been used off-label in the treatment of traumatic brain injury and depression in the elderly. [36]

Table 3c. Food and Drug Administration-Approved Indication-Central α-Agonists[24,25]

Indication	Clonidine	Guanfacine
Treatment of attention deficit/hyperactivity disorder as monotherapy and as adjunctive therapy to stimulant medications	a	a

Clonidine (immediate-release) is used off-label in a variety of conditions including alcohol withdrawal syndrome, diabetic diarrhea, hot flashed, hyperhidrosis, insomnia, methadone withdrawal, postherpetic neuralgia, migraine prophylaxis, restless legs syndrome, smoking cessation, tardive dyskinesia, Tourette syndrome and ulcerative colitis. Guanfacine has also been use in the treatment of Tourette syndrome.[36]

Table 3d. Food and Drug Administration-Approved Indication-Central Nervous System Agents-Miscellaneous[23]

Indication(s)	Atomoxetine
Treatment of attention deficit/hyperactivity disorder	a

In addition the Food and Drug Administration-approved indications listed above, atomoxetine has been used off label in the treatment of binge eating disorder, nocturnal enuresis and obesity, while sodium oxybate has been used in the treatment of fibromyalgia and fatigue.[36]

Pharmacokinetics

Table 4a. Pharmacokinetics-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines[1-10]

Drug	Absorption	Distribution	Metabolism	Elimination
Amphetamine	Bioavailability: not reported Cmax: not reported	VD: nd Protein binding: nd	Method: Liver Metabolites (active): 4-hydroxy-amphetamine	Route: renal (30 to 40% unchanged) Half-life: not reported (IR); 12 to 15 hours (ER)
Amphetamine/ dextro-amphetamine salts	Bioavailability: percent not reported (well-absorbed) (food: unaffected) Cmax: nd Tmax: 3 hours (IR), 7 hours (ER)	Vd: nd Protein binding: nd	Method: Liver (variable) Metabolites (active): 4-hydroxy-amphetamine, norephedrine	Route: renal (30 to 40% [unchanged], 50% [changed]) (ER) Half-life: 9 to 14 hours (ER) Cl: nd
Dextro-amphetamine	Bioavailability: percent not reported (well-absorbed) (food: unaffected) Cmax: nd	Vd: 6.11 L/kg Protein binding: nd	Method: liver (extensive) Metabolites: hippuric acid, benzoic acid, norephedrine, 4-hydroxy-	Route: renal (17 to 73%) Half-life: 10 to 12 hours Cl: nd

Drug	Absorption	Distribution	Metabolism	Elimination
	Tmax: 2 to 3 hours (IR), 8 hours (ER)		norephedrine, benzyl methyl ketone (activity not reported)	
Lisdex-amfetamine	Bioavailability: percent not reported (rapidly absorbed) (food: increased Tmax by 1 hour) Cmax: nd Tmax: 3.5 to 3.8 hours	Vd: nd Protein binding: nd	Method: blood Metabolites: dextro-amphetamine (active), L-lysine (inactive)	Route: renal (96%) fecal (0.3%) Half-life: <1 hour Cl: nd
Meth-amphetamine	Bioavailability: percent not reported (rapidly absorbed) (food: nd) Cmax: nd Tmax: nd	Vd: nd Protein binding: nd	Method: liver (aromatic hydroxylation, N-dealkylation, and domination) Metabolites: 7 metabolites have been identified (activity not reported)	Route: Renal (62%) Half-life: 4 to 5 hours Cl: nd

Cl=clearance, Cmax=maximum concentration, ER=extended-release, IR=immediate-release, nd=no data, Tmax=time to maximum concentration, Vd=volume of distribution

Table 4b. Pharmacokinetics-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous[11-22]

Drug	Absorption	Distribution	Metabolism	Elimination
Dexmethyl-phenidate	Bioavailability: 22 to 25% (ER) (food: delayed absorption [IR]) Cmax: nd Tmax: 1.0 to 1.5 hours (IR), 1.5 hours (first peak) and 6.5 hours (second peak) (ER)	Vd: 2.65 L/kg (ER) Protein binding: 12 to 15%	Method: Liver (extensive) (IR) Metabolites (inactive): d-ritalinic acid (IR)	Route: renal (90%) Half-life: 2.0 to 4.5 hours Cl: nd
Methylphenidate	Bioavailability: 10 to 52% (food: high fat meals delays Tmax by 1 hour and may increase AUC up to 30% [IR, ER capsule, ER tablet], no effect [transdermal patch]) Cmax: 4.2 to 15.3 ng/mL (IR), 10.9 to 16.8 ng/mL (ER capsule), 3.7	Vd: 1.80 to 2.65 L/kg (ER capsule) Protein binding: 10 to 33% (ER capsule)	Method: tissues (ER capsule) Metabolites (inactive): ritalinic acid, methylphenidate hydrochloride, hydroxy-methylphenidate, hydroxyritalinic acid (ER capsule)	Route: renal (90%) fecal (1 to 3%) (ER capsule) Half-life: 2.5 to 3.5 hours (ER capsule), 3 to 4 hours (transdermal patch) Cl: 0.4 to 0.73 L/hour/kg (ER capsule)

Drug	Absorption	Distribution	Metabolism	Elimination
	ng/mL (ER tablet) 39 ng/mL (transdermal patch) Tmax: 1 to 2 hours (IR), 1.5 to 3.0 hours (first peak) and 4.5 to 6.6 hours (second peak) (ER capsule), 6.8 hours (ER tablet), 4.7 hours (SR), 7.5 to 10.5 hours (transdermal patch)			

AUC=area under the curve, Cl=clearance, Cmax=maximum concentration, ER=extended-release, IR=immediate-release, nd=no data, SR=sustained release, Tmax=time to maximum concentration, Vd=volume of distribution

Table 4c. Pharmacokinetics-Central α-Agonist[24,25]

Drug	Absorption	Distribution	Metabolism	Elimination
Clonidine	Bioavailability: 89% (food: minimal effect) Cmax: nd Tmax: 6.5 hours	Vd: nd Protein binding: 20 to 40%	Method: Liver (50%) Metabolites: nd	Route: renal (40 to 60%) Half-life: 12 to 16 hours Cl: nd
Guanfacine	Bioavailability: 80% (food: increased exposure with high fat foods) Cmax: 1 ng/mL (1 mg) Tmax: 6 hours (range, 4 to 8 hours)	Vd: nd Protein binding: 70%	Method: Liver (50%) Metabolites: guanfacine hydrochloride (activity not reported)	Route: renal (percent not reported) Half-life: 16 hours Cl: nd

Cl=clearance, Cmax=maximum concentration, nd=no data, Tmax=time to maximum concentration, Vd=volume of distribution

Table 4d. Pharmacokinetics-Central Nervous System Agents-Miscellaneous[23]

Drug	Absorption	Distribution	Metabolism	Elimination
Atomoxetine	Bioavailability: 63 to 94% (food: extent of absorption unaffected) Cmax: nd Tmax: 1 to 2 hours	Vd: 74 to 250 L Protein binding: 98%	Method: liver (CYP2D6) Metabolites: 4-hydroxy-atomoxetine (active), noratomoxetine (inactive), N-desmethyl-atomoxetine (inactive)	Route: renal Half-life: 4 to 5 hours (extensive metabolites), 22 hours (poor metabolizers) Cl: 0.3 to 0.5 L/hour/kg

Cl=clearance, Cmax=maximum concentration, CYP=cytochrome P450 isoenzyme, nd=no data, Tmax=time to maximum concentration, Vd=volume of distribution

Clinical Trials

Clinical trials demonstrating the safety and efficacy of the attention deficit/hyperactivity disorder (ADHD) agents and stimulants in Food and Drug Administration (FDA)-approved indications are outlined in Table 5.[37-124]

The efficacy of amphetamine extended-release suspension (Dyanavel XR®) was evaluated in a laboratory classroom study conducted in 108 pediatric patients (aged 6 to 12 years) with ADHD. During the five-week, open-label dose optimization period amphetamine extended-release was titrated weekly to an optimum dose between 2.5 and the maximum dose of 20 mg/day. Subjects then entered a one-week randomized, double-blind treatment with the individually optimized dose of amphetamine extended-release or placebo. The primary efficacy endpoint was change from pre-dose Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) rating scale combined score at four hours post-dosing at the end of the week. SKAMP-combined change scores from pre-dose demonstrated a statistically significant improvement at all time points (1, 2, 4, 6, 8, 10, 12, 13 hours) post-dosing with amphetamine extended-release compared to placebo. At hour four, the placebo-subtracted difference in SKAMP-combined score was -14.8 (95% CI, -17.9 to -11.6, P value not reported).[2]

The efficacy of methylphenidate extended-release (Aptensio XR®) for the treatment of ADHD was established in a randomized, double-blind, single center, placebo-controlled, flexible-dose, cross-over trial in pediatric patients aged 6 to 12 years (study one) and a second randomized, double-blind, multicenter, placebo-controlled, fixed–dose trial in pediatric patients 6 to 17 years (study two). In study one, following a two to four week open-label dose optimization phase, patients received one week of treatment and evaluated over a period of 12 hours. Subsequently, patients were given the opposite treatment for one week and returned for the second evaluation. Patients could then enter an open-label extension phase for up to 21 months. The primary efficacy endpoint was the average SKAMP Total Score, comparing methylphenidate extended-release (Aptensio XR®) to placebo. The SKAMP Total Scores were statistically significantly lower for methylphenidate extended-release (Aptensio XR®) than for placebo at the test day average and at all time points (1, 2, 3, 4.5, 6, 7.5, 9, 10.5 and 12 hours) post-dosing (P values not reported). In study two, the primary efficacy endpoint was the mean decrease from baseline to the end of week one in the ADHD-Rating Scale-IV (ADHD-RS-IV) Total Score. Four methylphenidate extended-release (Aptensio XR®) doses were compared to placebo at the end of week one. ADHD-RS-IV Total Score was significantly improved in the 20 mg/day and 40 mg/day groups when compared to placebo, but not for the 10 mg/day or the 15 mg/day doses when compared to placebo (P value not reported).[14]

Data from several clinical trials demonstrate that the ADHD agents and stimulants are effective in the treatment of ADHD, as measured by significant decreases in ADHD rating scale scores compared to placebo. Although comparative trials have been conducted, it is difficult to interpret the results of these trials due to design flaws (e.g., small population, short treatment duration or variable outcomes). Overall, there is insufficient evidence to suggest that one ADHD agent and stimulant is more efficacious than another for the treatment of ADHD.[37-125]

The majority of efficacy data supporting the use of the ADHD agents and stimulants is derived from placebo-controlled trials. In addition, the majority of trials were conducted in the pediatric population. Limited data exists to demonstrate the efficacy of a variety of cerebral stimulants (amphetamine/dextroamphetamine, dexmethylphenidate and lisdexamfetamine) and atomoxetine in the adult population.[42,50,68,93,94,109] In a large study by Goodman et al (N=725), adults 18 years of age or older were administered amphetamine/dextroamphetamine salts extended-release 10 to 60 mg daily for 10 weeks. By 10 weeks, the mean ADHD rating scale (ADHD-RS) scores significantly decreased in the amphetamine/dextroamphetamine salts extended-release group compared to baseline, regardless of dose (P<0.0001).[42] In a four-year open label study in adults diagnosed with ADHD, treatment with atomoxetine reduced mean Conners Adult ADHD Rating Scale–Investigator Rated: Screening Version total ADHD symptom scores by 30.2% from baseline to endpoint (-8.8; P<0.001). In a study by Weisler and colleagues, treatment with lisdexamfetamine improved ADHD-RS total scores as early as week one of treatment and continued throughout the eleven month treatment period (P<0.001).[91] In adult patients

who were stabilized on immediate-release methylphenidate at baseline, switching to methylphenidate extended-release (Concerta®) has had no effect on Adult ADHD investigator system symptom report scale (AISRS) after six weeks of treatment (11.2 vs 10.7; P=0.80).[109]

Clonidine extended-release and guanfacine extended-release are FDA-approved for use in ADHD as monotherapy and as adjunctive treatment to stimulants.[24,25] In children with ADHD, treatment with clonidine extended-release 0.2 or 0.4 mg daily significantly improved ADHD-RS from baseline at eight weeks compared to placebo (P<0.001).[66] In a six-week study evaluating the effect of guanfacine extended-release on psychomotor functioning, there were no significant differences between guanfacine extended-release and placebo groups on measures of psychomotor functioning or alertness on the Cambridge Neuropsychological Test Automated Battery-Choice Reaction Time scale (mean difference, 2.5; P=0.80 for choice reaction time, 2.5; P=0.84 for correct responses, 15.5; P=0.30 for movement time and -8.2; P=0.72 for total time). Moreover, guanfacine extended-release was associated with a significant improvement in ADHD symptoms compared to placebo (P=0.001).[76] In a study by Sallee and colleagues, adolescents randomized to receive guanfacine extended-release 1 to 4 mg daily achieved statistically significant reductions in ADHD-RS-IV total scores from baseline compared to placebo. The placebo-adjusted mean endpoint changes from baseline were -6.75 (P=0.0041), -5.41 (P=0.0176), -7.34 (P=0.0016), and -7.88 (P=0.0006) in the guanfacine extended-release 1, 2, 3 and 4 mg groups, respectively.[75] Guanfacine extended-release was shown to significantly improve scores on the oppositional subscale of the Conners' parent rating scale-revised: long form compared to placebo over nine weeks of treatment (P<0.001). The mean percentage reductions from baseline were 56.3% with guanfacine extended-release and 33.4% with placebo (P<0.001).[80] With regard to monotherapy, these agents have been shown to significantly improve ADHD rating scale scores compared to placebo. Both clonidine extended-release and guanfacine extended-release have only been evaluated in pediatric patients (six to 17 years of age).[64,74-80,83] Similarly, use of these agents as adjunctive treatment to stimulant therapy has been shown to significantly improve ADHD rating scale scores compared to stimulant monotherapy.[65,81] Prior to FDA-approval of clonidine extended-release and guanfacine extended-release, the immediate-release formulations of these agents were evaluated, and demonstrated variable efficacy for the treatment of ADHD.[63,73,112]

Table 5. Clinical Trials

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Attention Deficit Hyperactivity Disorder				
McCracken et al[36] AMP-IR (Adderall®) 10 mg daily vs AMP-XR (Adderall XR®) 10 to 30 mg daily vs placebo	DB, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD (combined or hyperactive-impulsive subtype)	N=51 5 weeks	Primary: SKAMP scales Secondary: Examination of the time course of AMP-XR	Primary: AMP-IR and AMP-XR were judged to have similar efficacy, and both exceeded placebo on attention and deportment SKAMP scales (P<0.0001). Secondary: The AMP-XR group displayed continued efficacy (in SKAMP score improvements) at time points beyond that of the AMP-IR group (i.e., 12 hours post dose).
Pliszka et al[37] AMP-IR (Adderall®) 12.5 mg daily vs MPH-IR 25 mg daily vs placebo	DB, PC, PG, RCT Children in grades one through five diagnosed with ADHD	N=58 3 weeks	Primary: CGI-S (parent and teacher) Secondary: Not reported	Primary: More responders were reported with AMP-IR than MPH-IR or placebo on both CGI-S scores (P<0.05). Behavioral effects of AMP-IR appeared to persist longer than with MPH-IR. Fourteen (70%) patients in the AMP-IR group required only a single morning dose, and 17 (85%) patients in the MPH-IR group received two or more doses per day (P=0.003). Secondary: Not reported
Pelham et al[38] AMP-IR (Adderall®) 7.5 or 12.5 mg BID vs MPH-IR (Ritalin®) 10 or	DB, PC, RCT, XO Children five to 12 years of age diagnosed with ADHD	N=25 6 weeks	Primary: Time course and dose-dependent response information Secondary:	Primary: Both doses of AMP-IR were generally more efficacious in reducing negative behaviors and improving academic productivity than low-dose MPH-IR (10 mg BID) throughout the course of the entire day. The differences were more pronounced when the effects of MPH-IR were wearing off at midday and late afternoon/early evening (P<0.025). Conversely, AMP-IR 7.5 mg BID and MPH-IR 17.5 mg BID produced equivalent

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
17.5 mg BID vs placebo			Not reported	behavioral changes throughout the entire day. The doses of AMP-IR that were assessed produced greater improvement than did the assessed doses of MPH-IR, particularly the lower dose of MPH-IR (P<0.01). Both drugs produced low and comparable levels of clinically significant side effects. Secondary: Not reported
Faraone et al[39] AMP-IR (Adderall®) vs MPH-IR	MA (4 trials) Patients diagnosed with ADHD	N=216 3 to 8 weeks	Primary: CGI-S (parent, teacher and investigator) Secondary: Not reported	Primary: Combined results showed slightly greater efficacy with AMP-IR vs MPH-IR in clinician and parent ratings (P<0.05). No statistically significant difference was found in CGI-S scores with teacher ratings (P≥0.26). Secondary: Not reported
Biederman et al[40] AMP-XR (Adderall XR®) 10 to 30 mg daily vs placebo	DB, MC, PC, RCT Children six to 12 years of age diagnosed with ADHD (hyperactive-impulsive or combined subtypes)	N=584 3 weeks	Primary: CGI-S (teachers and parents) Secondary: Variation in responses based on morning and afternoon assessments	Primary: Each AMP-XR treatment group had a statistically significant improvement in both CGI-S teacher and parent scales (P<0.001). Secondary: The CGI-S teacher scores calculated for the morning and afternoon assessments showed all doses of AMP-XR to be more effective than placebo (P<0.001) at each assessment. The CGI-S teacher scores in the AMP-XR group were statistically significantly improved at all time points compared to those in the placebo group (P<0.001).
Goodman et al[41] AMP-XR (Adderall XR®) 10 to 60 mg daily	MC, OL, PRO Adults ≥18 years of age diagnosed with ADHD (any subtype)	N=725 10 weeks	Primary: ADHD-RS, CGI-I Secondary: SF-36	Primary: At the end of the study, the mean ADHD-RS scores significantly decreased in the AMP-XR group regardless of dose compared to baseline (P<0.0001). Statistical analysis comparing the individual AMP-XR doses was not performed. At the end of the study, most patients obtained CGI-I ratings of much/very much

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				improved (522/702; 74.4%). Secondary: At the end of the study, the AMP-XR groups reported significant improvements in all quality of life measurements (P<0.0001 for all) measured by the SF-36, including physical functioning and mental health parameters.
Biederman et al[42] Atomoxetine 1.2 to 1.8 mg/kg/day vs placebo	2 DB, MC, PC, RCT Females seven to 13 years of age diagnosed with ADHD	N=51 9 weeks	Primary: ADHD-RS Secondary: CPRS-R, CGI-S (parents)	Primary: Atomoxetine significantly decreased ADHD-R:S scores compared to placebo (P<0.05) for the entire duration of the study. Secondary: Atomoxetine statistically significantly decreased the parent-rated CPRS-R index scores compared to placebo (10.3 vs 1.0; P<0.001). Atomoxetine also statistically significantly decreased the parent-rated CGI-S scores compared to placebo (1.5 vs 0.6; P<0.001).
Durell et al[43] Atomoxetine vs placebo	DB, PC, RCT Young adults 18 to 30 years of age with ADHD	N=445 12 weeks	Primary: CAARS-Inv: SV total ADHD symptoms score with adult prompts Secondary: AAQoL-29, CGI-S, Patient Global Impression-Improvement, CAARS self report, BRIEF-Adult Version Self Report and asessments of depression,	Primary: Compared to placebo, treatment with atomoxetine resulted in a greater improvement in CAARS: Inv: SV (-13.6±0.8 vs -9.3±0.8; 95% CI, -6.35 to -2.37; P<0.001). Secondary: Compared to placebo, treatment with atomoxetine resulted in a greater improvement in CGI-S (-1.1±0.1 vs -0.7±0.1; 95% CI, -0.63 to -0.24; P<0.001) and CAARS Self-Report (-11.9±0.8 vs -7.8±0.7; 95% CI, -5.94 to -2.15; P<0.001) but not on the Patient Global Impression-Improvement score. Treatment with atomoxetine was superior to placebo on the AAQoL-29 and BRIEF-Adult Version Self-Report.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
			anxiety, sleepiness, driving behaviors, social adaptation and substance abuse	
Michelson et al[44] Atomoxetine 1.2 to 1.8 mg/kg/day vs placebo	MC, OL, PC, RCT Children eight to 18 years of age diagnosed with ADHD	N=297 8 weeks	Primary: ADHD-RS Secondary: CPRS-R, CHQ	Primary: Significant reduction in ADHD-RS was seen in both active groups (P<0.001). No difference was seen between the 1.2 and the 1.8 mg/kg/day treatment arms. Secondary: Atomoxetine 1.2 mg/kg showed significant decreases in all scales of CPRS-R (P<0.05). Atomoxetine 1.8 mg/kg showed significant increase in all scales of CHQ (P<0.05).
Kratochvil et al[45] Atomoxetine 0.5 to 1.8 mg/kg/day vs placebo	DB, MC, PC, RCT Children five to six years of age diagnosed with ADHD	N=101 8 weeks	Primary: ADHD-RS Secondary: CGI-S, CGI-I	Primary: Atomoxetine significantly reduced mean parent (P<0.009) and teacher (P=0.02) ADHD-RS total score compared to placebo. Secondary: A total of 40% of children treated with atomoxetine and 22% of children who received placebo had CGI-I scores much too very much improved (P=0.1) with no significant differences between groups. A total of 62% of children treated with atomoxetine had CGI-S scores of moderately or severely ill at the end of the study compared to 77% of children who received placebo. Common adverse events included decreased appetite, gastrointestinal upset, and sedation. Most adverse events were considered mild or moderate by the study investigator.
Spencer et al[46]	DB, MC, PC,	N=291	Primary:	Primary:

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Atomoxetine up to 90 mg daily vs placebo	RCT (pooled data) Children seven to 13 years of age diagnosed with ADHD	9 weeks	ADHD-RS Secondary: CPRS-R:S, CGI-S	Significant mean reductions in both active groups in all scales were reported (both studies) for ADHD-RS (P<0.001) and CPRS-R:S (P=0.023 for study one and P<0.001 for study two). Secondary: Atomoxetine displayed a significant mean reduction in CPRS-R:S index over placebo in both studies (study 1: -5.7 vs -2.6; P=0.023 and study 2: -8.8 vs -2.1; P<0.001). Atomoxetine displayed a statistically significant mean change in CGI-S scores over placebo in both studies (study 1: -1.2 vs -0.5; P=0.023 and study 2: -1.5 vs -0.7; P=0.001).
Dittmann et al[47] Atomoxetine 0.5 mg/kg/day for seven days, followed by 1.2 mg/kg/day (fast titration) vs atomoxetine 0.5 mg/kg/day for seven days, followed by 0.8 mg/kg/day for seven days, followed by 1.2 mg/kg/day (slow titration) vs placebo	DB, PC, RCT Patients six to 17 years of age ADHD with comorbid ODD or conduct disorder	N=181 9 week	Primary: SNAP-ODD, SNAP-ADHD Secondary: CGI-S	Primary: Treatment with atomoxetine once daily at week nine, using either fast or slow titration to a target dose of 1.2 mg/kg/day, was significantly better compared to placebo in reducing ODD symptoms measured by SNAP-ODD scores (P<0.001). Comparing fast and slow titration separately, the decrease in ODD symptoms severity was significant for both individual titration groups (atomoxetine-fast: 8.6; 95% CI, 7.2 to 9.9; atomoxetine-slow: 9.0; 95% CI, 7.7 to 10.3; and placebo: 12.0; 95% CI, 10.6 to 13.5). Atomoxetine was significantly more effective than placebo in reducing the severity of ADHD symptoms measured by SNAP-ADHD scores. Scores reflecting severity of conduct disorder symptoms, attention-deficit and disruptive behavior, were significantly reduced after nine weeks of atomoxetine treatment. Secondary: CGI-S and individual treatment behaviors showed were significantly reduced after treatment with atomoxetine. The most common adverse events included fatigue, sleep disorders, nausea, and gastrointestinal complaints and were reported the first three weeks of treatment in 60.0% of atomoxetine-fast, 44.3% of atomoxetine-slow, and 18.6% of placebo group

