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

Eaton C, Yong K, Walter V, Mbizvo GK, Rhodes S, Chin RFM

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[Intervention Review]

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.

PLAIN LANGUAGE SUMMARY

Stimulant and non-stimulant drug therapy for people with Attention Deficit Hyperactivity Disorder and epilepsy

What is the aim of this review?

The aim of this Cochrane Review was to find out if stimulant and non-stimulant medications are effective and safe in treating people with both Attention Deficit Hyperactivity Disorder (ADHD) and epilepsy. Cochrane Review authors collected and analysed all relevant studies to answer this question.

Background

Epilepsy is a disease where the brain is predisposed to generating seizures. ADHD is a condition where daily life is affected by inattention, hyperactivity and impulsivity. It is common for a person with epilepsy to also have a diagnosis of ADHD. Both these diagnoses together can have a negative impact on education, occupation and family and social relationships.

ADHD can be managed with drug therapy. This consists of stimulant drugs such as methylphenidate and non-stimulant drugs such as atomoxetine. These drugs act on different neurotransmitters within the brain to improve concentration and impulse control. It is suggested that stimulant drugs, particularly methylphenidate, may aggravate epilepsy or cause seizures. Both stimulant and non-stimulant drugs continue to be prescribed with a warning that they might worsen seizures.

We do not know if stimulant and non-stimulant drugs are effective and safe in treating people with ADHD and epilepsy. We also do not know if these drugs have intolerable side effects that stop people from taking them daily.

What are the main results of the review?

We found two relevant studies involving children with both ADHD and epilepsy: one American study looked at osmotic-release oral system methylphenidate (OROS-MPH) and was funded by a government grant; one Iranian study looked at omega-3 and was funded by a university grant.

In the first study, children at an American outpatient clinic received either OROS-MPH of increasingly higher doses or placebo. This study suggests that children receiving OROS-MPH:

• may have an increased risk of seizures with higher doses of OROS-MPH, although we are not certain of this.

• are probably twice as likely to stop taking OROS-MPH due to side effects (e.g. worsening emotional lability and seizures), although we are only moderately confident in this result.

• may improve their ADHD symptoms, although we are not certain of this.

In the second study, children at an Iranian outpatient clinic received either omega-3, the anti-psychotic drug risperidone and usual anti-seizure medication (ASM) or risperidone and usual ASM only. This study suggests that children receiving omega-3:

• may have fewer seizures (children who received omega-3 had six or seven fewer seizures per month on average compared to children who did not receive omega-3), although we are not certain of this.

• may be less likely to stop taking omega-3 due to side effects (sleepiness, diarrhoea and nausea and vomiting), although we are uncertain of this. However, the effects of omega-3 vary, and it is possible that omega-3 makes little or no difference.

The review authors did not find any studies that looked at the effect of omega-3 on ADHD symptoms.
The review authors did not find any studies that looked at adults with ADHD and epilepsy, and other types of stimulant and non-stimulant medication.

Key messages

The stimulant drug OROS-MPH may improve ADHD symptoms but may also increase the risk of adverse events such as seizures and emotional lability. The non-stimulant drug omega-3 may be safe to be used by children with both ADHD and epilepsy; however, we do not know if it is effective in treating the symptoms of ADHD. These conclusions should be interpreted with caution due to study biases, indirect outcome measures, small numbers of events and large confidence intervals. We still need more high-quality studies including studies involving adults with both ADHD and epilepsy and more types of stimulant and non-stimulant medications.

How up-to-date is this review?

The review authors searched for studies that had been published up to October 2020.

SUMMARY OF FINDINGS

Summary of findings 1. Osmotic-release oral system methylphenidate compared to placebo for people with ADHD and epilepsy

Osmotic-release oral system methylphenidate compared to control for people with ADHD and epilepsy

Patient or population: people with ADHD and epilepsy

Settings: outpatients

Intervention: osmotic-release oral system methylphenidate (OROS-MPH)

Comparison: placebo

Outcomes	Illustrative absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with OROS-MPH				
Seizure frequency	In logistic regression models calculating the odds of a seizure, significant predictors included the number of days of exposure to placebo or OROS-MPH (P < 0.005), the drug dose (P < 0.005) and the interaction between them (P = 0.002 when drug dose examined as mg/kg/day and P < 0.001 when examined as absolute dose). Cox proportional hazard models exploring time to seizure and hazard at each dose found that a higher mg/kg/day dose predicted a greater hazard of a seizure (P < 0.001). Days of exposure was not significant, but the interaction between days of exposure and dose was (P < 0.05).	-		33 (1 RCT)	⊕⊕⊖⊖ LOW[a,b]	
Proportion of people withdrawing from treatment	152 per 1000	424 per 1000 (173 to 1000)	RR 2.80 (1.14 to 6.89)	33 (1 RCT)	⊕⊕⊕⊖ MODERATE[a]	
Seizure severity	No participant experienced significant worsening of epilepsy in either the OROS-MPH or the placebo arm.	-		33 (1 RCT)	⊕⊕⊖⊖ LOW[a,c]	
Proportion of people experiencing 50% or	-	-		-	-	Not measured

greater reduction in seizure frequency					
ADHD symptoms	Descriptively, a greater proportion of participants received 'much improved' or 'very much improved' scores for ADHD symptoms on the CGI-ADHD-I in the OROS-MPH arm relative to the placebo arm. Total ADHD-RS score dropped across both the OROS-MPH and placebo arms (week of treatment, P < 0.0001), but dropped more rapidly in the OROS-MPH arm (significant interaction between week of treatment and OROS-MPH/placebo arm, P < 0.0001).	-		33 (1 RCT)	⊕⊕⊖⊖ LOW [a,d]
Proportion of people experiencing adverse drug events	No participants in either the OROS-MPH or placebo arm experienced serious adverse events.	-	-	33 (1 RCT)	⊕⊕⊕⊖ MODERATE[a]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
ADHD: attention deficit hyperactivity disorder; ADHD-RS: attention hyperactivity disorder-rating scale; CGI-ADHD-I: Clinical Global Impressions for ADHD—Improvement; CI: confidence interval; OROS-MPH: osmotic-release oral system methylphenidate; RCT: randomised controlled trial; RR: risk ratio

GRADE Working Group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

[a]Risk of bias: downgraded by one level. This study was rated 'unclear' for random sequence generation and allocation concealment, as well as high for other bias - several authors received funding from McNeil Consumer Health, the provider of active OROS methylphenidate and matching placebo for this study.
[b]Indirectness: downgraded by one level. This study did not explore seizure frequency (change from baseline) as an outcome; instead it explored measures of seizure risk (the odds of a seizure on each day of exposure and the number of days of exposure until a seizure occurred).
[c]Indirectness: downgraded by one level. This study did not explore seizure severity (change from baseline) as a continuous outcome; instead, seizure severity formed part of the dichotomous outcome 'worsening of epilepsy'. This was defined as (1) a doubling of the highest 14-day or highest 2-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 2 years, or (3) a clinically meaningful intensification in seizure duration or severity.
[d]Indirectness: downgraded by one level. This study does not present the exact proportion of participants showing improvement in ADHD symptoms, or exact numbers for the change in total ADHD-RS score. Data are provided in figures, preventing accurate estimates and therefore precluding risk ratio and mean difference calculations in this review.

Summary of findings 2. Omega-3 (with risperidone and previous ASM) compared to risperidone and previous ASM only for people with ADHD and epilepsy

Omega-3 (with risperidone and previous ASM) compared to risperidone and previous ASM only for people with ADHD and epilepsy

Patient or population: people with ADHD and epilepsy

Settings: outpatients

Intervention: omega-3 (with risperidone and previous ASM)

Comparison: risperidone and previous ASM only

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with risperidone & ASM only	Risk with omega-3 (with risperidone & ASM)				
Seizure frequency (monthly, postintervention) Follow-up: 3 months	The mean seizure frequency was 17 seizures per month	MD 6.6 seizures per month lower (8.96 lower to 4.24 lower)	-	56 (1 RCT)	⊕⊕⊖⊖ LOW [a,b]	
Proportion of individuals withdrawing from treatment	100 per 1000	65 per 1000 (12 to 359)	RR 0.65 (0.12 to 3.59)	61 (1 RCT)	⊕⊕⊖⊖ LOW [a,c]	
Seizure severity	-	-	-	-	-	Not measured
Proportion of people achieving 50% or greater reduction in monthly seizure frequency (change from baseline) Follow-up: 3 months	111 per 1000	310 per 1000 (93 to 1000)	RR 2.79 (0.84 to 9.24)	56 (1 RCT)	⊕⊕⊖⊖ LOW [a,d]	
ADHD symptoms	-	-	-	-	-	Not measured
Proportion of people experiencing adverse drug events Follow-up: 3 months	148 per 1000	207 per 1000 (65 to 655)	RR 1.40 (0.44 to 4.42)	56 (1 RCT)	⊕⊕⊖⊖ LOW [a,e]	

The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
ADHD: attention deficit hyperactivity disorder; ASM: anti-seizure medication; CI: Confidence interval; MD: Mean difference; RCT: randomised controlled trial; RR: Risk ratio

GRADE Working Group grades of evidence
High certainty: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate certainty: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: We are very uncertain about the estimate.

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[a]Risk of bias: downgraded by one level. Study rated as high risk of bias for 'blinding of participants and study personnel' and 'incomplete outcome data'.
[b]Imprecision: downgraded by one level. Statistical analysis was not paired between baseline and end-of-study outcome.
[c]Imprecision: downgraded by one level. Only a small number of adverse events occurred, and confidence intervals for the effect on adverse events are consistent with both and appreciable benefit and appreciable harm, so we lowered the certainty.
[d]Imprecision: downgraded by one level. Five participants who were randomised were excluded from analyses. Best-and-worst-case sensitivity analyses which made assumptions about 50% or greater reduction in seizure frequency in these participants provided mixed results: confidence intervals of risk ratios suggested both an increase and decrease in the likelihood of 50% or greater reduction.
[e]Imprecision: downgraded by one level. Only a small number of adverse events occurred and confidence intervals for the effect on adverse events are consistent with both an appreciable benefit and appreciable harm, so we lowered the certainty.

BACKGROUND

Epilepsy is defined as "a disease of the brain characterised by an enduring predisposition to generate epileptic seizures, and by the neurobiologic, cognitive, psychologic, and social consequences of this disease" (Fisher 2014a). Living with epilepsy can have devastating effects on health and lifestyle, particularly as seizures are associated with increased risk of death, serious injuries, depression, stigma, unemployment, and social exclusion (Mlinar 2016; Sander 2009). Anti-seizure medication (ASM) should not only reduce seizure frequency, but should also be tolerable in terms of adverse effects. The drugs used to treat co-occurring conditions managed alongside epilepsy should, ideally, not lower seizure threshold or interact with ASM (Cardamone 2013). Attention Deficit Hyperactivity Disorder (ADHD) can co-occur with epilepsy in 23% of the epilepsy population (Russ 2012), and people with epilepsy have a 3.5-fold increased risk of ADHD compared to people without epilepsy (Brikell 2018). This review examines the effect of stimulant and non-stimulant drug treatment in adults and children with ADHD and co-occurring epilepsy, in terms of the symptoms of ADHD, seizure frequency, seizure severity, adverse effects, and drug withdrawal.

