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Cochrane Database of Systematic Reviews 2017, Issue 11. Art. No.: CD011144.
DOI: 10.1002/14651858.CD011144.pub2.

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[Intervention Review]

Methylphenidate for children and adolescents with autism spectrum disorder

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Editorial group: Cochrane Developmental, Psychosocial and Learning Problems Group
Publication status and date: New, published in Issue 11, 2017.

Citation: Sturman N, Deckx L, van Driel ML. Methylphenidate for children and adolescents with autism spectrum disorder. *Cochrane Database of Systematic Reviews* 2017, Issue 11. Art. No.: CD011144. DOI: 10.1002/14651858.CD011144.pub2.

ABSTRACT

Background

Children with autistic spectrum disorder (ASD) frequently present with inattention, impulsivity and hyperactivity, which are the cardinal symptoms of attention deficit hyperactivity disorder (ADHD). The effectiveness of methylphenidate, a commonly used ADHD treatment, is therefore of interest in these children.

Objectives

To assess the effects of methylphenidate for symptoms of ADHD (inattention, impulsivity and hyperactivity) and ASD (impairments in social interaction and communication, and repetitive, restricted or stereotypical behaviours) in children and adolescents aged 6 to 18 years with ASD.

Search methods

In November 2016, we searched CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL, 11 other databases and two trials registers. We also checked reference lists and contacted study authors and pharmaceutical companies.

Selection criteria

Randomised controlled trials (RCTs) that investigated the effect of methylphenidate versus placebo on the core symptoms of ASD or ADHD-like symptoms, or both, in children aged 6 to 18 years who were diagnosed with ASD or pervasive developmental disorder. The primary outcome was clinical efficacy, defined as an improvement in ADHD-like symptoms (inattention, impulsivity and hyperactivity) and in the core symptoms of ASD (impaired social interaction, impaired communication, and stereotypical behaviours), and overall ASD. Secondary outcomes examined were: rate of adverse events; caregiver well-being; need for institutionalisation, special schooling or therapy to achieve learning outcomes; and overall quality of life.

Data collection and analysis

We used standard Cochrane methodological procedures. We combined outcome measures that used different psychometric scales, where clinically appropriate. We used a coefficient of 0.6 to calculate standard deviations and adjust for the studies' cross-over design. We considered a standardised mean difference (SMD) of 0.52 as the minimum clinically relevant inter-treatment difference. We applied the GRADE rating for strength of evidence for each outcome.

Main results

The studies: we included four cross-over studies, with a total of 113 children aged 5 to 13 years, most of whom (83%) were boys. We included two studies with five-year-old children since we were unable to obtain the disaggregated data for those aged six years and above,

and all other participants were in our target age range. All participants resided in the USA. The duration of treatment in the cross-over phase was one week for each dose of methylphenidate. Studies used a range of outcome scales, rated by parents, teachers or both; clinicians; or programme staff. We report parent-rated outcomes separately.

Risk of bias: we considered three trials to be at high risk of bias due to selective reporting and all trials to be at unclear risk of bias for blinding of participants and assessors, due to the potential for recognising the side effects of methylphenidate. We judged all trials to be at low or unclear risk of bias for other items.

Primary outcomes: the meta-analysis suggested that high-dose methylphenidate (0.43 mg/kg/dose to 0.60 mg/kg/dose) had a significant and clinically relevant benefit on hyperactivity, as rated by teachers (SMD −0.78, 95% confidence interval (CI) −1.13 to −0.43; 4 studies, 73 participants; P < 0.001; low-quality evidence) and parents (mean difference (MD) −6.61 points, 95% CI −12.19 to −1.03, rated on the hyperactivity subscale of the Aberrant Behviour Checklist, range 0 to 48; 2 studies, 71 participants; P = 0.02; low-quality evidence). Meta-analysis also showed a significant but not clinically relevant benefit on teacher-rated inattention (MD −2.72 points, 95% CI −5.37 to −0.06, rated on the inattention subscale of the Swanson, Nolan and Pelham, Fourth Version questionnaire, range 0 to 27; 2 studies, 51 participants; P = 0.04; low-quality evidence). There were inadequate data to conduct a meta-analysis on the symptom of impulsivity. There was no evidence that methylphenidate worsens the core symptoms of ASD or benefits social interaction (SMD −0.51, 95% CI −1.07 to 0.05; 3 studies, 63 participants; P = 0.07; very low-quality evidence), stereotypical behaviours (SMD −0.34, 95% CI −0.84 to 0.17; 3 studies, 69 participants; P = 0.19; low-quality evidence), or overall ASD (SMD −0.53, 95% CI −1.26 to 0.19; 2 studies, 36 participants; P = 0.15; low-quality evidence), as rated by teachers. There were inadequate data to conduct a meta-analysis on the symptom of impaired communication.