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				study patients.
Hammerness et al[48] Atomoxetine 0.5 to 1.4 mg/kg/day	OL, PRO Children six to 17 years of age diagnosed with ADHD who had a prior trial of stimulant treatment	N=34 6 weeks	Primary: ADHD-RS, CGI Secondary: Not reported	Primary: There was a significant reduction in ADHD RS symptoms compared to baseline. There was a significant reduction in ADHD-RS symptoms score from baseline to the second week of atomoxetine treatment. There was a significant reduction in ADHD symptoms of inattention (-8.1; P<0.001) and hyperactivity (-5.7; P<0.001) at the end of atomoxetine treatment. A total of 56% of patients met criteria for the a priori definition of response; much or very much improved on the CGI plus >30% reduction in ADHD-RS symptoms. Commonly reported adverse events (>10%) included gastrointestinal problems, headache and sedation. Secondary: Not reported
Adler et al[49] Atomoxetine 60 to 120 mg/day	MC, OL Adults diagnosed with ADHD	N=384 4 years	Primary: CAARS-Inv:SV total ADHD symptom score Secondary: CAARS-Self:SV, CGI-ADHD-S, HAM-D-17, HAMA, WRAADDS, SDS	Primary: The mean CAARS-Inv:SV total ADHD symptom scores decreased 30.2% from baseline to endpoint (-8.8; P<0.001). Secondary: Significant decreases were found on the CAARS-Inv:SV subscales, and the CAARS-Self:SV total and subscales (P<0.001). CGI-ADHD-S and WRAADDS scores improved significantly from baseline (-1.1 and -5.0, respectively; P<0.001 for both). SDS total and subscale scores improved 25.3% (-3.8; P<0.001). A slight increase was noted in HAM-D-17 scores (0.8; P=0.004), but this small change is not likely clinically relevant. There was no significant change in HAMA scores (0.4; P=0.216).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				HR, DBP, SBP increased. Weight loss over the course of the study was statistically significant (-0.94 kg; P<0.001).
Wietecha et al[50] Atomoxetine 40 mg daily titrated to 100 mg daily after two weeks vs placebo	DB, PC, RCT Adults with ADHD having both a spouse/partner and child	N=502 24 weeks	Primary: CAARS-Inv: SV and CGI-S Secondary: Not reported	Primary: Treatment with atomoxetine resulted in a greater improvement in CAARS-Inv: SV (-16.43 vs -8.65; P<0.001) and CGI-S compared to placebo at week 24 (P<0.001). Secondary: Not reported.
Biederman et al[51] Atomoxetine 0.5 to 1.2 mg/kg/day vs AMP-XR (Adderall XR®) 10 to 30 mg daily	DB, FD, MC, RCT Females six to 12 years of age diagnosed with ADHD	N=57 18 days	Primary: SKAMP-A SKAMP-D Academic testing Secondary: Adverse events	Primary: The AMP-XR group experienced significantly greater mean changes in SKAMP-D scores from baseline compared to the atomoxetine group (-0.48 vs -0.04; P<0.001). The AMP-XR group experienced significantly greater mean changes in SKAMP-A scores from baseline compared to the atomoxetine group (-0.45 vs -0.05; P<0.001). Both AMP-XR and atomoxetine groups experienced a significant increase in the mean number of math problems attempted and answered correctly from baseline (P<0.001), but patients in the AMP-XR group attempted a significantly greater number of math problems than those in the atomoxetine group (P=0.04). Secondary: Both AMP-XR and atomoxetine were well tolerated. The number of adverse events was similar in both groups. Most adverse events reported were of mild or moderate severity.
Kemner et al[52] Atomoxetine 0.5 mg/kg once daily vs MPH-ER (Concerta®)	MC, OL, PRO, RCT Children six to 12 years of age diagnosed with ADHD	N=1,323 3 weeks	Primary: Investigator-related ADHD-RS and CGI-I, performed at weeks one, two, and three; PSQ	Primary: The ADHD-RS change from baseline measured at each time point showed that both treatments were effective. MPH-ER produced significantly greater improvements in ADHD-RS scores at weeks, one, two, and three (P<0.001). At week three, rates of treatment response (i.e., ≥25% reduction in ADHD-RS score)

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
18 mg once daily			Secondary: Not reported	were significantly greater with MPH ER than were seen with atomoxetine (P<0.001). Significantly more children treated with MPH ER than with atomoxetine achieved a CGI-I score ≤2 after week three (P<0.001). Parent-rated PSQ scores revealed statistically significantly greater improvements with MPH-ER than with atomoxetine. Secondary: Not reported
Newcorn al[53] Acute Comparison Trial: Atomoxetine 0.8 to 1.8 mg/kg/day administered BID vs MPH-ER (Concerta®) 18 to 54 mg once daily vs placebo XO Trial: Atomoxetine 0.8 to 1.8 mg/kg/day administered BID Patients on MPH-ER were switched to atomoxetine during the XO trial.	DB, PC, RCT, XO Children six to 16 years of age diagnosed with ADHD (any subtype)	Acute Comparison Trial: N=516 6 weeks XO Trial: N=178 6 weeks	Primary: ADHD-RS Secondary: CGI-S, CPRS, CHQ, and Daily Parent Ratings of Evening and Morning Behavior-Revised	Acute Comparison Trial Primary: The proportion of patients responding to atomoxetine (45%) was significantly higher than the rate for placebo (24%; P=0.003). MPH-ER (56%) was also more effective than placebo (24%; P≤0.001). MPH-ER was found to be more effective than atomoxetine (P=0.02). Secondary: Atomoxetine and MPH-ER produced greater improvements in CGI-S, CPRS and CHQ compared to placebo. MPH-ER also produced greater improvements compared to atomoxetine on CGI-S, CPRS and CHQ (P=0.004, P=0.003, P=0.02, respectively). XO Trial The responses to the two treatments in these patients were as follows: 34% responded to either atomoxetine or MPH-ER, but not both; 44% responded to both treatments; 22% did not respond to either treatment. Of the 70 patients who did not respond to MPH-ER in the initial trial, 43% subsequently responded to atomoxetine in the XO trial. Of the 69 patients who did not respond to atomoxetine in the second trial, 42% had previously responded to MPH-ER. Of the patients classified as MPH-ER, 36% showed significantly worse response on atomoxetine, 18% showed significantly better response on atomoxetine, and 46% showed roughly the same response to treatment with atomoxetine. Of the 70 patients classified as MPH-ER nonresponders, 10% showed significantly worse response, 51% showed significantly better response, and 39% showed roughly the

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				same response to treatment with atomoxetine.
Starr et al[54] Atomoxetine 0.5 mg/kg once daily vs MPH-ER (Concerta®) 18 mg once daily	OL, RCT African-American children six to 12 years of age diagnosed with ADHD	N=183 3 weeks	Primary: Investigator-related ADHD-RS and CGI-I, performed at weeks one, two, and three; PSQ Secondary: Not reported	Primary: For the ADHD-RS scores, both treatment groups achieved significant improvements from baseline at all time points (P<0.001). Improvements from baseline, defined as ADHD-RS score reductions of ≥30% or ≥50%, were significantly greater in the MPH ER group starting at week three (P<0.03 for ≥30% reduction, P<0.006 for ≥50% reduction). Significantly more children treated with MPH ER than atomoxetine achieved a CGI-I score ≤2 after week three (P<0.01). Parent-rated PSQ scores revealed statistically significantly greater improvements with MPH ER than with atomoxetine. Secondary: Not reported
Wang et al[55] Atomoxetine 0.8 to 1.8 mg/kg/day vs MPH-IR 0.2 to 0.6 mg/kg/day administered BID	DB, MC, RCT Children six to 16 years of age diagnosed with ADHD	N=330 8 weeks	Primary: ADHD-RS Secondary: CPRS-R:S, CGI-S, treatment-emergent adverse events, weight	Primary: Atomoxetine was not significantly different than MPH in improving ADHD symptoms based on ADHD-RS scores (atomoxetine, 77.4%; MPH, 81.5%; P=0.404). Secondary: Both atomoxetine and MPH-IR treatment groups significantly improved CPRS-R:S and CGI-S scores from baseline (P<0.001 for all), the groups were not statistically significant from each other in both measures (P>0.05). Treatment-emergent adverse events that occurred significantly more frequently in the atomoxetine group, compared to the MPH group, included anorexia (37.2 vs 25.3%; P=0.024), nausea (20.1 vs 10.2%; P=0.014), somnolence (26.2 vs 3.6%; P<0.001), dizziness (15.2 vs 7.2%; P=0.024) and vomiting (11.6 vs 3.6%; P=0.007), most of which were of mild or moderate severity. Patients in the atomoxetine group experienced a small but significantly greater mean weight loss at the end of eight weeks compared to those in the MPH group (-1.2 vs -0.4 kg; P<0.001).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Kratochvil et al[56] Atomoxetine titrated up to 2 mg/kg/day vs MPH-IR titrated up to 60 mg/day	MC, OL Males seven to 15 years of age and females seven to nine year of age diagnosed with ADHD	N=228 10 weeks	Primary: ADHD-RS Secondary: CPRS-R, CGI-S, safety	Primary: Both atomoxetine and MPH-IR were associated with marked improvement in inattentive and hyperactive-impulsive symptom clusters but were not statistically different (P=0.66). Secondary: There were no statistically significant differences between treatment groups on all of the CPRS-R and CGI-S outcome measures (P<0.001). Tolerability was also similar between the two drugs with no statistical differences in discontinuations (P=0.18). Statistically significant increases in pulse and BFI were seen with both atomoxetine and MPH-IR (P<0.05).
Sutherland et al[57] Atomoxetine 40 to 100 mg/day vs atomoxetine 40 to 100 mg/day and buspirone 15 to 45 mg/day vs placebo	DB, MC, PC, RCT Men and women 18 to 60 years of age diagnosed with ADHD	N=241 8 weeks	Primary: AISRS Secondary: Not reported	Primary: There was a significantly greater decrease in the AISRS total score for atomoxetine plus buspirone than placebo at weeks one to seven, with an estimated mean difference of -4.80 (P=0.001). There was a greater decrease in the AISRS total score for atomoxetine plus buspirone than for atomoxetine at weeks one to seven, but only statistically significant at week four (P<0.09). The most commonly reported adverse events from both treatment groups included insomnia, dry mouth, headache, and asthenia. Dizziness was most commonly reported for the atomoxetine plus buspirone treatment group. Discontinuations due to treatment-related adverse events were 15.5% for atomoxetine plus buspirone, 11.3% for atomoxetine and 14.9% for placebo. Secondary: Not reported
Ni et al[58] Atomoxetine titrated up	OL, RCT Patients 18 to 50	N=63 8 to 10	Primary: ASRS, CGI-ADHD-S,	Primary: At visit one (weeks four and five), both the MPH-IR and atomoxetine treatment groups experienced statistically significant reductions from baseline in ASRS scores

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
to 1.2 mg/kg/day vs MPH-IR titrated up to 60 mg/day	years of age diagnosed with ADHD	weeks	AAQoL, WFIRS-S and safety Secondary: Not reported	for inattention (-5.77 and -8.93, respectively; P<0.001 for both) and hyperactivity-impulsivity (-3.69 and -8.11, respectively; P<0.001). The differences between the treatment groups was significant, favoring treatment with atomoxetine (P<0.05). Significant reductions from baseline in ASRS scores were apparent at visit two (eight to 10 weeks) for both the inattention (-9.25 and -10.20, respectively; P<0.001) and hyperactivity-impulsivity subtypes (-6.21 and -7.80, respectively; P<0.001); however, differences between treatment groups were not statistically significant. Both treatment groups experienced improved CGI-ADHD-S scores at all time points compared to baseline values (P<0.001 for all); however, differences between groups were not statistically significant. The mean AAQoL scores significantly increased from baseline to visit one (weeks four and five) and visit two (weeks eight to 10) for both treatment groups. The effect sizes as assessed by Cohen's d ranged from 0.59 to 1.63 (P<0.01). Both treatment groups experienced significant improvements in the severity of functional impairment (WFIRS-S) from baseline to visit one (weeks four to five) or (weeks eight to 10). Cohen's d ranged from 0.49 to 1.70 for the MPH-IR group and 0.42 to 1.11 for the atomoxetine group. Differences between the treatment groups were not statistically significant. Decreased appetite, vomiting and palpitation were frequently reported in both treatment groups. There was no significant difference in the occurrence of adverse events between treatment groups. Moreover, there was no significant change in body weight, BP, or HR during the study period (P>0.05 for all). Secondary: Not reported
Sutherland et al[59] Atomoxetine 40 to 100 mg/day vs	DB, MC, PC, RCT Patients 18 to 60 years of age diagnosed with	N=241 8 weeks	Primary: AISRS Secondary: Not reported	Primary: There was a significantly greater decrease in the AISRS total score for atomoxetine plus buspirone than placebo at weeks one to seven, with an estimated mean difference -4.80 (P=0.001). There was a greater decrease in the AISRS total score for atomoxetine plus

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
atomoxetine 40 to 100 mg/day plus buspirone 15 to 45 mg/day vs placebo	ADHD			buspirone than for atomoxetine at weeks one to seven, but only statistically significant at week four (P<0.09). The most commonly reported adverse events from both treatment groups included insomnia, dry mouth, headache, and asthenia. Dizziness was most commonly reported for the atomoxetine plus buspirone treatment group. Discontinuations due to treatment-related adverse events were 15.5% for atomoxetine plus buspirone, 11.3% for atomoxetine, and 14.9% for placebo. Secondary: Not reported
Prasad et al[60] Atomoxetine 0.5 to 1.8 mg/kg/day vs standard current therapy	MC, OL, RCT Children seven to 15 years of age diagnosed with ADHD	N=201 10 weeks	Primary: CHIP-CE Secondary: ADHD-RS, CGI-S, CGI-I, HSPP, FBIM	Primary: Quality of life greatly improved over the 10 weeks in the atomoxetine group vs the standard current therapy group as demonstrated by the significant increase in CHIP-CE (P<0.001). Secondary: ADHD-RS, CGI-S, and CGI-I scores were significantly improved in the atomoxetine group over the standard current therapy group (P<0.001 for all). The atomoxetine group was significantly better in improving the HSPP Social Acceptance domain over the standard current therapy group (P=0.03), but the groups were not significantly different in the other five HSPP domains (P>0.05). There was not a statistically significant difference between groups in reduction in FBIM scores (P>0.05).
Cheng et al[61] Atomoxetine vs placebo	MA (9 trials) Patients diagnosed with ADHD	N=1,828 Variable duration	Primary: ADHD-RS Secondary: CTRS-RS, CPRS-R:S, CGI-S, CHQ	Primary: Atomoxetine significantly improved ADHD-RS scores compared to placebo (P<0.01 for all). Secondary: Atomoxetine significantly improved CTRS-RS, CPRS-R:S, and CGI-S scores compared to placebo (P<0.01 for all).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				Atomoxetine significantly improved quality of life as measured by the CHQ compared to placebo (P<0.01).
Hazell et al[62] Clonidine 0.1 to 0.2 mg/day vs placebo	PC, RCT, TB Children six to 14 years of age with ADHD and co-morbid ODD or conduct disorder	N=67 6 weeks	Primary: CBC (subscales conduct and hyperactive index) Secondary: Not reported	Primary: Significantly more children treated with clonidine than placebo improved on the CBC-Conduct scale (21 of 37 vs 6 of 29; P<0.01) but not the Hyperactive Index (13 of 37 vs 5 of 29; P=0.16). Compared to placebo, clonidine was associated with a greater reduction in standing SBP measured and with transient sedation and dizziness. Study patients treated with clonidine have a greater reduction in a number of unwanted effects associated with psychostimulant treatment compared to placebo. Secondary: Not reported
Jain et al[63] Clonidine ER 0.2 mg/day vs Clonidine ER 0.4 mg/day vs placebo	DB, PC, RCT Patients six to 17 years of age diagnosed with ADHD	N=236 8 weeks	Primary: ADHD-RS (total score) Secondary: ADHD-RS (inattention and hyperactivity), CPRS-R:S, CGI-S, CGI-I, PGA, treatment-emergent adverse events	Primary: Improvement from baseline to week five in ADHD-RS total score was significantly greater in both clonidine ER groups vs placebo (P<0.001). A significant improvement in ADHD-RS total score occurred beginning week one for the clonidine ER 0.2 mg/day group (P=0.02) and week two for the clonidine ER 0.4 mg/day group (P<0.0001) as compared to the placebo group and continued throughout the treatment period. Secondary: A significant improvement in mean change in ADHD-RS inattention score at week five vs baseline was -7.7 for both clonidine ER groups vs -3.4 for the placebo group (P<0.001 for clonidine ER 0.2 mg/day; P<0.006 for clonidine ER 0.4 mg/day). Improvements from baseline to week five in ADHD-RS hyperactivity score were -4.1 in the placebo group, -7.9 in the clonidine ER 0.2-mg/day group, and -8.8 in the clonidine ER 0.4-mg/day group (P<0.0012). Mean improvement in CPRS-R total score was significantly greater than placebo in both clonidine ER groups (P<0.01) at weeks three and five.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				Improvement in CGI-S and CGI-I from baseline to week five was significantly greater in both treatment groups vs placebo (P<0.0001 for CGI-S and P<0.003 for CGI-I). Significant improvement in PGA score from baseline in both treatment groups vs placebo was observed at week two (P<0.001) and was maintained through week seven (P<0.02) in the clonidine ER 0.2 mg/day group and through week five in the clonidine ER 0.4 mg/day group (P<0.009). The most common treatment-emergent adverse event was mild-to-moderate somnolence. Changes on ECG were minor and due to the pharmacology of clonidine.
Kollins et al[64] Clonidine ER 0.1 to 0.4 mg/day plus psychostimulant vs placebo plus psycho-stimulant	DB, MC, PC, RCT Children and adolescents diagnosed with hyperactive or combined subtype ADHD who had inadequate response to their psychostimulant therapy	N=198 8 weeks	Primary: ADHD-RS (total score) Secondary: ADHD-RS (hyperactivity and inattention), CPRS, CGI-S, CGI-I, PGA	Primary: At week five, study patients in the clonidine ER plus psychostimulant group experienced a greater improvement in ADHD-RS total score compared to patients in the placebo plus psychostimulant group (P=0.009). Secondary: Scores from baseline ADHD-RS hyperactivity and inattention subscale (P=0.014 and P=0.017, respectively), CPRS (P<0.062), CGI-S (P=0.021), CGI-I (P=0.006), and PGA (P=0.001) were significantly improved in the clonidine ER plus psychostimulant group compared to the placebo plus psychostimulant group. The most commonly treatment-emergent adverse event reported were mild to moderate in severity and included somnolence, headache, fatigue, upper abdominal pain, and nasal congestion.
Wigal et al[65] DXM (Focalin®) 2.5 to 10 mg BID vs MPH-IR 5 to 20 mg BID	DB, MC, PC, RCT Children six to 17 years of age diagnosed with ADHD (any subtype)	N=132 4 weeks	Primary: SNAP-T Secondary: SNAP-P, CGI-I Math test performance (clinic and home)	Primary: Both DXM and MPH-IR significantly improved SNAP-T scores compared to placebo (P=0.004 and P=0.0042, respectively) Secondary: The DXM group decreased SNAP-P scores at both 3 and 6 PM assessments compared to placebo (P<0.0001 and P=0.0003 respectively). The MPH-IR group significantly decreased 3 PM SNAP-P assessments compared to the placebo group (P=0.0073) but did not reach statistical significance at the 6 PM assessment

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				(P=0.064). Both DXM and MPH-IR improved CGI-I scores in significantly more patients than the placebo group (67% [P=0.0010] and 49% [P=0.0130] compared to 22%, respectively). Both DXM and MPH-IR significantly improved clinic-based math test scores compared to placebo (P=0.001 and P=0.0041 respectively). DXM significantly improved home-based math test scores compared to placebo (P=0.0236). MPH-IR did not reach statistical significance compared to placebo.
Greenhill et al[66] DXM-XR (Focalin XR®) 5 to 30 mg/day vs placebo	DB, MC, PC, RCT Children six to 17 years of age diagnosed with ADHD (any subtype)	N=97 7 weeks	Primary: CADS-T Secondary: CADS-P, CGI-I, CGI-S, CHQ (physical and psychosocial)	Primary: DXM-XR significantly increased CADS-T scores from baseline compared to placebo (16.3 vs 5.7; P<0.001). Secondary: DXM-XR significantly increased CADS-P scores from baseline compared to placebo (17.6 vs 6.5; P<0.001). DXM-XR improved overall CGI-I scores in a greater percent of patients compared to placebo (67.3 vs 13.3%; P<0.001). DXM-XR significantly improved CGI-S scores in a greater percent of patients than placebo (64.0 vs 11.9%; P<0.001). There was not a statistical difference between DXM-XR and placebo on the mean change in CHQ physical scores. DXM-XR did significantly improve mean CHQ psychosocial scores compared to placebo (11.9 vs 4.3; P<0.001).
Spencer et al[67] DXM-XR (Focalin XR®) 20 to 40 mg/day vs	DB, MC, PC, RCT Adults 18 to 60 years of age diagnosed with ADHD (any	N=184 5 weeks	Primary: ADHD-RS Secondary: ADHD-RS, CGI-I, CGI-S, CAARS, Q-LES-	Primary: All doses of DXM-XR significantly improved ADHD-RS scores from baseline compared to placebo (P<0.05). Secondary: The 20 and 40 mg doses of DXM-XR achieved improved ADHD-RS scores ≥30% and were significant compared to placebo, the 30 mg group did not reach statistical

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
placebo	subtype), childhood onset of symptoms, and a baseline ADHD-RS score ≥24		Q	significance. The percent of patients who achieved ≥30% were as follows: DXM-XR 20 mg, 57.9% (P=0.017); DXM-XR 30 mg, 53.7% (P=0.054); DXM-XR 40 mg, 61.1% (P=0.007); and placebo, 34.0%. All doses DXM-XR significantly improved CGI-I scores over placebo (P<0.05 for all). The 20 and 40 mg doses of DXM-XR improved CGI-S scores in a greater percent of patients compared to placebo, but the 30 mg group did not reach statistical significance. The percents of patients were as follows: 20 mg, 68.4% (P=0.09); 30 mg, 61.1% (P value not significant); 40 mg, 64.8% (P=0.031); and placebo, 41.5%. All doses of DXM-XR significantly improved CAARS scores compared to placebo (P<0.05 for all). None of the groups improved Q-LES-Q scores from baseline nor were there significant differences between groups.
Adler et al[68] DXM-XR (Focalin XR®) 20 to 40 mg/day vs placebo After completion of DB phase, patients could enter an OL extension phase with flexible dosing 20 to 40 mg/day for six months.	DB, MC, RCT Patients 18 to 60 years of age diagnosed with ADHD	N=103 6 months	Primary: Long-term safety and tolerability Secondary: ADHD-RS, CGI-I	Primary: DXM-XR was well tolerated; the most common adverse events were headache (27.6%), insomnia (20.0%), and decreased appetite (17.6%). Most adverse events were considered mild or moderate by the study investigator. Secondary: Mean improvements in ADHD-RS scores were -10.2 for study patients switched from placebo to DXM-XR and -8.4 for those maintained on DXM-XR. Improvements in CGI-I scores were reported in 95.1% of study patients switched from placebo to DXM-XR and 95.0% of study patients maintained on DXM-XR.
Brams et al[69] DXM-XR 20 mg/day	DB, RCT, XO Children 6 to 12 years of age with	N=165 3 weeks	Primary: Change in average SKAMP-	Primary: The mean change from pre-dose in SKAMP-combined score was significantly greater in the DXM-XR 30 mg group compared to the DXM-XR 20 mg group (-4.47 vs -2.02; P=0.002). Significantly greater improvement in ADHD symptoms was

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs DXM-XR 30 mg/day vs placebo	ADHD previously stabilized on MPH (40 mg to 60 mg/day) or DXM (20 mg to 30 mg/day)		combined score from pre-dose to 10, 11 and 12 hours post-dose Secondary: Not reported	observed in the DXM-XR 30 mg group compared to the DXM-XR 20 mg group at hours 10 through 12. Secondary: Not reported
Stein et al[70] DXM-XR (Focalin XR®) 10 to 30 mg/day vs AMP-XR (Adderall XR®) 10 to 30 mg/day	DB, PC, RCT Patients nine to 17 years of age with ADHD	N=56 8 weeks	Primary: ADHD-RS, CGI-I, CGI-S, WFIS, SERS Secondary: Not reported	Primary: There were significant dose-related decreases in total and hyperactive-impulsive symptom scores (P<0.001 and P<0.001, respectively) that did not differ by type of stimulant. There were significant dose-related decreases for Inattention symptoms (P<0.001) that were more modest and did not differ by type of stimulant. There were significant dose-related decreases in CGI-S scores (P<0.001) that did not differ by type of stimulant. There were significant effects of dose on the WFIS total score (P=0.008), on the Family (P=0.010), Learning (P=0.002), Social Activities (P=0.018), and Risk Taking (P=0.050) subscales, but not on the Living Skills or Self-Esteem subscales. The most common adverse events were mild to moderate in severity and included decreased appetite and insomnia. Adverse events were more common at higher dose levels for both stimulants. Secondary: Not reported
Muniz et al[71] DXM-XR (Focalin XR®) 20 mg/day vs	DB, MC, RCT Children six to 12 years of age diagnosed with ADHD and stabilized on	N=84 10 weeks	Primary: SKAMP Secondary: Not reported	Primary: Mean change in combined SKAMP score at two hours post-dose was significantly larger for MPH-ER 20 vs 36 mg/day (P<0.001). MPH-ER 20 and 30 mg doses have a more rapid onset and a greater effect in the morning relative to MPH-ER 36 and 54 mg doses while MPH-ER 36 and 54 mg had a greater effect at the end of the 12 hour day.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
DXM-XR (Focalin XR®) 30 mg/day vs MPH-ER (Concerta®) 36 mg/day vs MPH-ER (Concerta®) 54 mg/day vs placebo	MPH ≥2 weeks			All active treatments provided a significant benefit over placebo at most time points to 12 hours post-dosing. Secondary: Not reported
Scahill et al[72] Guanfacine 0.5 mg at bedtime, day four added 0.5 mg in the morning, day eight added 0.5 mg afternoon dose vs placebo	DB, PC, PG, RCT Children seven to 15 years of age diagnosed with ADHD and tic disorder	N=34 8 weeks	Primary: ADHD-RS, CGI-I, CPRS-R (hyperactivity index), YGTSS, CPT Secondary: Not reported	Primary: Guanfacine was associated with a mean improvement of 37% in the teacher-rated ADHD-RS total score compared to 8% improvement for placebo (P<0.01). Nine of 17 patients who received guanfacine were rated on the CGI-I as either much improved or very much improved, compared to 0 of 17 patients who received placebo. The mean CPRS-R on the parent-rated hyperactivity index improved by 27% in the guanfacine group and 21% in the placebo group, not a significant difference. Tic severity decreased by 31% in the guanfacine group, compared to 0% in the placebo group (P=0.05). For CPT, commission errors decreased by 22% and omission errors by 17% in the guanfacine group, compared to increases of 29% in commission errors and of 31% in omission errors in the placebo group. No significant adverse events were observed; one study patient taking guanfacine withdrew with sedation. Guanfacine was associated with an insignificant decrease in

