Stimulant and non-stimulant drug therapy for people with attention deficit hyperactivity disorder and epilepsy

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Abstract

Background: Attention Deficit Hyperactivity Disorder (ADHD) can co-occur in up to 40% of people with epilepsy. There is debate about the efficacy and tolerability of stimulant and non-stimulant drugs used to treat people with ADHD and co-occurring epilepsy.

Objectives: To assess the effect of stimulant and non-stimulant drugs on children and adults with ADHD and co-occurring epilepsy in terms of seizure frequency and drug withdrawal rates (primary objectives), as well as seizure severity, ADHD symptoms, cognitive state, general behaviour, quality of life, and adverse effects profile (secondary objectives).

Search methods: We searched the following databases on 12 October 2020: Cochrane Register of Studies (CRS Web), MEDLINE (Ovid, 1946 to 9 October 2020), CINAHL Plus (EBSCOhost, 1937 onwards). There were no language restrictions. CRS Web includes randomised or quasi-randomised controlled trials from PubMed, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Specialised Registers of Cochrane Review Groups including Epilepsy. SELECTION CRITERIA: We included randomised controlled trials of stimulant and non-stimulant drugs for people of any age, gender or ethnicity with ADHD and co-occurring epilepsy.

Data collection and analysis: We selected articles and extracted data according to predefined criteria. We conducted primary analysis on an intention-to-treat basis. We presented outcomes as risk ratios (RRs) with 95% confidence intervals (CIs), except for individual adverse effects where we quoted 99% CIs. We conducted best- and worst-case sensitivity analyses to deal with missing

data. We carried out a risk of bias assessment for each included study using the Cochrane risk of bias tool and assessed the overall certainty of evidence using the GRADE approach.

Main results: We identified two studies that matched our inclusion criteria: a USA study compared different doses of the stimulant drug osmotic-release oral system methylphenidate (OROS-MPH) with a placebo in 33 children (mean age 10.5 ± 3.0 years), and an Iranian study compared the non-stimulant drug omega-3 taken in conjunction with risperidone and usual anti-seizure medication (ASM) with risperidone and ASM only in 61 children (mean age 9.24 ± 0.15 years). All children were diagnosed with epilepsy and ADHD according to International League Against Epilepsy and Diagnostic and Statistical Manual of Mental Disorders, fourth edition, criteria, respectively. We assessed both studies to be at low risk of detection and reporting biases, but assessments varied from low to high risk of bias for all other domains. OROS-MPH No participant taking OROS-MPH experienced significant worsening of epilepsy, defined as: 1. a doubling of the highest 14-day or highest two-day seizure rate observed during the 12 months before the trial; 2. a generalised tonic-clonic seizure if none had been experienced in the previous two years; or 3. a clinically meaningful intensification in seizure duration or severity (33 participants, 1 study; low-certainty evidence). However, higher doses of OROS-MPH predicted an increased daily risk of a seizure ($P < 0.001$; 33 participants, 1 study; low-certainty evidence). OROS-MPH had a larger proportion of participants receiving 'much improved' or 'very much improved' scores for ADHD symptoms on the Clinical Global Impressions for ADHD-Improvement tool (33 participants, 1 study; low-certainty evidence). OROS-MPH also had a larger proportion of people withdrawing from treatment (RR 2.80; 95% CI 1.14 to 6.89; 33 participants, 1 study; moderate-certainty evidence). Omega-3 Omega-3 with risperidone and ASM were associated with a reduction in mean seizure frequency by 6.6 seizures per month (95% CI 4.24 to 8.96; 56 participants, 1 study; low-certainty evidence) and an increase in the proportion of people achieving 50% or greater reduction in monthly seizure frequency (RR 2.79, 95% CI 0.84 to 9.24; 56 participants, 1 study; low-certainty evidence) compared to people on risperidone and ASM alone. Omega-3 with risperidone and ASM also had a smaller proportion of people withdrawing from treatment (RR 0.65, 95% CI 0.12 to 3.59; 61 participants, 1 study; low-certainty evidence) but a larger proportion of people experiencing adverse drug events (RR 1.40, 95% CI 0.44 to 4.42; 56 participants, 1 study; low-certainty evidence) compared to people on risperidone and ASM alone.

Authors' conclusions: In children with a dual-diagnosis of epilepsy and ADHD, there is some evidence that use of the stimulant drug OROS-MPH is not associated with significant worsening of epilepsy, but higher doses of it may be associated with increased daily risk of seizures; the evidence is of low-certainty. OROS-MPH is also associated with improvement in ADHD symptoms. However, this treatment was also associated with a large proportion of treatment withdrawal compared to placebo. In relation to the non-stimulant drug omega-3, there is some evidence for reduction in seizure frequency in children who are also on risperidone and ASM, compared to children who are on risperidone and ASM alone. Evidence is inconclusive whether omega-3 increases or decreases the risk of adverse drug events. We identified only two studies - one each for OROS-MPH and omega-3 - with low to high risk of bias. We assessed the overall certainty of evidence for the outcomes of both OROS-MPH and omega-3 as low to moderate. More studies are needed. Future studies should include: 1. adult participants; 2. a wider variety of

stimulant and non-stimulant drugs, such as amphetamines and atomoxetine, respectively; and 3. additional important outcomes, such as seizure-related hospitalisations and quality of life. Clusters of studies which assess the same drug - and those that build upon the evidence base presented in this review on OROS-MPH and omega-3 - are needed to allow for meta-analysis of outcomes.

Trial registration: ClinicalTrials.gov NCT00323947.