Supplementary Appendix

ADHD pharmacologic treatment

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Section 1. Effects sizes of approved ADHD medications (listed in alphabetic order) relative to efficacy on ADHD core symptoms (inattention, hyperactivity, and impulsivity), tolerability, and acceptability as reported in Cortese et al.[1] (outcomes closest to 12 weeks in the main dose analysis).

EFFICACY

Values are reported as standardized mean differences (SMD) with their 95% confidence interval. SMDs, and their 95% CI, < 0 indicate that the medication is significantly more efficacious than placebo. Significant values are bolded.

Clinicians' Ratings

Medication	Children and adolescents	Adults
Amphetamines	**-1.02 (-1.19, -0.85)**	**-0.79 (-0.99, -0.58)**
Atomoxetine	**-0.56 (-0.66, -0.45)**	**-0.45 (-0.58, -0.32)**
Clonidine *	**-0.71 (-1.17, -0.24)**	-
Guanfacine *	**-0.67 (-0.85, -0.50)**	-
Methylphenidate	**-0.78 (-0.93, -0.62)**	**-0.49 (-0.64, -0.35)**

*immediate or extended release (Note: the FDA has approved for ADHD only the extended-release)

Teachers' Ratings

Medication	Children and adolescents	Adults
Amphetamines	-	-
Atomoxetine	-0.32 (-0.82, 0.18)	-
Clonidine	-	-
Guanfacine	-0.63 (-1.62, 0.35)	-
Methylphenidate	**-0.82 (-1.16, -0.48)**	-

Parents' Ratings

Medication	Children and adolescents	Adults
Amphetamines	**-1.07 (-1.36, -0.79)**	-
Atomoxetine	**-0.60 (-0.71, -0.50)**	-
Clonidine	-	-
Guanfacine	-0.23 (-0.90, 0.45)	-
Methylphenidate	**-0.84 (-0.95, -0.72)**	-

Self-ratings

Medication	Children and adolescents	Adults
Amphetamines	-	**-0.45 (-0.70, -0.20**
Atomoxetine	-	**-0.37 (-0.47, -0.27)**
Clonidine	-	-
Guanfacine	-	**-0.70 (-1.30, -0.09)**
Methylphenidate	-	**-0.41 (-0.50, -0.33)**

TOLERABILITY (drop outs due to side effects)

Values are reported as odd ratios (OR) with their 95% confidence interval. ORs and their 95% CI > 1 indicate significantly worse tolerability of medication versus placebo. Significant values are bolded.

Medication	Children and adolescents	Adults
Amphetamines	**2.30 (1.36,3.89)**	**3.26 (1.54,6.92)**
Atomoxetine	1.49 (0.84, 2.64)	**2.33 (1.28,4.25)**
Clonidine	4.52 (0.75, 27.03)	-
Guanfacine	**2.64 (1.20, 5.81)**	-
Methylphenidate	1.44 (0.90,2.31)	**2.39 (1.40,4.08)**

ACCEPTABILITY (total drop outs)

Values are reported as odd ratios (OR) with their 95% confidence interval. ORs and their 95% CI < 1 indicate significantly better acceptability of medication versus placebo

Medication	Children and adolescents	Adults
Amphetamines	0.78 (0.56,1.09)	**0.68 (0.49,0.95)**
Atomoxetine	0.85 (0.61,1.18)	1.28 (0.97,1.70)
Clonidine	0.60 (0.26,1.37)	-
Guanfacine	0.81 (0.54,1.23)	-
Methylphenidate	**0.69 (0.52,0.91)**	1.06 (0.81,1.38)

Section 2. Heart rate values in Vitiello et al. 2012 [2]

At follow-up year 8, mean heart rate values were 66.4 ± 8.7 bpm in never medicated individuals *vs.* 70.4 ± 11.7 bpm in those continuously medicated with the highest cumulative dose. These differences were significant before ($p < 0.001$) and even after controlling for current medication use ($p < 0.001$). Differences in mean heart rate between never medicated individuals and those continuously medicated with the highest cumulative dose at follow-up year 3 were significant before ($p = 0.019$) but not after ($p = 0.084$) controlling for current medication use.

