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COCHRANE CORNER

Are stimulant and non-stimulant drugs effective and safe for treating ADHD co-occurring with epilepsy in children? A Cochrane Review summary with commentary

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The aim of this commentary is to discuss from a rehabilitation perspective the Cochrane Review 'Stimulant and non-stimulant drug therapy for people with attention deficit hyperactivity disorder and epilepsy' by Eaton et al.,[1]* published by The Cochrane Epilepsy Group. This Cochrane Corner is produced in agreement with *Developmental Medicine & Child Neurology* by Cochrane Rehabilitation with views[a] of the review summary author in the 'implications for practice' section.

BACKGROUND

Epilepsy is a group of neurological disorders wherein abnormal electrical activity in the brain triggers unprovoked and recurrent seizures.[1] The burden of psychological and physical comorbidity is high.[2] People with epilepsy may experience neuropsychological deficits resulting in memory loss, affective dysfunction, difficulty learning, slower processing speed, and attention and sleep problems.[3,4] Population-based studies have estimated a prevalence of attention-deficit/hyperactivity disorder (ADHD) between 23% and 50% in this population.[5] Children with both epilepsy and ADHD are at high risk of additional cognitive, psychosocial, and emotional difficulties.[5]

First-line management for ADHD relies on psychological interventions; if these fail and symptoms are persistent and severe, they can be supplemented with stimulant or non-stimulant drugs.[1,6] However, there remains uncertainty about the safety and effectiveness of drug treatments as they have been associated with a risk of increased seizure frequency.[1] Therefore, Eaton et al.[1] conducted a systematic review to appraise the state of evidence and clinical gaps in research on stimulant and non-stimulant drugs for children with ADHD and co-occurring epilepsy.

STIMULANT AND NON-STIMULANT DRUG THERAPY FOR PEOPLE WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER AND EPILEPSY[1]

What is the aim of this Cochrane Review?

This Cochrane Review[1] aimed to assess the effects of stimulant and non-stimulant drugs on seizure frequency and rate of withdrawal in patients with epilepsy with co-occurring ADHD. The secondary objective was to examine the effects of stimulant and non-stimulant drugs on seizure severity, ADHD symptoms, cognition, behavior, quality of life, and adverse events.

What was studied in the Cochrane Review?

The population addressed in this review[1] was children and adults with a diagnosis of epilepsy and ADHD according to the DSM-IV or ICD. No sociodemographic restrictions were applied. The studied interventions were stimulant and non-stimulant drugs administered for ADHD. Eligible

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[a] The views expressed in the summary with commentary are those of the Cochrane Corner author (different than the original Cochrane Review authors) and do not represent the Cochrane Library or Wiley.

comparators were control, stimulant drugs, and non-stimulant drugs. The primary outcomes were seizure frequency (change from baseline) and number of people withdrawing from treatment. The secondary outcomes were changes from baseline regarding seizure severity, number of episodes of status epilepticus, and hospitalizations, ADHD symptoms, cognition, behavior, quality of life, and proportion of people achieving 50% or greater reduction in seizure frequency.

How up to date is the Cochrane Review?

The authors[1] searched for randomized or quasi-randomized-controlled trials through October 2020 in 14 databases, including MEDLINE, CINAHL Plus, the Specialized Registers of Cochrane Review Groups including Epilepsy, the Cochrane Central Register of Controlled Trials, MEDLINE Ovid, Embase Ovid, the World Health Organization International Clinical Trials Registry Platform, and ClinicalTrials.gov. The language of publication was not a search restriction.

What are the main results of the Cochrane Review?

The review[1] included two randomized-controlled trials ($n = 94$). All children had a diagnosis of epilepsy according to International League Against Epilepsy criteria[7] and ADHD according to DSM-IV criteria.[8] Gonzalez-Heydrich et al.[9] reported on osmotic-release oral system methylphenidate (OROS-MPH) among the pediatric population (mean = 10 years 6 months [SD 3 years]; range 6 years 5 months–17 years 6 months). Fallah et al.[10] examined the effectiveness of omega-3 fatty acid supplementation plus risperidone on children with refractory epilepsy (mean = 9 years 3 months [SD 2 months]; range 7–11 years). Both studies had a higher percentage of males (59.8% and 57.6% respectively) than females. The overall certainty of evidence was judged to be low in both studies.

