JAMA Clinical Evidence Synopsis

Methylphenidate for Attention-Deficit/Hyperactivity Disorder in Children and Adolescents

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CLINICAL QUESTION Is treatment with methylphenidate associated with benefits or harms for children and adolescents with attention-deficit/hyperactivity disorder (ADHD)?

BOTTOM LINE Methylphenidate is associated with improvement in ADHD symptoms, general behavior, and quality of life; however, due to the very low quality of the evidence, the magnitude of the associated improvement is uncertain. Methylphenidate was associated with an increased risk of nonserious adverse events. There are too few data to assess the association with serious adverse events.

This JAMA Clinical Evidence Synopsis summarizes a Cochrane review[1] that assessed the use of methylphenidate for children and adolescents with ADHD. This disorder affects 3.4% of children and adolescents wordwide.[2] It is characterized by inattention, hyperactivity-impulsivity, or both, which impairs functioning or development in children before 12 years of age.[3,4] Methylphenidate is commonly prescribed for ADHD.[5]

Summary of Findings

Methylphenidate was associated with improved teacher-rated ADHD symptoms (standardized mean difference [SMD], −0.77 [95% CI, −0.90 to −0.64] in 19 trials with 1698 participants; **Figure**). This corresponds to a mean difference (MD) of −9.6 points (95% CI, −13.75 to −6.38 points) on an ADHD rating scale (point range, 0 to 72). Methylphenidate was not associated with increases in serious adverse events (risk ratio [RR], 0.98 [95% CI, 0.44 to 2.22] in 9 trials with 1532 participants); however, only a few trials evaluated this association. Methylphenidate was associated with improved teacher-rated general behavior (SMD, −0.87 [95% CI, −1.04 to −0.71] in 5 trials with 668 participants). This corresponds to an MD of 5.0 on the Conners Global Index scale (point range, 0 to 30). Methylphenidate was associated with improved parent-reported quality of life (SMD, 0.61 [95% CI, 0.42 to 0.80] in 3 trials with 514 participants). This corresponds to an MD of 8.0 points (95% CI, 5.49 to 10.46 points) on the Child Health Questionnaire (point range, 0 to 100).[1,6]

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Methylphenidate was associated with an increased risk of nonserious adverse events (RR, 1.29 [95% CI, 1.10-1.51] in 21 trials with 3132 participants); there were events in 52.6% of the methylphenidate group vs 40.8% of the control group. The most common nonserious adverse events were sleep problems, such as difficulty falling asleep (RR, 1.60 [95% CI, 1.15-2.23] in 13 trials with 2416 participants; there were events in 6% of the methylphenidate group vs 3.9% of the control group) and decreased appetite (RR, 3.66 [95% CI, 2.56-5.23] in 16 trials with 2962 participants; there were events in 19% of the methylphenidate group vs 5.6% of the control group). All evidence was assessed as very low quality by the Grading of Recommendations Assessment, Development and Evaluation due to high risk of bias, imprecision, and heterogeneity.[1,6]

Discussion

Methylphenidate was associated with improved teacher-reported symptoms of ADHD and general behavior and parent-reported quality of life. However, given the risk of bias in the included trials, and the low quality of evidence, the magnitude of improvement is uncertain. Methylphenidate is associated with an increased risk of nonserious adverse events. There are too few data to assess the association with serious adverse events.

Limitations

This report has several limitations, including the potential for unblinding because methylphenidate is associated with easily recognizable adverse effects, outcome reporting bias, heterogeneity, and low quality

Evidence Profile

No. of randomized controlled trials: 38 parallel-group trials and 147 cross-over trials

Study years: Published from 1981-2014 (most recent study conducted in 2012)

No. of participants: 12 245

Male sex: 8808 (79%) **Female sex:** 2376 (21%); 172 trials reported sex for 11 184 participants

Race/ethnicity: Not reported

Age, mean (range): 9.7 years (3-21 years)

Settings: Outpatient clinics, classroom setting, research unit at a hospital, summer treatment program, in-patient wards, and laboratory classroom setting

Countries: United States, Canada, United Kingdom, Australia, Brazil, Israel, Germany, Sweden, New Zealand, Norway, and the Netherlands

Comparison: Placebo (175 trials) or no intervention (10 trials)

Primary outcomes: ADHD symptoms and serious adverse events (life threatening)

Secondary outcomes: Nonserious adverse events, general behavior, quality of life

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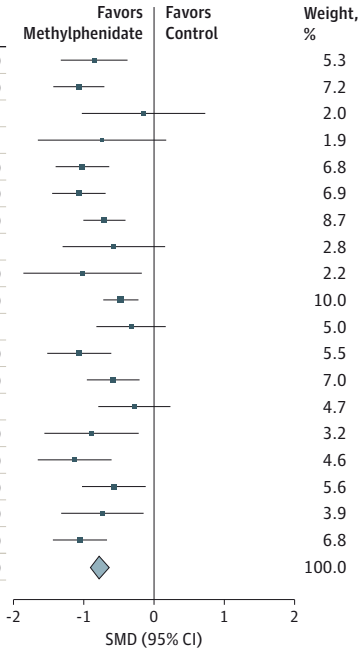
Figure. Teacher-Rated Attention-Deficit/Hyperactivity Disorder (ADHD) Symptoms