Description of the condition

Epilepsy is one of the most common neurologic diseases worldwide, affecting 70 million people and contributing to 0.7% of the global burden of disease (Murray 2012). It is defined as having two or more unprovoked seizures and is further classified by the International League Against Epilepsy (ILAE) according to seizure and epilepsy type (Fisher 2017; Scheffer 2017). The incidence of epilepsy is 50 per 100,000 people per year in high-income countries (defined as countries with an annual gross national income (GNI) per capita of USD 12,476 or more) (World Bank 2018). This rises to somewhere between 100 and 190 per 100,000 people per year in lower- and middle-income countries (defined as countries with an annual GNI of USD 1025 or less, and USD 1026 to USD 12,475, respectively) (Sander 2003; World Bank 2018). The prevalence of epilepsy in high-income countries is 5.8 per 1000 people, and between 10.3 and 15.4 per 1000 people for low- and middle-income countries (Ngugi 2010). In the majority of cases (60% to 75%), the cause of epilepsy is unknown. However, it is increasingly being recognised, with more modern classification systems, that a proportion of the unknown causes are probably genetic in nature with complex inheritance patterns and single-gene mutations on susceptibility alleles (a component of a gene making it more likely that one will develop certain medical diseases) (Epilepsy Foundation 2013; Ottman 2005). In cases where the cause of epilepsy is known, there is normally an association with the age of onset of epilepsy, of which there are two peak ages of onset. The first peak occurs in the early years of life, particularly at less than 10 years of age. This early peak is in close association with the incidence of birth defect-related complications, perinatal (birth) complications, and infections. The incidence of epilepsy then peaks again in the sixth decade of life, due to the increased incidence of secondary changes in brain structure, led by cerebrovascular diseases and brain tumours (Epilepsy Foundation 2013; Sander 2003).

Epilepsy and ADHD often co-occur. ADHD is a condition characterised by inattention, hyperactivity and impulsivity to such an extent that function or development is impaired, and activities of daily life interfered with (DSM-V; ICD-10 1992; NIMH 2016). The most established diagnostic classification systems for ADHD are the *International Classification of Diseases, 10th Revision* (ICD-10 1992) and the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) (DSM-V; ICD-10 1992). These classification systems recognise 18 symptoms indicative of inattention, hyperactivity and impulsivity. The criteria of the ICD-10 1992 and the DSM-V require that inattention, hyperactivity and impulsivity are pervasive (i.e. present in a range of situations for at least six months) and present before six years (ICD-10 1992), or 12 years of age (DSM-V). Some impairments resulting from these symptoms should be observed in two or more settings, and there should also be impairment in social, academic or occupational functioning (DSM-IV; DSM-IV-TR; DSM-V; ICD-10 1992). Research has identified the cognitive difficulties to be broader than attention and to include executive functions, memory and self-regulation difficulties (Coghill 2014; Rhodes 2004; Rhodes 2005; Rhodes 2012). The diagnostic process should include an assessment of needs, co-existing conditions, social, familial and educational or occupational circumstances, and physical health (NICE 2008). The cause(s) of ADHD are not known. However, there are possible correlations with abnormalities in brain structure or function, genetic involvement, and pre- or postnatal environmental risks such as maternal cigarette smoking and the early parent-child relationship, respectively (Kaufmann 2009; NHS 2016; Thapar 2013).

Symptoms of ADHD are normally present at the time of, or before, someone's first seizure. This suggests that ADHD is a co-occurring condition rather than a condition caused by the seizure disorder or its treatments (Hesdorffer 2004; Williams 2016). Co-occurring ADHD and epilepsy continue into adolescence and adulthood in around two-thirds of patients. Together, they have an increasingly negative impact on academic achievement, occupational status, as well as social and family relationships (CDC 2017; National Alliance on Mental Illness 2017; Radziuk 2015). The prevalence of ADHD in the paediatric epilepsy population is as high as 23% to 40% (Cohen 2013; Russ 2012), compared with a prevalence rate of between 2% and 8% in the non-epileptic control population, depending on the country studied (Czamara 2013; Marcus 2012; Russell 2014), with a worldwide average of around 5% (Polanczyk 2007; Sayal 2018). In the adult population, the prevalence of ADHD is 4% (National Alliance on Mental Illness 2017), and the prevalence of epilepsy ranges from 4 to 10 per 1000 people (Picot 2008). There are several proposed mechanisms for the high prevalence of ADHD in the epilepsy population. These include a common genetic propensity, adrenergic system dysfunction causing both epilepsy and ADHD, and psychosocial risk factors. Furthermore, people with ADHD have a higher-than-normal rate of electroencephalogram (EEG) abnormalities, even without a history of epilepsy. Such epileptiform discharges are associated with cognitive impairment and manifestation of ADHD symptoms such that in some cases, ASM use may not only abolish epileptiform discharges, but also improve ADHD symptoms (Kaufmann 2009).

There are some subtle differences between ADHD in children and adults. Hyperactivity - but not impulsivity - seems to become a less evident component of the disorder in adults. Impulsivity may be a distinct source of impairment compared to hyperactivity in adults (Martel 2012). This may change how the disease causes impairment and how it is managed between children and adults. The impact of seizures and their underlying abnormal neural substrate are different in the developing paediatric brain and the mature adult brain such that there may be contrasting

patterns of neuropsychological performance in children and adults with epilepsy (Smith 2010). This may differentially confound the phenotype of ADHD in children and adults with epilepsy such that subgroup analysis of outcomes between these two groups following treatment may be helpful.

Description of the intervention

Drug therapy in ADHD should form part of a wider treatment programme that includes lifestyle support. Psychological interventions should be offered to all children with ADHD. In children with moderate symptoms of ADHD, drug therapy should be used when psychological interventions have been unsuccessful or are unavailable (BNF 2017). In children with severe and persistent symptoms of ADHD, drug therapy should be commenced routinely alongside psychological interventions. Drug therapy for ADHD consists of central nervous system (CNS) stimulant and non-stimulant drugs. Stimulant drugs include the amphetamines (e.g. dexamfetamine and lisdexamfetamine) and related drugs (e.g. methylphenidate). These drugs increase the action of dopamine in the basal ganglia and prefrontal cortex by preventing its reuptake. The drugs work by improving self-regulation (Rhodes 2006), memory (Coghill 2014; Rhodes 2004), and executive functions (De Sousa 2012; Gau 2010; Hosenbocus 2012; Rosenau 2021). The basal ganglia are in charge of modifying motor control and determining when it is appropriate to perform an action. People with ADHD are believed to have dysfunctional basal ganglia. Therefore, increasing levels of dopamine, by drug therapy, allows the brain in ADHD to function more effectively (Leisman 2014). Adverse effects related to stimulant drugs are primarily insomnia, irritability, gastrointestinal discomfort or nausea, as well as increases in heart rate and blood pressure (BNF 2017). Non-stimulant drugs include atomoxetine, clonidine, guanfacine, lofexidine, and bupropion (Brown 2013); the most widely used is atomoxetine. Atomoxetine works as a selective noradrenaline reuptake inhibitor, increasing levels of dopamine and noradrenaline in the prefrontal cortex; it has less of an effect in the basal ganglia (Shier 2013).

The choice of drug in ADHD therapy should take into account the drug's effect on a person's comorbidities. Comorbidities commonly seen with ADHD include Autistic Spectrum Disorder, Developmental Coordination Disorder/dyspraxia, tic disorders, Tourette's syndrome, and epilepsy (Gnanavel 2019; Goulardins 2015; Leitner 2014; Russ 2012). The choice of ADHD drug should also be influenced by its adverse effect profile, potential for drug misuse, tolerance and dependence, as well as patient/carer preference (BNF 2017). The National Institute for Health and Care Excellence (NICE) recommend the following choices for drug therapy in children with ADHD:

1. methylphenidate for ADHD without significant comorbidity;
2. methylphenidate for ADHD with comorbid conduct disorder (severe behavioural problems);
3. methylphenidate or atomoxetine when tics, Tourette's syndrome, anxiety disorder, stimulant misuse or risk of stimulant diversion are present;
4. atomoxetine if methylphenidate has been tried and has been ineffective at the maximum tolerated dose, or the child is intolerant to low or moderate doses of methylphenidate (NICE 2008).

For adults with ADHD, NICE recommends that methylphenidate should be tried first. Atomoxetine or dexamfetamine are recommended if symptoms do not respond to methylphenidate or the person is intolerant to it after an adequate trial (approximately six weeks). Atomoxetine should be the first-line choice if there are concerns about drug misuse (NICE 2008).

In the context of ADHD and epilepsy, the recommendation is that if seizures are exacerbated or new seizures emerge following the introduction of methylphenidate or atomoxetine, the drug should be discontinued immediately. Dexamfetamine may be considered as an alternative in consultation with a regional tertiary specialist treatment centre (NICE 2008).

How the intervention might work

Stimulant drugs are able to bypass the blood-brain barrier and work by increasing the level of catecholamines, dopamine and noradrenaline in both the peripheral and central nervous systems. Amphetamines can do this in a variety of ways. Firstly, they act as competitive inhibitors to the monoamine reuptake transporters (DAT and NET), reducing the reuptake of dopamine and noradrenaline into nerve terminals. Moreover, amphetamines enter the synaptic cleft (space between nerve endings) via diffusion or active reuptake. They then interact with vesicular monoamine pumps (VMAT-2), which prevent the catecholamines present in the cytoplasm (material in a cell outside its nucleus) from being taken up into synaptic storage vesicles. Finally, at high concentrations, amphetamines can inhibit the action of monoamine oxidase (an enzyme), thereby preventing the breakdown of catecholamines (Markowitz 2001; Rang 2011).

Methylphenidate acts similarly to amphetamines, by inhibiting monoamine reuptake inhibitors, but it cannot enter nerve terminals. Therefore, it acts by producing a prolonged increase in catecholamines in the synaptic cleft (Rang 2011; Markowitz 2001).

Slow-release formulations of these drugs are used in ADHD to prevent the euphoric side effects seen with stimulants. They are taken orally and absorbed through the gastrointestinal tract. Amphetamines are rapidly absorbed and have a half-life that varies from five to 30 hours. They are metabolised primarily through deamination (the removal of an amino group from an amino acid) and converted into benzoic acid and hippuric acid in the kidneys before being excreted in urine. Methylphenidate is absorbed more slowly, and 80% is metabolised into ritalinic acid prior to entering the systemic circulation. The half-life of methylphenidate is only two to four hours, and the 20% that enters the systemic circulation is metabolised by carboxylesterase (Rang 2011).

Atomoxetine is a highly selective noradrenaline reuptake inhibitor and increases noradrenaline concentrations outside the cell. The drug is absorbed through the gastrointestinal tract and has a half-life of anywhere from five to 22 hours. The half-life is dependent on the activity of CYP2D6, which metabolises the drug. Atomoxetine is excreted through the kidneys (FDA 2006; Rang 2011). The pharmacokinetics (movements of the drug within the body) of atomoxetine are affected by concomitant use with paroxetine, which decreases its excretion and therefore results in an increased systemic concentration of atomoxetine (Sauer 2005).