Section 3. Annual prevalence of ADHD medication use in adults with ADHD

Tables S1-S4 show the annual prevalence of ADHD medication use in adults as reported in Raman et al.[3] The estimated prevalence of ADHD in adults in the meta-analysis by Simon et al.[4] was 2.5%. With the exception of the United States, the prevalence of ADHD medication use in adults was substantially lower than the estimated prevalence of ADHD in adults.

Section 4. Duration of response

Determining the exact duration of response to ADHD medications is challenging. Currently, duration of response to stimulants is commonly assessed based on hourly changes of symptoms severity measured with the scale SKAMP [5] or PERMP [6] in an artificial environment such as the analog classroom studies. However, these scales do not assess the early morning or evening. Another caveat to consider is that studies usually report SKAMP or PERMP measures at select time points after dosing, so caution should be used in interpreting data when a significant difference from placebo is first observed and in considering the spacing between assessed time points. Additionally, duration of action may change according to age groups. Finally, there is individual variability in the duration of response.

Therefore, the values reported in Table 1 in the main text should be considered cautiously.

The values in Table 1 reflect those reported in the FDA-approved patient labeling (retrieved from https://www.accessdata.fda.gov/scripts/cder/daf/), usually based on studies conducted with the SKAMP or PERMP. When such values were not reported in the FDA-approved patient labeling, studies on stimulants using the SKAMP or PERMP in analog classroom studies or

quantifying the duration of response of non-stimulants via other questionnaires were searched. The following studies provided additional information on the duration of response for some compounds for which the duration of response was not reported in the FDA approved patient labeling:

Methylphenidate immediate release (tablet)	Wigal SB, Gupta S, Guinta D, Swanson JM. Reliability and validity of the SKAMP rating scale in a laboratory school setting. Psychopharmacol Bull1998;34:47-53.
Methylphenidate extended release (long acting)	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;5:545-55.
Methylphenidate controlled delivery	Swanson J, Wigal S, Wigal T, et al. A comparison of once-daily extended-release methylphenidate formulations in children with attention-deficit/hyperactivity disorder in the laboratory school (The COMACS Study). Pediatrics 2004;113: 206-16
Mixed amphetamine salts extended - release	Biederman J, Boellner SW, Childress A, Lopez FA, Krishnan S, Zhang Y. Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: a double-blind, placebo-controlled, crossover analog classroom study. Biol Psychiatry 2007;62:970-6.
Amphetamine extended-release XR-ODT	Childress AC, Kollins SH, Cutler AJ, Marraffino A, Sikes CR. Efficacy, Safety, and Tolerability of an Extended-Release Orally Disintegrating Methylphenidate Tablet in Children 6-12 Years of Age with Attention-

Deficit/Hyperactivity Disorder in the Laboratory Classroom Setting. J Child Adolesc Psychopharmacol 2017;27:66-74.

Racemic amphetamine sulphate ODT — Childress AC, Brams M, Cutler AJ et al. The Efficacy and Safety of Evekeo, Racemic Amphetamine Sulfate, for Treatment of Attention-Deficit/Hyperactivity Disorder Symptoms: A Multicenter, Dose-Optimized, Double-Blind, Randomized, Placebo-Controlled Crossover Laboratory Classroom Study. J Child Adolesc Psychopharmacol 2015;25:402-14.

Atomoxetine — Block SL, Kelsey D, Coury D et al. Once-daily atomoxetine for treating pediatric attention-deficit/hyperactivity disorder: comparison of morning and evening dosing. Clin Pediatr (Phila) 2009;48:723-33.

Extended-release guanfacine — Biederman J, Melmed RD, Patel A et al.; SPD503 Study Group. 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.

Section 5. Mechanisms of action of ADHD medications

The mechanisms of action reported in Table 1 in the main text are detailed in the following publications:

Amphetamines and methylphenidate: Faraone SV. The pharmacology of amphetamine and methylphenidate: Relevance to the neurobiology of attention-deficit/hyperactivity disorder and other psychiatric comorbidities. Neurosci Biobehav Rev 2018;87:255-270.

Atomoxetine: Bymaster FP, Katner JS, Nelson DL et al. Atomoxetine increases extracellular levels of norepinephrine and dopamine in prefrontal cortex of rat: a potential mechanism for efficacy in attention deficit/hyperactivity disorder. Neuropsychopharmacology 2002;27:699-711.