Studies With High Risk of Bias	Methylphenidate: Total No. of Participants	Methylphenidate: Teacher-Rated ADHD Symptoms, Mean (SD)	Control: Total No. of Participants	Control: Teacher-Rated ADHD Symptoms, Mean (SD)	Teacher-Rated ADHD Symptoms, SMD (95% CI)	Weight, %
Arnold 2004	35	0.7 (0.7)	40	1.4 (0.9)	-0.85 (-1.33 to -0.38)	5.3
Biederman 2003	63	16.3 (12.1)	71	31.3 (15.4)	-1.07 (-1.43 to -0.71)	7.2
Brown 1985	10	15.1 (4.6)	10	15.7 (2.9)	-0.15 (-1.03 to 0.73)	2.0
Butter 1983	10	30.5 (17.3)	10	42.7 (14.2)	-0.74 (-1.65 to 0.17)	1.9
Childress 2009	57	16.4 (13.4)	63	30.0 (13.1)	-1.02 (-1.40 to -0.64)	6.8
Findling 2006	120	4.3 (3.2)	39	7.7 (3.1)	-1.07 (-1.45 to -0.69)	6.9
Findling 2008	94	18.3 (17.4)	88	31.6 (20.1)	-0.71 (-1.01 to -0.41)	8.7
Firestone 1981	18	8.9 (4.9)	13	11.8 (4.8)	-0.57 (-1.30 to 0.16)	2.8
Ialongo 1994	13	7.5 (7.4)	12	15.3 (7.3)	-1.02 (-1.86 to -0.17)	2.2
Jensen 1999 (MTA)	134	0.8 (0.7)	119	1.1 (0.8)	-0.47 (-0.72 to -0.22)	10.0
Kollins 2006 (PATS)	32	1.1 (0.8)	32	1.4 (0.8)	-0.33 (-0.82 to 0.17)	5.0
Lehmkuhl 2002	43	0.9 (0.7)	42	1.6 (0.6)	-1.06 (-1.52 to -0.61)	5.5
Moshe 2012	57	58.0 (10.3)	57	64.7 (12.5)	-0.58 (-0.96 to -0.21)	7.0
Palumbo 2008	29	-5.1 (6.8)	30	-3.2 (6.4)	-0.28 (-0.79 to 0.23)	4.7
Pliszka 2000	20	0.8 (0.6)	18	1.5 (0.9)	-0.89 (-1.56 to -0.22)	3.2
Schachar 1997	37	0.9 (0.7)	29	1.7 (0.7)	-1.13 (-1.65 to -0.60)	4.6
Taylor 1987	39	0.5 (1.0)	39	1.2 (1.3)	-0.57 (-1.03 to -0.12)	5.6
Van der Meere 1999	24	73.6 (12.7)	24	83.1 (12.7)	-0.73 (-1.32 to -0.15)	3.9
Wolraich 2001	81	5.7 (3.8)	46	9.9 (4.1)	-1.05 (-1.44 to -0.67)	6.8
Total (95% CI)	916		782		-0.77 (-0.90 to -0.64)	100.0

Heterogeneity: $\tau^2 = 0.03$; $\chi^2_{18} = 28.78$; $P = .05$; $I^2 = 37\%$

Test for overall effect: $z = 11.23$; $P < .001$



The trials were assessed as high risk of bias due to vested interest (eg, industry sponsorship or potential conflicts of interest were reported by trial authors), lack of blinding of participants, lack of outcome assessor blinding, selective outcome reporting, or selection bias. Some but not all bias risks were present in most trials. The size of the data markers indicates the weight of the study. SMD indicates standardized mean difference.

of evidence of the included trials. Methylphenidate was not associated with an increase in serious adverse events, but the analysis lacked statistical power. The median duration of drug treatment was less than 2 months and few trials had a treatment duration greater than 6 months. Therefore, conclusions cannot be made regarding the benefits and harms of methylphenidate for less than or more than 6-month follow-up because of the very low quality of evidence in the included trials.

Comparison of Findings With Current Practice Guidelines

Guidelines from the National Institute for Health and Care Excellence, the clinical practice guideline for the Diagnosis, Evaluation, and Treatment of Attention-Deficit/Hyperactivity Disorder in Children and Adolescents, and other guidelines recommend methylphenidate for children and adolescents with ADHD.[5,7] The findings from our review suggest that the recommendations in these guidelines should be reevaluated because of the very low quality of evidence in the included trials.

Areas in Need of Future Study

Randomized nocebo tablet (active placebo)-controlled high-quality clinical trials with longer follow-up are necessary. We recommend that nocebo-controlled trials should be conducted first in adults with ADHD.

ARTICLE INFORMATION

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REFERENCES

1. Storebø OJ, Ramstad E, Krogh HB, et al. Methylphenidate for children and adolescents with attention deficit hyperactivity disorder (ADHD). *Cochrane Database Syst Rev*. 2015;11(11):CD009885.

2. Polanczyk GV, Salum GA, Sugaya LS, et al. Annual research review. *J Child Psychol Psychiatry*. 2015;56(3):345-365.

3. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. Arlington, VA: American Psychiatric Association; 2013.

4. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva, Switzerland: World Health Organization; 1992.

5. National Institute for Health and Care Excellence. Attention deficit hyperactivity disorder. https://www.nice.org.uk/guidance/cg72. Accessed March 31, 2016.

6. Storebø OJ, Krogh HB, Ramstad E, et al. Methylphenidate for attention-deficit/hyperactivity disorder in children and adolescents. *BMJ*. 2015;351:h5203.

7. Wolraich M, Brown L, Brown RT, et al. ADHD. *Pediatrics*. 2011;128(5):1007-1022.

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