

# Methylphenidate for attention deficit hyperactivity disorder (ADHD) in children and adolescents - assessment of adverse events in non-randomised studies (Review)

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## ABSTRACT

### Background

Attention deficit hyperactivity disorder (ADHD) is a common neurodevelopmental disorder in childhood. The psychostimulant methylphenidate is the most frequently used medication to treat it. Several studies have investigated the benefits of methylphenidate, showing possible favourable effects on ADHD symptoms, but the true magnitude of the effect is unknown. Concerning adverse events associated with the treatment, our systematic review of randomised clinical trials (RCTs) demonstrated no increase in serious adverse events, but a high proportion of participants suffered a range of non-serious adverse events.

### Objectives

To assess the adverse events associated with methylphenidate treatment for children and adolescents with ADHD in non-randomised studies.

### Search methods

In January 2016, we searched CENTRAL, MEDLINE, Embase, PsycINFO, CINAHL, 12 other databases and two trials registers. We also checked reference lists and contacted authors and pharmaceutical companies to identify additional studies.

### Selection criteria

We included non-randomised study designs. These comprised comparative and non-comparative cohort studies, patient-control studies, patient reports/series and cross-sectional studies of methylphenidate administered at any dosage or formulation. We also included methylphenidate groups from RCTs assessing methylphenidate versus other interventions for ADHD as well as data from follow-up periods in RCTs. Participants had to have an ADHD diagnosis (from the 3rd to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders or the 9th or 10th edition of the International Classification of Diseases, with or without comorbid diagnoses. We required that at least 75% of participants had a normal intellectual capacity (intelligence quotient of more than 70 points) and were aged below 20 years. We excluded studies that used another ADHD drug as a co-intervention.

### Data collection and analysis

Fourteen review authors selected studies independently. Two review authors assessed risk of bias independently using the ROBINSI tool for assessing risk of bias in non-randomised studies of interventions. All review authors extracted data. We defined serious adverse events according to the International Committee of Harmonization as any lethal, life-threatening or life-changing event. We considered all other adverse events to be non-serious adverse events and conducted meta-analyses of data from comparative studies. We calculated meta-analytic estimates of prevalence from non-comparative cohorts studies and synthesised data from patient reports/series qualitatively. We investigated heterogeneity by conducting subgroup analyses, and we also conducted sensitivity analyses.

### Main results

We included a total of 260 studies: 7 comparative cohort studies, 6 of which compared 968 patients who were exposed to methylphenidate to 166 controls, and 1 which assessed 1224 patients that were exposed or not exposed to methylphenidate during different time periods; 4 patient-control studies (53,192 exposed to methylphenidate and

19,906 controls); 177 non-comparative cohort studies (2,207,751 participants); 2 cross-sectional studies (96 participants) and 70 patient reports/series (206 participants). Participants' ages ranged from 3 years to 20 years. Risk of bias in the included comparative studies ranged from moderate to critical, with most studies showing critical risk of bias. We evaluated all non-comparative studies at critical risk of bias. The GRADE quality rating of the evidence was very low.

#### Primary outcomes

In the comparative studies, methylphenidate increased the risk ratio (RR) of serious adverse events (RR 1.36, 95% confidence interval (CI) 1.17 to 1.57; 2 studies, 72,005 participants); any psychotic disorder (RR 1.36, 95% CI 1.17 to 1.57; 1 study, 71,771 participants); and arrhythmia (RR 1.61, 95% CI 1.48 to 1.74; 1 study, 1224 participants) compared to no intervention. In the non-comparative cohort studies, the proportion of participants on methylphenidate experiencing any serious adverse event was 1.20% (95% CI 0.70% to 2.00%; 50 studies, 162,422 participants). Withdrawal from methylphenidate due to any serious adverse events occurred in 1.20% (95% CI 0.60% to 2.30%; 7 studies, 1173 participants) and adverse events of unknown severity led to withdrawal in 7.30% of participants (95% CI 5.30% to 10.0%; 22 studies, 3708 participants).

#### Secondary outcomes

In the comparative studies, methylphenidate, compared to no intervention, increased the RR of insomnia and sleep problems (RR 2.58, 95% CI 1.24 to 5.34; 3 studies, 425 participants) and decreased appetite (RR 15.06, 95% CI 2.12 to 106.83; 1 study, 335 participants). With non-comparative cohort studies, the proportion of participants on methylphenidate with any non-serious adverse events was 51.2% (95% CI 41.2% to 61.1%; 49 studies, 13,978 participants). These included difficulty falling asleep, 17.9% (95% CI 14.7% to 21.6%; 82 studies, 11,507 participants); headache, 14.4% (95% CI 11.3% to 18.3%; 90 studies, 13,469 participants); abdominal pain, 10.7% (95% CI 8.60% to 13.3%; 79 studies, 11,750 participants); and decreased appetite, 31.1% (95% CI 26.5% to 36.2%; 84 studies, 11,594 participants). Withdrawal of methylphenidate due to non-serious adverse events occurred in 6.20% (95% CI 4.80% to 7.90%; 37 studies, 7142 participants), and 16.2% were withdrawn for unknown reasons (95% CI 13.0% to 19.9%; 57 studies, 8340 participants).

#### Authors' conclusions

Our findings suggest that methylphenidate may be associated with a number of serious adverse events as well as a large number of non-serious adverse events in children and adolescents, which often lead to withdrawal of methylphenidate. Our certainty in the evidence is very low, and accordingly, it is not possible to accurately estimate the actual risk of adverse events. It might be higher than reported here. Given the possible association between methylphenidate and the adverse events identified, it may be important to identify people who are most susceptible to adverse events. To do this we must undertake large-scale, high-quality RCTs, along with studies aimed at identifying responders and non-responders.