mnhd *Movement and Nutrition in Health and Disease*

Methylphenidate benefits and harms in children and adolescents with attention deficit/hyperactivity disorder: Two Cochrane systematic reviews

| Review

Ole Jakob Storebø[1,2], Erik Simonsen[1,3], Christian Gluud[4]

[1] Psychiatric Research Unit, Region Zealand Psychiatry, Slagelse, Denmark

[2] Department of Psychology, University of Southern Denmark, Odense, Denmark

[3] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Denmark

[4] Copenhagen Trial Unit, Centre for Clinical Intervention Research, Rigshospitalet, Copenhagen University Hospital, Copenhagen, Denmark

E-mail: ojst@regionsjaelland.dk

Received 23 May 2019; Accepted 9 June 2019; Published 26 June 2019

Abstract: The evidence regarding the benefits and harms of methylphenidate in children and adolescents with ADHD remains inconclusive. Between 2012 and 2018, we conducted two Cochrane systematic reviews on methylphenidate for ADHD. All procedures, such as searches, data extraction and quality assessment followed Cochrane guidelines. The first review included 185 randomised clinical trials. We observed possible beneficial effects of methylphenidate versus placebo or no-intervention, but methodological flaws, such as lack of blinding, outcome reporting bias and heterogeneity, prevented the effective evaluation of the magnitude of intervention effects. The meta-analysis of serious adverse events was considerably underpowered to identify a difference in these events, preventing the drawing of firm conclusions. Methylphenidate increased the risk of non-serious adverse events, with the most common events being appetite suppression and difficulty sleeping. This review has been heavily exposed in many critical articles and editorials. We have rebutted the criticism and have shown that the evidence base for the use of methylphenidate for children and adolescents is indeed flawed. The second review included 260 non-randomised studies, with over 2.2 million participants. Methylphenidate significantly increased the risk of serious adverse events compared to no-intervention. More than 50% of the participants treated with methylphenidate experienced one or more adverse events considered to be non-serious. Our comprehensive reviews of methylphenidate in children and adolescents with ADHD indicate that much of the ADHD research to date is seriously undermined by avoidable methodological flaws that could lead to an overestimation of benefits and an underestimation of harms of methylphenidate.

Keywords: Attention-deficit/hyperactivity disorder; methylphenidate; Cochrane systematic review; meta-analyses.

1. Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a common childhood psychiatric disorder with estimated global prevalence rates between 3% and 5%, depending on the classification used [1,2]. ADHD is characterised by a persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development [3]. Children, adolescents and adults with ADHD are at increased risk of a broad spectrum of co-

occurring conditions [4,5], which frequently result in negative outcomes later in life [5,6].

For more than 60 years, methylphenidate has been recommended as the first-choice pharmacological treatment for ADHD in many countries [7,8]. However, recent reviews reveal a weak evidence base for the use of methylphenidate in children and adolescents with ADHD due to lack of assessment of trial quality, risk of bias, risk of random errors and insufficient reporting of adverse events [9−18].

The evidence regarding the benefits and harms of methylphenidate in children and adolescents with ADHD remains inconclusive. In 2015 and 2018, we published two Cochrane systematic reviews on methylphenidate in ADHD, one based on benefits and harms in randomised clinical trials and the other based on harms in observational studies [19,20].

2. The Cochrane systematic review of randomised clinical trials

The review [19] included 185 randomised clinical trials, with a mean participant age of 9.7 years, a median treatment duration of 49 days (range 1 to 425) in 147 crossover trials, and a median of 14 days (range 1 to 56) in 38 parallel group trials. We observed possible beneficial effects of methylphenidate versus placebo or no-intervention on teacher-rated symptoms (SMD -0.78; 95% CI -0.92 to -0.64; 19 trials; n=1,698), general behaviour (SMD -0.87; 95% CI -1.04 to -0.71; 5 trials; n=668), and quality of life (SMD 0.61; 95% CI 0.42 to 0.80; 3 trials; n=514). However, all included trials were at high risk of bias using Cochrane standards, and the GRADE evidence certainty was rated very low on all outcomes.

Methodological flaws, such as lack of blinding, outcome reporting bias and heterogeneity, prevented the effective evaluation of the magnitude of intervention effects. The median duration of drug treatment was less than two months, and therefore the long-term benefits of methylphenidate in children and adolescents remain unclear.