Clonidine extended-release: Croxtall JD. Clonidine extended-release in attention-deficit hyperactivity disorder: profile report. CNS Drugs 20121;26(3):277-9.

Guanfacine extended-release: Alamo C, López-Muñoz F, Sánchez-García J. Guanfacine extended-release: a postsynaptic differential approach to the

treatment of attention deficit hyperactivity disorder (ADHD). Actas Esp Psiquiatr 2016;44:107-12.

Section 6. Additional details on the management of adverse events

Refer to pediatric endocrinologist/growth specialist if height and weight values are below the following critical thresholds [7]

Height: 1.5 standard deviations (SDs) below the average of mother's and father's height;

2. Height: 2 SDs below the population mean plus 1- year height velocity 1 SD below the mean, or a 1- year decrease of 0.5 SDs;

3. 1-year height velocity 2 SDs below the mean, or 2- year height velocity 1.5 SDs below the mean.

Management of psychotic symptoms

In a large study,[8] psychotic events occurred in approximately 1 in 660 patients with ADHD treated with stimulants. The percentage of patients who had an episode of psychosis (defined as a new diagnosis code for psychosis and a prescription for an antipsychotic medication) was significantly higher in the amphetamine group than in the methylphenidate group (0.21% vs. 0.10%), and psychotic episodes occurred a median of 128 days after exposure to the medication. Analyses of Food and Drug Administration data and case reports[9] have shown that psychotic symptoms are short-lived and resolve after discontinuation of the stimulant in 92% of patients, even without treatment with antipsychotic medications.

Figure S1. Recommendations for blood pressure monitoring

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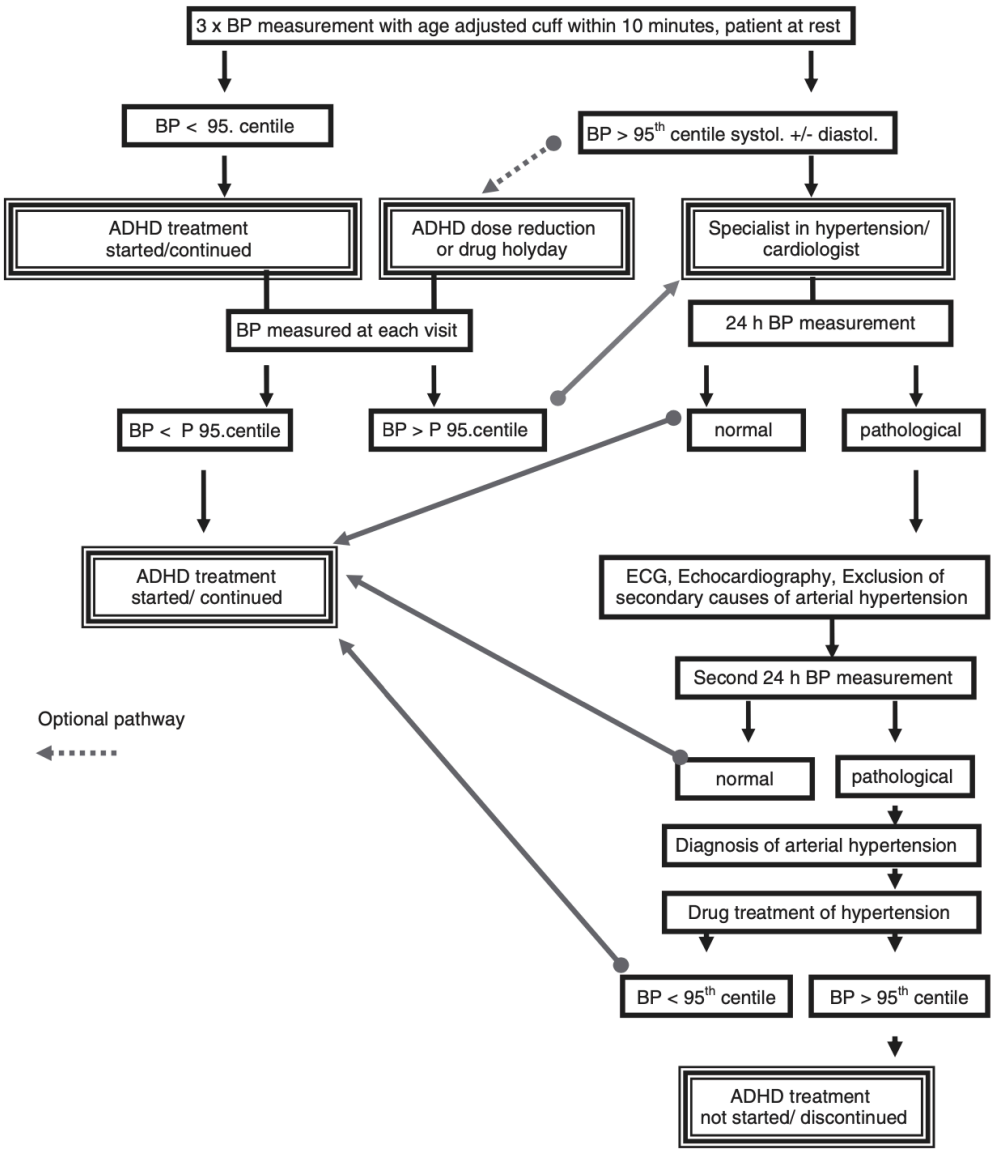