Osmotic-release oral system methylphenidate versus placebo

Seizure frequency: Children in both arms experienced an increased risk of daily seizures: eight seizures on 7 of a total 1058 days of placebo or OROS-MPH, three seizures during 565 placebo days (0.53 seizures/100 days), one seizure during 194 days for 10 mg or 18 mg OROS-MPH (0.52 seizures/100 days), two seizures during 170 days for 36 mg OROS-MPH (1.12 seizures/100 days), and two seizures during 87 days for 54 mg OROS-MPH (2.30 seizures/100 days). A regression model assessing day of exposure and dose (i.e. 18, 36, and 54 mg daily) found that the risk of daily seizure was positively correlated with the use of OROS-MPH ($p < 0.001$).

Treatment withdrawal: The OROS-MPH group recorded a significantly higher treatment withdrawal rate than the control group ($p = 0.007$); 42.4% of the children discontinued therapy in the OROS-MPH group compared with 15.2% in the placebo group (risk ratio = 2.80; 95% confidence interval [CI] 1.14–6.89).

Severity of seizure: No changes in seizure severity were recorded.

ADHD symptoms: ADHD symptoms decreased at a faster rate in children treated with OROS-MPH than in the control group when measured using the Clinical Global Impression-ADHD-Improvement ($p < 0.001$).

Adverse events: No severe adverse events were reported. Mild individual adverse events included worsening of emotional liability in four (12.1%) patients in the OROS-MPH group compared with two (6.1%) in the control group.

Omega-3 plus risperidone versus risperidone

Seizure frequency: Children in the omega-3 plus risperidone (0.5 mg) group reported a significantly lower number of seizures (mean = 10.4 [SD 3.92]) compared with the risperidone (0.5 mg) group (17.0 [SD 4.98]; $p = 0.003$). The mean difference was −6.6 in the omega-3 group compared with the control group (95% CI −8.96 to −4.24).

Treatment withdrawal: Two children discontinued omega-3 plus risperidone treatment (risk ratio = 0.65; 95% CI 0.12–3.59), and three children discontinued treatment with risperidone alone (risk ratio = −0.04; 95% CI −0.17 to 0.1).

Adverse events: The following adverse events were recorded in the omega-3 plus risperidone group: sleepiness ($n = 2$), diarrhea ($n = 2$), and nausea and vomiting ($n = 2$) (risk ratio = 1.40; 95% CI 0.44–4.42). Four (14.8%) children in the control group experienced sleepiness ($n = 2$), anorexia ($n = 1$), and constipation ($n = 1$).

None of the studies reported the number of hospitalizations, episodes of status epilepticus, and effects on cognition, behavior, and overall quality of life. Fallah et al. did not report on ADHD symptoms.[10]

What did the authors conclude?

Only one stimulant (OROS-MPH) and one non-stimulant (omega-3 plus risperidone) intervention were investigated in this review to treat ADHD in children with epilepsy. The authors concluded that, while stimulant drugs may decrease ADHD-related symptoms, they were associated with increased frequency of seizures, which may exacerbate cognitive, behavioral, and emotional impairments and other adverse events. Preliminary data suggest that polytherapy with omega-3, risperidone, and antiseizure medication may reduce the frequency of seizures; however, the effect on ADHD symptoms and risk of adverse events are unclear. The authors stress that the findings should be interpreted with caution due to the low certainty of evidence and high risk of bias.

What are the implications of the Cochrane evidence for practice in rehabilitation?

People with epilepsy have a higher likelihood of being diagnosed with ADHD than the general population.[5,6] The low certainty of evidence paired with the limited number of studies included in the review prevented the recommendation of OROS-MPH and omega-3 plus risperidone as safe and effective treatment options. In contrast with children with only ADHD, risk factors of ADHD in children with epilepsy include ictal and interictal epileptiform discharges, sleep problems, and antiseizure medication adverse effects, which highlights the need for increased scrutiny when developing treatment plans for these patients.[6] Current pediatric recommendations consider behavioral therapy as the first treatment choice in managing ADHD symptoms, especially in children ≤6 years of age.[1,6] Timely detection of symptoms, development of a multimodal and patient-centered treatment plan, and regular follow-up remain the most effective approaches to mitigate adverse events and augment functioning and quality of life in young children who are at increased risk of behavioral and psychological issues.

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DATA AVAILABILITY STATEMENT

Not required.

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