Methylphenidate did not seem to increase serious adverse events in the randomised clinical trials (risk ratio 0.98; 95% CI 0.44 to 2.22; 9 trials; n=1,532). The Trial Sequential Analysis-adjusted confidence interval was, however, 0.02 to 33.2. The meta-analysis of serious adverse events was considerably underpowered to identify a difference in these events, preventing the drawing of firm conclusions.

Methylphenidate increased the risk of adverse events considered to be non-serious (risk ratio 1.29; 95 CI 1.10 to 1.51; 21 trials; n=3,132), with the most common events being appetite suppression and difficulty sleeping.

Our review has been heavily exposed in many critical articles and editorials [21−29]. We have rebutted the criticism and have shown that the evidence base for the use of methylphenidate for children and adolescents is indeed flawed [30–36].

3. The Cochrane systematic review of non-randomised studies

Together with other authors, we have also conducted a Cochrane systematic review on the adverse events of methylphenidate in ADHD in non-randomised studies [20].

Non-randomised studies are of limited use in establishing benefits, but appear more reliable in establishing harms. Since authors tend to distance themselves from adverse events [37], it is likely that their descriptions of such effects are reliable. Our Cochrane review included 260 non-randomised studies: four patient-controlled studies, seven comparative cohort studies, 177 cohort studies, two cross-sectional studies, and 70 patient reports, with over 2.2 million participants. The studies lasted between one day and 11 years. We searched all relevant databases using a very broad search strategy. We did not limit our searches by language, year of publication, or type of publication. We contacted experts in the field and pharmaceutical companies for published and unpublished data and checked reference lists for relevant reviews, meta-analyses, and additional studies. Finally, we searched for unpublished data on the websites of the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) [20]. Quality assessment of the included studies, including risk of bias ratings, followed the Cochrane Collaboration's guidelines [20].

In contrast to our former review of randomised clinical trials [19], methylphenidate significantly increased the risk of serious adverse events in comparative studies, compared to no-intervention (risk ratio 1.36; 95% CI 1.17 to 1.58; 2 studies; n=72,005). Furthermore, 1.2% (95% CI 0.60% to 2.30%, 7 studies; n=1,173) of the participants discontinued methylphenidate due to serious adverse events. Moreover, another 7.30% (95% CI 5.30% to 10.0%; 22 studies; n=3,708) of the participants discontinued the drug due to adverse events of "unknown seriousness".

The meaning of unknown seriousness and whether such harms are serious or non-serious is unclear.

Regarding non-serious adverse events, 51.2% (41.2% to 61.1%; 49 studies; n=13,978) of the participants treated with methylphenidate experienced one or more adverse events considered to be non-serious. These included sleep difficulties (17.9%); abdominal pain (10.7%); decreased appetite (31.1%); anxiety (18.4%); and sadness (16.8%). Furthermore, 16.2% (95% CI 13.0% to 19.9%; 57 studies; n=8,340) discontinued methylphenidate due to 'unknown' reasons and another 6.20% (4.90% to 8.00%; 37 studies; n=7,142) due to non-serious adverse events. Many studies were excluded due to missing data on adverse events, despite considerable efforts to contact the study authors (we reached out to 171 authors, and received responses from 109 of them).

According to GRADE, all outcomes had low certainty of evidence. The low-certainty evidence can partly be explained by methodological issues with non-randomised studies: many do not employ control interventions, and their observational nature leads to confounding variables that would otherwise be corrected for in randomised clinical trials. Nonetheless, non-randomised studies may be preferable in assessing rare and late occurring adverse events, because randomised clinical trials are often underpowered to detect such events; they may only occur after longer duration of methylphenidate administration; and they may be subject to distorted and insufficient reporting [38]. Non-randomised studies can be much larger and can follow patients for considerably longer periods compared to randomised clinical trials, allowing for detection of rare and late adverse events [20].

Subgroup analyses suggested that adverse events considered non-serious and observed in the non-randomised studies were not dependent on comorbidity, age of participants, dose or duration of methylphenidate administration or study design [20].