BP: Blood pressure

Table S1. Annual prevalence of ADHD medication use in adults (Asia and Oceania Region) [3]

Year	Australia	Hong Kong	Japan	Taiwan
	Prevalence (per 100)	Prevalence (per 100)	Prevalence (per 100)	Prevalence (per 100)
2001	--	0.003 (0.002 to 0.003)	--	--
2002	--	0.002 (0.002 to 0.003)	--	0.02 (0.02 to 0.02)
2003	--	0.002 (0.002 to 0.002)	--	0.02 (0.02 to 0·03)
2004	--	0.003 (0.003 to 0.004)	--	0.03 (0.02 to 0.03)
2005	--	0.004 (0.004 to 0.005)	--	0.03 (0.03 to 0.04)
2006	--	0.003 (0.003 to 0.004)	--	0.03 (0.02 to 0.03)
2007	--	0.004 (0.004 to 0.005)	--	0.03 (0.03 to 0.04)
2008	--	0.005 (0.004 to 0.005)	--	0.04 (0.03 to 0.04)
2009	0.15 (0.15 to 0.15)	0.005 (0.005 to 0.006)	--	0.04 (0.03 to 0.04)
2010	0.16 (0.16 to 0.17)	0.006 (0.005 to 0.006)	0.003 (0.002 to 0.004)	0.04 (0.03 to 0.04)
2011	0.18 (0.18 to 0.18)	0.006 (0.006 to 0.007)	0.003 (0.002 to 0.004)	--
2012	0.20 (0.20 to 0.20)	0.007 (0.006 to 0.007)	0.009 (0.007 to 0.01)	--
2013	0.22 (0.21 to 0.22)	0.008 (0.007 to 0.008)	0.02 (0.02 to 0.03)	--
2014	0.23 (0.22 to 0.23)	0.01 (0.01 to 0.01)	0.05 (0.04 to 0.05)	--

2015	--	0.01 (0.01 to 0.02)	0.05 (0.05 to 0.05)	--

Table S2. Annual prevalence of ADHD medication use in adults (North America Region) [3]

Year	US MarketScan	US Medicaid
	Prevalence (per 100)	Prevalence (per 100)
2001	0.52 (0.52 to 0.53)	0.35 (0.34 to 0.35)
2002	0.52 (0.52 to 0.53)	0.37 (0.37 to 0.37)
2003	0.61 (0.61 to 0.62)	0.52 (0.51 to 0.52)
2004	0.80 (0.80 to 0.81)	0.71 (0.70 to 0.71)
2005	0.93 (0.93 to 0.94)	0.77 (0.76 to 0.77)
2006	0.86 (0.85 to 0.86)	0.78 (0.78 to 0.79)
2007	0.93 (0.93 to 0.94)	0.84 (0.84 to 0.85)
2008	1.12 (1.11 to 1.12)	0.95 (0.94 to 0.95)
2009	1.36 (1.36 to 1.37)	1.11 (1.11 to 1.12)
2010	1.48 (1.48 to 1.49)	1.35 (1.34 to 1.36)
2011	1.68 (1.67 to 1.68)	--
2012	1.88 (1.87 to 1.88)	--
2013	2.04 (2.04 to 2.05)	--
2014	2·11 (2.11 to 2.12)	--
2015	--	--