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				BP and pulse. Secondary: Not reported
Kollins et al[73] Guanfacine ER 1 to 3 mg once daily vs placebo	DB, MC, PC, RCT Patients six to 17 years of age diagnosed with ADHD	N=182 6 weeks	Primary: CANTAB-CRT Secondary: CANTAB-SWM, DSST, PERMP	Primary: There were no significant differences between guanfacine ER and placebo groups on measures of psychomotor functioning or alertness on the CANTAB-CRT (mean difference, 2.5; P=0.8 for CRT, 2.5; P=0.84 for correct responses, 15.5; P=0.30 for movement time, and -8.2; P=0.72 for total time). Secondary: Guanfacine ER treatment was associated with significant improvement in ADHD symptoms (P=0.001) Most sedative adverse events were mild to moderate and occurred during dose titration, decreased with dose maintenance, and resolved during the study period.
Sallee et al[74] Guanfacine ER 1 to 4 mg once daily vs placebo	DB, MC, PC, RCT Patients six to 17 years of age with ADHD and a baseline score of 24 on the ADHD-RS-IV	N=324 9 weeks	Primary: ADHD-RS-IV total score Secondary: CPRS-R, CGI-I, PGA	Primary: The mean reduction in ADHD-RS-IV total scores from baseline to endpoint across all guanfacine ER dose groups was -19.6 compared to -12.2 for the placebo group. The placebo-adjusted mean endpoint changes from baseline were -6.75 (P=0.0041), -5.41 (P=0.0176), -7.34 (P=0.0016), and -7.88 (P=0.0006) in the guanfacine ER 1, 2, 3, and 4 mg groups, respectively. Placebo-adjusted mean baseline-to-endpoint changes for symptoms of inattentiveness were: -4.2 (P=0.002), -3.0 P=0.02), -3.5 (P=0.007), and -4.0 (P=0.002) for guanfacine ER 1, 2, 3, and 4 mg, respectively. Placebo-adjusted mean baseline-to-endpoint changes for symptoms of hyperactivity/impulsivity were: -2.7 (P=0.028), -2.5 (P=0.03), -3.9 (P=0.001), and -4.0 (P=0.0008) for guanfacine ER 1, 2, 3, and 4 mg, respectively. Secondary: Using placebo-adjusted LSMD in change from baseline at endpoint in CPRS-R total scores, the 4 mg guanfacine ER dose demonstrated significant efficacy at eight hours (-10.2; P=0.004) and 12 hours (-7.5; P=0.04). The 3 mg guanfacine ER dosage group demonstrated significant improvements in CPRS-R results at eight (-

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				11.8; P=0.002), 12 (-9.6; P=0.01), and 14 hours (-9.8; P=0.0156) postdose. The 2 mg guanfacine ER dosage group demonstrated significant improvements in CPRS-R scores at eight hours (-9.0; P=0.01) postdose. For the 1 mg guanfacine ER dosage group, the placebo-adjusted LSMD in CPRS-R at eight, 12, 14, and 24 hours were -12.8 (P=0.0004), -11.4 (P=0.002), -10.4 (P=0.0077), and -8.9 (P=0.02), respectively. Based on CGI-I scores, the percentages of the patients showing clinical improvement were 30% (placebo), 54% (guanfacine ER 1 mg; P=0.007 vs placebo), 43% (guanfacine ER mg; P=0.1404 vs placebo), 55% (guanfacine ER mg; P=0.006 vs placebo), and 56% (guanfacine ER mg; P=0.004 vs placebo). Improvements in PGA scores were 30% (placebo), 51% (guanfacine ER 1 mg; P=0.030 vs placebo), 36% (guanfacine ER 2 mg; P=0.4982 vs placebo), 62% (guanfacine ER mg; P=0.002 vs placebo), and 57% (guanfacine ER 4 mg; P=0.0063 vs placebo). Mild to moderate treatment-emergent adverse events in patients taking guanfacine ER were somnolence, headache, fatigue, sedation, dizziness, irritability, upper abdominal pain, and nausea. There were no significant differences in sleepiness between the patients taking placebo and guanfacine ER. Guanfacine ER was not associated with abnormal changes in height or weight. SBP, DBP, and pulse rate decreased as the guanfacine ER dose increased and then increased during dose maintenance and tapering. The range of mean changes from baseline for seated SBP for the placebo group was -1.30 to -0.48 mm Hg and -7.38 to 0.54 mm Hg for the guanfacine ER randomized dose groups.
Sallee et al[75] Guanfacine ER 1 to 4 mg once daily	ES, OL Patients six to 17 years of age with ADHD and a baseline score of 24 on the ADHD-RS-IV	N=257 24 months	Primary: ADHD-RS-IV, CPRS-R, CGI-I, CHQ-PF50, CTRS-R, PGA Secondary: Not reported	Primary: Somnolence (30.5%), headache (24.3%), upper respiratory tract infection (17.8%), nasopharyngitis (14.3%), fatigue (13.9%), upper abdominal pain (12.7%) and sedation (11.2%) were the most frequently reported adverse events. The majority of somnolence, sedation, or fatigue events was moderate or mild in severity and resolved by end of treatment. Hypotension was reported in 5.0% of patients. Decreased DBP was found in 3.5% of patients, decreased BP in 2.7% of patients, and decreased SBP in 2.3% of patients. Decreased appetite (13.2%), irritability (13.2%), and pharyngitis (11.3%) were

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				among the most common treatment-emergent adverse events that differed in the subgroup coadministered psychostimulants relative to monotherapy or the overall safety population. Mean changes in ADHD-RS-IV total score from baseline to end point showed significant improvement: overall, -20.1 (P<0.001), and for all guanfacine ER dose groups, -23.8, -22.5, -20.0, and -18.4 for the 1, 2, 3, and 4 mg dose groups, respectively (P<0.001 for each). CPRS-R mean changes from baseline to end point were statistically significant in the overall treatment group (-18.2; P<0.001). The overall mean change from baseline demonstrated significant improvement in CPRS-R scores at each postdose assessment (P<0.001). Investigator-rated CGI-I scores at end point showed that investigators rated the majority of patients very much improved (29.3%) or much improved (28.8%). For the PGA, 59.7% of patients were rated as very much or much improved at end point. Mean changes in CHQ-PF50 Physical Summary Scores from baseline to end point were not statistically significant. CHQ-PF50 Psychosocial Summary Scores demonstrated significant improvement from baseline to end point for the overall full analysis set (P<0.001). Secondary: Not reported
Sallee et al[76] Guanfacine ER 1 to 4 mg/day vs placebo	DB, PC, RCT (Post-hoc analysis) Patients 6 to 17 years of age with ADHD	N=631 Variable duration	Primary: Change in ADHD-RS total scores Secondary: Not reported	Primary: For patients with the predominantly inattentive subtype of ADHD, patients treated with guanfacine ER achieved significantly greater mean reductions from baseline in ADHD-RS total scores compared to placebo (P≤0.020). For patients with combined-type ADHD, patients treated with guanfacine ER achieved significantly greater reductions in ADHD-RS total score from baseline compared to placebo at treatment weeks one through five and at study end (P≤0.011). Secondary:

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Connor et al[77] Guanfacine ER 1 to 4 mg once daily vs placebo	DB, MC, PC, RCT Patients six to 12 years of age with a diagnosis of ADHD and the presence of oppositional symptoms	N=217 9 weeks	Primary: Change from baseline to endpoint in the oppositional subscale of the CPRS-R:L Secondary: Change in ADHD-RS-IV total score and safety	Primary: The mean change from baseline in the oppositional subscale of the CPRS-R:L was -10.9 for those receiving guanfacine ER and -6.8 for those receiving placebo (P<0.001). The mean percentage reductions from baseline were 56.3% with guanfacine ER and 33.4% with placebo (P<0.001). Secondary: The mean decrease from baseline to endpoint in ADHD-RS-IV total score was 23.8 points for guanfacine ER compared to 11.5 for placebo (P<0.001). The mean percentage reductions from baseline were 56.7% with guanfacine ER and 26.5% with placebo (P<0.001). Adverse events were reported in 84.6% of those receiving guanfacine ER group and 60.3% of those receiving placebo. Treatment-emergent adverse events occurred more frequently with guanfacine ER than with placebo (83.8 vs 57.7%, respectively). The most common treatment-emergent adverse events in the guanfacine ER group were somnolence (50.7%), headache (22.1%), sedation (13.2%), upper abdominal pain (11.8%) and fatigue (11.0%).
Biederman et al[78] Guanfacine ER 2 to 4 mg once daily vs placebo	DB, MC, PC, RCT Patients six to 17 years of age with ADHD combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype	N=345 8 weeks	Primary: ADHD-RS-IV total score observed during the last treatment week of the dosage escalation period (weeks one to five) Secondary: CGI-S, CGI-I, PGA, CPRS-R, and CTRS-R observed during	Primary: The mean reduction in ADHD-RS-IV score at end point across all guanfacine ER groups was -16.7 compared to -8.9 for placebo. Placebo-adjusted LS mean end point changes from baseline in the guanfacine ER 2, 3, and 4 mg groups were -7.70 (P=0.0002), -7.95 (P=0.0001), and -10.39 (P<0.0001), respectively. Mean changes from baseline in hyperactivity/impulsivity in the placebo and guanfacine ER 2, 3, and 4 mg groups were -3.51, -7.33 (P=0.0002 vs placebo), -7.32 (P=0.0002 vs placebo), and -9.31, (P<0.0001 vs placebo) respectively. Mean changes from baseline in inattentiveness were -4.92, -8.7 (P=0.0011 vs placebo), -9.11 (P=0.0006 vs placebo), and -9.44 (P=0.0002 vs placebo), respectively. Secondary: Significant improvement in CGI-I scores at end point was shown in 25.64, 55.95, 50.00, and 55.56% of patients in the placebo and guanfacine ER 2, 3, and 4 mg groups, respectively. Improvement in CGI-I scores was significant in the guanfacine

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
			the last treatment week of the dosage escalation period (weeks one to five)	ER 2 mg group compared to the placebo group by week two (P=0.0194) and in all guanfacine ER groups by week three continuing through week five (P<0.05). Significant improvement in PGA scores at end point was shown in 23.08, 62.12, 50.82, and 66.10% of patients in the placebo and guanfacine ER 2, 3, and 4 mg groups, respectively. On the CPRS-R, placebo-adjusted LS mean day total end point changes from baseline were -6.55 in the 2 mg group (P=0.0448), -7.36 in the 3 mg group (P=0.0242), and -12.70 in the 4 mg group (P<0.0001). On the CTRS-R, placebo-adjusted LS mean day total end point changes from baseline were -11.57 (P<0.0001), -13.48 (P<0.0001), and -12.53 (P<0.0001), for the 2, 3, and 4 mg doses, respectively. The most commonly reported treatment-emergent adverse events were somnolence, fatigue, upper abdominal pain and sedation. The incidence of somnolence in patients who were receiving guanfacine ER 1, 2, 3, and 4 mg doses was 12.7, 11.4, 20.9, and 17.5%, respectively. SBP, DBP, and pulse rate decreased as guanfacine ER dosages increased, then increased as dosages stabilized and tapered down. The greatest mean changes from baseline in SBP and DBP for patients who were receiving guanfacine ER 2, 3, and 4 mg doses were -7.0 mm Hg (week 3) and -3.8 mm Hg (week 2), -7.0 mm Hg (week 3) and -4.7 mm Hg (weeks three and five), and -10.1 mm Hg (week four) and -7.1 mm Hg (week four), respectively. The greatest mean changes from baseline in pulse rate for patients who were receiving guanfacine ER 2, 3, and 4 mg doses were -5.7 beats per minute (week three), -8.1 beats per minute (week three), and -8.0 beats per minute (week four), respectively. Mean changes in height and weight from baseline to end point were not significant across the treatment groups.
Biederman et al[79] Guanfacine ER 2 to 4 mg once daily	ES, OL Patients six to 17 years of age with ADHD combined subtype, predominantly	N=240 24 months	Primary: Safety Secondary: ADHD-RS-IV, PGA, CHQ-PF50	Primary: Somnolence (30.4%), headache (26.3%), fatigue (14.2%), and sedation (13.3%) were the most frequently reported adverse events. Changes from baseline to endpoint in SBP, DBP, and pulse rate were -0.8 mm Hg, -0.4 mm Hg, and -1.9 beats per minute, respectively. Mean changes in pulse rate and QRS intervals were generally unchanged across study visits.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
	inattentive subtype, or predominantly hyperactive-impulsive subtype			Hypotension was reported in 2.9% of patients and bradycardia was reported in 2.1% of patients. There were no unexpected changes in mean height or weight. Approximately 7.0% of patients reported weight increase possibly or probably related to study drug. Weight decrease was not reported. Appetite increase was reported by 2.1% of patients, appetite decrease by 3.3% of patients, and anorexia by 0.8% of patients. Secondary: The mean ADHD-RS-IV total score was significantly reduced from baseline to endpoint (-18.1; P<0.001 vs baseline). Mean reductions in ADHD-RS-IV scores were significant for both the inattention (-9.5; P<0.001 vs baseline) and the hyperactivity/impulsivity (-8.5; P<0.001 vs baseline) subscales. For PGA scores, 58.6% of patients were 'improved' at endpoint compared to baseline of the preceding study. For the CHQ-PF50, physical summary scores did not change significantly from baseline to endpoint overall or in any dose or age group.
Spencer et al[80] Guanfacine ER 1 to 4 mg once daily, added to existing stimulant therapy	MC, OL Patients six to 17 years of age with ADHD (combined, predominantly inattentive, or predominantly hyperactive-impulsive subtype) and who were on a stable regimen of	N=75 9 weeks	Primary: ADHD-RS-IV, CPRS-R, CGI-I, CGI-S, CHQ-PF50, and PGA Secondary: Not reported	Primary: The most common treatment-related adverse events were fatigue (34.7%), headache (33.3%), upper abdominal pain (32.0%), irritability (32.0%), somnolence (18.7%), and insomnia (16.0%). Most adverse events were mild to moderate in severity. The incidences of the treatment-emergent adverse events were comparable between both psychostimulant subgroups except for fatigue (28.6% in the guanfacine ER plus MPH subgroup vs 18.2% in the guanfacine ER plus AMP subgroup) and irritability (14.3% in the guanfacine ER plus MPH subgroup vs 33.3% in the guanfacine ER plus AMP subgroup). Twenty patients have a decrease in BP judged to be of clinical interest. Twelve patients exhibited orthostatic BP decreases. None of the patients with BP decreases

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
	either MPH or AMP ≥1 month with suboptimal control of ADHD symptoms			reported syncope or lightheadedness. At baseline, the mean PDSS score was 15.0. Decreases were observed at visit six (-4.8) and end point (-3.1). During treatment, there was an increase from screening in the number of patients reporting clinically significant dullness, tiredness, and listlessness on the PSERS. There was a decrease in the number of patients with clinically significant loss of appetite and trouble sleeping. The psychostimulant subgroups were generally comparable. Significant decreases from baseline (psychostimulant only) to end point in ADHD-RS-IV total score were observed overall and in both psychostimulant combination subgroups, indicating improvement in ADHD symptoms (overall, -16.1; guanfacine ER plus MPH group, -17.8; guanfacine ER plus AMP group, -13.8; P<0.0001 for all). The mean percentage reduction from baseline to end point in ADHD-RS-IV score overall was 56.0%. Improvement was significant for the mean day CPRS-R total score (-19.8; P<0.0001), as well as for all three time points (-23.2 at 12 hours postdose, -18.5 at 14 hours postdose, and -17.8 at 24 hours postdose; P<0.0001 for all). The percentage of patients showing improvement at end point on the CGI was 73.0%. On the PGA, 84.1% of patients showed improvement. No significant improvement occurred at end point in the CHQ-PF50 physical summary score. Mean improvement for the CHQ-PF50 psychosocial score was 10.2 (P<0.0001). Secondary: Not reported
Wilens et al[81] Guanfacine ER 1 to 4 mg/day in the morning plus placebo at	DB, MC, PC, RCT Children and adolescents six	N=461 9 weeks	Primary: ADHD-RS Secondary: CGI-S, CGI-I	Primary: At the end of the study, guanfacine ER treatment groups showed significantly greater improvement from baseline ADHD-RS total scores compared to placebo plus psychostimulant (guanfacine ER in the morning; P=0.002; guanfacine ER in the evening; P<0.001).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
bedtime vs placebo in the morning and guanfacine ER 1 to 4 mg/day in the afternoon vs placebo Patients continued stable dose of psycho-stimulant given in the morning.	to 17 years of age diagnosed with ADHD			Secondary: Significant benefits of guanfacine ER treatment compared to placebo plus psychostimulant were observed on the CGI-S (guanfacine ER in the morning; P=0.013, guanfacine ER in the evening; P<0.001) and CGI-I (guanfacine ER in the morning; P=0.024, guanfacine ER in the evening; P=0.003). At study endpoint, small mean decreases in pulse, SBD, and DBP were observed in guanfacine ER treatment groups compared to placebo plus psychostimulant group. The most common treatment-emergent adverse events were mild to moderate in severity and included headache, somnolence and upper respiratory infections.
Faraone et al[82] Guanfacine ER 1 to 4 mg once daily	MA Patients six to 17 years of age with ADHD (combined subtype, predominantly inattentive subtype, or predominantly hyperactive-impulsive subtype)	N=813 6 to 9 weeks	Primary: Predictors of efficacy and sedation using various models Secondary: Not reported	Primary: Actual Dose Model The presence or absence of ADHD symptoms was influenced by the actual doses of medication received by the participants (P=0.006). In participants with residual ADHD symptoms, greater total ADHD-RS symptom scores were significantly related to shorter treatment duration (P<0.001) and higher baseline total ADHD-RS symptom scores (P<0.001). The only significant influence on the frequency of sedation-related adverse events was treatment duration (P=0.034). mg/kg Dose Model: The presence or absence of ADHD symptoms was significantly influenced by the dose of medication received by the participant as expressed in mg/kg (P=0.001). Treatment duration (P<0.001) and baseline total ADHD-RS symptom scores (P<0.001) were predictors of weekly total ADHD-RS symptom scores. The only significant influence on the frequency of sedation-related adverse events was treatment duration (P=0.034).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				Titration Rate Dose Model: The presence or absence of ADHD symptoms was significantly influenced by the titrated dose of medication received by the participant (P=0.005). The number of symptoms was significantly influenced by treatment duration (P<0.001) and baseline total ADHD-RS scores (P<0.001). The only significant influence on the frequency of sedation-related adverse events was treatment duration (P=0.034). Secondary: Not reported
Adler et al[83] LDX 30 to 70 mg/day vs placebo	DB, PC, RCT Adults 18 to 55 years of age with a primary diagnosis of ADHD and executive function deficits (assessed by baseline BRIEF-A GEC T-scores ≥65)	N=161 10 weeks	Primary: BRIEF-A scales (GEC, index and clinical subscales) Secondary: Not reported	Primary: At week 10 or early termination, treatment with LDX was associated with significantly greater reductions from baseline in mean BRIEF-A GEC T-scores compared to placebo (P<0.0001) and significantly greater reductions from baseline in mean T-scores for both BRIEF-A index scales (metacognition scale) and all nine clinical subscales (P≤0.0056 for all). At week 10 or early termination, patients treated with LDX had mean T-scores for BRIEF-A indices and clinical subscales that were below levels of clinically significant deficits in executive function. The mean GEC T-scores were 57.2 and 68.3 for the LDX and placebo groups, respectively. Secondary: Not reported
Babcock et al[84] LDX 30 to 70 mg/day vs placebo	DB, MC, RCT (Post-hoc analysis) Adults with ADHD who remained symptomatic on AMP therapy	N=36 4 weeks	Primary: Mean change in ADHD-RS score from baseline Secondary: Change in CGI-S, CGI-I	Primary: At study end, the change from baseline in mean ADHD-RS scores for LDX -treated patients was similar in the AMP group and the overall study group. The prior AMP non-responders in the placebo group had a change from baseline in ADHD-RS total score of -13.5. In the overall efficacy population, the placebo group experienced a change from baseline of -7.8. Secondary: Mean CGI scores were similar between the prior AMP subgroup and overall efficacy

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
	prior to enrollment in a four-week trial			population in the LDX groups. In addition, the percentage of clinical responders and symptomatic remitters was comparable at all time points assessed in both LDX groups.
Biederman et al[85] LDX 30 to 70 mg/day vs placebo	DB, MC, PC, RCT Children six to 12 years of age diagnosed with ADHD and with an ADHD-RS score ≥28	N=209 4 weeks	Primary: ADHD-RS Secondary: CPRS-R, CGI-S, CGI-I	Primary: ADHD-RS scores were significantly greater with each of the three LDX doses compared to placebo (P<0.001). The greatest efficacy was seen in the 70 mg group with a mean ADHD-RS change of -4.91 from baseline between the 30 and 70 mg groups (P<0.05). Secondary: Each LDX group significantly improved CPRS-R scores throughout the day compared to the placebo group (P<0.01 for all). Mean CGI-S scale scores significantly improved from baseline to treatment end point for all LDX groups compared to the placebo group (P<0.001 for all). CGI-I ratings were either “very much improved” or “much improved” in ≥70% of patients in the LDX groups compared to 18% of patients in the placebo group (P<0.001 for all).
Biederman et al[86] LDX 30 to 70 mg/day vs placebo AMP-XR 10 to 30 mg was used as a control arm.	DB, MC, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD	N=52 12 weeks	Primary: SKAMP scale Secondary: PERMP, CGI-I	Primary: SKAMP scores significantly improved in both the LDX and AMP-XR groups compared to the placebo group (P<0.0001 for both). Secondary: PERMP scores for both the LDX and AMP-XR groups significantly decreased compared to the placebo group (P<0.0001 for both). The CGI-I scores significantly improved in the both LDX and AMP-XR groups compared to the placebo group (P<0.0001).
Brams et al[87] LDX 30 to 70 mg/day vs	DB, RCT Withdrawal study Adults 18 to 55 years of age with	N=116 6 weeks	Primary: Proportion of patients with symptom relapse (≥50%	Primary: At study end, 8.9% of patients in the LDX group and 75.0% of patients in the placebo group experienced symptom relapse (P<0.0001), with most patients showing relapse after one and two weeks of the randomized withdrawal period.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
placebo	baseline ADHD-RS with adult prompt total scores <22 and CGI-S ratings of 1, 2 or 3		increase in ADHD-RS score and ≥2 rating-point increase in CGI-S score) Secondary: Not reported	Secondary: Not reported
Coghill et al[88] LDX 30 to 70 mg/day vs MPH-ER (Concerta®) 18 to 54 mg/day vs placebo	DB, MC, PC, PG, RCT Children and adolescents six to 17 years of age diagnosed with ADHD	N=336 7 weeks	Primary: ADHD-RS Secondary: CGI-I	Primary: The LS mean change from baseline in ADHD-RS total score was significantly greater for patients treated with LDX (-24.3±1.2) and MPH-ER (-18.7±1.1) compared to placebo (-5.7±1.1; P<0.001 for both). The LS mean change from baseline in ADHD-RS total score was significantly greater with LDX or MPH-ER compared to placebo at every time point evaluated (P<0.001 for all visits). Effect sizes based on the difference in LS mean change in ADHD-RS total score from baseline to endpoint were 1.80 and 1.26 for LDX and MPH-ER, respectively. The decreases in both the ADHD-RS hyperactivity/impulsivity and inattention subscale scores from baseline were also significantly greater for patients treated with LDX or MPH-ER compared to placebo. The LS mean change from baseline to endpoint in hyperactivity/impulsivity was significantly greater with LDX compared to placebo (-8.7; 95% CI -10.3 to -7.2; P<0.001) as was the change in inattention score (-9.9; 95% CI, -11.5 to -8.3; P<0.001). The LS mean change from baseline to endpoint significantly favored MPH-ER compared to placebo for hyperactivity/impulsivity (-6.0; 95% CI, -7.5 to -4.5; P<0.001) and inattention (-7.0; 95% CI, -8.6 to -5.4; P<0.001) scores. Secondary: The proportions of patients with a CGI-I rating of 'very much improved' or 'much improved' after seven weeks of treatment were 78 and 61% for patients treated with LDX or MPH-ER, respectively, compared to 14% of patients treated with placebo (P<0.001 for both).
Findling et al[89]	DB, PC, RCT	N=314	Primary:	Primary:

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
LDX 30 to 70 mg/day vs placebo	Adolescents 13 to 17 years of age diagnosed with ADHD	4 weeks	ADHD-RS Secondary: CGI-I, YQOL-R, treatment-emergent adverse events	Differences in ADHD-RS total scores favored all LDX doses compared to placebo at all weeks (P<0.0076). Secondary: Patients were rated much or very much improved at the end of the study with all doses of LDX (69.1%) compared to placebo (39.5%; P<0.0001). YQOL-R scores at the end of the study indicated improvement with LDX treatment, but did not result in significant differences compared to placebo. The most common treatment-emergent adverse events for all combined LDX doses included decreased appetite, headache, insomnia, decreased weight, and irritability. The severity of treatment-emergent adverse events was generally mild or moderate Clinically insignificant mean increases in pulse, BP and ECG changes were noted with LDX.
Findling et al[90] LDX 30 to 70 mg/day	MC, OL, SA Children six to 12 years of age diagnosed with ADHD	N=274 12 months	Primary: ADHD-RS Secondary: CGI-S	Primary: Mean ADHD-RS total score improved by 27.2 points (P<0.001). Mean ADHD-RS inattentive subscale score improved by 13.4 points (P<0.001). Mean ADHD-RS hyperactivity score improved by 13.8 points (P<0.001). After improvements during the first four weeks, improvements in ADHD-RS scores were maintained throughout eleven months of treatment. Secondary: Improvement in scale scores seen in >80% of study patients at endpoint and >95% of completers at 12 months were rated as improved. Adverse event included insomnia and vomiting and considered mild or moderate by the study investigator. There were no clinical meaningful changes in BP or electrocardiographic parameters.
Jain et al[91] LDX 20 to 70 mg/day	OL, PC, RCT, SA, XO (Post-hoc	N=150 Variable	Primary: Study 1 Change in	Study 1 Primary: Of patients treated with LDX, the mean change from baseline in ADHD-RS total score