4. Discussion

In August 2018, a network meta-analysis on drug-treatment of ADHD was published [38]. The study was sponsored by Eunethydis, a European network of ADHD-researchers connected to the European ADHD guidelines group, and was authored by many of the same researchers who criticised our Cochrane review published in 2015 [38]. Network meta-analyses integrate networks of direct and indirect comparisons of interventions, and allows for treatment comparisons that have not been directly compared in a clinical trial [39].

This publication was a systematic review with network-meta-analysis of 133 RCTs considering tolerability and efficacy of drug treatment for ADHD using clinician-rated symptoms as primary outcome in children and adults. The network analysis wished to study the effects of administration of medication for 12, 26, and 52 weeks, but, in the absence of sufficient data, restricted the analysis to a period of 12 weeks. The authors concluded that there is good evidence for using methylphenidate in children/adolescents, and that this should be the first pharmacological choice for ADHD for a treatment-period of 12 weeks [38]. A drawback of this study is that few adverse events were assessed. The severity of the reported harm measures on tolerability and acceptability is difficult to interpret because of the dichotomous nature of the data. Additional assessment of serious and non-serious adverse events would have been informative. Furthermore, the study excluded potentially valuable studies to limit risk of bias and statistical and methodological assumptions might have increased the risks of selection bias. A further risk of bias in this analysis is that the participants in the medication groups could have been subject to systematic unblinding, given the known adverse events of ADHD medications compared with placebo interventions [21,40].

The authors of this network meta-analysis asserted that their findings were in line with the NICE guidelines. A closer look at the NICE guideline [7], however, reveals several problems. Strong clinical practice recommendations for the ADHD medications are informed by studies with low certainty of evidence and the guideline itself includes serious methodological limitations, including selective reporting, inadequate adjustments for multiple comparisons, and short-term data [40,41]. Another network meta-analysis on the efficacy and safety of drugs for ADHD in children and adolescents published in 2018 suffered from several methodological shortcomings, such as selection bias and erratic quality assessment [42,43].

A further concern in respect of research on drug treatment for ADHD is the potential bias resulting from vested interests. Of 185 trials in our Cochrane review evaluating treatment-effects of methylphenidates for ADHD, nearly 40% (n=72) were funded by industry [19]. In the second Cochrane review evaluating adverse events, as many as 62% of the included studies had affiliations to industry [20]. Studies have shown that researchers funded by industry may overestimate benefits and underestimate harms [37,44].

5. Conclusions

Our comprehensive analysis of methylphenidate in children and adolescents with ADHD [19,20] indicates that much of the ADHD research to date is seriously undermined by avoidable methodological flaws, which could lead to an overestimation of benefits and an underestimation of harms of methylphenidate. Our systematic review of non-randomised studies helps shed light on the long-term safety profile of the drug [20]. Before physicians commence patients on methylphenidate administration, they should inform them and their parents of the uncertainty surrounding evidence of benefits and risks associated with the drug. More well-powered, methodologically sound, and better reported randomised clinical trials are needed. Blinding (through use of active placebo to control for the adverse events typically occurring with methylphenidate administration), *a priori* published trial protocols that reduce publication bias, and action to reduce vested interests should be secured. Non-randomised studies can be advantageous for assessing rare and late adverse events, until these potential harms are evaluated in well-designed, adequately blinded randomised clinical trials.

Acknowledgements

We thank our co-authors Helle B. Krogh, Erica Ramstad, Nadia Pedersen, Maja Lærke Kielsholm, Signe Sofie Nielsen, Carlos R. Moreira-Maia, Frederik L. Magnusson, Mathilde Holmskov, Trine Danvad Nilausen, Maria Skoog, Susanne Rosendal, Camilla Groth, Donna Gillies, Kirsten Buch Rasmussen, Dorothy Gauci, Richard Kirubakaran, Sasja J. Håkonsen, and Lise Aagaard for invaluable help in conducting our two Cochrane systematic reviews [19,20].

Funding

This study received funding from Region Zealand Research Foundation, Psychiatric Research Unit, Region Zealand Psychiatry, Roskilde, Denmark, and the Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Copenhagen, Denmark.

Conflict of interest

All authors declare no competing interest.

References

1 Schahill L, Schwab-Stone M. Epidemiology of ADHD in school-age children. Child Adolesc Psychiatr Clin N Am 2000; 9: 541−555.