Why it is important to do this review

There is clinical debate about the efficacy and safety of stimulant and non-stimulant drugs used to treat ADHD in people with co-occurring epilepsy (De Sousa 2012). It is suggested that stimulant drugs, particularly methylphenidate, may induce new-onset epilepsy, aggravate existing epilepsy, or lower the seizure threshold in people with epilepsy or an abnormal EEG (Gonzalez-Heydrich 2010; Kattimani 2011). However, the mechanism of these possible effects is as yet undescribed and the aggravation of seizures, or the onset of new ones, may be a coincidental part of the normal course of the epileptic disease. Methylphenidate affects the presynaptic reuptake of noradrenaline and dopamine but has no effect on neurotransmitters such as gamma aminobutyric acid (GABA), glutamate and aspartic acid, or sodium and calcium channels, which are associated with the pathophysiology of epilepsy. Methylphenidate and the other stimulant drugs continue to be prescribed with a warning that they may increase seizures, and clinicians are advised to discontinue these drugs if seizure frequency increases (Kaufmann 2009). Methylphenidate is also thought to increase the plasma concentration of several ASM, including fosphenytoin, phenobarbital, phenytoin, and primidone (BNF 2017). Such interactions are a reason why older ASM are now less commonly used in clinical practice (French 2011).

Atomoxetine has virtually no affinity for other transport mechanisms or receptors, including those implicated in the pathogenesis of epilepsy. Therefore, based on its chemistry and pharmacology, there is no reason to believe it to be epileptogenic. A recent review of the literature found that atomoxetine does not appear to increase the risk of seizures (Williams 2016). However, atomoxetine continues to be prescribed with a warning that it may increase seizures, and clinicians are advised to discontinue the drug if seizure frequency increases (Kaufmann 2009). There are no reported interactions between ASM and atomoxetine (BNF 2017).

ADHD is managed using stimulant and non-stimulant drugs and, although there are warnings surrounding the use of these in ADHD and co-occurring epilepsy, the evidence is conflicting and remains to be appraised in a systematic review and meta-analysis (Brown 2013; Kaufmann 2009). This review aims to address this gap in appraisal by systematically evaluating clinical trials of both stimulant and non-stimulant drugs in people with ADHD and co-occurring epilepsy. Outcomes of interest include seizure frequency and severity, symptoms of ADHD, adverse effects as well as drug withdrawal.

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).

METHODS

Criteria for considering studies for this review

Types of studies

We included studies that met the following criteria.

1. Intervention studies (we excluded observational studies)
2. Randomised control trials (RCTs): the trial was described by the study author(s) as a 'randomised controlled trial' (or words to that effect), or a process of random allocation into intervention groups was described.
3. Placebo-, active- or usual-treatment controlled
4. Double-blind, single-blind, or unblinded
5. Parallel or cross-over design

Types of participants

We included participants that met the following criteria.

1. Any age, gender, ethnicity, and country
2. A diagnosis of both ADHD, according to a recognised classification system such as the DSM or the ICD, and epilepsy. A diagnosis of epilepsy must have been stated, and we noted any particular classification system used.

Types of interventions

We included trials that reported testing the following interventions.

1. The use of CNS stimulant drugs including, but not exclusively, the amphetamines (dexamfetamine and lisdexamfetamine) and related drugs (e.g. methylphenidate).
2. The use of non-stimulant CNS drugs including, but not exclusively, atomoxetine, clonidine, guanfacine, lofexadine, and bupropion.

Trials with at least one of the following comparisons were eligible.

1. Stimulant therapy versus control
2. Non-stimulant therapy versus control
3. Stimulant therapy versus non-stimulant therapy
4. Stimulant therapy versus non-stimulant therapy versus control
5. Stimulant therapy 1 versus stimulant therapy 2
6. Non-stimulant therapy 1 versus non-stimulant therapy 2

Types of outcome measures

Primary outcomes

1. Seizure frequency (change from baseline)
2. Proportion of people withdrawing from treatment

Secondary outcomes

1. Seizure severity (change from baseline)
2. Number of episodes of status epilepticus (change from baseline)
3. Number of seizure-related hospitalisations (change from baseline)
4. Proportion of people achieving 50% or greater reduction in seizure frequency
5. ADHD symptoms (change from baseline): attention, hyperactivity and impulsivity, measured by psychometric instruments or by observations of behaviour, using, for example, Conners' Rating Scales (Conners 2008). Raters could be teachers, independent assessors or parents.
6. Proportion of people experiencing adverse drug events
7. Cognitive effects, as changes from baseline in scores on neuropsychological tests such as the Wechsler Adult Intelligence

Scale (WAIS, Wechsler 1997), and the Wide Range Assessment of Memory and Learning-2 (WRAML-2, Sheslow 2003).

8. General behaviour effects, as changes from baseline in scores on psychometric instruments such as the Child Behaviour Checklist (CBCL; Achenbach 1991).
9. Quality of life (QoL) scores (change from baseline), as measured by psychometric instruments such as the Child Health Questionnaire (CHQ; Landgraf 1998), and Quality of Life in Epilepsy Inventory (QOLIE-31, Cramer 1998). Raters could be teachers, independent assessors or parents.

Search methods for identification of studies

Electronic searches

We searched the following databases on 12 October 2020.

1. Cochrane Register of Studies (CRS Web), using the search strategy shown in Appendix 1.
2. MEDLINE (Ovid), 1946 to 9 October 2020, using the search strategy shown in Appendix 2.
3. CINAHL Plus (Cumulative Index to Nursing and Allied Health Literature), 1937 onwards (EBSCOhost), using the search strategy shown in Appendix 3.

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. In MEDLINE (Ovid) the coverage end date always lags a few days behind the search date.

Searching other resources

We identified other potentially eligible trials by searching the reference lists of included trials and any relevant reviews found.

Data collection and analysis

Selection of studies

Two review authors (CE and KY) independently screened the titles and abstracts of papers to exclude any that were not relevant to the study. They then screened articles in full to remove any that were irrelevant or did not meet the inclusion criteria. Authors used the Covidence systematic review software for both title and abstract screening and full-text review. For papers excluded at the full-text stage, authors recorded their bibliographic data along with the reason(s) for exclusion. A third review author (RFMC) resolved any disagreements that arose.

Data extraction and management

Two review authors (CE and KY) independently extracted the following information, where available, from published manuscripts. A third review author (RFMC) resolved any disagreements that arose. Authors extracted data using the Cochrane Effective Practice and Organisation of Care data collection form (EPOC 2017).

1. **Publication details**
   a. Author(s)
   b. Year of publication
   c. Funding source/type
   d. Whether a conflict of interest statement was made
2. **Methodological/trial design**
   a. Country(s) of study
   b. Type of study
   c. Study setting (e.g. inpatient or outpatient)
   d. Inclusion/exclusion criteria
   e. Length of recruitment period
   f. Method of randomisation (random sequence generation): authors extracted all reported information on the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.
   g. Method of randomisation concealment (allocation concealment): authors extracted all available information on the method used to conceal the allocation sequence in sufficient detail to help determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.
   h. Methods of blinding, including, where reported, whether these applied to each main outcome (or class of outcomes), and whether there was blinding of participants, study personnel (e.g. treating clinicians), and outcome assessors. Authors extracted sufficient information about the blinding methods, where reported, to assist in making a judgement about whether the intended blinding was effective.
   i. Whether any randomised participants had been excluded from reported analyses (for each outcome). Authors extracted reasons for attrition/exclusions, where reported.
   j. Duration of any baseline period during which seizure frequency or ADHD symptoms were assessed
   k. Duration of treatment period (including recording any drug titration periods)
   l. Description of control methods used (i.e. details of the placebo/active control/usual care used)
   m. Any evidence of selective reporting of outcomes
3. **Participants**
   a. Number of participants
   b. Age of participants
   c. Gender of participants
   d. How ADHD was diagnosed (i.e. according to which criteria)
   e. Duration of ADHD
   f. Severity of ADHD (any reported scale)
   g. How epilepsy was diagnosed (i.e. according to which criteria)
   h. Duration of epilepsy
   i. Type of epilepsy (as described in manuscript)
   j. Type of seizures (as described in manuscript)
   k. Baseline seizure frequency
   l. Comorbidity and concurrent drugs or interventions, including name and dose of ASM

4. **Interventions**
   a. Name of stimulant or non-stimulant drug(s) used during trial
   b. Dose of stimulant or non-stimulant drug(s) used during trial
   c. Frequency of stimulant or non-stimulant drug(s) used during trial
5. **Outcomes:** we used change from baseline data where available. If such data were not available, we either used the separate baseline data and end of follow-up estimates described by the study authors, or calculated these ourselves. If studies did not report baseline data or end of follow-up data, it was not possible for review authors to calculate effect estimates.
6. **Analysis**
   a. Statistical methods used, including whether analysis was by intention-to-treat (ITT)
   b. What was done with missing or incomplete data and dropout participants
   c. Effect sizes (including variance, proportions, difference in proportions, risk ratios (RRs), odds ratios, difference in mean/median seizure severity scores)
   d. P values and confidence intervals quoted

Assessment of risk of bias in included studies

Two review authors (CE and KY) independently assessed risk of bias for each study across the domains outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). A third review author (RFMC) resolved any disagreements that arose. We graded each potential source of bias as high, low or unclear, and provided a quote from the study report together with a justification for our judgement in the risk of bias table. We summarised the risk of bias judgements across different studies for each of the bias domains.

Cochrane's risk of bias domains are as follows.

1. **Selection bias:** were there adequate methods of random sequence generation and allocation concealment? Methods considered to confer a low risk of selection bias include those using random numbers tables/electronically generated random numbers for random sequence generation, and those using allocation of sequentially numbered sealed packages of medication, sealed opaque envelopes, or central/telephone randomisation for allocation concealment.
2. **Performance bias:** was knowledge of the allocated interventions by study participants and personnel (e.g. treating clinicians) adequately prevented during the study? Methods considered to confer a low risk of performance bias include using packaging and tablets that are identical for intervention and control agents.
3. **Detection bias:** was knowledge of the allocated interventions by outcome assessors prevented during the study? Studies were regarded as possessing low risks of this bias when it was specifically described that investigators/outcome assessors were blinded to treatment assignment.
4. **Attrition bias:** were incomplete outcome data adequately addressed? Studies were regarded as possessing low risks of this bias when it is clear all participants (including missing participants and missing data) were accounted for by authors, e.g. by explaining reasons for missing data, participants, and changing denominators.
5. **Reporting bias:** risk of selective reporting was judged to be low when the results of all outcomes measured were also published.

We also assessed whether bias from study funding may be present, and described this under the 'Other bias' section of the risk of bias table. This is summarised below.

Funding bias: bias related to funding source resulting from systematic influences on how the study was conducted. This largely relates to pharmaceutical industry-sponsored studies. These are more likely to have favourable efficacy and harm results than studies not sponsored by industry (Lundh 2017). Therefore, we judged industry-sponsored studies to have a high risk of funding bias if we deemed their methodology to have been conducted differently to standard accepted methods (i.e. following CONSORT guidelines) or differently to non-industry-funded studies testing the same drug.

Measures of treatment effect

We summarised dichotomous outcomes as risk ratios (RRs) with 95% confidence intervals (CIs), and calculated the risk difference (RD). Where different trials used the same instrument to measure a particular continuous outcome, we calculated mean differences (MD) with 95% CIs. Where trials used different measurement tools, we planned to calculate standardised mean differences (SMDs) with 95% CIs. If trials did not report means and standard deviations but did report other values (such as t-tests or P values), we transformed these into standard deviations.

The primary outcome of interest was whether stimulants or non-stimulants alter seizure outcomes. Therefore, we defined treatment harm or effect as any increase or decrease (compared to baseline), respectively, in seizure frequency (continuous outcome), severity scores (continuous outcome), number of episodes of status epilepticus (continuous outcome), number of seizure-related hospitalisations (continuous outcome), and proportion of people not achieving 50% or greater reduction in seizure frequency (dichotomous outcome). We defined secondary outcome treatment effects as change from baseline in ADHD symptom scores (continuous outcome), general behaviour scores (continuous outcome), cognitive effect scores (continuous outcome), and QoL scores (continuous outcome). We also compared treatments and controls for significant differences in the proportion of people experiencing adverse drug events and drug withdrawal (dichotomous outcomes). We reported 95% CIs for all comparisons except for the comparison of individual adverse effects, where we reported 99% CIs to make allowance for multiple testing.