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo	analysis) Children 6 to 12 years of age with ADHD and baseline ADHD-RS IV total score ≥28 who had received MPH within six months of study enrollment	duration	ADHD-RS total score from baseline Study 2 Mean SKAMP-D subscore over the course of a laboratory school day Secondary: Study 1 CGI-S, EESC, BRIEF-Parent form Study 2 SKAMP-A, PERMP math scores, ADHD-RS and CGI scores	was similar for the overall study population and the prior MPH group, with a 64.9% improvement observed in the prior MPH group. Secondary: Of patients treated with LDX, the mean change in BRIEF scores from baseline were similar for the overall study population and the prior MPH group. The mean change in CGI-I scores, EESC total scores and the BRIEF index subscale scores from baseline were similar between the overall study population and the prior MPH group. In addition, the BRIEF index subscale scores were normalized at endpoint. The rates of symptomatic remission were similar between the overall study population and the prior MPH group; however, the prior MPH group had numerically lower remission rates compared to the overall group. A clinical response was achieved in 89.6% and 86.7% of the overall population and the prior MPH group, respectively. Study 2 Primary: Improvements in SKAMP-D subscores were similar for both the overall study population and the prior MPH group. For both groups, SKAMP-D scores were improved at all post-dose time points from 1.5 hours to 13 hours with LDX vs placebo ($P \leq 0.0046$ and $P \leq 0.0284$ for all time points in the overall study population and prior MPH group, respectively). Secondary: Improvements in SKAMP-A scores were similar in the overall study population and prior MPH group from 1.5 hours to 13 hours post-dose with LDX vs placebo ($P < 0.0001$ and $P \leq 0.0114$ for all time points in the overall study population and prior MPH group, respectively). The PERMP-A and PERMP-C scores were improved to a similar degree in both the overall study population and the prior MPH group at all post-dose time points from 1.5 to 13.0 hours with LDX vs placebo ($P < 0.0001$ for all time points in the overall study population and prior MPH group, respectively, for both PERMP-A and PERMP-C). The change from baseline in mean ADHD-RS total scores for the overall study population and the prior MPH groups were similar when taking LDX and placebo during the XO phase (57.1 and 18.1% for patients who had previously received MPH in the LDX group and the placebo group, respectively). At visit five during the XO

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				period, mean CGI-I scores were 1.7 and 3.5 for patients taking LDX and placebo, respectively, for the overall study population and 1.7 and 3.7, respectively, for the prior MPH group who had received ≥1 mg/kg/day of MPH.
Weisler et al[92] LDX 30 to 70 mg/day	DB, PC, RCT, SA Adults aged 18 to 55 years of age diagnosed with ADHD	N=349 12 months	Primary: ADHD-RS Secondary: CGI-S, CGI-I	Primary: Mean ADHD-RS total scores improved at week one of treatment and sustained throughout the eleven month treatment period (P<0.001). Mean ADHD-RS total scores improved by 24.8 points from baseline to study endpoint (P<0.001). Secondary: All study patients rated as moderately ill with a mean CGI-S of 4.8 with improvement in their mean score of 1.7 at endpoint. At weeks one, two, three, and four, the proportion of study patients rated as improved on the CGI-I was 43.9, 68.3, 83.4 and 89.1%, respectively. At month 12, 92.6% were improved on the CGI-I. Common adverse events included upper respiratory tract infection, insomnia, headache, dry mouth, decreased appetite and irritability. Most adverse events were considered mild or moderate by the study investigator. Small but statistically significant increases in pulse and BP noted at treatment endpoint.
Mattingly et al[93] LDX 30 to 70 mg/day	Post-hoc analysis of Weisler et al[82] Adults aged 18 to 55 years of age diagnosed with ADHD who had completed ≥2 weeks of treatment with LDX	N=345 12 months	Primary: ADHD-RS-IV Secondary: Not reported	Primary: Baseline ADHD-RS-IV total scores were lower in the predominantly inattention and hyperactivity/impulsivity symptom cluster subgroups. LDX decreased ADHD-RS-IV total scores in all predominant symptom cluster subgroups. Mean percent reduction from baseline to endpoint was 55.9, 71.0, and 62.6% for the predominantly inattention, hyperactivity/impulsivity, and combined symptom cluster subgroups, respectively, and was 61.1% for the overall population. At trial end, 285/345 patients were classified as clinical responders (ADHD-RS-IV total score decrease of ≥30% from baseline and CGI-I score of one or two). Of the 93 patients with predominantly inattention symptom cluster at baseline, 74 were classified as clinical responders at trial end. All 13 patients who had predominantly hyperactivity/impulsivity symptom cluster at baseline were classified as clinical

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				responders at endpoint. At endpoint, 236 of patients who had combined type ADHD at baseline, 196 were classified as clinical responders. Secondary: Not reported
Wigal et al[94] MPH-ER (Concerta®) 18 to 54 mg/day vs placebo	DB, PC, RCT Children nine to 12 years of age diagnosed with ADHD	N=78 5 months	Primary: PERMP, SKAMP, TOVA, Finger Windows forward and backward subtest Secondary: Not reported	Primary: MPH-ER significantly improved performance on the number of problems attempted and number of problems correctly answered on the PERMP compared to placebo (P<0.001). MPH-ER significantly improved performance on inattention, deportment, and total ratings of the SKAMP measure (P<0.001) as compared to placebo. Children taking MPH-ER had statistically significantly better scores than children taking placebo on response time (P<0.000). MPH-ER significantly improved performance on memory as compared to placebo. Most common adverse effects included decreased appetite, upper abdominal pain, headache and irritability. Most adverse events were considered mild or moderate by the study investigator. Secondary: Not reported
Casas et al[95] MPH-ER (Concerta®) 54 to 72 mg/day vs placebo	DB, MC, PC, RCT Men and women 18 to 65 years of age diagnosed with ADHD	N=279 13 weeks	Primary: CAARS-Inv: SV Secondary: CGI-S, CGI-C, CAARS-Self: SV, SDS, AIMA-A	Primary: Improvements in CAARS-Inv:SV were significantly greater with MPH-ER 72 mg compared to placebo (P=0.0024). There was no significant difference between MPH-ER 54 mg and placebo. Secondary: Mean improvement in CGI-S score was significantly greater with MPH-ER 72 mg than placebo (P<0.001); however, there was no significant difference with MPH-ER 54 mg compared to placebo. Median improvement in CGI-C score was significantly greater with MPH-ER 72 mg

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				(2.0) compared to placebo (3.0; P=0.0018); however, there was no significant difference with MPH-ER 54 mg (2.5) compared to placebo. CAARS-Self:SV scores decreased significantly compared to placebo in both MPH-ER treatment groups (P<0.05). There was no significant change in SDS score from baseline in either treatment group. Significant benefit compared to placebo was observed on several AIM-A subscales, which included performance and daily functioning, communication and relationships, living with ADHD and general well-being. The most common adverse events with MPH-ER were mild to moderate in severity and included headache, decreased appetite, dry mouth and nausea.
Wigal et al[96] MPH-ER suspension (Quillivant XR®) 20 to 60 mg/day vs placebo	DB, MC, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD	N=45 2 weeks	Primary: SKAMP combined score Secondary: Onset of action and duration of clinical effect, subscale scores for SKAMP, PERMP, CGI-S and CGI-I	Primary: Children treated with MPH-ER suspension experienced a statistically significant improvement in SKAMP combined score at four hours post-dose compared to children treated with placebo. The LS mean SKAMP combined score was 7.12 in children receiving MPH-ER suspension compared to 19.58 in children receiving placebo (LS mean difference, -12.46; P<0.0001). Secondary: There were statistically significant improvements from baseline with MPH-ER suspension compared to placebo at each time point tested (45 minutes, two, four, eight, 10 and 12 hours), with the onset of action at 45 minutes post-dose and a duration of effect continuing to be significant compared to placebo at 12 hours post-dose. The results of the remaining secondary endpoints were not presented in this study.
Wilens et al[97] MPH-ER (Concerta®) 18 to 54 mg/day	MC, OS, PRO Children six to 13 years of age diagnosed with	N=432 1 year	Primary: HR and BP after one year Secondary:	Primary: Compared to baseline, MPH-ER was associated with minor clinical, although statistically significant, DBP elevations (1.5 mm Hg; P<0.001), SBP elevations (3.3 mm Hg; P<0.001) and HR (3.9 beats per minute; P<0.0001) at the 12-month end point.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
	ADHD		Not reported	Secondary: Not reported
Mattos et al[98] MPH-ER (Concerta®) 18 to 72 mg/day	MC, OL Men and women 18 to 65 years of age diagnosed with ADHD	N=60 12 weeks	Primary: ASRS, AAQoL, STAI, HAMD, CGI-I Secondary: Not reported	Primary: ADHD symptom severity improved with the ASRS scores (total score, inattention and hyperactivity) significantly reduced from baseline to weeks four, eight, and 12 (P<0.001). AAQoL subscales (P<0.001), as well as AAQoL total score (P<0.001), significantly improved from baseline to week 12. A significant reduction in STAI, CGI-I, and HAMD, scores were observed (P<0.0001). The most common adverse events included appetite changes (25%), dry mouth (16.7%), headache (11.7%), irritability (5%) and insomnia (5%). Adverse events were mild to moderate in severity as reported by the study investigators. Secondary: Not reported
Cox et al[99] MPH-ER (Concerta®) 36 mg once daily on days one to five, followed by 72 mg once daily on days six to 17 vs AMP-XR (Adderall XR®) 15 mg once daily on days one to five, followed by 30 mg once daily on days six to 17	DB, PC, RCT, XO Adolescents 16 to 19 years of age diagnosed with ADHD and licensed to drive	N=35 21 to 38 days	Primary: IDS, assessed using an Atari Research Driving Simulator on days 10 and 17; subjective ratings of driving performance by participants and investigators Secondary: Not reported	Primary: Overall IDS values were significantly better than with placebo with MPH-ER (P<0.001), but not with AMP-ER (P=0.24). Simulator-rated driving performance as indicated by IDS was also significantly better in the MPH-ER group than in those receiving AMP-ER (P=0.03). MPH-ER was significantly better than placebo in the categories off-road excursions (P=0.02), speeding (P=0.01), SD speed (P=0.02), and time at a stop sign deciding where to turn (P=0.003). AMP-ER was significantly better than placebo in the category of inappropriate braking (P=0.04). Subjective ratings of driving performance by participants and investigators rated MPH-ER as better for driving performance (P=0.008).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				Secondary: Not reported
Yang et al[100] MPH-ER 18 to 54 mg/day vs atomoxetine 0.5 to 1.4 mg/kg/day	RCT, SB Children and adolescents seven to 14 years of age diagnosed with ADHD	N=142 4 to 6 weeks	Primary: RCFT, Digit span, Stroop color word test Secondary: Not reported	Primary: Both MPH-ER and atomoxetine significantly improved visual memory, verbal memory, and word inference time. Visual and verbal memory was not significantly different from the control group at post-treatment assessment (P>0.05). Although word interference time was more improved than the control group, there was no statistically significant difference (P>0.05). Secondary: Not reported
Wolraich et al[101] MPH-ER (Concerta®) 18 to 54 mg/day vs MPH-IR 5 to 15 mg TID vs placebo	DB, PC, PG, RCT Children six to 12 years of age diagnosed with ADHD (any subtype)	N=282 28 days	Primary: Iowa Conners I/O and O/D rating scale (parents and teachers) Secondary: SNAP-IV scores (teachers and parents), CGI-I scores (investigators), global assessment of efficacy (parents and teachers)	Primary: Both MPH-ER and MPH-IR demonstrated a statistically significant improvement in the Iowa Conners I/O and O/D rating scale scores compared to placebo at week one and at the end of the study (P<0.001). There was no significant difference in the mean Iowa Conners scale scores between the MPH-ER and MPH-IR groups at week one (P=0.838) or at the end of the study (P=0.539). Secondary: Teacher and parent SNAP-IV scores were significantly better for patients in the MPH-ER and MPH-IR groups than for those in the placebo group (P<0.001). There was not a significant difference in SNAP-IV scores between the MPH-ER and MPH-IR groups. CGI-I scores significantly improved in the MPH-ER and MPH-IR groups compared to the placebo group (P<0.001).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				Both the parent and teacher global assessment of efficacy scores were significantly higher with the MPH-ER and MPH-IR groups than the placebo group (P<0.001).
Pelham et al[102] MPH-ER (Concerta®) 18 to 54 mg/day vs MPH-IR 5 to 15 mg TID vs placebo	DB, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD (any subtype) who were taking MPH prior to study entry	N=68 1 week	Primary: Iowa Conners I/O and O/D rating scales (teacher and parents), SKAMP scale (teacher) Secondary: Not reported	Primary: MPH-ER and MPH-IR were better than placebo in the Iowa Conners I/O and O/D rating scale scores from teachers and parents (P<0.05). MPH-ER scored significantly better than MPH-IR in the parent Iowa Conners I/O rating scales (P<0.05). In the SKAMP scales, MPH-ER and MPH-IR were similar in efficacy, but both were significantly better than placebo. Secondary: Not reported
Gau et al[103] MPH-ER (Concerta®) 18 to 36 mg/day vs MPH-IR 5 to 10 mg TID	OL, RCT Children six to 15 years of age diagnosed with ADHD (any subtype) who were taking MPH (10 to 40 mg/day)	N=64 28 days	Primary: CTRS-RS, CPRS-RS, SKAMP-A, SKAMP-D Secondary: SAICA, CGI	Primary: Each of the four groups displayed a significant decrease in all measures of CTRS-RS, CPRS-RS, SKAMP-A, SKAMP-D at each of the follow-up visits (P<0.001 for all) compared to baseline, but there were no significant differences between the groups (P>0.05 for all). Secondary: Patients in both the MPH-XR and MPH-IR groups experienced significant improvements from baseline in academic performance and less severe problems at school (P<0.05). Patients in the MPH-XR group also significantly improved from baseline in attitude toward their teachers, school social interaction, and relationships with peers and siblings (P<0.05). The MPH-XR group had a significantly greater number of patients being very much or much improved (84.4%) than the MPH-IR group (56.3%) (P=0.014) based on the CGI score.
Lopez et al[104] MPH-ER (Concerta®)	DB, PC, RCT Children six to 12	N=36 28 days	Primary: SKAMP scales	Primary: Both MPH-ER and MPH-XR statistically improved SKAMP scale scores compared to placebo (P<0.001).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
18 to 36 mg/day vs MPH-XR (Ritalin LA®) 20 mg/day vs placebo	years of age diagnosed with ADHD who were previously stabilize on MPH (equivalent dose of 10 mg BID)		Secondary: Not reported	Secondary: Not reported
Swanson et al[105] MPH-ER (Concerta®) 18 to 54 mg/day vs MPH-XR (Metadate CD®) 20 to 60 mg/day vs placebo	DB, MC, PC, RCT, XO Children six to 12 years of age diagnosed with ADHD (inattentive type, hyperactive-impulsive type, or combined type) being treated with MPH in doses of 10 to 60 mg/day	N=184 7 weeks	Primary: SKAMP scales, PERMP Secondary: Not reported	Primary: MPH-ER and MPH-XR demonstrated similar efficacy, and both were better than placebo in SKAMP and PERMP scores (P<0.016). Secondary: Not reported
Silva et al[106] MPH-ER (Concerta®) 18 mg vs MPH-ER (Concerta®) 36 mg	MC, RCT, SB, XO Children six to 12 years of age diagnosed with ADHD and stabilized on MPH (20 to 40 mg/day)	N=54 6 weeks	Primary: SKAMP-A rating subscale Secondary: SKAMP-D and SKAMP-C rating subscales and written math tests	Primary: All doses of the study medications significantly improved SKAMP-A scores from baseline at all time points, compared to placebo (P<0.038). ER-MPH 20 and 40 mg showed significantly greater differences from predose on the SKAMP-A than did MPH ER, 36 mg at two hours postdose, and also when scores were integrated over zero to four hours (P=0.022 for the 20 mg dose and P=0.001 for the 40 mg dose), but showed no significant improvement over eight to 12 hours. Secondary:

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs MPH-ER (ER-MPH) 20 mg vs MPH-ER 40 mg vs placebo All medications were dosed once per study day (6 consecutive Saturdays). Patients continued their regular ADHD medications on Sunday through Thursday of the study weeks, with no medications allowed on Friday.				Single morning doses of ER-MPH and MPH ER, were effective in improving SKAMP-D scores and academic productivity for the majority of the 12-hour classroom session.
Jahromi et al[107] MPH-IR 0.125 mg/kg/ dose BID for one week (low dose) vs MPH-IR 0.25 mg/kg/ dose BID for one week (medium dose)	DB, RCT, XO Children five to 13 years of age with PDD and hyperactivity	N=33 4 weeks	Primary: JAMES, Caregiver-Child Interaction measure (competing demands and clean-up task) captured social communication, self-regulation	Primary: Significant positive effect of MPH was seen on social communication (P<0.05); comparing each of the three MPH doses of MPH compared to placebo, the low dose showed significant improvement compared to placebo (P<0.05); no significant differences found between placebo and the medium or high doses. No significant improvement in self-regulation for the competing demands task when comparing best dose MPH to placebo (P=0.09); significant improvement in self-regulation behaviors comparing low dose MPH (P<0.05) and medium dose effect (P<0.01) compared to placebo; no improvement found in high dose MPH over placebo.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
vs MPH-IR 0.50 mg/kg/ dose BID for one week (high dose) vs placebo for one week			and affective behavior Secondary: Not reported	No significant improvement in self-regulation behaviors for the clean-up task for any of the three dose levels of MPH compared to placebo, or between placebo and the best dose of MPH (P>0.05). Significant improvement in affective behavior for the competing demands task when comparing medium MPH dose (P <0.05) and high MPH dose compared to placebo (P<0.05); no improvement found in best dose of MPH compared to placebo (P=0.09); or low dose (P=0.07). No significant improvement on affective behavior for the clean-up task and any MPH dose (P>0.05). Secondary: Not reported
Spencer et al[108] MPH-IR TID vs MPH-ER once daily (Concerta®)	PG, RCT, SB Patients 19 to 60 years of age diagnosed with ADHD who were on stable therapy with MPH-IR	N=61 6 weeks	Primary: AISRS Secondary: Not reported	Primary: MPH-IR responders randomized to MPH-IR or MPH-ER had no effect on AISRS score at the study endpoint (11.2 vs 10.7; P=0.80). Study patients stabilized on MPH-IR and switched to MPH-ER remained satisfied over 71% of the time. MPH-IR treatment group missed significantly more doses than the MPH-ER treatment group (7.3 vs 3.3; P=0.02). Secondary: Not reported
Efron et al[109] MPH-IR 0.3 mg/kg/ dose BID vs DEX-IR 0.15 mg/kg/	DB, RCT, XO Children five to 15 years of age diagnosed with ADHD	N=125 4 weeks	Primary: SERS Secondary: Not reported	Primary: There was a statistically significant decrease in the mean number of side effects in the MPH-IR group vs the DEX-IR group (8.19 vs 7.19; P=0.03) based on the results of the SERS questionnaire which assess the 17 most common side effects of stimulants including trouble sleeping, decreased appetite and anxiousness. Mean severity of side effects statistically significantly improved in the MPH-IR group compared to the DEX-IR group (3.24 vs 3.73; P<0.01).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
dose BID Patients received one drug for two weeks then XO to the other stimulant for two weeks.				A majority of parents rated their children as improved compared to their "usual selves" in both of the treatment groups (68.8% in the DEX-IR groups and 72% in the MPH-IR). Secondary: Not reported
Pelham et al[110] MPH-IR 10 mg BID vs MPH-SR (Ritalin SR®) 20 mg/day vs DEX-SR (Dexedrine®) 10 mg/day vs pemoline 56.25 mg/day vs placebo	DB, PC, RCT, XO Males eight to 13 years of age diagnosed with ADHD	N=22 8 weeks	Primary: Evaluated social behavior during activities, classroom performance, and performance on a continuous performance task Secondary: Not reported	Primary: Each of the active treatment groups were more effective than placebo on most measures of social behavior from the medication assessment (P<0.05). DEX-SR and pemoline tended to produce the most consistent effects. The continuous performance task results showed that all four medications had an effect within two hours, and the effects lasted for nine hours vs placebo (P<0.025). Secondary: Not reported
Palumbo et al[111] MPH-IR 5 to 60 mg/day vs clonidine 0.05 to 0.6	DB, MC, PC, RCT Children seven to 12 years of age diagnosed with ADHD	N=122 16 weeks	Primary: CASQ-T Secondary: CASQ-P, CGAS	Primary: For CASQ-T, clonidine did not improve ADHD symptoms. Study patients treated with MPH showed significant improvement compared to those not treated with MPH. Secondary: Study patients treated with clonidine had greater improvements on the CASQ-P and CGAS, but a higher rate of sedation compared to patients not treated with clonidine.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
mg/day vs MPH-IR plus clonidine vs placebo				
Greenhill et al[112] MPH-XR (Metadate CD®) 20 to 60 mg/day vs placebo	DB, MC, PC, RCT Children six to 16 years of age diagnosed with ADHD	N=321 3 weeks	Primary: CGI-S (teacher) Secondary: CGI-S (parents), CGI-I scores, adverse events	Primary: CGI-S teacher scores significantly improved in the MPH-XR group (12.7±7.2 to 4.9±4.7) compared to the placebo group (11.5±7.3 to 10.3±6.9; P<0.001). Secondary: CGI-S parent scores significantly improved from 13.6±6.6 to 7.4±5.9 with MPH-XR vs 12.9±7.6 to 10.1±6.7 with placebo (P<0.001 for both scales). Eighty-one percent of the patients in the MPH-XR group compared to 50% of the patients in the placebo group were classified as responders based on their CGI-I scores (P<0.001). In the MPH-XR group, 52% of children reported at least one adverse event vs 38% from the placebo group (P=0.014). The rate of anorexia was more significant in the MPH-XR group vs the placebo group (9.7 vs 2.5%; P=0.007).
McGough et al[113] MPH transdermal patch 10 to 27 mg/day vs placebo	OL, RCT (first five weeks) then DB, PC Children six to 12 years of age diagnosed with ADHD	N=80 7 weeks	Primary: Evaluate time course effects of MPH transdermal patch vs placebo transdermal patch via SKAMP-A, SKAMP-D,	Primary: Mean SKAMP-D scores were improved with MPH transdermal patch vs placebo (mean score, 3.2 vs 8.0) and at all time points assessed including 12 hours post-application (P<0.01). Mean (SKAMP-A) scores were improved with MPH transdermal patch vs placebo (6.2±0.50 vs 9.9±0.50, respectively; P<0.0001). PERMP scale results: Mean number of math problems attempted and math problems correct were significantly higher with MPH transdermal patch vs placebo (113.8 vs 86.2 and 109.4 vs 80.7, respectively; P<0.0001).