Table S3. Annual prevalence of ADHD medication use in adults (Northern Europe) [3]

Year	Denmark	Finland	Iceland	Norway	Sweden
	Prevalence (per 100)	Prevalence (per 100)	Prevalence (per 100)	Prevalence (per 100)	Prevalence (per 100)
2001	0.03 (0.03 to 0.03)	--	--	--	--
2002	0.03 (0.03 to 0.04)	--	--	--	--
2003	0.04 (0·04 to 0·04)	--	0.53 (0.50 to 0.56)	--	--
2004	0.05 (0.05 to 0.06)	--	0.58 (0.56 to 0.62)	0.12 (0.12 to 0.13)	--
2005	0.07 (0.07 to 0.07)	0.03 (0.03 to 0.04)	0.64 (0.61 to 0.67)	0.20 (0.19 to 0.20)	--
2006	0.09 (0.09 to 0.10)	0.05 (0.05 to 0.05)	0.72 (0.68 to 0.75)	0.22 (0.22 to 0.23)	0.09 (0.09 to 0.09)
2007	0.14 (0.14 to 0.14)	0.07 (0.07 to 0.08)	0.78 (0.75 to 0.82)	0.27 (0.26 to 0.27)	0.13 (0.13 to 0.14)
2008	0.21 (0.21 to 0.22)	0.09 (0.09 to 0.10)	0.82 (0.79 to 0.86)	0.31 (0.30 to 0.32)	0.19 (0.19 to 0.20)
2009	0.33 (0.32 to 0.34)	0.10 (0.10 to 0.11)	0.94 (0.90 to 0.87)	0.35 (0.34 to 0·36)	0.27 (0.26 to 0.27)
2010	0.44 (0.43 to 0.45)	0.11 (0.11 to 0.11)	1.06 (1.02 to 1.10)	0.39 (0.38 to 0.39)	0.35 (0.35 to 0.36)
2011	0.50 (0.50 to 0.51)	0.08 (0.08 to 0.08)	1.15 (1.11 to 1.19)	0.40 (0.39 to 0.41)	0.44 (0.44 to 0.45)
2012	0.55 (0.55 to 0.56)	0.12 (0.12 to 0.13)	1.35 (1.30 to 1.39)	0.44 (0.43 to 0.44)	0.51 (0.51 to 0.52)
2013	0.52 (0.51 to 0.52)	--	1.56 (1.51 to 1·60)	0.47 (0.46 to 0.48)	0.58 (0.57 to 0.58)
2014	--	--	--	--	--
2015	--	--	--	--	--

Table S4. Annual prevalence of ADHD medication use in adults (Western/Southern Europe Region) [3]

Year	France	Spain	UK
	Prevalence (per 100)	Prevalence (per 100)	Prevalence (per 100)
2001	--	0.02 (0.01 to 0.03)	0.01 (0.01 to 0.01)
2002	--	0.02 (0.01 to 0.03)	0.01 (0.01 to 0.01)
2003	--	0.01 (0.01 to 0.02)	0.01 (0.01 to 0.01)
2004	--	0.02 (0.02 to 0.02)	0.01 (0.01 to 0.01)
2005	--	0.02 (0.02 to 0.02)	0.01 (0.01 to 0.01)
2006	0.01 (0.01 to 0.01)	0.02 (0.02 to 0.02)	0.01 (0.01 to 0.02)
2007	0.01 (0.01 to 0.01)	0.02 (0.02 to 0.03)	0.02 (0.02 to 0.02)
2008	0.01 (0.01 to 0.01)	0.03 (0.03 to 0.03)	0.02 (0.02 to 0.02)
2009	0.01 (0.01 to 0.01)	0.03 (0.03 to 0.04)	0.02 (0·02 to 0·02)
2010	0.01 (0.01 to 0.01)	0.04 (0.03 to 0.04)	0.03 (0.02 to 0.03)
2011	0.02 (0.01 to 0.02)	0.06 (0.06 to 0.07)	0.03 (0.03 to 0.03)
2012	0.02 (0.02 to 0.02)	0.07 (0.07 to 0.08)	0.04 (0.04 to 0.04)
2013	0.02 (0.02 to 0.02)	0.09 (0.09 to 0.10)	0.04 (0.04 to 0.05)
2014	0.02 (0.02 to 0.02)	0.11 (0.10 to 0.12)	0.05 (0.05 to 0.05)
2015	--	--	--