Unit of analysis issues

For cross-over studies, we only used data from the first treatment phase when there was evidence of significant carryover of treatment effect into the second treatment phase. We judged there to have been a significant carryover of effect when this was stated to be the case by authors, or when there was no return to baseline seizure frequency during the second baseline/washout period.

Dealing with missing data

Primary analysis was on an intention-to-treat (ITT) basis. For this, we analysed all randomised participants in the treatment group to which they had been allocated, irrespective of the treatment that

they actually received. We obtained any missing data for this by contacting trial authors. When missing data were unobtainable, we conducted analyses using the available published data (Storebø 2015), with the assumption that data were missing at random (Higgins 2011). In order to assess the impact of missing data on the overall conclusions through attrition and reporting biases, we carried out sensitivity analysis that excluded data from trials judged to have high risks of bias for incomplete outcome data and selective reporting.

In addition, we conducted best- and worst-case sensitivity analyses to deal with missing dichotomous data for the outcomes of 50% reduction in seizure frequency and treatment withdrawal.

1. Worse-case analysis: participants randomised but excluded from analysis (e.g. for not completing follow-up) were assumed to have failed to achieve 50% or greater reduction in seizure frequency or to have withdrawn from treatment in the intervention group, and achieved 50% or greater reduction in seizure frequency or not withdrawn from treatment in the control group.
2. Best-case analysis: participants randomised but excluded from analysis (e.g. for not completing follow-up) were assumed to have achieved 50% or greater reduction in seizure frequency or to have not withdrawn from treatment in the intervention group, and failed to achieve 50% or greater reduction in seizure frequency or to have withdrawn from treatment in the control group (Higgins 2011).

Assessment of heterogeneity

Where possible, we planned to check statistical heterogeneity between trials for each outcome using a Chi^2 test for heterogeneity and the I^2 statistic, interpreted as follows:

1. heterogeneity may not be important (I^2 values 0% to 40%);
2. moderate heterogeneity (I^2 values 30% to 60%);
3. substantial heterogeneity (I^2 values 50% to 90%); and
4. considerable heterogeneity (I^2 values 75% to 100%) (Higgins 2011).

Provided no significant heterogeneity was present ($P < 0.05$ on the Chi^2 test, or the I^2 statistic < 50%), we planned to conduct meta-analysis using a fixed-effect model. Where significant heterogeneity existed, we planned to conduct meta-analysis using a random-effects model and explore heterogeneity using subgroup analyses, as described in the Subgroup analysis and investigation of heterogeneity section, according to the various demographic, clinical and trial characteristics (Higgins 2011).

Due to the small number of included studies, we were unable to undertake the above.

Assessment of reporting biases

We judged the risk of selective reporting to be low when the results of all outcomes measured by trialists were also published. We requested unpublished data from authors of those papers that we judged to have a high risk of reporting bias, to help increase the size of the evidence base for analysis.

Data synthesis

For each study, we reported the overall effect of the stimulant or non-stimulant drugs used on the primary and secondary outcomes described. We also planned to use these results to perform a meta-analysis, where possible. Where heterogeneity precluded the provision of precise estimates, we planned to provide a descriptive analysis of the overall trends in evidence, and use subgroup analyses to help identify factors that may help explain the heterogeneity (see Subgroup analysis and investigation of heterogeneity).

Subgroup analysis and investigation of heterogeneity

Where possible, subgroup analyses on the following groups were planned to help identify whether these groups were affected by stimulant/non-stimulant drugs differently, or to help investigate heterogeneity.

1. Children versus adults: the cutoff age for childhood is 16 or 18 years in different countries, where 16 to 18 years is described as adolescence. We planned to group children and adolescents together.
2. Males versus females
3. Comorbidity: participants with ADHD and epilepsy with additional comorbid disorders versus those without additional comorbid disorders;
4. Type of epilepsy: we planned to compare: generalised epilepsy, focal epilepsy, generalised and focal epilepsy, and unknown if generalised or focal epilepsy.
5. Type of ADHD: participants with predominantly inattentive subtype versus participants with predominantly combined subtype (Storebø 2015)
6. Study location: we planned to group studies together by continent and compare the different continents.
7. Intervention: we planned to group studies and compare them by the particular stimulant or non-stimulant drug used, when more than one study had used the same drug.
8. Studies at low risk of bias versus studies at unclear or high risk of bias: we planned to group studies with low risk of bias (all domains) together and compare these against studies with unclear or high risk of bias.
9. Industry and non-industry studies: we planned to group together studies funded by the pharmaceutical industry and compare them against studies without industry funding.

Due to the small number of included studies, we were unable to undertake the above.

Sensitivity analysis

We planned to conduct best- and worst-case sensitivity analyses as described above to deal with missing dichotomous data (see Dealing with missing data).

Due to the small number of included studies (one study for each drug), we were unable to perform a sensitivity analysis in which we would have excluded data from studies with high or unclear risk of bias from the analysis, in order to assess the impact of these biases on the overall conclusions.

Summary of findings and assessment of the certainty of the evidence

We interpreted findings using the GRADE approach (Schunemann 2019). We used GRADEPro GDT software, into which we imported data from Review Manager 5 (Review Manager 2020), to create summary of findings tables for each comparison included in the review for the following outcomes.

1. Seizure frequency
2. Proportion of people experiencing drug withdrawal
3. Seizure severity
4. Proportion of people achieving 50% or greater reduction in seizure frequency
5. ADHD symptoms
6. Proportion of people experiencing adverse drug events

RESULTS

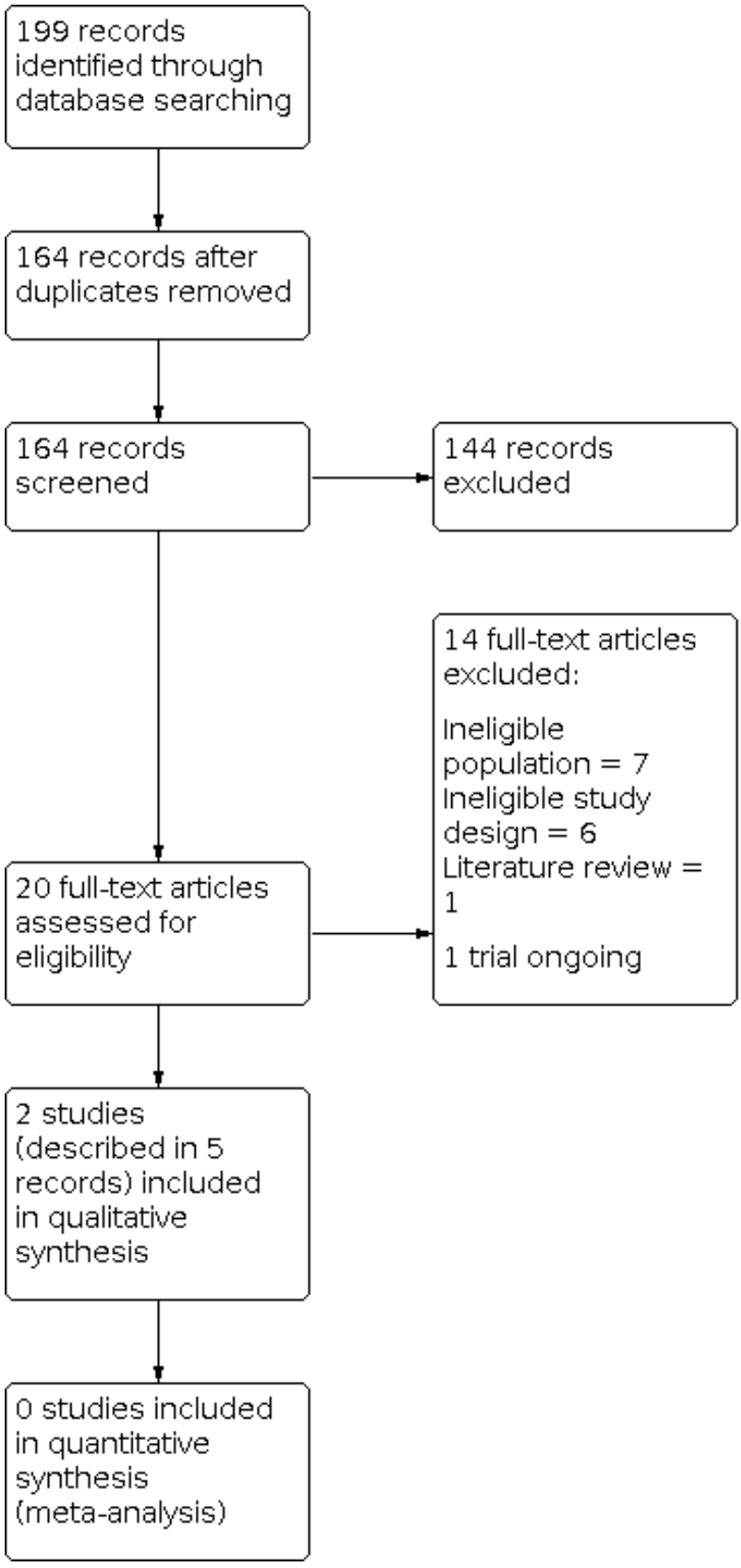
Description of studies

See Characteristics of included studies, Characteristics of excluded studies and Characteristics of ongoing studies for the details of the studies considered for this review.

Results of the search

The search identified 199 records. After removal of duplicates, 164 records remained. Review authors screened the titles and abstracts of these records and selected 20 to be assessed in full-text. On full-text review, an additional 14 records were excluded (see Characteristics of excluded studies). We identified one study which we classified as ongoing. We contacted the authors, who responded informing us that this study was completed and was currently being prepared for publication (see Characteristics of ongoing studies). We included two studies, described in five records, in our review. The study selection process is summarised in Figure 1.

Figure 1. Study flow diagram



Included studies

We included two studies with a total of 94 participants (Gonzalez-Heydrich 2010; Fallah 2018).

Study design

Both trials were RCTs, randomising at the participant level.

The aim of Gonzalez-Heydrich 2010 was to pilot a trial of osmotic-release oral system methylphenidate, known as OROS methylphenidate (OROS-MPH), to treat people with ADHD and epilepsy. Thirty-three people took part in the double-blind placebo-controlled cross-over trial.

Participants were randomised to either the active treatment (OROS-MPH) or placebo arm of the study, and crossed over to the opposite arm after a one-week washout period. Given the sustained release of OROS-MPH, the study employed an adaptive phase-I dosing escalation strategy to find the maximum acceptable dose and to explore safety problems in a small number of participants. Three groups of participants were assessed sequentially: in the first group, the maximum dose was 18 mg per day, the second was 36 mg and the third 54 mg. Recruitment into the 36 mg group could not begin until at least three participants had completed the cross-over trial for the 18 mg dose without a significant worsening of epilepsy or a serious adverse event, with this process repeated for the 54 mg group. It is important to note that the maximum dose was the lesser of 54 mg or 2 mg/kg/day, therefore even if a higher dose group had begun recruiting (e.g. group II), the participant could still be assigned to the lower group (e.g. group I) to ensure the maximum dose remained below 2 mg/kg/day. If at any of the three dose levels two participants had significant worsening of epilepsy (see Characteristics of included studies for a definition) during the active arm, the dose level immediately below would be fixed as the maximum dose for the rest of the study (this did not occur and so all three dose levels were tested).