Secondary outcomes: no data were available for the secondary outcomes of caregiver well-being; need for institutionalisation, special schooling options or therapy to achieve learning outcomes; or overall quality of life. No trials reported serious adverse events. The only adverse effect that was significantly more likely with treatment was reduced appetite as rated by parents (risk ratio 8.28, 95% CI 2.57 to 26.73; 2 studies, 74 participants; P < 0.001; very low-quality evidence). Subgroup analysis by dose did not identify any significant differences in effect on our primary outcomes between low-, medium- or high-dose ranges.

Authors' conclusions

We found that short-term use of methylphenidate might improve symptoms of hyperactivity and possibly inattention in children with ASD who are tolerant of the medication, although the low quality of evidence means that we cannot be certain of the true magnitude of any effect. There was no evidence that methylphenidate has a negative impact on the core symptoms of ASD, or that it improves social interaction, stereotypical behaviours, or overall ASD. The evidence for adverse events is of very low quality because trials were short and excluded children intolerant of methylphenidate in the test-dose phase. Future RCTs should consider extending the duration of treatment and follow-up. The minimum clinically important difference also needs to be confirmed in children with ASD using outcome scales validated for this population.

PLAIN LANGUAGE SUMMARY

Effect of methylphenidate for inattentiveness, impulsivity and/or hyperactivity in children aged 6 to 18 years with autistic spectrum disorder

Children with autistic spectrum disorder (ASD) often have trouble paying attention, acting impulsively and sitting still. Methylphenidate, a stimulant drug, is often prescribed to treat children with attention deficit hyperactivity disorder (ADHD) who also have these problems, so it is important to know how well it works for children with ASD.

What is the aim of this review?

The aim of this Cochrane Review was to find out if methylphenidate is helpful for children with ASD. We collected and analysed all relevant studies to answer this question and found four studies.

Key messages

Methylphenidate may improve hyperactivity in children with ASD in the short term, although there was no evidence that methylphenidate improves or worsens ASD symptoms. Some children cannot tolerate the medication's side effects.

What was studied in the review?

We looked for studies that compared children receiving methylphenidate at any dose to placebo (a dummy pill which looks like methylphenidate but has no known effects). We were most interested in investigating the effect of the drug on symptoms of ADHD (inattention, impulsivity and hyperactivity) and ASD (impairments in social interaction and communication, and repetitive, restricted or stereotypical behaviours), but we also looked for information on side effects, caregiver well-being, the need for special schooling or institutionalisation, and children's overall quality of life.

What are the main results of the review?

We found four studies involving 113 children aged 5 to 13 years and comparing methylphenidate versus placebo. We included two studies with five-year-old children because we were unable to separate the data for those aged six years and above, and all other participants were in our target age range. In all of these studies, children took different doses of methylphenidate (low, medium or high) for one week and placebo for another week, and their caregivers (including parents, teachers and clinicians) rated their symptoms at the end of each week. Children who could not tolerate methylphenidate in the test-dose week (where a dose of medication is given to test the safety and tolerability of the drug) did not participate in the study. All of the studies took place in the USA.

We found that methylphenidate may improve hyperactivity, as assessed by parents and teachers, in the short term. Teachers also tended to report an improvement in children taking methylphenidate in relation to inattention, social interaction, repetitive behaviours, and overall ASD symptoms. However, the studies only lasted for about four weeks, so we do not know if there are any benefits or risks in the long term. There was not enough evidence to say whether methylphenidate has any effect on impulsivity or communication. Teachers and clinicians tended to report more improvement than parents.

We cannot be confident about these findings, mainly because parents and teachers may have recognised which treatment the children were on. The size of the improvement was not very large, except in the case of hyperactivity, where it was probably large enough to really notice the difference. Most of the improvements, except for the improvements in hyperactivity and inattention, could have happened by chance even if methylphenidate is not really effective. We cannot say anything about the likelihood of any harmful effects from methylphenidate, partly because children who had harmful effects prior to the studies, or in the test-dose phase, are less likely to have participated in the studies.

How up-to-date is this review?

The evidence is current to November 2016.