Table S5. Medications approved by the Food and Drug Administration (FDA) for the treatment of ADHD.[a]

Preparation	FDA approved age (years)	Dose range (mg)	Form	Approximate duration of response (h) [b]
STIMULANTS				
Amphetamines				
Mixed amphetamine salts	≥ *3*	*3-5 years: 2.5-not specified; ≥ 6 years: 5-40*	*Tablet*	*4-6*
Racemic amphetamine sulfate	>3	3-5 years: 2.5-not specified; ≥ 6 years: 5-40	Tablet	4-6
Dextroamphetamine sulfate	≥ *3*	3-5 *years*: 2.5-not specified; ≥ 6 *years*: 5-40	*Tablet/solution*	*4-6*
Racemic amphetamine sulfate ODT	6-17	5-40	Tablet	10
Methamphetamine	≥ 6	5-25	Tablet	Not reported

Dextroamphetamine sulfate extended-release	6-16	5-40	Capsule	Not reported
Mixed amphetamine salts extended-release	≥ 6	6-17 years: 10 (max 30 in 6-12 years old); adults: 20	Capsule	12
Extended-release 1) XR-OS and 2) XR-ODT	≥ 6	6-12 years: 6.3-18.8; 13-17 years: 6.3-12.5 adults:12.5	1) Suspension 2) Tablet	12 [c]
Lisdexamfetamine	≥ 6	30-70	Capsule Chewable tablet	13
Extended-release EROS	≥ 6	2.5-20	Suspension	13

Tripled bead mixed amphetamine salts extended-release	≥ 13	13-17 years: 12.5-25; adults: 12.5-50	Capsule	16
Methylphenidate				
Immediate release	≥ 6	10-60	Tablet	4
Immediate release [d]	≥ 6	10-60	Solution	Not reported
Dexmethylphenidate	Not stated [e]	5-20	Tablet	4
Extended-release	≥ 6	10-60	Tablet	8
Extended-release	≥ 6	20-60	Chewable tablet	8
Extended release (long-acting)	6-12	20-60	Capsule	8
Controlled delivery	≥ 6	20-60	Capsule	8

Transdermal system	6-17	10-30	Patch	Depends on wear time (max 9) [f]
Delayed-release and extended-release	≥ 6	20-100	Capsule	11 [g]
Osmotic-release oral system (OROS)	≥ 6 and ≤ 65	Children: 18-54; adolescents: 18-72 adults: 18 or 36-72	Tablet	12
Extended-release, ODT	6-17	17.3-51.8	Tablet	12
Extended-release	≥ 6	20-60	Suspension	12
Dexmethylphenidate extended release	Not stated [e]	Pediatric patients: 5-30; adults: 10-40	Capsule	12
Multilayer extended-release (*Aptensio XR ®)*	≥ 6	10-60	Capsule	12
Multilayer extended-release (*Adhansia XR* ®)	≥ 6	Pediatric patients: 25-70; adults: 25-85	Capsule	13-16
NON-STIMULANTS				

Atomoxetine	≥ 6	Children/adolescents < 70 Kg: 0.5-1.4 mg/kg Children/adolescents >70 Kg and adults: 40-100 mg	Capsule	24
Extended-release clonidine	6-17	0.1-0.4 mg/day	Tablet	Not reported
Extended-release guanfacine	6-17	1-7 mg	Tablet	24

[a] *As to April 1, 2020, under a New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) (in italics compounds available only as ANDA, with data from corresponding NDA), retrieved from https://www.accessdata.fda.gov/scripts/cder/daf/. Compounds listed as "discontinued" are not included in the table* [b] *Additional details on the duration of response are provided in Section 4;* [c] *Value reported for* XR-ODT; [d] *Available also as chewable tablet (ANDA);* [e] *According to the package insert,* safety and effectiveness in patients < 6 years have not been established [f] *Response may persist for 2-3 hours after patch removal;* [g] After delayed onset (10-12 hr post dose)

The range of available preparations of amphetamines and methylphenidate allows prescribers to tailor the onset and duration of response as well as the type of formulation to the specific needs of the patient

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