Participants spent a week on the maximum dose before endpoint measures for that arm were taken, and the participant crossed over to the opposite arm. Therefore, for group I, the treatment period lasted for three weeks (one week of 18 mg OROS-MPH, one week of washout, one week of placebo), for group II, five weeks (one week of 18 mg OROS-MPH, one week of 36 mg OROS-MPH, one week washout, two weeks of placebo) and for group III, seven weeks, (one week of 18 mg OROS-MPH, one week of 36 mg OROS-MPH, one week of 54 mg OROS-MPH, one week washout, three weeks placebo). In all three groups, on the first day of the active arm, participants were given 5 mg or immediate-release (IR) in the morning and at noontime. If the participant tolerated this, they moved on to completing the remaining six days on 18 mg of OROS-MPH. The baseline period was not reported, although the authors did take a seizure history over the previous two years.

Fallah 2018 employed a single-blind parallel-group design, whereby participants were randomised to receive either omega-3 with risperidone and previous ASM, or risperidone with previous ASM only. The treatment period lasted for three months, with outcome measures taken monthly. The duration of the baseline period was not reported.

Setting

Gonzalez-Heydrich 2010 was conducted in the USA and Fallah 2018 was conducted in Iran.

In Gonzalez-Heydrich 2010, participants were patients in the clinics of neurologists at Children's Hospital Boston. In Fallah 2018, participants were patients of the Pediatric Neurology Clinic of Shahid Sadoughi Hospital, Yazd, Iran.

Participants

In both included studies, participants had a dual-diagnosis of ADHD and epilepsy; 33 in Gonzalez-Heydrich 2010 and 61 in Fallah 2018 (although data were reported for only 56 (five participants who were randomised subsequently discontinued medication after three to four weeks). We contacted the authors of Fallah 2018 to request the relevant outcome data from these five participants, however, the authors did not respond to our request. Both studies diagnosed epilepsy according to the International League Against Epilepsy (ILAE) definition; in Fallah 2018, the diagnosis was refractory epilepsy specifically (ILAE 1989; Fisher 2014b). In both studies, ADHD was diagnosed according to DSM-IV criteria (DSM-IV); in Fallah 2018, participants were additionally required to have a score of at least 20 on an ADHD diagnostic rating scale, conducted via parent interview (Urion 2016). Please see Characteristics of included studies for additional inclusion/exclusion criteria. The mean age of participants was 9.24 years (range 7 to 11 years) in Fallah 2018 and 10.5 years (range 6 to 18 years) in Gonzalez-Heydrich 2010. Both studies recruited a majority of male participants, 57.6% in Gonzalez-Heydrich 2010 and 58.9% in Fallah 2018. In Gonzalez-Heydrich 2010, participants were taking ASM and had a last seizure one to 60 months prior to starting study medication.

Interventions

Gonzalez-Heydrich 2010 used a stimulant drug, whereas Fallah 2018 used a non-stimulant drug.

Gonzalez-Heydrich 2010 investigated the safety and efficacy of OROS-MPH, a sustained-release stimulant drug. As described in 'Study Design', different dose levels of the drug were tested to establish a maximum acceptable dose; 18 mg, 36 mg and 54 mg (or no more than 2 mg/kg/per day), with the participant remaining on the maximum dose for one week. The drug was administered orally on a daily basis in the morning. Before testing OROS-MPH, participants were initially given 5 mg of IR-MPH on the first day of the active arm at morning and at noontime to see if they tolerated this dose. Participants in the control arm received a placebo.

Fallah 2018 explored the safety and efficacy of fish oil (omega-3), from 21st Century Co., USA. Each capsule contained 1000 mg of fish oil, 180 mg of eicosapentaenoic acid and 120 mg of docosahexaenoic acid. Each day, participants in the active arm received one capsule, along with a 1 mg of risperidone (Abdi Co., Iran) divided into two doses, and their usual regimen of ASM. In the control arm, participants received only the risperidone and previous ASM. Drugs were delivered by the mothers of the participants and continued for three months.

Outcomes

Gonzalez-Heydrich 2010 assessed outcome measures after the participant had remained on the maximum dose of OROS-MPH or

placebo for one week, except where noted. Fallah 2018, assessed outcomes measures on a monthly basis for three consecutive months.

Primary outcomes

Seizure frequency

Gonzalez-Heydrich 2010 provided data on the total number of seizures that occurred in the OROS-MPH and placebo arms, as well as by dose in the OROS-MPH group. Fallah 2018 measured the mean monthly seizure frequency across the three-month research period, and compared this between the omega-3 and placebo arms. Neither study included a comparison to baseline when exploring seizure frequency.

Proportion of people withdrawing from treatment

Both Gonzalez-Heydrich 2010 and Fallah 2018 provided data on the proportion of people withdrawing from treatment. Gonzalez-Heydrich 2010 included this as an outcome within their study and compared this variable between the OROS-MPH and placebo arms. Fallah 2018 reported the number of randomised participants who discontinued medication after three to four weeks, but did not include this as an outcome or compare this between the omega-3 and placebo arms in their analyses.

Secondary outcomes

Seizure severity

Gonzalez-Heydrich 2010 included a measure of seizure severity as part of their assessment of whether participants experienced 'significant worsening of epilepsy' during treatment. This was defined as: 1) a doubling of the highest 14-day or two-day seizure rate observed during the 12 months preceding the trial; 2) the occurrence of a generalised tonic-clonic seizure if the participant had not experienced one in the previous two years; or, 3) an intensification of seizure severity or frequency determined to be clinically meaningful.

Proportion of people achieving 50% or greater reduction in seizure frequency

Fallah 2018 measured the proportion of participants who achieved 50% or greater reduction in seizure frequency (relative to baseline) in the omega-3 and control groups.

ADHD symptoms

Gonzalez-Heydrich 2010 measured ADHD symptoms using the ADHD Rating Scale IV Home Version (ADHD-RS, DuPaul 1998), which consists of 18 items, with each item corresponding to one of the DSM-IV ADHD criteria. The Principal Investigator (PI) read out each item to the participant's guardian and then rated the participant's symptom severity over the preceding week. In addition, this study used the 'Severity' and 'Improvement' subscales of the Clinical Global Impressions for ADHD scale (CGI-ADHD, Guy 1976) to assess symptom severity and symptom improvement after the intervention, respectively. Both subscales are single-item ratings, given by a clinician. The 'Severity' subscale reflects a clinician's assessment of the global severity of the child's ADHD symptoms in relation to total experience with them, and uses a 7-point scale: 1 = normal, not at all, and 7 = among the most extremely ill patients. The 'Improvement' subscales measure the global change in the child's ADHD symptoms; in this study, the clinician provided the rating at the final visit of each arm. A score of either 1 = very much improved or 2 = much improved were collectively defined as 'response'.

Proportion of people experiencing adverse drug events

Both trials measured the proportion of participants experiencing adverse drug effects. In Gonzalez-Heydrich 2010, the PI rated adverse events from mild to life-threatening and also measured the severity of these events using the Barkley Side Effects Checklist-Modified (BSCEM, Barkley 1990). This assesses 24 side effects linked to stimulant medication use. The authors defined a 'dose limiting adverse-event' (in which the participant would discontinue the arm of the cross-over they were currently participating in) if one of the BSCEM items was elevated above baseline at a moderate or higher level.

Funding sources

Both studies reported information on their source of funding; Gonzalez-Heydrich 2010 was funded by an NIMH Grant K23 MH066835 and Fallah 2018 was funded by a grant from the Deputy for Research of Shahid Sadoughi University of Medical Sciences, Yazd, Iran.

Excluded studies

We excluded 14 studies. In seven studies, participants did not have a dual-diagnosis of ADHD and epilepsy, six had an ineligible study design (they were not randomised controlled trials) and one was a literature review.

Risk of bias in included studies

See also Figure 2 and Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

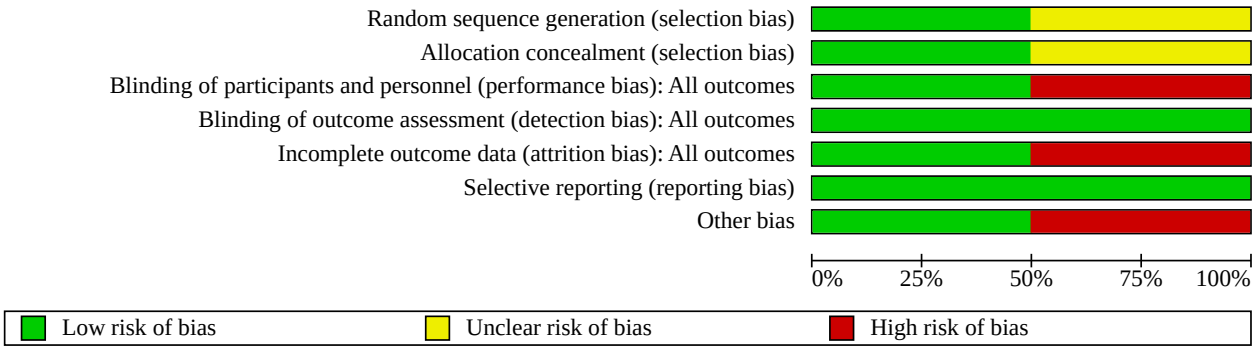
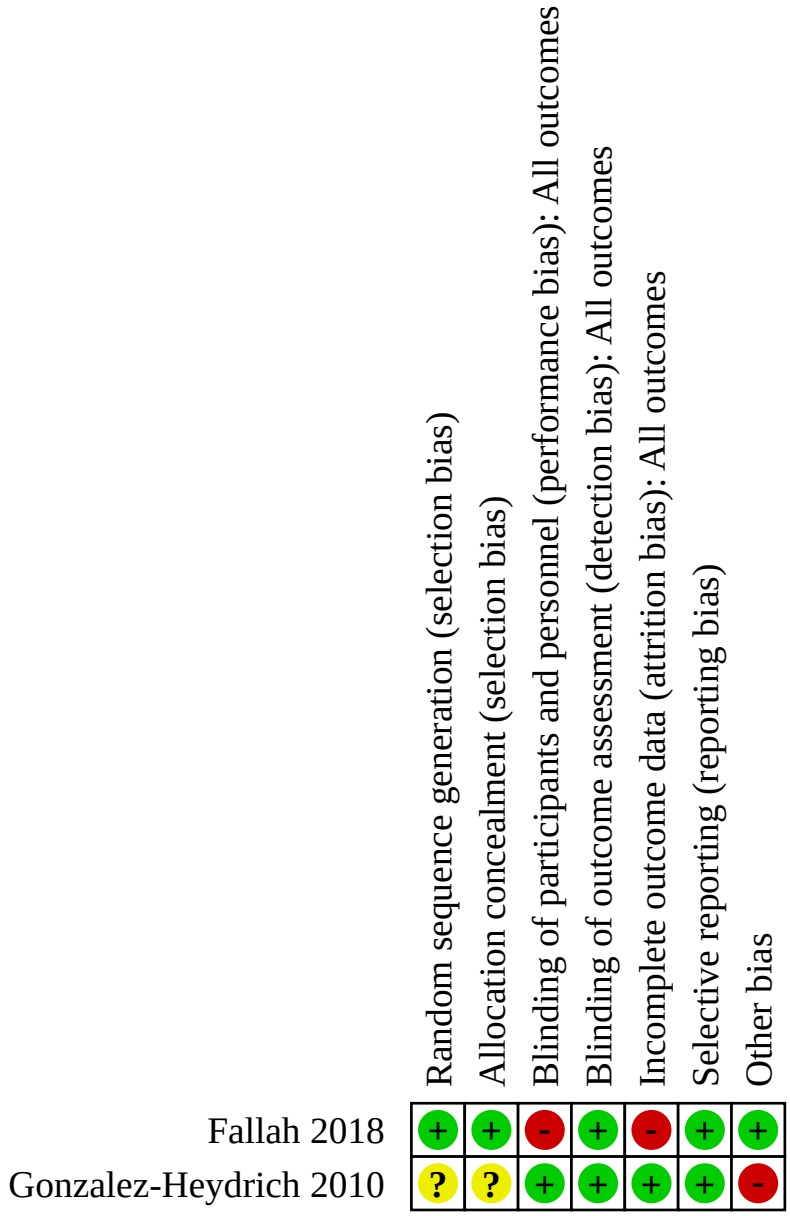