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
			PERMP, ADHD-RS-IV, CPRS-R, CGI-I, and PGA rating scales Secondary: Acute efficacy and tolerability of MPH transdermal patch	Across the double-blind period, mean scores for the ADHD-RS-IV and CPRS-R scales were significantly improved with MPH transdermal patch vs placebo (P<0.0001). Those in the MPH transdermal patch group (79.8%) were more likely to be deemed improved on clinician rated CGI-I scores vs those in the placebo group (79.85 and 11.6%, respectively; P<0.0001). Statistically significant differences were observed with PGA ratings; 71.1% of MPH transdermal patch participants and 15.8% of placebo participants were rated as improved (P<0.0001). Secondary: More treatment-emergent adverse events were recorded with MPH transdermal patch therapy (39 events, 24 participants) vs placebo therapy (25 events, 18 participants). The most common treatment-related adverse events were decreased appetite, anorexia, headache, insomnia, and upper abdominal pain, all reported by less than 5% of study participants.
Pelham et al[114] MPH transdermal patch: 6.25 cm^2 (0.45 mg/hour), 12.5 cm^2 (0.9 mg/hour), and 25 cm^2 (1.8 mg/hour), worn for ≥12 hours daily Each patient received single applications of MPH transdermal patch 6.25 cm^2, 12.5 cm^2 or 25 cm^2 patches or placebo in a random	DB, DR, MC, RCT Children seven to 12 years of age diagnosed with ADHD	N=36 8 days	Primary: MPH transdermal patch efficacy and influence of exposure time on morning effects Secondary: Not reported	Primary: All doses of MPH transdermal patches were significantly improved vs placebo on measures of social behavior in recreational settings, classroom functioning, and parent ratings of evening behavior (P<0.05). Beneficial effects of MPH transdermal patches were observed at all time points after application of the patch and were still seen for three hours after the patch had been removed (i.e., throughout the 12-hour assessment). Incidence of skin rash was reported as 40 to 50%. Secondary: Not reported

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
order on separate days and at two time points (6 or 7 AM).				
Pelham et al[115] MPH transdermal patch: 12.5 cm^2, 25 cm^2, and 37.5 cm^2 plus behavior modification Each participant had two days on each treatment without concomitant behavior modification and four days on each treatment with behavior modification.	DR, RCT Children aged six to 12 years diagnosed with ADHD	N=27 6 weeks	Primary: Proportion that reached individual target goals in Daily Report Card scores Secondary: Not reported	Primary: The percentage of individualized target criteria met by children in their Daily Report Card assessment was significantly (P<0.05 for all) higher with MPH transdermal patch 12.5, 25, and 37.5 cm^2 vs placebo, both without behavior modification (41.9, 63.1, and 66.2 vs 20.8%) and with behavior modification (73.7, 87.5, and 86.2 vs 54.7%; all P<0.05). Response rates were higher in the MPH transdermal patches 25 cm^2 group than in the 12.5 cm^2 group, both with and without behavior modification (P<0.05 for both); increasing the size of the patch to 37.5 cm^2 added no further advantage. Secondary: Not reported
Faraone et al[116] MPH transdermal patch 10 to 30 mg/day worn for nine hours per day or MPH-ER (Concerta®) 18 to 54 mg/day vs placebo	DB, MC, PC, RCT Children six to 12 years of age diagnosed with ADHD (predominantly hyperactive-impulsive, predominantly inattentive, or combined type)	N=268 5 weeks	Primary: CSHQ Secondary: Not reported	Primary: No significant difference in the severity of sleep problems was observed among the treatment and placebo groups (P≥0.233). No significant differences in the numbers of sleep problems were observed between MPH transdermal patch/MPH-ER and placebo (P≥0.554). There was no significant effect of MPH dosage on sleep problems (P=0.135). The effects of each MPH treatment and the various doses of these treatments on each CSHQ subscale were identical to the effects observed for the total CSHQ scale. Secondary: Not reported
Findling et al[117]	DB, PC, RCT	N=282	Primary: ADHD-RS	Primary: Mean total ADHD-RS scores were similar between MPH transdermal patch, MPH-

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
MPH transdermal patch 10 to 30 mg/day or MPH-ER (Concerta®) 18 to 54 mg/day vs placebo	Children six to 12 years of age diagnosed with ADHD	7 weeks	Secondary: CTRS-R, CPRS-R, CGI-S, CGI-I	ER, and placebo at baseline (43.0, 43.8, and 41.9, respectively), but not at endpoint (18.8, 21.8, and 32.1, respectively). Mean change from baseline in ADHD-RS scores was greater in study patients receiving MPH transdermal patch and MPH-ER compared to patients receiving placebo (P<0.001). There was a two-fold improvement of ADHD symptoms in active treatments compared to placebo from baseline to study endpoint. Secondary: MPH transdermal patch and MPH-ER showed improvements over placebo in mean total parent and teacher scores from baseline to endpoint. More study patients receiving MPH transdermal patch and MPH-ER compared to placebo were rated as improved by clinicians and parents (P<0.001). Adverse events included decreased appetite, nausea, vomiting and insomnia. Most adverse events were considered mild or moderate by the study investigator.
Chou et al[118] MPH-ER (Concerta®) 18, 36, or 54 mg once daily	OS Children six to 19 years of age with ADHD who have received MPH-IR for ≥1 month	N=521 10 weeks (six weeks forced-titration phase to achieve remission, followed by a four week main-tenance phase)	Primary: Symptomatic remission Secondary: Changes in efficacy and satisfaction, safety	Primary: Using the forced-titration of MPH-ER dosage to increase the dosage during the first six weeks, the remission rate significantly increased with time from 4.8% (at baseline), 25% (week two), 44.2% (week four), 58.8% (week six), up to 59.6% (week 10) among 507 ITT patients. Among 439 patients who completed the 10 week follow-up assessments, 290 (66.1%) patients achieved symptomatic remission (95% CI, 61.6 to 70.5). The non-remission group had higher mean daily doses compared to the remission group from visit two to trial end. Secondary: Among the 439 patients who completed the treatment, there was a significant decrease in the total score and three sub-scores of the Chinese SNAP-IV (P<0.001), CGI-ADHD-S (P<0.001), and CGI-ADHD-I (P<0.001) as intra-individual comparison from the baseline to each visit through the trial period. Among the items on the Barkley SERS, poor appetite was the only one exacerbated on visit three, but improved on later visits. The other side effects gradually decreased in intensity throughout the trial period, and the difference from baseline reached significance from visit three to trial end.

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
				At trial end, there was a decrease in both mean body weight (-0.85 kg) and mean respiratory rate (-0.44/minute), and an increase in mean pulse rate (5.09 beats per minute) in comparison with baseline with significance (P<0.001). Five percent of patients withdrew from the trial because of adverse events, and these patients mostly left due to poor appetite and insomnia. Three patients experienced at least one serious adverse event that was not deemed to be treatment-related.
Faraone et al[119] AMP-IR, AMP-XR, atomoxetine, bupropion, DEX-IR, DEX-ER, DEXM-IR, modafinil, MPH-ER, MPH-IR, MPH-XR, MPH transdermal patch, pemoline	MA (29 trials) Patients diagnosed with ADHD	N=2,988 Variable duration	Primary: Effect sizes Secondary: Not reported	Primary: All of the drugs groups produced a significant measure of effect compared to the placebo group (P<0.0001). The effect sizes for non stimulant medications were significantly less than those for immediate-release stimulants (P<0.0001) or long-acting stimulants (P=0.0008). The two classes of stimulant medications (short acting and long acting) did not differ significantly from one another (P=0.14). Secondary: Not reported
Schelleman et al[120] ADHD medications vs nonusers	RETRO Children three to 17 years of age who were dispensed a prescription for an AMP, atomoxetine, or MPH	N=241,417 Variable duration	Primary: Sudden cardiac death, or ventricular arrhythmia, stroke, MI Secondary: All-cause death	Primary and Secondary: No statistically significant difference between incident users and nonusers was observed in the rate of validated sudden death or ventricular arrhythmia (HR, 1.6; 95% CI, 0.19 to 13.60) or all-cause death (HR, 0.76; 95% CI, 0.52 to 1.12). None of the strokes identified during exposed time to ADHD medications were validated. No MIs were identified in study patients who used ADHD medication. No statistically significant difference between prevalent users and nonusers was observed for validated sudden death or ventricular arrhythmia (HR, 1.43; 95% CI, 0.31 to 6.61); stroke (HR, 0.89; 95% CI, 0.11 to 7.11); stroke/MI (HR, 0.72; 95% CI, 0.09 to 5.57); or all-cause death (HR, 0.77; 95% CI, 0.56 to 1.07).
Olfson et al[121]	RETRO	N=171,126	Primary: Cardiac events	Primary: There were 0.92 new cardiac events and 3.08 new cardiac symptoms per 1,000,000

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
AMP and MPH vs nonusers	Patients six to 21 years of age diagnosed with ADHD who were prescribed AMP or MPH	Variable duration	(inpatient diagnosis of chest pain, cardiac dysrhythmia or transient cerebral ischemia) and cardiac symptoms (tachycardia, palpitations, or syncope) Secondary: Not reported	days of current stimulant use. Current stimulant use compared to no stimulant use was not associated with less severe cardiovascular event (adjusted OR, 0.69; 95% CI, 0.42 to 1.12). Past stimulant use compared to no stimulant use was not associated with less severe cardiovascular event (adjusted OR, 1.18; 95% CI, 0.83 to 1.66). The adjusted ORs for cardiac symptoms were 1.18 (95% CI, 0.89 to 1.59) for current and 0.93 (95% CI, 0.71 to 1.21) for past stimulant use when compared to no stimulant use. Current and past stimulant use was not associated with cardiac symptoms. No significant differences were observed in risks of cardiovascular events (adjusted OR, 2.14; 95% CI, 0.82 to 5.63) or symptoms (adjusted OR, 1.08; 95% CI, 0.66 to 1.79) for current MPH use compared to AMP use. Secondary: Not reported
Schelleman et al[122] AMP, atomoxetine, MPH	RETRO Patients three to 17 years of age with a prescription for an AMP, atomoxetine, or MPH	N=219,954 Variable duration	Primary: Sudden death, ventricular arrhythmia, stroke, MI Secondary: Not reported	Primary: No significant difference between incident users and nonusers was observed in the rate of sudden death or ventricular arrhythmia (HR, 1.60; 95% CI, 0.19 to 3.60) or all-cause death (HR, 0.76; 95% CI, 0.52 to 1.12). None of the strokes identified during exposed time to ADHD medications were validated. No MIs were identified in ADHD medication users. No significant difference between prevalent users and nonusers was observed (HR for validated sudden death or ventricular arrhythmia, 1.43; 95% CI, 0.31 to 6.61; stroke, 0.89; 95% CI, 0.11 to 7.11; stroke/MI, 0.72; 95% CI, 0.09 to 5.57; and all-cause death, 0.77; 95% CI, 0.56 to 1.07). Secondary: Not reported

Study and Drug Regimen	Study Design, Study Rating, and Demographics	Sample Size and Study Duration	End Points	Results
Hanwella et al[123] Atomoxetine vs MPH	MA (five trials) Children and adolescents six to 16 years of age diagnosed with ADHD	N=2,762 Variable duration	Primary: ADHD-RS Secondary: Not reported	Primary: The MA did not find a significant difference in efficacy between MPH and atomoxetine when comparing SMD in ADHD-RS scores (SMD, 0.09; 95% CI, -0.08 to 0.26). There was no significant difference in response rates between the two medications (RR, 0.93; 95% CI, 0.76 to 1.14). Treatment effects between the formulations of MPH showed a significant SMD in ADHD-RS favoring OROS-MPH (SMD, 0.32; 95% CI, 0.12 to 0.53). MPH-IR was not superior to atomoxetine (SMD, -0.04; 95% CI, -0.19 to 0.12). There was no significant difference in acceptability between atomoxetine and MPH (RR, 1.22; 95% CI, 0.87 to 1.71). Secondary: Not reported
Bloch et al[124] ADHD medications	MA (11 trials) Children diagnosed with ADHD and Tourette's	N=77 Variable duration	Primary: ADHD severity (ADHD-RS, CADS-P, CADS-T, CTRS-R) and tic severity (YGTSS, STSSS, HMVTS, and GTSS) Secondary: Not reported	Primary: MPH, α-2 agonists, desipramine, and atomoxetine demonstrated efficacy in improving ADHD symptoms in children with co-morbid tics. α-2 agonists and atomoxetine significantly improved co-morbid tic symptoms. There was evidence that supratherapeutic doses of DXM worsened tics; however, there was no evidence that MPH worsened tic severity in the short term. Secondary: Not reported

Drug regimen abbreviations: AMP=mixed amphetamine salts, BID=twice a day, DEX=dextroamphetamine, DXM=dexmethylphenidate, ER=extended release, IR=immediate release, LDX=lisdexamfetamine, MPH=methylphenidate, OROS=osmotic-release oral system, SR=sustained release, TID=three times a day, XR=extended release
Study regimen abbreviations: CI=confidence interval, DB=double blind, DR=dose ranging, ES=extension study, FD=forced dose, HR=hazard ratio, LS=least squares, LSMD=least squares mean difference, MA=meta-analysis, MC=multicenter, OL=open-label, OR=odds ratio, OS=observational study, PC=placebo-controlled, PG=parallel-group, PRO=prospective trial, RCT=randomized-controlled trial, RETRO=retrospective, RR=relative risk, SA=single arm, SB=single blind, SD=standard deviation, SMD=standardized mean difference, TB=triple blind, XO=cross-over trial
Miscellaneous abbreviations: AAQoL=Adult ADHD quality of life scale, ADHD=attention deficit hyperactivity disorder, ADHD-RS=ADHD rating scale, AIM-A=ADHD impact module-adult, AISRS=Adult ADHD investigator system symptom report scale, ASRS=Adult self-rating scale, BFI=Brief Fatigue Inventory, BP=blood pressure, BRIEF=Behavior Rating Inventory of Executive Function, BRIEF-A=Behavior Rating

Inventory of Executive Function-Adult Version, CAARS=Conners adult ADHD rating scale, CAARS-Inv:SV=Conner's Adult ADHD Rating Scale–Investigator Rated: Screening Version, CAARS-Self:SV=Conners Adult ADHD Rating Scale–Self Rated: Screening Version, CADS-T=Conners ADHD/DSM IV scale-teacher version, CADS-P=Conners ADHD/DSM IV scale-parent version, CANTAB-CRT=Cambridge Neuropsychological Test Automated Battery-Choice Reaction Time, CANTAB-SWM=Cambridge Neuropsychological Test Automated Battery-Working Memory and Strategy Performance, CASQ-P=Conner's abbreviated symptom questionnaire for parents, CASQ-T=Conner's abbreviated symptom questionnaire for teachers, CBC=Conner's behavior checklist, CGAS=Children's Global Assessment Scale, CGI=Clinical Global Impression, CGI-ADHD-I=Clinical Global Impressions-ADHD-Improvement scale, CGI-ADHD-S=Clinical Global Impressions-ADHD-Severity scale, CGI-C= Clinical Global Impressions of change, CGI-I=Clinical Global Impressions of improvement, CGI-S= Clinical Global Impressions of severity, CHIP-CE=Child Health and Illness Profile-Child Edition, CHQ=Child Health Questionnaire, CHQ-PF50=Child Health Questionnaire-Parent Form, CPRS=Conners parent rating scale, CPRS-R=Conners parent rating scale-revised, CPRS-R:S=Conners parent rating scale: short form, CPRS-R:L=Conners' parent rating scale-revised: long form, CPT=Continuous performance test, CSHQ=Children's Sleep Habits Questionnaire, CTRS-R=Conners teacher rating scale–revised, DBP=diastolic blood pressure, DSM-IV=Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, DSST=Digit Symbol Substitution Task/Coding Test, ECG=electrocardiogram, EESC=Expression and Emotion Scale for Children, FBIM=Family Burden of Illness Module, GTSS=Global tic severity scale, HAMA=Hamilton Anxiety Rating Scale, HAMD=Hamilton Depression Rating Scale, HAM-D-17=Hamilton 17-item Depression Rating scale, HR=heart rate, HSPP=Harter Self-Perception Profile, HMVTS=Hopkins motor/vocal tic scale, I/O=inattention/over activity, IDS=Impaired Driving Score, ITT=intention to treat, JAMES=Joint Attention Measure from the EScs (Early and Social Communication Scale), MI=myocardial infarction, mm Hg=millimeters per mercury, O/D=oppositional/defiance, ODD=oppositional defiant disorder, PDSS=Pediatric Daytime Sleepiness Scale, PDD=pervasive developmental disorders, PERMP=permanent product measure of performance, PGA=parent global assessment, PSERS=Pittsburgh Side Effects Rating Scale, PSQ=Parental Satisfaction Questionnaire, Q-LES-Q=quality of life, enjoyment, and satisfaction questionnaire, SBP=systolic blood pressure, RCFT=Rey Complex Figure Test, SAICA=Social Adjustment Scale for Children and Adolescents, SDS=Sheehan disability scale, SF-36=36-item Short Form Health Survey, SERS=side effect ratings scale, SKAMP=Swanson, Kotkin, Agler, M-Flynn, and Pelham, SKAMP-A=SKAMP-Attention, SKAMP-D=SKAMP-Deportment, SNAP=Swanson, Nolan and Pelham, SNAP-ODD=Swanson, Nolan and Pelham-oppositional defiant disorder, SNAP-P=Swanson, Nolan and Pelham-parent rating scale, SNAP-T=Swanson, Nolan and Pelham-teacher rating scale, STAI=State and trait anxiety inventory, STSS=Shapiro Tourette syndrome severity scale, TOVA=test of variables of attention, WFIS=Weiss Functional Impairment Scale, WFIRS-S=Weiss Functional Impairment Rating Scale Self-Report, WRAADDS=Wender-Reimherr Adult Attention-Deficit Disorder Scale, YGTSS=Yale global tic severity scale, YQOL-R=Youth quality of life-research version

Table 6. Special Populations[1-25]

Drug	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines					
Amphetamine	Safety and efficacy in elderly patients not reported. Safety and efficacy in children <3 years of age have not been established (IR). Safety and efficacy in children <6 years of age have not been established (ER).	No dosage adjustment required.	No dosage adjustment required.	C	Yes; advise to refrain from nursing.
Amphetamine/ dextro-amphetamine salts	Not studied in elderly patients (IR). Safety and efficacy in children <3 years of age have not been established (IR). Safety and efficacy in children <6 years of age have not been established (ER).	No dosage adjustment required.	No dosage adjustment required.	C	Yes; advise to refrain from nursing.
Dextro-amphetamine	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children <3 years of age have not been established (IR, solution). Safety and efficacy in children <6 years of age have not been established (ER).	No dosage adjustment required.	No dosage adjustment required.	C	Yes; advise to refrain from nursing.

Drug	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Lisdexamfetamine	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children <6 years of age have not been established.	No dosage adjustment required.	No dosage adjustment required.	C	Yes; advise to refrain from nursing.
Methamphetamine	Safety and efficacy for the treatment of ADHD in children <6 years of age have not been established. Safety and efficacy for use as an anorectic agent in children <12 years of age have not been established.	No dosage adjustment required.	No dosage adjustment required.	C	Yes; advise to refrain from nursing.
Agents and Respiratory and Cerebral Stimulants-Miscellaneous					
Dexmethyl-phenidate	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children <6 years of age have not been established.	Not studied with renal dysfunction.	Not studied with hepatic dysfunction.	C	Unknown; use with caution.
Methylphenidate	Safety and efficacy in elderly patients have not been established. Safety and efficacy in children <6 years of age have not been established.	Not studied with renal dysfunction.	Not studied with hepatic dysfunction.	C	Unknown; use with caution.
Central α-Agonists					
Clonidine	Safety and efficacy have not been established.	Dose adjustment based on degree of	Not studied in hepatic dysfunction.	C	Yes; use with caution.

Drug	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	Safety and efficacy in children <6 years of age have not been established.	impairment is recommended; monitor patients.			
Guanfacine	Safety and efficacy have not been established. Safety and efficacy in children <6 years of age have not been established.	Dose adjustment may be required in patients with significant renal impairment; monitor patients.	Not studied in hepatic dysfunction.	B	Unknown; use with caution.
Central Nervous Agents-Miscellaneous					
Atomoxetine	Safety and efficacy have not been established. Safety and efficacy in children <6 years of age have not been established; potential risks with clinical need must be balanced when used in children or adolescents.	No dosage adjustment required.	Hepatic dosage adjustment required; with moderate dysfunction, initial and target doses should be reduced to 50% of the normal dose; with severe dysfunction, initial and target doses should be reduced to 25% of normal.	C	Unknown; use with caution.

ADHD=attention deficit hyperactivity disorder, CrCl=creatinine clearance, ER=extended-release, IR=immediate-release

Adverse Drug Events

Table 7a. Adverse Drug Events (%)-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines[1-10]

Adverse Events	Amphetamine	Amphetamine/ Dextroam-phetamine Salts	Dextro-amphetamine	Lisdex-amfetamine	Meth-amphetamine
Cardiovascular					
Blood pressure increased	a	-	-	3	-
Cardiomyopathy	a	a *	a	a	-
Heart rate increased	a	-	a	2	a
Hypertension	a	a *	a	a	a

Adverse Events	Amphetamine	Amphetamine/ Dextroam-phetamine Salts	Dextro-amphetamine	Lisdex-amfetamine	Meth-amphetamine
Myocardial infarction	a	a †	a	a	a
Palpitations	a	a */2 to 4†	a	a	a
Peripheral vascular disease	a	-	a	-	-
Raynaud's disease	a	-	a	-	a
Sudden death	a	a †	a	a	a
Tachycardia	a	a */6†	a	a	a
Central Nervous System					
Aggressive behavior	a	a *†	a	-	-
Agitation	-	8†	-	3	-
Anxiety	-	8†	-	6	-
Depression	-	a *†	-	a	-
Dizziness	a	2 to 7†	a	5	a
Dyskinesia	a	a *†	a	a	-
Dysphoria	a	a *†	a	a	a
Euphoria	a	a *†	a	a	a
Fever	-	5†	-	2	-
Headache	a	a */2†	a	12	a
Insomnia	a	12 to 27†	a	13 to 27	a
Irritability	-	a *†	-	10	-
Labile affect	-	-	-	3	-
Mania	a	-	a	a	a
Nervousness	-	6 to 13†	-	-	-
Overstimulation	a	a *	a	a	a
Psychotic episodes	a	a *	a	a	a
Restlessness	a	a *†	a	3	a
Seizures	-	a †	-	a	a
Somnolence	-	2 to 4†	-	2	-
Speech disorder	-	2 to 4†	-	-	-
Stroke	-	a †	a	a	a
Tic exacerbation	a	a *†	a	2	a
Tourette's exacerbation	a	a *†	a	a	a
Tremor	a	a *†	a	2	a
Twitching		2 to 4†	-	-	-
Dermatological					
Diaphoresis	-	2 to 4†	-	-	-
Hyperhidrosis	-	-	-	3	-
Photosensitivity	-	2 to 4†	-	-	-
Rash	-	a *†	a	3	a
Stevens-Johnson syndrome	-	a *†	-	a	-
Toxic epidermal necrolysis	-	a *†	-	a	-
Urticaria	a	a *†	a	a	a
Gastrointestinal					
Abdominal pain	-	11 to 14†	-	12	-

Adverse Events	Amphetamine	Amphetamine/ Dextroam-phetamine Salts	Dextro-amphetamine	Lisdex-amfetamine	Meth-amphetamine
Anorexia	a	-	a	5	a
Appetite decreased	-	22 to 36†	-	27 to 39	-
Constipation	a	a */2 to 4†	a	a	a
Diarrhea	a	2 to 6†	a	7	a
Dry mouth	a	2 to 35†	a	5 to 26	a
Dyspepsia	-	2 to 4†	-	-	-
Nausea	-	2 to 8†	-	6 to 7	a
Other gastrointestinal disturbances	a	-	a	-	a
Unpleasant taste	a	a *†	a	a	a
Vomiting	-	2 to 7†	-	9	a
Weight loss	a	4 to 11†	a	9	a
Genitourinary					
Changes in libido	a	2 to 4†	a	≤2	a
Impotence	a	2 to 4†	a	a	a
Prolonged Erections	a	-	-	-	-
Urinary tract infection	-	5†	-	-	-
Other					
Anaphylaxis	a	a †	-	a	-
Blurred vision	a	a *†	a	a	-
Dysmenorrhea	-	2 to 4†	-	-	-
Dyspnea	-	2 to 4†	-	2	-
Growth suppression	a	-	a	a	a
Hypersensitivity reactions	a	-	-	a	-
Infection	-	2 to 4†	-	-	-
Rhabdomyolysis	a	-	-	-	-
Weakness	-	2 to 6†	-	-	-

* Immediate-release formulation.
†Extended-release formulation.
-Event not reported.
a Percent not specified.

Table 7b. Adverse Drug Events (%)-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous[11-22]

Adverse Event(s)	Dexmethylphenidate	Methylphenidate
Cardiovascular		
Angina	a	a
Cardiac arrhythmia	a	a
Chest pain	-	a
Hypertension	a	a
Hypotension	a	a
Myocardial infarction	-	a
Palpitations	a	a
Pulse increase/decrease	a	a
Raynaud's phenomenon	-	a
Sudden death	a	-
Systolic blood pressure increased	-	-

Adverse Event(s)	Dexmethylphenidate	Methylphenidate
Tachycardia	3	a
Vasodilation	-	-
Central Nervous System		
Aggressive behavior	a	a
Agitation	-	-
Anxiety	5 to 11	-
Attention disturbance	-	-
Cerebral arteritis	a	a
Cerebral occlusion	a	a
Depression	a	a
Dizziness	6	a
Drowsiness	a	a
Dyskinesia	a	a
Emotional instability	-	6†
Fatigue/lethargy	-	-
Fever	5	a
Hallucinations	-	a†
Headache	25 to 39	a /28†
Hyperkinesia	-	-
Hypertonia	-	-
Insomnia	a	a /13 to 30†
Jittery feeling	12	a
Labile affect	-	a
Mania	-	a
Migraine	-	-
Nervousness	a	a
Neuroleptic malignant syndrome	a	a
Overstimulation	-	-
Paresthesia	-	a
Psychotic episodes	-	-
Restlessness	12	-
Seizures	-	a†
Somnolence	-	-
Tic	-	a /7†
Tourette's exacerbation	a	a
Toxic psychosis	a	a
Tremor	-	-
Vertigo	-	-
Dermatological		
Alopecia	-	a
Application site reaction	-	a†
Dermatitis	-	-
Diaphoresis	-	-
Erythema	-	a
Erythema multiforme	a	a
Exfoliative dermatitis	a	a
Hair loss	a	a
Herpes simplex	-	-
Hyperhidrosis	-	a
Rash	a	a
Stevens-Johnson syndrome	-	-
Toxic epidermal necrolysis	-	a

Adverse Event(s)	Dexmethylphenidate	Methylphenidate
Urticaria	a	a
Gastrointestinal		
Abdominal pain	15	a
Anorexia	5 to 7	a /5 to 46[†]
Appetite decreased	30	a /26[†]
Bruxism	-	a
Constipation	-	a
Diarrhea	-	a
Dry mouth	7 to 20	a
Dyspepsia	5 to 9	a
Flatulence	-	-
Mouth ulceration	-	-
Nausea	9	a /12[†]
Stomach cramps	a	-
Thirst	-	-
Vomiting	-	a /10[†]
Weight loss	a	a / 9[†]
Genitourinary		
Abnormal urine	-	-
Erectile disturbance	-	a
Hematuria	-	-
Libido decreased	-	a
Polyuria	-	-
Hematologic		
Agranulocytosis	-	-
Anemia	a	a
Eosinophilia	-	-
Leukopenia	a	a
Pancytopenia	-	a
Thrombocytopenic purpura	a	a
Hepatic		
Hepatic coma	a	a
Liver function test abnormalities	a	a
Musculoskeletal		
Arthralgia	a	a
Back pain	-	-
Respiratory		
Cough	-	a
Dyspnea	-	a
Epistaxis	-	-
Lung disorder	-	-
Nasal congestion	-	a /6[†]
Nasopharyngitis	-	a /5[†]
Pharyngitis	-	a
Pharyngolaryngeal pain	4 to 7	a
Respiratory tract infection	-	a
Rhinitis	-	a
Sinusitis	-	a
Special Senses		
Abnormal vision	-	-
Accommodation difficulties	a	a
Amblyopia	-	-

Adverse Event(s)	Dexmethylphenidate	Methylphenidate
Blurred vision	a	a
Dry eyes	-	a
Eye pain	-	-
Mydriasis	-	a
Other		
Accidental injury	-	a
Allergic contact sensitization	-	a †
Anaphylaxis	-	a †
Dysmenorrhea	-	a
Edema	-	-
Flu-like syndrome	-	-
Growth suppression	-	a
Hypersensitivity reactions	a	a
Necrotizing vasculitis	a	a
Pain	-	-
Viral infection	-	28†

†Transdermal formulation.
-Event not reported.
a Percent not specified.