2 Polanczyk G, Rohde. Epidemiology of attention-deficit/hyperactivity disorder across the lifespan. Curr Opin Psychiatry 2007; 20: 386−392.

3 American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). 5th Edition. Washington, DC: American Psychiatric Association, 2013.

4 Newcorn JH. Co-morbidity in adults with ADHD. CNS Spectrums 2008; 13 (Suppl 12): 12−15.

5 Schmidt S, Petermann F. Developmental psychopathology: attention deficit hyperactivity disorder (ADHD). BMC Psychiatry 2009; 9: 58.

6 Jensen PS, Hinshaw SP, Kraemer HC, et al. ADHD comorbidity findings from the MTA study: comparing comorbid subgroups. J Am Acad Child Adolesc Psychiatry 2001; 40: 147−158.

7 NICE. Attention deficit hyperactivity disorder: diagnosis and management (NG87). National Institute for Health and Care Excellence, 2018. Available: nice.org.uk/guidance/ng87. Accessed August 28, 2018.

8 Trip AM, Visser ST, Kalverdijk LJ, de Jong-van den Berg LT. Large increase of the use of psycho-stimulants among youth in the Netherlands between 1996 and 2006. Br J Clin Pharmacol 2009; 67: 466−468.

9 Bloch MH, Panza KE, Landeros-Weisenberger A, Leckman JF. Meta-analysis: treatment of attention-deficit/ hyperactivity disorder in children with comorbid tic disorders. J Am Acad Child Adolesc Psychiatry 2009; 48: 884−893.

10 Charach A, Carson P, Fox S, Ali MU, Beckett J, Lim CG. Interventions for preschool children at high risk for ADHD: a comparative effectiveness review. Pediatrics 2013; 131: e1584−e1604.

11 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: 468−473.

12 Faraone SV, Biederman J, Spencer TJ, Aleardi M. Comparing the efficacy of medications for ADHD using meta-analysis. MedGenMed 2006; 8: 4.

13 Faraone SV. Using meta-analysis to compare the efficacy of medications for attention-deficit/hyperactivity disorder in youths. P T 2009; 34: 678−694.

14 Faraone SV, Glatt SJ. A comparison of the efficacy of medications for adult attention-deficit/hyperactivity disorder using meta-analysis of effect sizes. J Clin Psychiatry 2010; 71: 754−763.

15 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.

16 Kambeitz J, Romanos M, Ettinger U. Meta-analysis of the association between dopamine transporter genotype and response to methylphenidate treatment in ADHD. Pharmacogenomics J 2014; 14: 77−84.

17 King S, Griffin S, Hodges Z, et al. A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents. Health Technol Assess 2006; 10: iii-iv, xiii-146.

18 Maia CR, Cortese S, Caye A, et al. Long-term efficacy of methylphenidate immediate-release for the treatment of childhood ADHD: a systematic review and meta-analysis. J Atten Disord 2017; 21: 3–13.

19 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: CD009885.

20 Storebø O, Pedersen N, Ramstad E, et al. Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents − assessment of adverse events in non-randomised studies. Cochrane Database Syst Rev 2018; 5: CD012069.

21 Shaw P. Quantifying the benefits and risks of methylphenidate as treatment for childhood attention-deficit/hyperactivity disorder. JAMA 2016; 315: 1953−1955.

22 Romanos M, Reif A, Banaschewski T. Methylphenidate for attention-deficit/hyperactivity disorder. JAMA 2016; 316: 994−995.

23 Levy F. Methylphenidate for attention-deficit/ hyperactivity disorder: the longest debate. Aust N Z J Psychiatry 2016; 50: 616–617.

24 Hoekstra PJ, Buitelaar JK. Is the evidence base of methylphenidate for children and adolescents with attention-deficit/hyperactivity disorder flawed? Eur Child Adolesc Psychiatry 2016; 25: 339–340.

25 Banaschewski T, Gerlach M, Becker K, et al. Trust, but verify. The errors and misinterpretations in the Cochrane analysis by O. J. Storebo and colleagues on the efficacy and safety of methylphenidate for the treatment of children and adolescents with ADHD. Z Kinder Jugendpsychiatr Psychother 2016; 44: 307−314.

26 Banaschewski T, Buitelaar J, Chui CSL, et al. Methylphenidate for ADHD in children and adolescents: throwing the baby out with the bathwater. Evid Based Ment Health 2016; 19: 97−99.