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Allocation

In Gonzalez-Heydrich 2010, randomisation lists for each of the three dose groups were prepared by a statistician and maintained by the study research pharmacist. However, there was no report of how these lists were randomised, nor the process for allocation concealment. We therefore considered both sequence generation and allocation concealment to be at unclear risk in Gonzalez-Heydrich 2010. By contrast, in Fallah 2018, an investigator with no clinical involvement in the trial randomly allocated participants into either the intervention or control group using computer-generated equal simple randomisation by random numbers. Numbered, sealed opaque envelopes containing the group number for each child were used for concealment, opened by the paediatric neurologist in the research study immediately before study enrolment. We therefore rated both sequence generation and allocation concealment as low risk in Fallah 2018.

Blinding

In Gonzalez-Heydrich 2010, the participants, study personnel and the outcome assessor were all blind to medication status. We considered Gonzalez-Heydrich 2010 to be at low risk for blinding of participants and study personnel, as well as blinding of outcome assessors. In Fallah 2018, we considered blinding of participants and study personnel to be at high risk as, given the design of the study (i.e. no placebo), the mothers in the intervention arm of the trial were aware they were administering omega-3 to their child. All outcome assessors were, however, kept blinded to the allocation, so we rated the 'Blinding of outcome assessors' domain as low risk.

Incomplete outcome data

We considered Gonzalez-Heydrich 2010 to be at low risk of incomplete outcome data; all 33 randomised participants were included in the analyses. By contrast, we rated Fallah 2018 as high risk in this domain; five participants who had been randomised were excluded as a result of discontinuing medication after three to four weeks.

Selective reporting

We considered both Gonzalez-Heydrich 2010 and Fallah 2018 to be at low risk for selective outcome reporting, as all analyses and planned outcomes described in the methods section were subsequently reported in the results.

Other potential sources of bias

Several of the Gonzalez-Heydrich 2010 study authors received funding from McNeil Consumer Health, who provided the active OROS methylphenidate and matching placebo for the study. Therefore, we considered this trial to be at high risk of funding bias. We considered Fallah 2018 to be at low risk of funding bias, as university departmental funding was declared (a grant from the Deputy for Research of Shahid Sadoughi University of Medical Sciences, Yazd, Iran).

Effects of interventions

See: **Summary of findings 1** Osmotic-release oral system methylphenidate compared to placebo for people with ADHD and epilepsy; **Summary of findings 2** Omega-3 (with risperidone and previous ASM) compared to risperidone and previous ASM only for people with ADHD and epilepsy

The diversity of stimulant/non-stimulant drugs measured, study design and reported outcomes meant that we were unable to pool data from the two studies included in our review. We therefore did not conduct analyses of statistical heterogeneity or any of the subgroup analyses (see items 1 to 9 in Subgroup analysis and investigation of heterogeneity). We present data on key outcomes for each of the two key comparisons in this review, and describe our confidence in the results based on GRADE criteria (Schunemann 2019).

OROS-MPH versus control

See Summary of findings 1.

Primary outcomes

1. Seizure frequency (change from baseline)

Gonzalez-Heydrich 2010 found that eight seizures occurred on seven out of a total 1058 days of placebo or OROS-MPH. Three seizures occurred during 565 placebo days (rate = 0.53 seizures/100 days). One seizure occurred during 194 days of either 10 mg or 18 mg OROS-MPH (0.52 seizures/100 days). Two seizures occurred during 170 days of 36 mg OROS-MPH (1.12 seizures/100 days). Two seizures occurred during 87 days of 54 mg OROS-MPH (2.30 seizures/100 days).

Given that, if the participant experienced a seizure in either the OROS-MPH or control arm, they discontinued that arm, the authors used logistic regression models to explore the odds of a seizure on each day of exposure to OROS-MPH or placebo. They found that significant predictors of seizure risk were: the number of days of exposure to placebo or OROS-MPH ($P < 0.005$), the drug dose ($P < 0.005$), and the interaction between them ($P = 0.002$ when drug dose examined as mg/kg/day and $P < 0.001$ when examined as absolute dose). The authors also used Cox proportional hazard models to explore time to seizure and hazard at each dose. They found a higher mg/kg/day dose predicted a greater hazard of a seizure ($P < 0.001$). Days of exposure was not significant in this model, but the interaction between days of exposure and dose was ($P < 0.05$). We had low confidence in these findings. We downgraded certainty by one level due to risk of bias: this study was rated 'unclear' for random sequence generation and allocation concealment, as well as high for other bias - several authors received funding from McNeil Consumer Health, the provider of active OROS methylphenidate and matching placebo for this study. We downgraded certainty by another level due to indirectness: this did not compare the mean seizure frequency (change from baseline) as an outcome between the OROS-MPH and the placebo arms.

2. Proportion of people withdrawing from treatment

Gonzalez-Heydrich 2010 explored the proportion of people withdrawing from treatment. If a dose-limiting adverse event occurred (if one of the BSCEM items was elevated above baseline at a moderate or higher level), the participant withdrew from the OROS-MPH/placebo arm of the cross-over they were participating in. Fourteen out of 33 (42.4%) participants discontinued OROS-MPH and 5/33 (15.2%) discontinued the placebo. This difference was statistically significant ($P = 0.007$). The risk ratio was 2.80 (95% CI 1.14 to 6.89) (Analysis 1.1), and the risk difference was 0.27 (95% CI 0.06 to 0.48). We had moderate certainty in these findings, and downgraded certainty by one level due to risk of bias.

Secondary outcomes

1. Seizure severity (change from baseline)

Gonzalez-Heydrich 2010 included a measure of seizure severity as part of their assessment of whether participants had 'worsening of epilepsy' during the study. They defined significant worsening of epilepsy as: 1) a doubling of the highest 14-day or two-day seizure rate observed during the 12 months preceding the trial; 2) the occurrence of a generalised tonic-clonic seizure if the participant had not experienced one in the previous two years; or, 3) an intensification of seizure severity or frequency determined to be clinically meaningful. No participants in either the OROS-MPH or placebo arms experienced significant worsening of epilepsy. We had low certainty in these findings, and downgraded certainty by

one level due to risk of bias and another level due to indirectness because the study did not explore seizure severity (change from baseline) as a continuous outcome, instead, seizure severity formed part of the dichotomous outcome 'worsening of epilepsy'.

2. Number of episodes of status epilepticus (change from baseline)

Gonzalez-Heydrich 2010 did not measure the number of episodes of status epilepticus.

3. Number of seizure-related hospitalisations (change from baseline)

Gonzalez-Heydrich 2010 explored the proportion of people who experienced serious adverse events, but did not provide a further breakdown of whether this included seizure-related hospitalisations.

4. Proportion of people achieving 50% or greater reduction in seizure frequency (change from baseline)

Gonzalez-Heydrich 2010 did not measure the proportion of people achieving a 50% or greater reduction in seizure frequency.

5. ADHD symptoms

Gonzalez-Heydrich 2010 found that a greater proportion of participants received 'much improved' or 'very much improved' scores for ADHD symptoms on the CGI-ADHD-I in the OROS-MPH arm relative to the placebo arm (descriptive comparison only). Total ADHD-RS scores dropped across both the OROS-MPH and placebo arms (week of treatment, P < 0.0001), but dropped more rapidly in the OROS-MPH arm (significant interaction between week of treatment and OROS-MPH/placebo arm, P < 0.0001). We had low confidence in these findings; we downgraded certainty by one level due to risk of bias and by one level due to indirectness: this study did not present the exact proportion of participants showing improvement in ADHD symptoms, or exact numbers for the change in total ADHD-RS score. Data were provided in figures, which prevented accurate estimates and therefore precluded risk ratio and mean difference calculations in this review. We contacted the study authors and asked to obtain these data, but the authors did not respond.

6. Proportion of people experiencing adverse events during follow-up

No participants in either the OROS-MPH or control arms experienced serious adverse events. We had moderate certainty in these findings, and downgraded certainty by one level due to risk of bias.

This study measured milder, individual adverse affects across the OROS-MPH and placebo arms. Four participants in the OROS-MPH arm experienced worsened emotional lability (4/33, 12.1%) compared to two in the control arm (2/33, 6.1%). The risk ratio was 2.0 (99% CI 0.24 to 16.98) (Analysis 1.2) and the risk difference was 0.06 (99%% CI 0.06 to 0.24). Four participants experienced a seizure in the OROS-MPH arm (4/33, 12.1%) compared to three in the control arm (3/33, 9.1%). The authors found this difference was not statistically significant. The risk ratio was 1.33 (99% CI 0.21 to 8.58) (Analysis 1.2) and the risk difference was 0.03 (99% CI -0.16 to 0.23).

Omega-3 versus control

See Summary of findings 2.

Primary outcomes

1. Seizure frequency

Fallah 2018 compared mean monthly seizure frequency between the omega-3 and control groups over a three-month treatment period. The omega-3 group had a mean monthly seizure frequency of 10.4 (SD 3.92), which was significantly lower than that of the control group (17.0, SD 4.98; P = 0.003). The mean difference was -6.6 in the omega-3 group relative to control (95% CI -8.96 to -4.24) (Analysis 2.1. We had low confidence in these findings. We downgraded certainty by one level due to high risk of bias in the 'blinding of participants and study personnel' domain and the 'incomplete outcome data' domains. We also downgraded by one level due to indirectness; this study did not compare seizure frequency in omega-3 and control groups based on change from baseline. Importantly, a comparison of baseline seizure frequency between omega-3 and control revealed a descriptive trend towards a lower seizure frequency in the omega-3 group (mean 15.8, SD 8.49) relative to control (mean 16.7, SD 6.68) which approached significance (P = 0.09).

2. Proportion of individuals withdrawing from treatment

After three to four weeks of treatment, two participants in Fallah 2018 discontinued omega-3 and three participants in the control group discontinued risperidone. The risk ratio was 0.65 (95% CI 0.12 to 3.59) (Analysis 2.2) and the risk difference was -0.04 (95% CI -0.17 to 0.1). We had low confidence in these findings. We downgraded certainty by one level due to high risk of bias in the 'blinding of participants and study personnel' domain and the 'incomplete outcome data' domains. We also downgraded by one level due to imprecision; only a small number of participants withdrew from treatment and confidence intervals for the effect on withdrawal are consistent with both a decrease and increase in risk in the omega-3 group.