Table 7c. Adverse Drug Events (%)-Central α-Agonists[24,25]

Adverse Event(s)	Clonidine	Guanfacine
Cardiovascular		
Atrioventricular block	a	a
Bradycardia	≤4	-
Cardiac arrhythmia	a	-
Chest pain	a	-
Congestive heart failure	a	-
Electrocardiogram abnormalities	a	-
Hypertension	-	a
Hypotension	-	4
Orthostatic hypotension	a	-
Pallor	a	-
Palpitations	1	-
Raynaud's phenomenon	a	-
Sinus arrhythmia	-	a
Syncope	a	a
Tachycardia	1	-
Central Nervous System		
Abnormal sleep-related event	1 to 3	-
Aggressive behavior	a	-
Agitation	a	a
Anxiety	a	a
Behavioral change	a	-
Crying	1 to 3	-
Delirium	a	-
Depression	-	a
Dizziness	2 to 5	6 to 8
Emotional disorder	3 to 4	-
Fatigue/lethargy	12 to 15	14
Fever	a	-
Hallucinations	a	a
Headache	1 to 11	21 to 24

Adverse Event(s)	Clonidine	Guanfacine
Insomnia	≤5	12
Irritability	3 to 6	2
Malaise	a	-
Mental depression	1	-
Nervousness	1 to 3	-
Nightmares	a	a
Paresthesia	a	-
Restlessness	a	-
Seizure	-	a
Sleep terror	3	-
Somnolence	26 to 33	18 to 38
Tremor	a	-
Vivid dreams	a	-
Dermatological		
Flushing	a	-
Rash	1	-
Urticaria	a	-
Gastrointestinal		
Abdominal pain	≤3	10 to 11
Anorexia	1	-
Appetite decreased	-	2
Constipation	1 to 6	3
Diarrhea	≤1	-
Dry mouth	a	3
Dyspepsia	-	a
Nausea	1 to 4	4
Stomach discomfort	-	a
Thirst	1 to 3	-
Vomiting	a	a
Weight gain	<1	a
Genitourinary		
Dysuria	a	-
Enuresis	4	a
Erectile dysfunction	2 to 3	-
Gynecomastia	1	-
Libido decreased	a	-
Nocturia	1	-
Pollakiuria	3	-
Sexual disturbances	3	-
Hepatic		
Hepatitis	a	-
Liver function test abnormalities	≤1	-
Musculoskeletal		
Arthralgia	1	-
Leg cramps	≤1	-
Myalgia	1	-
Pain in extremities	a	-
Weakness	10	-
Respiratory		
Asthma	4	a
Epistaxis	3	-
Lower respiratory tract infection	2	-

Adverse Event(s)	Clonidine	Guanfacine
Nasal congestion	2 to 4	-
Nasal dryness	a	-
Nasopharyngitis	2	-
Upper respiratory tract infection	2 to 7	-
Special Senses		
Accommodation difficulties	a	-
Blurred vision	a	-
Dry eyes	a	-
Eye pain	a	-
Other		
Body temperature increase	≤2	-
Ear infection	a	-
Ear pain	4	-
Flu-like syndrome	≤3	-
Hypersensitivity reactions	-	a
Pallor	-	a
Throat pain	3 to 5	-
Thrombocytopenic purpura	a	-
Viral infection	≤3	-

-Event not reported.
a Percent not specified.

Table 7d. Adverse Drug Events (%)-Central Nervous System Agents-Miscellaneous[23]

Adverse Event(s)	Atomoxetine
Cardiovascular	
Chest pain	-
Diastolic blood pressure increased	4 to 22
Flushing	≥2
Hypertension	1 to 9
Hypotension	<2
Palpitations	3
QT prolongation	<1
Raynaud's phenomenon	a
Stroke	a
Systolic blood pressure increased	4 to 13
Tachycardia	2 to 24
Central Nervous System	
Abnormal dreams	4
Aggressive behavior	a
Agitation	a
Akathisia	a
Anxiety	a
Ataxia	-
Attention disturbance	-
Chills	3
Confusion	-
Crying	2
Depression	-
Disorientation	-
Dizziness	5 to 6
Early morning awakening	<2
Fatigue/lethargy	6 to 9
Fever	3

Adverse Event(s)	Atomoxetine
Headache	2 to 19
Hostility	a
Insomnia	2 to 15
Irritability	≤6
Jittery feeling	2
Mania	a
Mood swings	1 to 2
Nightmare	-
Panic disorder	a
Paresthesia	4
Rigors	3
Seizure	-
Sleep disorder	-
Sleep disturbance	3
Sleep paralysis	-
Sleep walking	-
Somnolence	4 to 11
Suicidal ideation	a
Syncope	a
Tremor	2
Dermatological	
Dermatitis	2 to 4
Diaphoresis	2
Flushing	2
Hyperhidrosis	4
Rash	2
Urticaria	a
Endocrine and Metabolic	
Dysmenorrhea	6
Hot flushes	8
Menstrual disturbances	2 to 3
Gastrointestinal	
Abdominal pain	7 to 18
Anorexia	<3
Appetite decreased	11 to 16
Constipation	1 to 9
Diarrhea	4
Dry mouth	4 to 21
Dyspepsia	4 to 6
Fecal incontinence	-
Flatulence	2
Nausea	7 to 26
Stomach discomfort	-
Vomiting	3 to 11
Weight loss	2 to 30
Genitourinary	
Dysuria	3
Ejaculatory disturbance	3
Enuresis	-
Erectile disturbance	9
Impotence	3
Libido decreased	4

Adverse Event(s)	Atomoxetine
Orgasm abnormal	2
Prostatitis	2
Urinary incontinence	-
Urinary retention	7
Hepatic	
Hepatotoxicity	a
Jaundice	a
Musculoskeletal	
Hypoesthesia	-
Myalgia	-
Myasthenia	-
Weakness	-
Respiratory	
Bronchitis	-
Cough	11
Dyspnea	-
Nasopharyngitis	-
Rhinitis	-
Rhinorrhea	4
Sinus headache	3
Sinusitis	6
Upper respiratory infection	-
Special Senses	
Amblyopia	-
Blurred vision	-
Mydriasis	<2
Tinnitus	-
Other	
Allergic contact sensitization	a
Ear infection	3
Ear pain	-
Flu-like syndrome	a
Hypersensitivity reactions	<1
Influenza	3
Pain	-
Pallor	-
Thirst	-
Viral infection	-

-Event not reported.
a Percent not specified.

Contraindications

Table 8a. Contraindications-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines[1-10]

Contraindication(s)	Amphetamine	Amphetamine/ Dextroam-phetamine Salts	Dextro-amphetamine	Lisdex-amfetamine	Meth-amphetamine
Advanced arteriosclerosis	a *	a	a	-	a
Agitated states	a *	a	a	-	a
Glaucoma	-	a	a	-	a

Contraindication(s)	Amphetamine	Amphetamine/ Dextroam-phetamine Salts	Dextro-amphetamine	Lisdex-amfetamine	Meth-amphetamine
Hypersensitivity	a	a	a	a	a
Hyperthyroidism	a *	a	a	-	a
Moderate to severe hypertension	a *	a	a	-	a
Patients receiving monoamine oxidase inhibitors	a	a	a	a	a
Patients with a history of drug abuse	a *	a	a	-	a
Symptomatic cardiovascular disease	a *	a	a	-	a

*Evekeo®

Table 8b. Contraindications-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous[11-22]

Contraindication(s)	Dexmethylphenidate	Methylphenidate
Anxiety, tension, and agitation	a	a
Family history or diagnosis of Tourette syndrome	a	a
Glaucoma	a	a
Hypersensitivity	a	a
Motor tics	a	a
Patients receiving monoamine oxidase inhibitors	a	a

Table 8c. Contraindications-Central α-Agonists[24,25]

Contraindication(s)	Clonidine	Guanfacine
Hypersensitivity	a	a

Table 8d. Contraindications-Central Nervous System Agents-Miscellaneous[23]

Contraindication(s)	Atomoxetine
Hypersensitivity	a
Narrow angle glaucoma	a
Patients receiving monoamine oxidase inhibitors	a
Pheochromocytoma or a history of pheochromocytoma	a
Severe cardiovascular disorders whose condition would be expected to deteriorate if they experience increases in blood pressure or heart rate that could be clinically important	a

Boxed Warnings

Boxed Warning for amphetamine and amphetamine/dextroamphetamine salts[36]

WARNING
Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of time may lead to drug dependence and must be avoided. Particular attention should be paid to the possibility of subjects obtaining amphetamines for non-therapeutic use or distribution to others, and the drugs should be prescribed or dispensed sparingly. Misuse of amphetamines may cause sudden death and serious cardiovascular adverse reactions.

Boxed Warning for atomoxetine[36]

WARNING
Suicidal ideation in children and adolescents: Atomoxetine increased the risk of suicidal ideation in short-term studies in children or adolescents with attention deficit hyperactivity disorder. Anyone considering the use of atomoxetine in a child or adolescent must balance this risk with the clinical need. Closely monitor patients who are started on therapy for suicidality (suicidal thinking and behavior), clinical worsening, or unusual changes in behavior. Advise families and caregivers of the need for close observation and communication with the prescribing health care provider. Atomoxetine is approved for attention deficit hyperactivity disorder in children and adults. Atomoxetine is not approved for major depressive disorder. Pooled analysis of short-term (six- to 18-week), placebo-controlled trials of atomoxetine in children and adolescents (12 trials involving more than 2,200 patients, including 11 trials in attention deficit hyperactivity disorder and one trial in enuresis) has revealed a greater risk of suicidal ideation early during treatment in those receiving atomoxetine compared to placebo. The average risk of suicidal ideation in patients receiving atomoxetine was 0.4% (5/1,357 patients), compared to none in placebo-treated patients (0/851 patients). No suicides occurred in these trials

Boxed Warning for dexmethylphenidate[36]

WARNING
Drug dependence: Give dexmethylphenidate cautiously to patients with a history of drug dependence or alcoholism. Chronic, abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during drug withdrawal from abusive use because severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

Boxed Warning for lisdexamfetamine[36]

WARNING
Potential for misuse, abuse, addiction, and diversion: Lisdexamfetamine dimesylate is a Schedule II controlled substance. Stimulants, such as amphetamines and methylphenidates, are subject to misuse abuse, addiction, and criminal diversion. Misuse of amphetamines may cause sudden death and serious cardiovascular adverse reactions.

Boxed Warning for methamphetamine[36]

WARNING
Methamphetamine has a high potential for abuse. It should thus be tried only in weight reduction programs for patients in whom alternative therapy has been ineffective. Administration of methamphetamine for prolonged periods of time in obesity may lead to drug dependence and must be avoided. Particular attention should be paid to the possibility of subjects obtaining methamphetamine for nontherapeutic use or distribution to others, and the drug should be prescribed or dispensed sparingly.

Boxed Warning for methylphenidate[36]

WARNING
Drug dependence: Give methylphenidate cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence, with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use because severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

Warnings/Precautions

Table 9a. Warnings and Precautions-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines[1-10]

Warning(s)/Precaution(s)	Amphetamine	Amphetamine/ Dextroamphet-amine Salts	Dextro-amphetamine	Lisdex-amfetamine	Meth-amphet-amine
Aggressive behavior or hostility; patients beginning therapy should be monitored for the appearance or worsening of aggressive behavior or hostility	a	a	a	a	a
Drug abuse and dependence; classified as a Schedule II controlled substance	a	a	a	a	a
Effects on growth; growth should be monitored during therapy	a	a	a	-	a
Emergence of new psychotic or manic symptoms; may develop with therapy	a	a	a	a	a
Fatigue; do not use to combat fatigue or to replace rest in healthy persons	-	-	-	-	a
Hazardous tasks; amphetamines may impair the ability of the patient to engage in potentially hazardous activities	a	a	a	a	a
Hypertension; stimulant medications cause a modest increase in blood pressure and heart rate	a	a	a	a	a
Peripheral vasculopathy has been reported and may result in digital ulceration and/or soft tissue breakdown; monitoring is recommended and discontinuation may be necessary	a	a	a	a	a
Preexisting psychosis; administration of stimulants may exacerbate symptoms of behavior disturbances and thought disorder in patient with preexisting psychotic disorder	a	a	a	a	a

Warning(s)/Precaution(s)	Amphetamine	Amphetamine/ Dextroamphet-amine Salts	Dextro-amphetamine	Lisdex-amfetamine	Meth-amphet-amine
Prescribing/dispensing; prescribe or dispense the least amount feasible at one time in order to minimize the possibility of overdosage	a	a	a	a	a
Screening patients for bipolar disorder; prior to initiating therapy, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder	a	a	a	a	a
Seizures; stimulants may lower the convulsive threshold in patients with a history of seizures, discontinue therapy in the presence of seizures	a	a	a	a	a
Serious cardiovascular events; sudden death, stroke, and myocardial infarction have been reported with therapy and patients should have a careful history and physical exam to assess for the presence of cardiac disease before initiating therapy	a	a	a	a	a
Tartrazine sensitivity; some products may contain tartrazine which may cause allergic-like reactions	-	-	a	-	-
Tics; amphetamines have been reported to exacerbate motor and phonic tics and Tourette syndrome	a	a	a	a	a
Tolerance; tolerance to the anorectic effect usually develops within a few weeks and when it occurs, the recommended dose should not be exceeded in an attempt to increase the effect	a	-	-	-	a
Visual disturbances; difficulties with accommodation and	a	a	a	a	a

Warning(s)/Precaution(s)	Amphetamine	Amphetamine/ Dextroamphet-amine Salts	Dextro-amphetamine	Lisdex-amfetamine	Meth-amphet-amine
blurring have been reported with stimulant treatment					

Table 9b. Warnings and Precautions-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous[11-22]

Warning(s)/Precaution(s)	Dexmethylphenidate	Methylphenidate
Aggressive behavior or hostility; patients beginning therapy should be monitored for the appearance or worsening of aggressive behavior or hostility	a	-
Angioedema and anaphylactoid reactions; discontinue therapy and immediately report any signs or symptoms suggesting angioedema or anaphylaxis	a	-
Cardiovascular system; therapy has not been evaluated in patients with a recent history of myocardial infarction or unstable angina, and such patients should be treated with caution	-	-
Contact sensitization; use of transdermal patch may lead to contact sensitization	-	a
Continuous positive airway pressure use in patients with obstructive sleep apnea; indicated as an adjunct to standard treatment(s) for the underlying obstruction	-	-
Depression; do not use transdermal patch to treat severe depression	-	a
Diagnosis of sleep disorders; therapy should be used only in patients who have had a complete evaluation of their excessive sleepiness, and in whom a diagnosis of either narcolepsy, obstructive sleep apnea, and/or shift-work disorder has been made in accordance with International Classification of Sleep Disorders or Diagnostic and Statistical Manual of Mental Disorders diagnostic criteria	-	-
Drug abuse and dependence; classified as a Schedule II controlled substance	a	a
Drugs affecting the central nervous system; may alter judgment, thinking, or motor skills	-	-
Effects on growth; growth should be monitored during therapy	a	a
Emergence of new psychotic or manic symptoms; may develop with therapy	a	-
External heat; avoid exposing transdermal patch application site to direct external heat sources while wearing the patch	-	a
Fatigue; do not use transdermal patch for the prevention or treatment of normal fatigue states	-	a
Hypertension; stimulant medications cause a modest increase in blood pressure and heart rate	a	a
Multi-organ hypersensitivity reactions; discontinue therapy if suspected	-	-
Patients using cyclosporine; blood levels of cyclosporine may be reduced with therapy	-	-

Warning(s)/Precaution(s)	Dexmethylphenidate	Methylphenidate
Patients using steroidal contraceptives; effectiveness of steroidal contraceptives may be reduced with therapy, alternative or concomitant methods of contraception are recommended	-	-
Peripheral vasculopathy has been reported and digital ulceration and/or soft tissue breakdown may result, monitoring is recommended and dosage adjustment or discontinuation may be necessary.	a	a
Persistent sleepiness; patients with excessive sleepiness should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or other potentially dangerous activity	-	-
Priapism has been reported with methylphenidate products in both pediatric and adult patients	a	a
Psychiatric symptoms have been reported	a	a
Screening patients for bipolar disorder; prior to initiating therapy, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder	a	-
Seizures; stimulants may lower the convulsive threshold in patients with a history of seizures, discontinue therapy in the presence of seizures	a	a
Serious cardiovascular events; sudden death, stroke, and myocardial infarction have been reported with therapy and patients should have a careful history and physical exam to assess for the presence of cardiac disease before initiating therapy	a	a
Serious rash, including Stevens-Johnson Syndrome; serious rash requiring hospitalization and discontinuation of treatment has been reported in adults and children	-	-
Visual disturbances; difficulties with accommodation and blurring have been reported with stimulant treatment	a	a

Table 9c. Warnings and Precautions-Central α-Agonists[24,25]

Warning(s)/Precaution(s)	Clonidine	Guanfacine
Abrupt discontinuation; do not discontinue therapy without consulting a healthcare professional due to the potential risk of withdrawal effects	a	a
Allergic reactions; substitution of oral therapy may elicit an allergic reaction in patients who developed allergic reactions from therapy with the transdermal system	a	-
Hypotension/bradycardia/syncope; treatment can cause dose-related decreases in blood pressure and heart rate	a	a
Other clonidine-containing products; do not use concomitantly	a	-
Other guanfacine-containing products; do not use concomitantly	-	a
Patients with vascular disease, cardiac conduction disease, or renal disease; use with caution	a	-
Sedation and somnolence; caution against operating heavy equipment or driving until response to treatment is known	a	a

Table 9d. Warnings and Precautions-Central Nervous System Agents-Miscellaneous[23]

Warning(s)/Precaution(s)	Atomoxetine
Aggressive behavior or hostility; patients beginning therapy should be monitored for the appearance or worsening of aggressive behavior or hostility	a

Warning(s)/Precaution(s)	Atomoxetine
Allergic events; although uncommon, allergic reactions have been reported	a
Central nervous system depression/respiratory depression; potential to impair respiratory drive, especially in patients with already-compromised respiratory function	-
Confusion/neuropsychiatric adverse events; emergence requires careful and immediate evaluation	-
Depression; emergence requires careful and immediate evaluation	-
Effects on blood pressure and heart rate; use with caution in patients whose underlying medical conditions could be worsened by increases in blood pressure or heart rate	a
Effects on growth; growth should be monitored during therapy	a
Effects on urine outflow from the bladder; rates of urinary retention and hesitation have been reported in adults	a
Emergence of new psychotic or manic symptoms; may develop with therapy	a
Incontinence; if urinary or fecal incontinence is reported, consider pursuing investigations to rule out underlying etiologies	-
Priapism; rare postmarketing cases have been reported	a
Rapid onset of central nervous system depressant effects; only administer at bedtime and while in bed	-
Screening patients for bipolar disorder; prior to initiating therapy, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder	a
Serious cardiovascular events; sudden death, stroke, and myocardial infarction have been reported with therapy and patients should have a careful history and physical exam to assess for the presence of cardiac disease before initiating therapy	a
Severe liver injury; postmarketing reports indicate therapy can cause severe liver injury and therapy should be discontinued in patients with jaundice or laboratory evidence of liver injury, and should not be restarted	a
Sleepwalking; episodes should be fully evaluated and appropriate interventions considered	-
Sodium intake; appropriate daily intake of sodium should be reviewed in patients with heart failure, hypertension, or compromised renal function (see approved package labeling)	-
Suicidal ideation; increased risk of suicidal ideation was observed in short-term trials in children and adolescents with attention deficit hyperactivity disorder	a

Drug Interactions

Table 10a. Drug Interactions-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines[1-10]

Description	Amphetamine	Amphetamine/ Dextroamphetamine Salts	Dextroamphetamine	Lisdexamfetamine	Methamphetamine
Furazolidone: increased sensitivity to central nervous system stimulants. If an interaction is suspected, monitor patients for signs and symptoms of toxicity, and reduce the dose of the central nervous system stimulant accordingly.	a	a	a	a	a
Guanethidine: central nervous system stimulants can reverse the	a	a	a	a	a

Description	Amphetamine	Amphetamine/ Dextroamphetamine Salts	Dextroamphetamine	Lisdexamfetamine	Methamphetamine
hypotensive effects of guanethidine. Monitor patients. If there is a loss of blood pressure control, discontinue the central nervous system stimulant or switch to alternative hypotensive therapy.					
Monoamine oxidase inhibitor: exaggerated pharmacologic effects caused by central nervous system stimulants. Avoid coadministration.	a	a	a	a	a
Serotonin Reuptake Inhibitors: increased sensitivity to sympathomimetic effects and increased risk of serotonin syndrome. If these agents must be used concurrently, monitor for increased central nervous system. Adjust therapy as needed.	a	a	a	a	a
Urinary alkalinizers: alkalinized urine may prolong the effects of central nervous system stimulants. Avoid agents that may alkalinize the urine, particularly in overdose situations.	a	a	a	a	a

Table 10b. Drug Interactions-Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous[11-22]

Description	Dexmethylphenidate	Methylphenidate
Monoamine oxidase inhibitors: hypertensive crisis. Dexmethylphenidate is contraindicated with monoamine oxidase inhibitors.	a	-
Monoamine oxidase inhibitors: hypertensive crisis. Monitor blood pressure during combination therapy.	-	a

Table 10c. Drug Interactions-Central α-Agonists[24,25]

Description	Clonidine	Guanfacine
β-blockers: potentially life-threatening increases in blood pressure. Closely monitor blood pressure after initiation or discontinuation of therapy or a β-blocker when they are given concurrently.	a	-
Tizanidine: potentially symptomatic additive hypotension.	a	-
Tricyclic antidepressants: antihypertensive effect of guanfacine may be decreased. Monitor blood pressure in patients receiving guanfacine when starting, stopping, or charging the dose of the tricyclic antidepressant or using an antihypertensive agent with a different mechanism	-	a

Description	Clonidine	Guanfacine
of action.		
Tricyclic antidepressants: loss of blood pressure control and possible life-threatening increases in blood pressure. Avoid combination if possible by using other agents.	a	-

Table 10d. Drug Interactions-Central Nervous System Agents-Miscellaneous[23]

Description	Atomoxetine
Barbiturates: increased sleep duration and central nervous system depression.	-
Benzodiazepines: increased sleep duration and central nervous system depression.	-
Buspirone: increased sleep duration and central nervous system depression.	-
Central nervous system depressants: increased sleep duration and central nervous system depression.	-
Monoamine oxidase inhibitors: increased risk of serious or fatal reactions. Coadministration is contraindicated.	a
Quinidine: increased plasma concentrations and pharmacologic effects.	a
Serotonin reuptake inhibitors: atomoxetine plasma concentrations may be relaxed, increasing the pharmacologic effects and adverse reactions. Closely monitor the patient when the dose of certain serotonin reuptake inhibitors is started, stopped, or changed. Adjust the dose of atomoxetine as needed.	a
Yohimbine: increased risk of new or worsened preexisting supine hypertension in patients with autonomic failure.	a
Zolpidem: increased sleep duration and central nervous system depression.	-

Table 11. Dosing and Administration[1-25]