27 Hollis C. Re: Methylphenidate for ADHD: have Cochrane got it wrong this time? March 2016. Available: nationalelfservice.net/mental-health/adhd/ methylphenidate-for-adhd-have-cochrane-got-it-wrong-this-time/#comment-1010366. Accessed June 1, 2019.

28 Swanson J. Risk-of-bias and quality-of-evidence for treatment of ADHD with stimulant medication. Clin Pharmacol Ther 2018; 104: 638–643.

29 Cortese S. Are the effects of methylphenidate uncertain? Ir J Psychol Med 2018; 35: 163–167.

30 Storebø OJ, Gluud C. Re: Methylphenidate for ADHD: have Cochrane got it wrong this time? Response to: Chris Hollis (Has Chris Hollis got it wrong again this time?). March 2016. Available: nationalelfservice.net/mental-health/adhd/methylphenidate-for-adhd-have-cochrane-got-it-wrong-this-time/#comment-1002564. Accessed June 1, 2019.

31 Storebø OJ, Simonsen E, Gluud C. Methylphenidate for attention-deficit/hyperactivity disorder − Reply. JAMA 2016; 316: 995.

32 Storebø OJ, Simonsen E, Gluud C. The evidence base of methylphenidate for children and adolescents with attention-deficit hyperactivity disorder is in fact flawed. Eur Child Adolesc Psychiatry 2016; 25: 1037–1038.

33 Storebø OJ, Zwi M, Moreira-Maia CR, et al. Response to "Trust, but verify" by Banaschewski et al. Z Kinder Jugendpsychiatr Psychotherap 2016; 44: 334−335.

34 Storebø OJ, Gluud C. Re: Trust, but verify. The errors and misinterpretations in the Cochrane analysis by O. J. Storebo and colleagues on the efficacy and safety of methylphenidate for the treatment of children and adolescents with ADHD [personal communication]. Response to: T BanaschewskI, M Gerlach, K Becker, M Holtmann, M Döpfner, M Romanos. June 24, 2016.

35 Storebø OJ, Zwi M, Krogh HB, et al. Evidence on methylphenidate in children and adolescents with ADHD is in fact of 'very low quality'. Evid Based Ment Health 2016; 19: 100−102.

36 Storebø OJ, Faltinsen E, Zwi M, et al. The jury is still out on the benefits and harms of methylphenidate for children and adolescents with attention deficit hyperactivity disorder. Clin Pharmacol Ther 2018; 104: 606–609.

37 Ioannidis JP. Adverse events in randomized trials: neglected, restricted, distorted, and silenced. Arch Intern Med 2009; 169: 1737–1739.

38 Cortese S, Adamo N, Giovane CD, et al. Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents and adults: a systematic review and network meta-analysis. Lancet Psychiatry 2018; 5: 727−738.

39 Faltinsen EG, Storebø OJ, Jakobsen JC, Boesen K, Lange T, Gluud C. Network meta-analysis: the highest level of medical evidence? BMJ Evid Based Med 2018; 23: 56−59.

40 Faltinsen EG, Gluud C, Simonsen E, Zwi M, Storebø OJ. Unbalanced risk-benefit analysis of ADHD drugs. Lancet Psychiatry 2018; 5: 870.

41 Faltinsen E, Zwi M, Castells X, Gluud C, Simonsen E, Storebø OJ. Updated 2018 NICE guideline on pharmacological treatments for people with ADHD: a critical look. BMJ Evid Based Med 2019; 24: 99–102.

42 Padilha SCOS, Virtuoso S, Tonin FS, Borba HHL, Pontarolo R. Efficacy and safety of drugs for attention deficit hyperactivity disorder in children and adolescents: a network meta-analysis. Eur Child Adolesc Psychiatry 2018; 27: 1335–1345.

43 Faltinsen EG, Storebø OJ, Gluud C. Methodological concerns with network meta-analysis on drugs for attention deficit hyperactivity disorder. Eur Child Adolesc Psychiatry 2019; 28: 145–146.

44 Lundh A, Lexchin J, Mintzes B, Schroll JB, Bero L. Industry sponsorship and research outcome. Cochrane Database Syst Rev 2017; 2: MR000033.