Secondary outcomes

1. Seizure severity (change from baseline)

Fallah 2018 did not measure seizure severity.

2. Number of episodes of status epilepticus (change from baseline)

Fallah 2018 did not measure the number of episodes of status epilepticus.

3. Number of seizure-related hospitalisations (change from baseline)

Fallah 2018 did not measure the number of seizure-related hospitalisations.

4. Proportion of people achieving 50% or greater reduction in monthly seizure frequency (change from baseline)

Fallah 2018 compared the proportion of people achieving 50% or greater reduction in seizure frequency, relative to baseline, in the omega-3 and control groups. They found that a significantly greater proportion of individuals in the omega-3 arm experienced ≥ 50% reduction (31%) than did individuals in the control group (11.1%). However, our calculations of the risk ratio (2.79, 95% CI 0.84 to 9.24; Analysis 2.3) and risk difference (0.20, 95% CI -0.01 to 0.41) indicated uncertainty about whether omega-3 increased or decreased the likelihood of achieving a 50% reduction in seizure frequency. We had low certainty in these findings, downgrading by one level due to high risk of bias in the 'blinding of participants and study personnel'

domain and the 'incomplete outcome data' domains and by one level due to imprecision, as a result of the mixed results from the best- and worst-case scenario sensitivity analyses (see below).

Given that five participants randomised in Fallah 2018 were excluded from the analysis due to discontinuing medication, we conducted best- and worst-case scenario sensitivity analyses for this outcome. In the best-case scenario, it was assumed that participants withdrawing from the omega-3 group did achieve a 50% or greater reduction in seizure frequency and those in the control group did not. The risk ratio was 3.55 (95% CI 1.10 to 11.48; Analysis 2.4) and the risk difference was 0.25 (95% CI 0.06 to 0.45), indicating an increase in the likelihood of achieving a 50% or greater reduction in seizure frequency. In the worst-case scenario, it was assumed that participants withdrawing from the omega-3 group did not achieve a 50% or greater reduction in seizure frequency and that those in the control group did. The risk ratio was 1.45 (95% CI 0.59 to 3.58; Analysis 2.5) and the risk difference was 0.09 (95% CI -0.12 to 0.30).

5. Proportion of people experiencing adverse events during follow-up

Fallah 2018 explored the proportion of participants in the omega-3 and control groups who experienced an adverse event over the three-month treatment period. Six participants in the intervention group (20.7%) experienced an adverse event: two experienced sleepiness, two diarrhoea and two nausea and vomiting. In the control group, four participants (14.8%) experienced an adverse event: two experienced sleepiness, one anorexia and one constipation. The trial authors found the proportion of participants experiencing an adverse event did not differ between the omega-3 and control group. The risk ratio for an adverse event in the omega-3 group was 1.40 (95% CI 0.44 to 4.42) (Analysis 2.6), and the risk difference was 0.06 (95% CI -0.14 to 0.26). We had low confidence in these findings and downgraded by one level due to high risk of bias in the 'blinding of participants and study personnel' domain and the 'incomplete outcome data' domain. We also downgraded by one level due to imprecision: only a small number of adverse events occurred, and confidence intervals for the effect of omega-3 are consistent with both appreciable harm and benefit.

Fallah 2018 also reported the proportion of participants with individual adverse effects across the omega-3 and control arms (Analysis 2.7). Two participants experienced sleepiness in the omega-3 arm (2/29, 6.9%), as did two participants in the control arm (2/27, 7.4%). The risk ratio was 0.93 (99% CI 0.08 to 11.14) and the risk difference was -0.01 (99% CI 0.18 to 0.17). Two participants suffered from diarrhoea in the omega-3 arm (2/27, 7.4%), compared to none in the control arm. The risk ratio was 4.67 (99% CI 0.09 to 238.19) and the risk difference was 0.07 (99% CI -0.08 to 0.21). Two participants experienced nausea and vomiting in the omega-3 arm (2/27, 7.4%) compared to none in the control arm. The risk ratio was 4.67 (99% CI 0.09 to 238.19) and the risk difference was 0.07 (99% CI -0.08 to 0.21). One participant experienced anorexia and one experienced constipation in the control arm; none of the participants in the omega-3 arm experienced these conditions. For both anorexia and constipation, the risk ratios were 0.31 (99% CI 0.00 to 19.76) and the risk differences were -0.04 (99% CI 0.16 to 0.09).

DISCUSSION

Summary of main results

This is the first study to systematically review the efficacy and tolerability of stimulant and non-stimulant drugs in people with a dual-diagnosis of ADHD and epilepsy, within clinical trials. Our review found only two RCTs which matched our inclusion criteria. Both studies focused on children with a dual-diagnosis of ADHD and epilepsy, but explored different drugs; Gonzalez-Heydrich 2010 explored the stimulant drug OROS-MPH, whereas Fallah 2018 explored the non-stimulant omega-3 fish oil. The two studies also employed different designs; Fallah 2018 employed a parallel-group design to compare omega-3 taken in tandem with risperidone and the participant's usual regiment of ASM with risperidone and ASM only, whereas Gonzalez-Heydrich 2010 employed a cross-over design to compare different doses of OROS-MPH with a placebo.

Gonzalez-Heydrich 2010 found that increasing the dose of OROS-MPH was associated with an increase in the daily risk of a seizure, although there is low certainty surrounding these findings. This reduced certainty is due to study biases, including funding bias and lack of information about method of randomisation and allocation concealment, and indirect outcomes which did not compare a change in mean seizure frequency between OROS-MPH and placebo arms. This study also provided evidence suggesting OROS-MPH increases the risk of adverse events and withdrawal from treatment relative to placebo. There was moderate certainty associated with these findings. Finally, Gonzalez-Heydrich 2010 provided evidence suggesting OROS-MPH improved ADHD symptoms relative to placebo, although there is low certainty associated with these findings, due to study biases and a lack of reporting of the exact change in ADHD symptom scores and the proportions showing improvement.

Whilst Fallah 2018 provided some evidence to suggest omega-3 was associated with improved seizure outcomes (by both a reduction in mean monthly seizure frequency and an increase in the likelihood of achieving 50% or greater reduction in seizure frequency), there was low certainty associated with these findings due to study biases, which concerned the participants' mothers who were administering the drug being unblinded to medication status. There was also indirectness due to a failure to include a change from baseline when exploring seizure outcomes and imprecision as a result of confidence intervals which crossed the threshold for an increase and decrease in the likelihood of seizure reduction. This study did not provide data on seizure outcomes for five participants who were randomised but who discontinued medication; best-case scenario sensitivity analysis indicated that omega-3 may increase the likelihood of a 50% or greater seizure frequency reduction, with worst-case scenario analysis proving inconclusive. Fallah 2018 also explored treatment withdrawal and adverse events associated with omega-3; again, findings were inconclusive about whether this drug increases or decreases the risk, due to study biases, a small number of adverse events and withdrawals occurring, and wide confidence intervals indicating both an appreciable treatment benefit or harm.

Overall completeness and applicability of evidence

Participants in our study had a dual-diagnosis of ADHD and epilepsy. In both studies, epilepsy diagnoses were made according to ILAE criteria Fisher 2014b and ADHD diagnoses made according to DSM-IV criteria DSM-IV. However, a number of participant

characteristics limit the generalisability of our findings. Firstly, our study did not include any adult participants, meaning that our findings can only be generalised to children with ADHD and epilepsy. Secondly, participants in both studies were recruited from clinic settings, so findings cannot be generalised to community settings.

As discussed previously, our review only explored two drugs (one stimulant and one non-stimulant), so we were unable to undertake a meta-analysis of the data.

The included studies did not explore several of the outcomes of interest in our review: the number of episodes of status epilepticus, the number of seizure-related hospitalisations and effects of stimulant/non-stimulant drugs on cognition, general behaviour and quality of life. Among those outcomes for which we had data, these often did not match the definitions set out in our protocol (Walter 2018); for example, in exploring seizure frequency, Fallah 2018 did not include change from baseline scores when comparing omega-3 and control groups.

For a study to be included in our review, the authors must have described it as a randomised controlled trial or have described a process of random allocation into intervention groups. Whilst this improves the quality of the evidence on the efficacy and safety of stimulant and non-stimulant drugs for people with ADHD and epilepsy, some studies will have been ineligible. For example, we did not include the studies by Feldman 1989, Gross-Tsur 1997 and Gucuyener 2003 (the Gucuyener 2003 study was not returned in our search results, but we considered it when searching through the reference list of a relevant review), all of which explored the efficacy and safety of MPH in children with ADHD and epilepsy, but which did not describe a process of random allocation into intervention groups. Our approach will also not have captured observational studies and case studies in this area.

Quality of the evidence

We used GRADE to assess the certainty of evidence for each outcome.

For the comparison of OROS-MPH versus placebo, certainty in outcomes ranged from low to moderate; for the comparison of omega-3 versus control, certainty in outcomes was low. Across both comparisons, key issues included study biases, indirect outcome measures and imprecision as a result of small numbers of events as well as confidence intervals which crossed the threshold for an increase and decrease in the likelihood of a given outcome.

In particular, it is important to highlight that the comparisons of individual adverse events between active and control arms of both Gonzalez-Heydrich 2010 and Fallah 2018 produced risk ratios with very wide confidence intervals, due to the very small number of individual adverse events occurring (e.g. in Fallah 2018, only two participants experienced nausea and vomiting in the active arm and none did so in the control arm). Our findings relating to the risk of individual adverse events associated with OROS-MPH and omega-3 should, therefore, be interpreted with caution.

Potential biases in the review process

We cannot rule out the possibility of publication bias. Gonzalez-Heydrich 2010 did not present the exact proportion of participants showing improvement in ADHD symptoms, or exact numbers for the change in total ADHD-RS score. Data were provided in figures, which prevented accurate estimates and therefore precluded risk ratio and mean difference calculations in this review. We contacted the study authors and asked to obtain these data, however the authors did not respond. We also contacted the authors of Fallah 2018 to request the relevant outcome data from five participants who were randomised but subsequently discontinued medication after three to four weeks; however, the authors did not respond to our request. We attempted to account for this missing data with best-and-worst-case sensitivity analyses of the proportion of individuals achieving 50% or greater reduction in monthly seizure frequency.

Agreements and disagreements with other studies or reviews

Torres 2008 conducted a literature review of pharmacological treatment in children with ADHD and epilepsy. Of relevance to this Cochrane Review, the authors summarised findings from Gonzalez-Heydrich 2010 (which was an ongoing study at the time of the literature review) as well as three additional prospective trials not included in this review due to no evidence of randomisation (Feldman 1989; Gross-Tsur 1997; Gucuyener 2003). Similar to our review, the authors found some evidence for OROS-MPH improving ADHD symptoms over a short-term period, but concluded that existing evidence used small sample sizes with relatively infrequent seizures, which may be underpowered to detect an effect of OROS-MPH on seizure risk.

AUTHORS' CONCLUSIONS

Implications for practice

Preliminary findings suggest that osmotic-release oral system methylphenidate (OROS-MPH) may reduce the severity of attention deficit hyperactivity disorder *(*ADHD) symptoms in children with a dual-diagnosis of ADHD and epilepsy. However, it is also possible that OROS-MPH may increase the risk of seizures and other adverse events (e.g. worsened emotional lability) in this population. These conclusions should be interpreted with caution due to the low certainty surrounding the evidence used to inform them. There is also some preliminary evidence that the non-stimulant drug omega-3, administered in tandem with risperidone and the participant's usual regimen of AEDs, may reduce seizure frequency in children with a dual-diagnosis of ADHD and epilepsy relative to risperidone and AEDs alone, although there is low certainty in this finding. It is also unclear whether this drug increases or decreases the risk of adverse events. Ultimately, more randomised controlled trials are needed to provide a more robust evidence base to better inform clinical practice about the safety and efficacy of stimulant and non-stimulant drugs in people with a dual-diagnosis of ADHD and epilepsy.