Generic Name	Adult Dose	Pediatric Dose	Availability
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Amphetamines			
Amphetamine	Treatment of ADHD (six years of age and older): Tablet: initial: 5 mg once or twice daily; maintenance: 30 mg daily; maximum: 40 mg once daily Extended-release suspension: initial, 2.5 to 5 mg once daily; maximum: 20 mg once daily Narcolepsy (12 years of age and older): Tablet: initial, maintenance: 5 to 60 mg	Treatment of ADHD (three to five years of age); Tablet: 2.5 mg daily Narcolepsy (six to 12 years of age): Tablet: 5 mg daily Exogenous Obesity: Safety and efficacy in children not established	Extended-release suspension 2.5 mg/mL Tablet: 5 mg 10 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	in divided doses Exogenous Obesity: Tablet: initial, maintenance: 30 mg daily in divided doses 30 to 60 minutes before meals		
Amphetamine/ dextro-amphetamine salts	Treatment of ADHD: Capsule: 20 mg once daily in the morning Tablet: 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day Narcolepsy: Capsule, tablet: 5 to 60 mg daily in divided doses	Treatment of ADHD: Capsule: 10 mg once daily in the morning; maximum, 30 mg/day Tablet: 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day Narcolepsy in children six to 12 years of age: Capsule, tablet: 5 mg once daily; may increase by 5 mg weekly until optimal response Narcolepsy in children 12 years of age and older: Capsule, tablet: 10 mg once daily; may increase by 10 mg weekly until optimal response	Capsule: 5 mg 10 mg 15 mg 20 mg 25 mg 30 mg Tablet: 5 mg 7.5 mg 10 mg 12.5 mg 15 mg 20 mg 30 mg
Dextro-amphetamine	Treatment of ADHD: Solution, tablet: initial, 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day Sustained-release capsule: initial, 5 mg once or twice daily; maintenance, up to 40 mg/day Narcolepsy: Solution, sustained-release capsule, tablet: 5 to 60 mg/day administered in divided doses	Treatment of ADHD in children six years of age and older: Solution, tablet: initial, 2.5 to 5 mg once or twice daily; maintenance, up to 40 mg/day Sustained-release capsule: initial, 5 mg once or twice daily; maintenance, up to 40 mg/day Narcolepsy in adolescents 12 years of age and older: Solution, sustained-release capsule, tablet: 5 to 60 mg/day administered in divided doses	Solution: 5 mg/5 mL Sustained-release capsule: 5 mg 10 mg 15 mg Tablet: 2.5 mg 5 mg 7.5 mg 10 mg
Lisdex-amfetamine	Treatment of ADHD: Capsule: initial, 30 mg once daily in the morning; maximum, 70	Treatment of ADHD in children six years of age and older: Capsule: initial, 30 mg once	Capsule: 20 mg 30 mg 40 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	mg/day	daily in the morning; maximum, 70 mg/day	50 mg 60 mg 70 mg
Meth-amphetamine	Exogenous obesity: Tablet: 5 mg taken one half hour before each meal Treatment of ADHD: Tablet: initial, 5 mg once or twice daily; maintenance, 20 to 25 mg/day	Exogenous obesity in children 12 years of age and older: Tablet: 5 mg taken one half hour before each meal Treatment of ADHD in children six years of age and older: Tablet: initial, 5 mg once or twice daily; maintenance, 20 to 25 mg/day	Tablet: 5 mg
Anorexigenic Agents and Respiratory and Cerebral Stimulants-Miscellaneous			
Dexmethyl-phenidate	Treatment of ADHD: Extended-release capsule (new starts): initial, 5 to 10 mg once daily in the morning; maximum, 40 mg/day Extended-release capsule (patients currently receiving methylphenidate): initial, half the dose of racemic methylphenidate Tablet (new starts): initial, 2.5 mg twice daily; maximum, 10 mg twice daily Tablet (patients currently receiving methylphenidate): initial, half the dose of racemic methylphenidate; maximum, 10 mg twice daily	Treatment of ADHD in children six years of age and older: Extended-release capsule (new starts): initial, 5 to 10 mg once daily in the morning; maximum, 30 mg/day Extended-release capsule (patients currently receiving methylphenidate): initial, half the dose of racemic methylphenidate Tablet (new starts): initial, 2.5 mg twice daily; maximum, 10 mg twice daily Tablet (patients currently receiving methylphenidate): initial, half the dose of racemic methylphenidate; maximum, 10 mg twice daily	Extended-release capsule: 5 mg 10 mg 15 mg 20 mg 25 mg 30 mg 35 mg 40 mg Tablet: 2.5 mg 5 mg 10 mg
Methylphenidate	Treatment of ADHD: Chewable tablet, solution, tablet: 20 to 30 mg/day administered in two or three divided doses Extended-release capsule (new starts): initial, 20 mg once daily in the morning; maximum, 60 mg/day	Treatment of ADHD: Chewable tablet, solution, tablet: initial, 5 mg twice daily; maintenance, increase dose gradually Extended-release tablet (new starts): initial, 18 mg once daily in the morning; maximum, 54 (children) and 72 mg/day (adolescents)	Chewable tablet: 2.5 mg 5 mg 10 mg Extended-release capsule (Aptensio XR®) 10 mg 15 mg 20 mg 30 mg 40 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Extended-release capsule (patients currently receiving methylphenidate): administer equivalent total daily doses Extended-release suspension: initial, 20 mg once daily in the morning; maximum, 60 mg/day Extended-release tablet (new starts): initial, 18 to 36 mg/day; maximum, 72 mg/day Extended-release tablet (patients currently receiving methylphenidate): dosing is based on current dose regimen and clinical judgment Extended-release tablet: may be used in place of tablets when the eight hour dosage of the sustained-release tablet corresponds to the titrated eight hour dosage with the tablets Sustained-release tablet: may be used in place of tablets when the eight hour dosage of the sustained-release tablet corresponds to the titrated eight hour dosage with the tablets Transdermal patch: initial, 10 mg; maintenance, titrate to effect <u>Narcolepsy:</u> Chewable tablet, solution, tablet (adults): 20 to 30 mg/day	Extended-release tablet (patients currently receiving methylphenidate): dosing is based on current dose regimen and clinical judgment Extended-release tablet: may be used in place of tablets when the eight hour dosage of the sustained-release tablet corresponds to the titrated eight hour dosage with the tablets Sustained-release tablet: may be used in place of tablets when the eight hour dosage of the sustained-release tablet corresponds to the titrated eight hour dosage with the tablets Transdermal patch: initial, 10 mg; maintenance, titrate to effect <u>Narcolepsy:</u> Chewable tablet, solution, tablet: initial, 5 mg twice daily; maintenance, increase dose gradually Extended-release tablet: may be used in place of tablets when the eight hour dosage of the sustained-release tablet corresponds to the titrated eight hour dosage with the tablets Sustained-release tablet: may be used in place of tablets when the eight hour dosage of the sustained-release tablet corresponds to the titrated eight hour dosage with the tablets	50 mg 60 mg Extended-release capsule (Metadate CD®, generic): 10 mg 20 mg 30 mg 40 mg 50 mg 60 mg Extended-release capsule (Ritalin LA®, generic): 10 mg 20 mg 30 mg 40 mg Extended-release suspension: 25 mg/ 5 mL Extended-release tablet (Concerta®, generic): 18 mg 27 mg 36 mg 54 mg Extended-release tablet (Metadate ER®, generic): 20 mg Solution: 5 mg/5 mL 10 mg/5 mL Sustained-release tablet (Ritalin SR®, generic): 20 mg Tablet: 5 mg 10 mg 20 mg Transdermal patch: 10 mg/9 hours (1.1.mg/hour) 15 mg/9 hours (1.6 mg/hour) 20 mg/9 hours (2.2 mg/hour)

Generic Name	Adult Dose	Pediatric Dose	Availability
	administered in two or three divided doses Extended-release tablet: may be used in place of tablets when the eight hour dosage of the sustained-release tablet corresponds to the titrated eight hour dosage with the tablets Sustained-release tablet: may be used in place of tablets when the eight hour dosage of the sustained-release tablet corresponds to the titrated eight hour dosage with the tablets		30 mg/9 hours (3.3 mg/hour)
Central α-Agonists			
Clonidine	Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications: Extended-release tablet: initial, 0.1 mg at bedtime; maintenance, 0.1 to 0.4 mg/day administered in two divided doses	Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications in children six years of age and older: Extended-release tablet: initial, 0.1 mg at bedtime; maintenance, 0.1 to 0.4 mg/day administered in two divided doses	Extended-release tablet: 0.1 mg 0.2 mg
Guanfacine	Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications: Extended-release tablet: initial, 1 mg once daily; maintenance, 1 to 4 mg/day	Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications in children six years of age and older: Extended-release tablet: initial, 1 mg once daily; maintenance, 1 to 4 mg/day	Extended-release tablet: 1 mg 2 mg 3 mg 4 mg
Central Nervous System Agents-Miscellaneous			
Atomoxetine	Treatment of ADHD: Capsule (>70 kg and adults): initial, 40 mg/day; maintenance, 80 mg/day; maximum, 100 mg/day	Treatment of ADHD: Capsule (≤70 kg): initial, 0.5 mg/kg/day; maintenance, 1.2 mg/kg/day; maximum, 1.4 mg/kg/day	Capsule: 10 mg 18 mg 25 mg 40 mg 60 mg 80 mg 100 mg

ADHD=attention deficit hyperactivity disorder

Clinical Guidelines

Table 12. Clinical Guidelines

Clinical Guideline	Recommendations
American Academy of Pediatrics: **Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit Hyperactivity Disorder in Children and Adolescents (2011)**[28]	Preschool-aged children (four to five years of age) · The primary care clinician should prescribe evidence-based parent- and/or teacher-administered behavior therapy as the first-line of treatment. · Methylphenidate may be prescribed if the behavior interventions do not provide significant improvement and there is moderate-to-severe continuing disturbance in the child's function. Elementary school-aged children (six to 11 years of age) · The primary care clinician should prescribe Food and Drug Administration (FDA)-approved medications for attention deficit-hyperactivity disorder (ADHD) and/or evidence-based parent and/or teacher-administered behavior therapy as treatment for ADHD, preferably both. · 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). Adolescents (12 to 18 years of age) · The primary care clinician should prescribe FDA-approved medications for ADHD with the assent of the adolescent and may prescribe behavior therapy as treatment for ADHD, preferably both. General considerations · Stimulant medications are highly effective for most children in reduction of core symptoms of ADHD. · Atomoxetine, extended-release guanfacine and extended-release clonidine reduce core symptoms; however, they have a smaller evidence base than stimulants. · Extended-release guanfacine and extended-release clonidine have evidence to support their use as adjunctive therapy with stimulant medications. · Before beginning medication treatment for adolescents with newly diagnosed ADHD, clinicians should assess these patients for symptoms of substance abuse. · Clinicians should monitor symptoms and prescription-refill requests for signs of misuse or diversion of ADHD medications and consider prescribing medications with no abuse potential, such as atomoxetine, extended-release guanfacine, or extended-release clonidine (which are not stimulants) or stimulant medications with less abuse potential, such as lisdexamfetamine, dermal methylphenidate, or osmotic-release oral system methylphenidate). · Primary care clinicians should titrate doses of medication for ADHD to achieve maximum benefit with minimum adverse effects.
Institute for Clinical Systems Improvement: **Attention Deficit Hyperactivity Disorder in Primary Care for School-Age Children and Adolescents**	· The Institute for Clinical Systems Improvement has endorsed with qualifications the American Academy of Pediatrics guideline, ADHD: Clinical Practice Guideline, and Supplement. · The primary care clinician should initiate an evaluation for ADHD for any child four through 18 years of age who presents with academic or behavioral problems and symptoms of inattention, hyperactivity, or impulsivity.

Clinical Guideline	Recommendations
(2014)[30]	· In the evaluation of a child for ADHD, the primary care clinician should include assessment for other conditions that might coexist 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 (e.g., tics, sleep apnea) conditions. · The primary care clinician 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. · Recommendations for treatment of children and youth with ADHD vary depending on the patient's age: o For preschool-aged children (four to five years of age), the primary care clinician should prescribe evidence-based parent- and/or teacher-administered behavior therapy as the first line of treatment 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. In areas where 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. o For elementary school–aged children (six to 11 years of age), the primary care clinician should prescribe approved medications for ADHD and/or evidence-based parent and/or teacher-administered behavior therapy as treatment for ADHD, preferably both. 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). The school environment, program, or placement is a part of any treatment plan. o For adolescents (12 to 18 years of age), the primary care clinician should prescribe approved medications for ADHD with the assent of the adolescent and may prescribe behavior therapy as treatment for ADHD preferably both. · The primary care clinician should titrate doses of medication for ADHD to achieve maximum benefit with minimum adverse effects.
National Institute for Health and Clinical Excellence: **Attention Deficit Hyperactivity Disorder: Diagnosis and Management of Attention Deficit Hyperactivity Disorder in Children, Young People, and Adults (2008)**[31]	Treatment for children and adolescents with ADHD · Methylphenidate, atomoxetine and dexamphetamine are recommended as options for the management of ADHD in children and adolescents. · The decision regarding which product to use should be based on the following: o The presence of comorbid conditions. o The different adverse effects of the drugs. o Specific issues regarding compliance identified for the individual child or adolescent. o The potential for drug diversion. o The preferences of the child/adolescent and/or his or her parent or guardian. · Healthcare professionals should consider the following treatment recommendations: o Methylphenidate for patients with ADHD without significant comorbidities.

Clinical Guideline	Recommendations
	o Methylphenidate for patients with ADHD with comorbid conduct disorder. o Methylphenidate or atomoxetine when tics, Tourette's syndrome, anxiety disorder, stimulant misuse or risk of stimulant diversion are present. o Atomoxetine if methylphenidate has been tried and has been ineffective at the maximum tolerated dose, or the child or young person is intolerant to low or moderate doses of methylphenidate. · Modified-release preparations should be considered for the following reasons: o Convenience. o Improving adherence. o Reducing stigma (because the child or young person does not need to take medication at school). o Reducing problems schools have in storing and administering controlled drugs. o Their pharmacokinetic profiles. · Immediate-release preparations may be considered if more flexible dosing regimens are required, or during initial titration to determine correct dosing levels. Treatment of adults with ADHD · Drug treatment is the first-line treatment for adults with ADHD with either moderate or severe levels of impairment. · Methylphenidate is recommended as the first-line drug. · If methylphenidate is ineffective or unacceptable, atomoxetine or dexamphetamine can be tried. · Caution should be exercised when prescribing dexamphetamine to those likely to be at risk of stimulant misuse or diversion.
American Academy of Child and Adolescent Psychiatry: **Practice Parameter for the Assessment and Treatment of Children and Adolescents With Attention-Deficit/ Hyperactivity Disorder (2007)**[27]	· Initial pharmacologic therapy should be with an agent approved by the FDA for the treatment of ADHD. This includes dextroamphetamine, methylphenidate, mixed salts of amphetamine, and atomoxetine. · Stimulants have been shown to be highly effective for the treatment of ADHD in many clinical trials. · Available evidence suggests that both methylphenidate and amphetamines are equally efficacious in the treatment of ADHD. · Immediate-release stimulant medications have the disadvantage that they must be taken two to three times per day to control ADHD symptoms throughout the day. · The long-acting formulations are equally efficacious as immediate-release formulations. · Long-acting formulations may be used as initial therapy. There is no need to titrate to the appropriate dose on short-acting forms and then transfer children to a long-acting form. Short-acting stimulants are often used as initial treatment in small children (<16 kg in weight), for whom there are no long-acting forms in a sufficiently low dose. · Once a medication is initiated, the dose should be titrated every one to three weeks until the maximum dose is reached, the symptoms of ADHD remit, or side effects prevent further titration. · It is recommended that the patient be in contact with the physician during the titration period and visit the physician after one month of therapy to assess effectiveness and determine long-term therapy plans. · Some patients may respond similarly to different stimulant classes;

Clinical Guideline	Recommendations
	whereas, other patients may preferentially respond to only one class of stimulants. There is no method to predict which stimulant will produce the best response in a given patient. · For the treatment of preschoolers, the available evidence suggests that the titration of stimulants be done slowly and that lower doses may be effective. This may be due to slower metabolism of methylphenidate in preschoolers. · In studies published comparing atomoxetine to stimulants, greater efficacy was seen in those patients treated with stimulants. · Atomoxetine may have less pronounced effects on appetite and sleep than stimulants, although they may produce relatively more nausea or sedation. · Atomoxetine may be considered as a first-line agent in patients with an active substance abuse problem, comorbid anxiety, tics, or in those who experience severe side effects while taking stimulants. · It is the choice of the family and the clinician as to which agent should be used for the patient's treatment and each patient's treatment must be individualized.
British Association of Psychopharmacology: **Evidence-Based Guidelines for the Pharmacological Management of Attention Deficit Hyperactivity Disorder: Update on Recommendations From the British Association for Psychopharmacology (2014)**[32]	Pharmacology of drug treatments for ADHD · Stimulants are first-line treatment for adults with ADHD. · Atomoxetine is considered first-line treatment in patients with substance use disorders. · Drug treatment should be continued as long as clinically useful. · Careful titration and monitoring of side effects is required, particularly when using stimulants. · Drug holidays may be useful to ascertain the need of continuation of treatment. · Co-administration of drugs is relatively common in clinical practice for resistant cases but there is a lack of studies investigating its efficacy. Treatment of ADHD in children · All children with severe ADHD (conceptualised as hyperkinetic disorder) should be offered pharmacological treatment. In addition, consider pharmacological treatment for children with moderate symptoms of ADHD who have not responded to psychological interventions. · The treatment of choice for children with severe ADHD or moderate ADHD non-responsive to psychological treatments is psychostimulant. · Atomoxetine can be used instead when there is a risk of misuse of psychostimulants by children or the adults supporting the child. · Appropriate child and family-based psychological interventions should be available to all children with ADHD. These interventions should be tailored to the child's needs and not depend on the local availability of services. · Teachers should be given evidence-based information about ADHD. · Patient and parental preferences should be taken into account when designing a psychological intervention for ADHD. · Every effort should be made to facilitate the transition from adolescence to adulthood. This should include education of parents, children and professionals involved in the care of these children and the development of appropriate services and shared care protocols to enable this transition. · Systems and protocols need to be implemented to allow early re-access to services for young people who may have dropped out of treatment at an early age, but still have significant symptoms and impairment.
American Academy of Sleep Medicine:	· Most of the agents used to treat excessive sleepiness have little effect on cataplexy or other rapid eye movement sleep associated symptoms. Most

Clinical Guideline	Recommendations
Practice Parameters for the Treatment of Narcolepsy and Other Hypersomnias of Central Origin (2007)[33]	antidepressants and anticataplectics have little effect on alertness. However, some compounds act on both symptoms. Compounds should be selected depending on the diagnosis and the targeted symptoms. Coadministration of two or more classes of compounds may be needed in some patients to adequately address their symptoms. · Modafinil is effective for treatment of daytime sleepiness due to narcolepsy. · Sodium oxybate is effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy. Sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis. · Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness due to narcolepsy. · Selegiline may be an effective treatment for cataplexy and daytime sleepiness. · Tricyclic antidepressants, selective serotonin reuptake inhibitors, and venlafaxine may be effective treatment for cataplexy. · Scheduled naps can be beneficial to combat sleepiness, but seldom suffice as primary therapy for narcolepsy.
European Federation of Neurological Sciences: **Guidelines on Management of Narcolepsy in Adults (2011)**[34]	<u>Excessive daytime sleepiness and irresistible episodes of sleep</u> · Modafinil should be prescribed when excessive daytime sleepiness is present. Modafinil should be dosed as 100 to 400 mg/day, given once in the morning or twice daily. · Sodium oxybate may be used when excessive daytime somnolence coexists with cataplexy and poor sleep. Depressed patients should not receive sodium oxybate. · Sodium oxybate should be initiated with 4.5 g/night, increasing by increments of 1.5 g at four-week intervals and should not be used with other sedatives, respiratory depressants or muscle relaxants. Monitor patients for possible development of sleep-disordered breathing. Adverse effects may limit the dose, and require slower titration. · The optimal response on excessive daytime sleepiness may take up to 12 weeks. · Supplementation with modafinil is generally more successful than sodium oxybate alone. · Methylphenidate may be considered if modafinil is insufficient and sodium oxybate is not recommended. · The short-acting effect of methylphenidate is of interest when modafinil needs to be supplemented at a specific time of the day, or in situations where maximum alertness is required. <u>Cataplexy</u> · First-line pharmacological treatment of cataplexy is sodium oxybate at a starting dose of 4.5 g/night divided into two equal doses of 2.25 g/night. The dose may be increased to a maximum of 9 g/night, divided into two equal doses of 4.5 g/night, by increments of 1.5 g at two-week intervals. · Adverse effects may limit the dose, and require slower titration and the optimal response on excessive daytime sleepiness may take up to 12 weeks. · Antidepressants are recommended as second-line pharmacological treatment. Tricyclic antidepressants, particularly clomipramine (10 to 75 mg), are potent anticataplectic drugs; however, anticholinergic adverse effects are common.

Clinical Guideline	Recommendations
	· Selective serotonin reuptake inhibitors are slightly less active but have fewer adverse effects. · Venlafaxine is widely used but clinical evidence supporting its use is limited. · Reboxetine and atomoxetine, also lack published clinical evidence. · Given the efficacy of sodium oxybate and antidepressants, the place for other compounds is fairly limited. · There is no accepted behavioral treatment of cataplexy. Poor sleep · Sodium oxybate appears to be the most appropriate to treat poor sleep. · Benzodiazepine or non-benzodiazepine hypnotics may be effective in consolidating nocturnal sleep, but objective evidence is lacking over intermediate- or long-term follow-up. · The improvement in poor sleep reported by some patients once established on modafinil is noteworthy. Obstructive sleep apnea/hypopnea syndrome, periodic limb movements in sleep, neuropsychiatric symptoms · Obstructive sleep apnea/hypopnea syndrome should be similarly in narcoleptic patients and general population, although continuous positive airway pressure does not improve excessive daytime sleepiness in most narcolepsy subjects. · There is usually no need to treat periodic limb movements in narcoleptic patients. Antidepressants and psychotherapy should be used in depressed narcoleptic patients as in non-narcoleptic depressed patients.
American Academy of Sleep Medicine: **Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders (2007)**[35]	Shift work disorder · Planned napping before or during the night shift is indicated to improve alertness and performance among night shift workers. · Timed light exposure in the work environment and light restriction in the morning, when feasible, is indicated to decrease sleepiness and improve alertness during night shift work. · Administration of melatonin prior to daytime sleep is indicated to promote daytime sleep among night shift workers. · Hypnotic medications may be used to promote daytime sleep among night shift workers. Carryover of sedation to the nighttime shift with potential adverse consequences for nighttime performance and safety must be considered. · Modafinil is indicated to enhance alertness during the night shift for shift work disorder. · Caffeine is indicated to enhance alertness during the night shift for shift work disorder.

Conclusions

There are several central nervous system agents that are Food and Drug Administration (FDA)-approved for the treatment of attention deficit/hyperactivity disorder (ADHD), including the cerebral stimulants (amphetamines and methylphenidate derivatives), atomoxetine (Strattera®), clonidine extended-release (Kapvay®) and guanfacine extended-release (Intuniv®).[1-25] The cerebral stimulants are classified as Schedule II controlled substances, and are associated with Boxed Warnings regarding risk of abuse.[1-22] Atomoxetine, clonidine extended-release and guanfacine extended-release are not classified as controlled substances.[23-25] Clonidine and guanfacine, extended-release formulations, are the first ADHD medications to achieve FDA-approval as adjunctive therapy with stimulant medications, but are also indicated for use as monotherapy.[24,25] Atomoxetine is associated with a Boxed Warning regarding an

increased risk of suicidal ideation observed in short-term trials in children and adolescents with ADHD.[23,36]

Most ADHD agents and stimulants are currently available generically. Agents that are available only as a brand name product include: lisdexamfetamine capsules (Vyvanse®), amphetamine tablets (Evekeo®) and extended-release suspension (Dyanavel XR®), atomoxetine capsules (Strattera®), dextroamphetamine solution (ProCentra®), methylphenidate patch (Daytrana®), and extended-release suspension (Quillivant XR®). Aptensio XR (methylphenidate extended-release) is also available only as a brand name product; however, other extended-release biphasic capsules are available generically.[29]

Several clinical trials have demonstrated the effectiveness of the ADHD agents and stimulants in their respective FDA-approved indications. Evidence consistently demonstrates that these agents significantly improve ADHD and sleepiness rating scales compared to placebo. There is insufficient evidence to suggest that one ADHD agent and stimulant is more efficacious than another. In addition, there is limited efficacy data regarding the treatment of ADHD in the adult population.[37-124] Guidelines recommend the use of FDA-approved agents for initial pharmacologic treatment of ADHD, and preference of one agent over another is not stated. Stimulant medications are still recognized as the most effective treatment option for most children with ADHD, and response to one stimulant dose not predict response to another. Other factors associated with treatment decisions include presence of comorbid conditions, patient/family preference, storage/administration issues at school, history and/or presence of substance abuse, pharmacokinetics and anticipated adverse events.[27,28,30-32] With regard to the use of non stimulant medications in the treatment of ADHD, atomoxetine is recognized as a good option for patients with comorbid anxiety, sleep initiation disorder, substance abuse, or tics, or if initially preferred by parents and/or the physician. Overall, atomoxetine, clonidine extended-release and guanfacine are effective in reducing ADHD core symptoms; however, these agents have a smaller evidence base compared to the cerebral stimulants.[28] With regard to the treatment of ADHD in adults, methylphenidate is recommended first-line, with atomoxetine and dexamphetamine recommended second line.[31,32]

References

1. Evekeo® [prescribing information]. Atlanta (GA): Arbor Pharmaceuticals, LLC; 2015 Feb.
2. Dyanavel XR® [prescribing information]. Monmouth Junction (NJ): Tris Pharma; 2015 Oct.
3. Adderall® [prescribing information]. Wayne (PA): Shire US Inc.; 2014 Apr.
4. Adderall XR® [prescribing information]. Wayne (PA): Shire US Inc.; 2013 Dec.
5. Dexedrine® Spansule® [prescribing information]. Research Triangle Park (NC): GlaxoSmithKline; 2013 Oct.
6. Dexedrine® [prescribing information]. Horsham (PA): Amedra Pharmaceuticals LLC; 2014 May.
7. Zenzedi® [prescribing information]. Atlanta (GA): Arbor Pharmaceuticals, Inc.; 2014 Jan
8. ProCentra® [prescribing information]. Newport (KY): Independence Pharmaceuticals, LLC; 2014 Apr.
9. Vyvanse® [prescribing information]. Wayne (PA): Shire US Inc.; 2014 Nov.
10. Desoxyn® [prescribing information]. Deerfield (IL): Ovation Pharmaceuticals, Inc.; 2013 Dec.
11. Focalin® [prescribing information]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2013 Dec.
12. Focalin XR® [prescribing information]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2013 Dec.
13. Daytrana® [prescribing information]. Miami (FL): Noven Therapeutics, LLC; 2013 Dec.
14. Aptensio XR® [prescribing information]. Coventry (RI): Rhodes Pharmaceuticals L.P.; 2015 May.
15. Concerta® [prescribing information]. Titusville (NJ): McNeil Pediatrics, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.; 2014 Jul.
16. Metadate CD® [prescribing information]. Smyrna (GA): UCB, Inc.; 2013 Dec.
17. Metadate ER® [prescribing information]. Smyrna (GA): UCB Manufacturing, Inc.; 2014 Jan.
18. Methylin® solution [prescribing information]. Atlanta (GA): Shionogi Pharma, Inc.; 2013 Dec.
19. Methylin® chewable tablets [prescribing information]. Atlanta (GA): Shionogi Pharma, Inc.; 2013 Dec
20. Quillivant XR® [prescribing information]. New York (NY): NextWave Pharmaceuticals Inc.; 2014 Oct.
21. Ritalin®, Ritalin-SR® [prescribing information]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2013 Dec.
22. Ritalin LA® [prescribing information]. East Hanover (NJ): Novartis Pharmaceuticals Corporation; 2013 Dec.
23. Strattera® [prescribing information]. Indianapolis (IN): Lilly USA, LCC; 2014 Feb.
24. Intuniv® [prescribing information]. Wayne (PA): Shire US Inc.; 2014 Nov.
25. Kapvay® [prescribing information]. Atlanta (GA): Shionogi Pharma Inc.; 2014 Nov.
26. Krull KR. Attention deficit hyperactivity disorder in children and adolescents: treatment with medications. In: Torchia MM (Ed). UpToDate [database on the internet]. Waltham (MA): UpToDate; 2014 [cited 2014 Dec 18]. Available from: .
27. American Academy of Child and Adolescent Psychiatry. Practice parameter for the assessment and treatment of children and adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2007;46:894-921.
28. American Academy of Pediatrics. ADHD: Clinical Practice Guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents. Pediatrics. 2011;128:1-16.
29. DRUGS@FDA.com [database on the internet]. Rockville (MD): U.S. Food and Drug Administration [cited 2014 Dec 18]. Available from: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm.
30. Institute for Clinical Systems Improvement. ADHD, Attention Deficit Hyperactivity Disorder in Primary Care for School-Age Children and Adolescents [guideline on the Internet]. 9th ed. Bloomington (MN): Institute for Clinical Systems Improvement; 2014 Apr [cited 2014 Dec 18] Available at: https://www.icsi.org/guidelines__more/catalog_guidelines_and_more/catalog_guidelines/catalog_behavioral_health_guidelines/adhd/.
31. National Institute for Health and Clinical Excellence. Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people, and adults [guideline on the Internet]. London (UK). 2008 Sep [cited 2014 Dec 18]. Available at: http://guidance.nice.org.uk/CG72.
32. Bolea-Alamañac B, Nutt DJ, Adamou M, Asherson P, Bazire S, Coghill D, Heal D, et al. Evidence-based guidelines for the pharmacological management of attention deficit hyperactivity disorder: Update on recommendations from the British Association for Psychopharmacology. J Psychopharmacol. March 2014;28:179-203.

33. Morgenthaler TI, Kapur VK, Brown T, Swick TJ, Alessi C, Aurora RN, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep. 2007;30:1705-11.
34. European Federation of Neurological Societies (EFNS). Management of narcolepsy in adults [guideline on the internet]. Vienna, Austria: European Federation of Neurological Societies; 2011 [cited 2014 Dec 18].Available from: http://www.efns.org/fileadmin/user_upload/guidline_papers/EFNS_guideline_2011_Management_of_narcolepsy_in_adults.pdf.
35. American Academy of Sleep Medicine. Practice Parameters for the Clinical Evaluation and Treatment of Circadian Rhythm Sleep Disorders. Sleep. 2007;30:1445-59.
36. Drug Facts and Comparisons 4.0 [database on the Internet]. St. Louis: Wolters Kluwer Health, Inc.; 2013 [cited 2014 Dec 18]. Available from: http://online.factsandcomparisons.com.
37. McCracken JT, Biederman J, Greenhill LL, Swanson JM, McGough JJ, Spencer TJ, et al. Analog classroom assessment of a once-daily mixed amphetamine formulation, SLL381 (Adderall XR) in children with ADHD. J Am Acad Child Adolesc Psychology. 2003;426(6):673-83.
38. Pliszka SR, Browne RG, Olvera RL, Wynne SK. A double-blind, placebo controlled study of Adderall and methylphenidate in the treatment of attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2000;39(5):619-26.
39. Pelham WE, Aronof HR, Midlam JL, Shapiro CJ, Gnagy EM, Chronis AM, et al. A comparison of Ritalin and Adderall; efficacy and time course in children with attention hyperactivity deficit disorder. Pediatrics. 1999;103:e43.
40. Faraone SV, Biederman J, Roe C. Comparative efficacy of Adderall and methylphenidate in attention-deficit/hyperactivity disorder: a meta-analysis. J Clin Psychopharmacol. 2002;22(5):468-73.
41. Biederman J, Lopez FA, Boellner SW, Chandler MC. A randomized, double blind, placebo controlled parallel group study of SLI381 (Adderall XR) in children with attention-deficit/hyperactivity disorder. Pediatrics. 2002;110:258-66.
42. Goodman DW, Ginsberg L, Weisler, RH, Cutler AJ, Hodgkins P. An Interim Analysis of the Quality of Life, Effectiveness, Safety, and Tolerability (QU.E.S.T.) Evaluation of Mixed Amphetamine Salts Extended Release in Adults With ADHD. CNS Spectr. 2005;10(Suppl 20):26-34.
43. Biederman J, Heiligenstein JH, Faries DE, Galil N, Dittmann R, Emslie GJ, et al. Atomoxetine ADHD Study Group. Efficacy of atomoxetine vs placebo in school-age girls with attention-deficit/hyperactivity disorder. Pediatrics. 2002;110(6):e75.
44. Durell TM, Adler LA, Williams DW, Deldar A, McGough JJ, Glaser PE, et al. Atomoxetine treatment of attention-deficit/hyperactivity disorder in young adults with assessment of functional outcomes: a randomized, double-blind, placebo-controlled clinical trial. J Clin Psychopharmacol. 2013 Feb;33(1):45-54.
45. Michelson D, Faries D, Wernicke J, Kelsey D, Kendrick K, Sallee FR, et al. Atomoxetine in the treatment of children and adolescents with attention deficit, hyperactivity disorder: A randomized, placebo controlled, dose response study. Pediatrics. 2001;108(5):e83.
46. Kratochvil CJ, Vaughan BS, Stoner JA, Daughton JM, Lubberstedt BD, Murray DW, et al. A double-blind, placebo-controlled study of atomoxetine in young children with ADHD. Pediatrics. 2011;127:e862-8.
47. Spencer T, Heiligenstein JH, Biederman J, Faries DE, Kratochvil CJ, Conners CK, et al. Results from two proof-of-concept, placebo-controlled studies of atomoxetine in children with attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2002;63:1140-7.
48. Dittmann RW, Schacht A, Helsberg K, Schneider-Fresenius C, Lehmann M, Lehmkuhl G, et al. Atomoxetine vs placebo in children and adolescents with attention-deficit/hyperactivity disorder and comorbid oppositional defiant disorder: a double-blind, randomized, multicenter trial in Germany. J Child Adolesc Psychopharmacol. 2011;21:97-110.
49. Hammerness P, Doyle R, Kotarski M, Georgiopoulos A, Joshi G, Zeitlin S, et al. Atomoxetine in children with attention-deficit hyperactivity disorder with prior stimulant therapy: a prospective open-label study. Eur Child Adolesc Psychiatry. 2009;18:493-8.
50. Adler LA, Spencer TJ, Williams DW, Moore RJ, Michelson D. Long-term, open-label safety and efficacy of atomoxetine in adults with ADHD: final report of a four-year study. J Atten Disord. 2008;12:248-53.

51. Wietecha L, Young J, Ruff D, Dunn D, Findling RL, Saylor K. Atomoxetine once daily for 24 weeks in adults with attention-deficit/hyperactivity disorder (ADHD): impact of treatment on family functioning. Clin Neuropharmacol. 2012 Juen;35(3):125-33.
52. Biederman J, Wigal SB, Spencer TJ, McGough JJ, Mays DA. A post hoc subgroup analysis of an 18-day randomized controlled trial comparing the tolerability and efficacy of mixed amphetamine salts extended release and atomoxetine in school-age girls with attention-deficit/hyperactivity disorder. Clin Ther. 2006;28(2):280–93.
53. Kemner JE, Starr HL, Ciccone PE, Hooper-Wood CG, Crockett RS. Outcomes of OROS methylphenidate compared to atomoxetine in children with ADHD: a multicenter, randomized prospective study. Adv Ther. 2005 Sep-Oct;22(5):498-512.
54. Newcorn JH, Kratochvil CJ, Allen AJ, Casat CD, Ruff DD, Moore RJ, et al. Atomoxetine and osmotically released methylphenidate for the treatment of attention deficit hyperactivity disorder: acute comparison and differential response. Am J Psychiatry. 2008;165:721-30.
55. Starr HL, Kemner J. Multicenter, randomized, open-label study of OROS methylphenidate vs atomoxetine: treatment outcomes in African-American children with ADHD. J Natl Med Assoc. 2005 Oct;97(10 Suppl):11S-16S.
56. Wang Y, Zheng Y, Du Y, Song DH, Shin YJ, Cho SC, et al. Atomoxetine vs methylphenidate in pediatric outpatients with attention deficit hyperactivity disorder: a randomized, double-blind comparison trial. Aust N Z J Psychiatry. 2007 Mar;41(3):222-30.
57. Kratochvil CJ, Heiligenstein JH, Dittmann R, Spencer TJ, Biederman J, Wernicke J, et al. Atomoxetine and methylphenidate treatment in children with ADHD: a prospective, randomized, open-label trial. J Am Acad Child Adolesc Psychiatry. 2002;41(7):776-84.
58. Sutherland SM, Adler LA, Chen C, Smith MD, Feltner DE. An 8-week, randomized controlled trial of atomoxetine, atomoxetine plus buspirone, or placebo in adults with ADHD. J Clin Psychiatry 2012 Jan 10.
59. Ni HC, Lin YJ, Gau SS M D Ph D, Huang HC, Yang LK. An Open-Label, Randomized Trial of Methylphenidate and Atomoxetine Treatment in Adults With ADHD. J Atten Disord. 2013 Mar 8. [Epub ahead of print].
60. Sutherland SM, Adler LA, Chen C, Smith MD, Feltner DE. An eight-week, randomized controlled trial of atomoxetine, atomoxetine plus buspirone, or placebo in adults with ADHD. J Clin Psychiatry. 2012 Apr;73(4):445-50.
61. Prasad S, Harpin V, Poole L, Zeitlin H, Jamdar S, Puvanendran K; The SUNBEAM Study Group. A multi-centre, randomized, open-label study of atomoxetine compared to standard current therapy in UK children and adolescents with attention-deficit/hyperactivity disorder (ADHD). Curr Med Res Opin. 2007 Feb;23(2):379-94.
62. Cheng JYW, Chen RYL, Ko JSN, Ng EML. Efficacy and safety of atomoxetine for attention-deficit/hyperactivity disorder in children and adolescents-meta-analysis and meta-regression analysis. Psychopharmacology. 2007;194:197-209.
63. Hazell PL, Stuart JE. A randomized controlled trial of clonidine added to psychostimulant medication for hyperactive and aggressive children. J Am Acad Child Adolesc Psychiatry. 2003;42:886-94.
64. Jain R, Segal S, Kollins SH, Khayrallah M. Clonidine extended-release tablets for pediatric patients with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2011;50:171-9.
65. Kollins SH, Jain R, Brams M, Segal S, Findling RL, Wigal SB, et al. Clonidine extended-release tablets as add-on therapy to psychostimulants in children and adolescents with ADHD. Pediatrics. 2011;127:e1406-13.
66. Wigal S, Swanson JM, Feifel D, Sangal RB, Elia J, et al. A double-blind, placebo-controlled trial of dexmethylphenidate hydrochloride and d,l-threo-methylphenidate hydrochloride in children with attention-deficit/hyperactivity disorder. J Am Acad Adolesc Psychiatry. 2004;43(11):1406-14.
67. Greenhill LL, Muniz R, Ball RR, Levine A, Pestreich L, et al. Efficacy and safety of dexmethylphenidate extended-release capsules in children with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2006;45(7):817-23.
68. Spencer TJ, Adler LA, McGough JJ, Muniz R, Jiang H, et al. Efficacy and safety of dexmethylphenidate extended-release capsules in adults with attention-deficit/hyperactivity disorder. Biol Psychiatry. 2007;61:1380-7.

69. Adler LA, Spencer T, McGough JJ, Jiang H, Muniz R. Long-term effectiveness and safety of dexmethylphenidate extended-release capsules in adult ADHD. J Atten Disord. 2009;12:449-59.
70. Brams M, Turnbow J, Pestreich L, Giblin J, Childress A, McCague K, et al. A randomized, double-blind study of 30 vs 20 mg dexmethylphenidate extended-release in children with attention-deficit/hyperactivity disorder. J Clin Psychopharmacol. 2012 Oct;32(5):637-44.
71. Stein MA, Waldman ID, Charney E, Aryal S, Sable C, Gruber R, et al. Dose effects and comparative effectiveness of extended release dexmethylphenidate and mixed amphetamine salts. J Child Adolesc Psychopharmacol. 2011;21:581-8.
72. Muniz R, Brams M, Mao A, McCague K, Pestreich L, Silva R. Efficacy and safety of extended-release dexmethylphenidate compared to d,l-methylphenidate and placebo in the treatment of children with attention-deficit/hyperactivity disorder: a 12-hour laboratory classroom study. J Child Adolesc Psychopharmacol. 2008;18:248-56.
73. Scahill L, Chappell PB, Kim YS, Schultz RT, Katsovich L, Shepherd E, et al. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. Am J Psychiatry. 2001;158:1067-74.
74. Kollins SH, López FA, Vince BD, Turnbow JM, Farrand K, Lyne A, et al. Psychomotor functioning and alertness with guanfacine extended release in subjects with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2011;21:111-20.
75. Sallee FR, McGough J, Wigal T, Donahue J, Lyne A, Biederman J, et al. Guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder: a placebo-controlled trial. J Am Acad Child Adolesc Psychiatry. 2009;48:155-65.
76. Sallee FR, Lyne A, Wigal T, McGough JJ. Long-term safety and efficacy of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2009;19:215-26.
77. Sallee FR, Kollins SH, Wigal TL. Efficacy of guanfacine extended-release in the treatment of combined and inattentive only subtypes of attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2012 June;22(3):206-14.
78. Connor DF, Findling RL, Kollins SH, et al. Effects of guanfacine extended release on oppositional symptoms in children aged six-12 years with attention-deficit hyperactivity disorder and oppositional symptoms: a randomized, double-blind, placebo-controlled trial. CNS Drugs. 2010;24:755-68.
79. Biederman J, Melmed RD, Patel A, McBurnett K, Konow J, Lyne A, et al. A randomized, double-blind, placebo-controlled study of guanfacine extended release in children and adolescents with attention-deficit/hyperactivity disorder. Pediatrics. 2008;121:e73-84.
80. Biederman J, Melmed RD, Patel A, McBurnett K, Donahue J, Lyne A. Long-term, open-label extension study of guanfacine extended release in children and adolescents with ADHD. CNS Spectr. 2008;13:1047-55.
81. Spencer TJ, Greenbaum M, Ginsberg LD, Murphy WR. Safety and effectiveness of coadministration of guanfacine extended release and psychostimulants in children and adolescents with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2009;19:501-10.
82. Wilens TE, Bukstein O, Brams M, Cutler AJ, Childress A, Rugino T, et al. A controlled trial of extended-release guanfacine and psychostimulants for attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2012;51:74-85.
83. Faraone SV, Glatt SJ. Effects of extended-release guanfacine on ADHD symptoms and sedation-related adverse events in children with ADHD. J Atten Disord. 2010;13:532-8.
84. Adler LA, Dirks B, Deas PF, Raychaudhuri A, Dauphin MR, Lasser RA, et al. Lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder who report clinically significant impairment in executive function: results from a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2013;74(7):694-702.
85. Babcock T, Dirks B, Adeyi B, Scheckner B. Efficacy of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder previously treated with amphetamines: analyses from a randomized, double-blind, multicenter, placebo-controlled titration study. BMC Pharmacology and Toxicology. 2012;13:18.
86. Biederman J, Krishnan S, Zhang Y, McCough JJ, Findling RL. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: A phase III, randomized, multicenter, double-blind, parallel-group study. Clin Ther. 2007;29:450–63.

87. Biederman J, Boellner SW, Childress A, Lopez FA, Krishnan S, et al. Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: A double-blind, placebo-controlled, crossover analog classroom study. Biol Psychiatry. 2007;62(9):970-6.
88. Brams M, Weisler R, Findling RL, Gasior M, Hamdani M, Ferreira-Cornweel MC, et al. Maintenance of efficacy of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder: randomzied withdrawal design. J Clin Psychiatry. 2012;73(7):977-83.
89. Coghill D, Banaschewski T, Lecendreux M, Soutullo C, Johnson M, Zuddas A, et al. European, randomized, phase 3 study of lisdexamfetamine dimesylate in children and adolescents with attention-deficit/hyperactivity disorder. Eur Neuropsychopharmacol. 2013 Jan 14. [Epub ahead of print].
90. Findling RL, Childress AC, Cutler AJ, Gasior M, Hamdani M, Ferreira-Cornwell MC, et al. Efficacy and safety of lisdexamfetamine dimesylate in adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2011;50:395-405.
91. Findling RL, Childress AC, Krishnan S, McGough JJ. Long-term effectiveness and safety of lisdexamfetamine dimesylate in school-aged children with attention-deficit/hyperactivity disorder. CNS Spect. 2008;13:614-20.
92. Jain R, Babcock T, Burtea T, Dirks B, Adeyi B, Scheckner B, et al. Efficacy and safety of lisdexamfetamine dimesylate in children with attention deficit/hyperactivity disorder and recent methylphenidate use. Adv Ther. 2013;30:472-86.
93. Weisler R, Young J, Mattingly G, Gao J, Squires L, Adler L, et al. Long-term safety and effectiveness of lisdexamfetamine dimesylate in adults with attention-deficit/hyperactivity disorder. CNS Spectr. 2009;14:573-85.
94. Mattingly G, Weisler R, Dirks B, Babcock T, Adeyi B, Scheckner B, et al. Attention deficit hyperactivity disorder subtypes and symptom response in adults treated with lisdexamfetamine dimesylate. Innov Clin Neurosci. 2012;9(5-6):22-30.
95. Wigal SB, Wigal T, Schuck S, Brams M, Williamson D, Armstrong RB, et al. Academic, behavioral, and cognitive effects of OROS® methylphenidate on older children with attention-deficit/hyperactivity disorder. J Child Adolesc Psychopharmacol. 2011;21:121-31.
96. Casas M, Rösler M, Sandra Kooij JJ, Ginsberg Y, Ramos-Quiroga JA, Heger S, et al. Efficacy and safety of prolonged-release OROS methylphenidate in adults with attention deficit/hyperactivity disorder: A 13-week, randomized, double-blind, placebo-controlled, fixed-dose study. World J Biol Psychiatry. 2011 Nov 22.
97. Wigal SB, Childress AC, Belden HW, Berry SA. NWP06, an extended-release oral suspension of methylphenidate, improved attention-deficit/hyperactivity disorder symptoms compared to placebo in a laboratory classroom study. J Child Adolesc Psychopharmacol. 2013 Feb;23(1):3-10.
98. Wilens TE. Biederman J. Lerner M. Concerta Study Group. Effects of once-daily osmotic-release methylphenidate on blood pressure and heart rate in children with attention-deficit/hyperactivity disorder: results from a one-year follow-up study. Journal of Clinical Psychopharmacology. 2004; 24(1):36-41.
99. Mattos P, Louzã MR, Palmini AL, et al. A Multicenter, Open-Label Trial to Evaluate the Quality of Life in Adults With ADHD Treated With Long-Acting Methylphenidate (OROS MPH): Concerta Quality of Life (CONQoL) Study. J Atten Disord. 2012 Feb 14. [Epub ahead of print].
100. Cox DJ, Merkel RL, Moore M, Thorndike F, Muller C, Kovatchev B. Relative benefits of stimulant therapy with OROS methylphenidate vs mixed amphetamine salts extended release in improving the driving performance of adolescent drivers with attention-deficit/hyperactivity disorder. Pediatrics. 2006 Sep;118(3):e704-10.
101. Yang L, Cao Q, Shuai L, Li H, Chan RC, Wang Y. Comparative study of OROS-MPH and atomoxetine on executive function improvement in ADHD: a randomized controlled trial. Int J Neuropsychopharmacol. 2011 Oct 21:1-12. [Epub ahead of print].
102. Wolraich ML, Greenhill LL, Pelham W, Swanson J, Wilens T, Palumbo D, et al. Randomized, controlled trial of OROS methylphenidate once a day in children with attention-deficit/hyperactivity disorder. Pediatrics. 2001;108:883-92.
103. Pelham WE, Gnagy EM, Burrows-Maclean L, Williams A, Fabiano GA, Morrisey SM, et al. Once-a-day Concerta -methylphenidate vs three times daily methylphenidate in laboratory and natural settings. Pediatrics. 2001;107:e105.

104. Gau SS, Shen HY, Soong WT, Gau CS. An open-label, randomized, active-controlled equivalent trial of osmotic release oral system methylphenidate in children with attention-deficit/hyperactivity disorder in Taiwan. J Child Adolesc Psychopharmacol. 2006 Aug;16(4):441-55.
105. Lopez F, Silva R, Pestreich L, Muniz R. Comparative efficacy of two once daily methylphenidate formulations (Ritalin LA and Concerta) and placebo in children with attention deficit hyperactivity disorder across the school day. Paediatr Drugs. 2003;5(8):545-55.
106. Swanson JM, Wigal SB, Wigal T, Sonuga-Barke E, Greenhill LL, Biederman J, et al. A comparison of one-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (the Comacs study). Pediatrics. 2004;113:e206-16.
107. Silva R, Muniz R, Pestreich LK, Brams M, Childress A, Lopez FA. Efficacy of two long-acting methylphenidate formulations in children with attention- deficit/hyperactivity disorder in a laboratory classroom setting. J Child Adolesc Psychopharmacol. 2005 Aug;15(4):637-54.
108. Jahromi LB, Kasari CL, McCracken JT, Lee LS, Aman MG, McDougle CJ, Scahill L, Tierney E, Arnold LE, Vitiello B, Ritz L, Witwer A, Kustan E, Ghuman J, Posey DJ. Positive effects of methylphenidate on social communication and self-regulation in children with pervasive developmental disorders and hyperactivity. J Autism Dev Disord. 2009;39:395-404.
109. Spencer TJ, Mick E, Surman CB, Hammerness P, Doyle R, Aleardi M, et al. A randomized, single-blind, substitution study of OROS methylphenidate (Concerta) in ADHD adults receiving immediate release methylphenidate. J Atten Disord. 2011;15:286-94.
110. Efron D, Jarman F, Barker M. Efficacy of methylphenidate and dextroamphetamine in children with attention hyperactivity disorder: a double blind crossover trial. Pediatrics. 1997;100:662-8.
111. Pelham WE, Greenslade KE, Vodde-Hamilton M, Murphy DA, Greenstein JJ, Gnagy EM, et al. Relative efficacy of long-acting stimulants on children with attention deficit-hyperactivity disorder: a comparison of standard methylphenidate, sustained-release methylphenidate, sustained-release dextroamphetamine, and pemoline. Pediatrics. 1990;86:226-37.
112. Palumbo DR, Sallee FR, Pelham WE Jr, Bukstein OG, Daviss WB, McDermott MP. Clonidine for attention-deficit/hyperactivity disorder: 1. Efficacy and tolerability of outcomes. J Am Acad Child Adolesc Psychiatry. 2008;47:180-8.
113. Greenhill LL, Findling RL, Swanson JM; ADHD Study Group. A double-blind, placebo-controlled study of modified-release methylphenidate in children with attention-deficit/hyperactivity disorder. Pediatrics. 2002;109:e39.
114. McGough JJ, Wigal SB, Abikoff H, Turnbow JM, et al. A randomized, double-blind, placebo-controlled, laboratory classroom assessment of methylphenidate transdermal system. J of Att Dis. 2006;9(3):476-85.
115. Pelham WE, Manos MJ, Ezzell CE, Tresco KE, et al. A dose-ranging study of methylphenidate transdermal system in children with ADHD. J Am Acad Adolesc. 2005;44(6):522-9.
116. Pelham WE, Burrows-MacLean L, Gnagy EM, Fabiano GA, et al. Transdermal methylphenidate, behavioral, and combined treatment for children with ADHD. Exp Clin Psychopharmacology. 2005;13:111-26.
117. Faraone SV, Glatt SJ, Bukstein OG, Lopez FA, Arnold LE, Findline RL. Effects of once-daily oral and transdermal methylphenidate on sleep behavior of children with ADHD. J Atten Disord. 2009; 12:308-15.
118. Findling RL, Bukstein OG, Melmed RD, López FA, Sallee FR, Arnold LE, Pratt RD. A randomized, double-blind, placebo-controlled, parallel-group study of methylphenidate transdermal system in pediatric patients with attention-deficit/hyperactivity disorder. J Clin Psychiatry. 2008;69:149-59.
119. Chou WJ, Chen SJ, Chen YS, Liang HY, Lin CC, Tang CS, et al. Remission in children and adolescents diagnosed with attention-deficit/hyperactivity disorder via an effective and tolerable titration scheme for osmotic release oral system methylphenidate. J Child Adolesc Psychopharmacol. 2012 Jun;22(3):215-25.
120. Faraone SV, Bierderman J, Spencer TJ, Aleardi M. Comparing the efficacy of medications for ADHD using meta-analysis. MedGenMed. 2006;8(4):4.

121. Schelleman H, Bilker WB, Strom BL, Kimmel SE, Newcomb C, Guevara JP, et al. Cardiovascular events and death in children exposed and unexposed to ADHD agents. Pediatrics. 2011;127:1102-10.
122. Olfson M, Huang C, Gerhard T, Winterstein AG, Crystal S, Allison PD, et al. Stimulants and cardiovascular events in youth with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry. 2012;51:147-56.
123. Schelleman H, Bilker WB, Kimmel SE, Daniel GW, Newcomb C, Guevara JP, et al. Methylphenidate and risk of serious cardiovascular events in adults. Am J Psychiatry. 2012;169:178-85.
124. Hanwella R, Senanayake M, de Silva V. Comparative efficacy and acceptability of methylphenidate and atomoxetine in treatment of attention deficit hyperactivity disorder in children and adolescents: a meta-analysis. BMC Psychiatry. 2011;11:176.