Implications for research

There is a dearth of randomised controlled trials exploring the efficacy and safety of stimulant and non-stimulant drugs for people with a dual-diagnosis of ADHD and epilepsy. More studies are needed. Future studies should include adult participants, as research to date has focused on children. A wider variety of stimulant and non-stimulant drugs needs to be assessed, for example, amphetamines (stimulants) and clonidine (non-stimulant), particularly those which are most commonly used

in clinical practice to treat ADHD, such as the non-stimulant atomoxetine. In addition, clusters of studies which assess the same drug are needed, in order to potentially allow for meta-analysis of outcomes. To build on the evidence base presented in this review, future studies could focus on OROS-MPH and omega-3 fish oil. Important outcomes such as occurrence of status epilepticus episodes, seizure-related hospitalisations, cognitive changes, changes in general behaviour and changes in quality of life scores need to be explored. Analysis of any change in seizure frequency should always be relative to baseline.

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- Sign-off Editor (final editorial decision): Tony Marson
- Managing Editor (provided editorial guidance to authors, edited the update, conducted editorial policy checks): Rachael Kelly
- Copy Editor (copy-editing and production): Andrea Takeda

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Fallah 2018

Study characteristics	
Methods	**Treatment allocation:** randomised controlled trial **Study design:** single-blind parallel group **Intervention period:** 3 months **Assessment period:** baseline seizure frequency was taken, but duration of baseline period was not reported. Participants were assessed monthly for 3 consecutive months during the intervention.
Participants	**Country:** Iran **Participants recruited from:** Paediatric Neurology Clinic of Shahid Sadoughi Hospital, Yazd, Iran **Number of participants randomised:** 61 **Number of participants included in the analysis:** 56 **Age of participants:** mean = 9.24 years (SD ± 0.15 years); range 7 to 11 years **Gender of participants:** 58.9% male overall; 55% male in active arm and 63% male in control arm **Diagnosis of epilepsy:** refractory epilepsy was diagnosed according to ILAE criteria **Duration of epilepsy:** NR **Type of epilepsy** • Cryptogenic 30.4% • Idiopathic 14.3% • Symptomatic 55.4% **Type of seizures** • Generalised 44.6% • Focal 17.9% • Mixed 37.5% **Baseline seizure frequency** (monthly)

Fallah 2018 *(Continued)*

- Omega 3: mean = 15.8 (SD ± 8.49)
- Control: mean = 16.7 (SD ± 6.68)

Diagnosis of ADHD: participants diagnosed according to DSM-IV criteria.

Duration of ADHD: NR

Severity of ADHD: all participants had a score of at least 20 on an ADHD diagnostic rating scale conducted via parental interview.

Comorbid conditions and developmental status

- Developmental delay 67.9%
- No developmental delay 32.1%

Medication use

- NR

Inclusion criteria

1. Children 7 to 11 years old
2. Diagnosis of refractory epilepsy according to ILAE classification
3. ADHD diagnosis according to DSM-IV criteria
4. Score of at least 20 in ADHD diagnostic rating scale conducted via parental interview (Urion 2016)
5. Able to walk

Exclusion criteria

1. Supplement use within previous 2 months
2. Diagnosis of any other psychiatric disorders
3. Status epilepticus during research period
4. Allergy to either omega-3 or risperidone
5. Change in antiepileptic drug regimen
6. Use of phenobarbital or topiramate
7. Irregular drugs usage and not taking omega-3 or risperidone for more than 1 week

Interventions	Participants in the active arm received one daily capsule of omega-3 fish oil (21st Centry Co., USA); containing 1000 mg of fish oil, 180 mg of eicosapentaenoic acid and 120 mg of docosahexaenoic acids. In addition, they received 1 mg of risperidone (Abdi Co., Iran) divided into two 0.5 mg doses, as well as their usual regimen of ASM. In the control arm, participants received only the risperidone and usual regimen of antiepileptic drugs. The drugs were delivered by the mothers of the participants, and continued for 3 months.
Outcomes	1. Proportion of participants experiencing > 50% reduction in monthly seizure frequency 2. Monthly seizure frequency at the end of the research period 3. Proportion of participants experiencing adverse drug events
Notes	**Funding:** the study was funded by a grant from the Deputy for Research of Shahid Sadoughi University of Medical Sciences, Yazd, Iran. **Conflict of interest**: the authors declared that there were no conflict of interests.

Fallah 2018 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated equal simple randomisation was used.
Allocation concealment (selection bias)	Low risk	Randomisation was completed by an investigator who had no clinical involvement in the trial. Allocation concealment was completed through the use of sealed opaque envelopes containing the number for each serially participating child. These were then opened by the study paediatric neurologist immediately before study enrolment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Mothers delivering the drug and the participants were not blinded to medication status, given the nature of the study design.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Data collectors and analysts, as well as outcome assessors, were blinded to medication status.
Incomplete outcome data (attrition bias) All outcomes	High risk	One exclusion criterion for the study was discontinuation of omega-3 or risperidone for more than a week. Five randomised participants dropped out on this basis; analysis should have been conducted on an ITT basis.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	Low risk	Low funding bias: funding source was declared and there were no apparent conflicts of interest.

Gonzalez-Heydrich 2010

Study characteristics

Methods	**Treatment allocation:** randomised controlled trial **Study design:** double-blind, placebo-controlled cross-over design. Three groups of participants were assessed sequentially to establish a maximum acceptable dose: in the first group, the maximum dose was 18 mg per day, the second 36 mg and the third 54 mg. **Intervention period:** for group I, the treatment period lasted for 3 weeks (1 week of 18 mg OROS-MPH, 1 week of washout, 1 week of placebo), for group II, 5 weeks (1 week of 18 mg OROS-MPH, 1 week of 36 mg OROS-MPH, 1 week washout, 2 weeks of placebo) and for group III, 7 weeks, (1 week of 18 mg OROS-MPH, 1 week of 36 mg OROS-MPH, 1 week of 54 mg OROS-MPH, 1 week washout, 3 weeks placebo). **Assessment period:** baseline assessments were taken prior to the intervention, but the length of the intervention period was not clearly defined (authors did, however, assess seizure history of the previous 2 years). Outcomes measures were assessed after participants had been on the maximum dose for their group for 1 week.
Participants	**Country:** USA **Participants recruited from:** neurology clinics at Children's Hospital Boston.

Gonzalez-Heydrich 2010 *(Continued)*

Number of participants randomised: 33

Number of participants included in the analysis: 33

Age of participants: 10.5 years (SD ± 3.0 years); range 6.4 to 17.5 years

Gender of participants: 57.6% male

Diagnosis of epilepsy: diagnosed according to ILAE criteria (Fisher 2014b) by PI (child and adolescent psychiatrist), after completing the Seizure Classification Interview, medical record review and consulting with the study neurologist.

Duration of epilepsy: at least 1 seizure within the previous 5 years

Type of epilepsy

- Cryptogenic 36.4%
- Idiopathic 39.4%
- Symptomatic 24.2%

Type of seizures

- Focal onset 78.8%
- Generalised onset 21.2%

Diagnosis of ADHD: diagnosed according to DSM-IV-TR criteria, after PI interviewed children and guardian

Duration of ADHD: NR

Severity of ADHD: all participants had a score >= 90th percentile or above on the ADHD-RS (DuPaul 1998) as a well as a score >= 4 on the Clinical Global Impressions for ADHD severity (Guy 1976), indicating moderate or greater severity)

Comorbid conditions and developmental status

- Full-scale IQ = 89.7 (SD ± 16.9, range 59 to 123)

Medication use

- Number of antiepileptic drugs at start of the study: mean 1.2 (SD ± 0.5, range 1 to 3)
- Valproate 42.4%
- Carbamazepine (18.2%)
- Lamotrigine (18.2%)
- Topiramate (12.1%)
- Levetiracetam (12.1%)
- Gabapentin (3%)
- Oxcarbazepine (6.1%)
- Ethosuximide (6.1%)
- Lorazepam (3%)
- Diazepam (3%)

Inclusion criteria

1. Diagnosis of epilepsy according to ILAE classification
2. ADHD diagnosis according to DSM-IV-TR
3. Stable regiment of AEDs
4. Had at least one seizure within the past five years
5. No seizures for one month prior to taking study medication

Exclusion criteria

Gonzalez-Heydrich 2010 *(Continued)*

1. Severe developmental delays or mental retardation
2. Non-English speaker
3. History of psychosis
4. Current major depression
5. History of bipolar disorder or currently being treated with medication for a mood disorder. This criterion applies to the first seven patients only, after the seventh, it was amended to include patients with a mood disorder that had remitted and patients who were taking mood stabilisers or antidepressants and were defined by the authors as in a stable condition.
6. CGI-ADHD-S rating less than 4 or score on ADHD RS-IV below the 90th percentile on Inattentive and Hyperactive-Impulsive scales, as well as total score.

Interventions	Participants in the active arm received a maximum dosage of either 18 mg, 36 mg or 54 mg of the sustained-release stimulant drug OROS methylphenidate (OROS-MPH), given on a daily basis in the morning. Before testing OROS-MPH, participants were firstly given 5 mg of IR-MPH on the first day of the active arm at morning and at noontime, to see if they tolerated this dose. Participants in the control arm received a placebo.
Outcomes	1. Seizure frequency (number of seizures occurring in OROS-MPH and control arms, by dose) 2. Proportion of participants withdrawing from treatment 3. Proportion of participants experiencing significant worsening of epilepsy 4. Proportion of participants experiencing adverse events 5. Proportion of participants classed as 'responders' with respect to ADHD symptom severity on CGI-ADHD-I (scores of 'much improved' and 'very much improved' at the last observation on that arm of the cross-over, relative to baseline) 6. Mean weekly ADHD-RS total score by dose level
Notes	Recruitment into the 36 mg group could not begin until at least 3 participants had completed the cross-over trial for the 18 mg dose without a significant worsening of epilepsy or a serious adverse event, with this process repeated for the 54 mg group. It is important to note that the maximum dose was the lesser of 54 mg or 2 mg/kg/day, therefore even if a higher dose group had begun recruiting (e.g. group II), the participant could still be assigned to the lower group (e.g. group I) to ensure the maximum dose remained below 2 mg/kg/day. If at any of the 3 dose levels 2 participants had significant worsening of epilepsy during the active arm, the dose level immediately below would be fixed as the maximum dose for the rest of the study (this did not occur and so all 3 dose levels were tested). Significant worsening of epilepsy was defined as 1) a doubling of the highest 14-day or 2-day seizure rate observed during the 12 months preceding the trial; 2) the occurrence of a generalised tonic-clonic seizure if the participant had not experienced one in the previous 2 years; 3) an intensification of seizure severity or frequency determined to be clinically meaningful. **Funding:** this study was supported by NIMH Grant K23 MH066835. **Conflict of interest:** the trial authors made the following declarations in the conflicts of interest statement:. "In the past year, Dr. Joseph Gonzalez-Heydrich, has been a consultant to AstraZeneca and received research support from Pfizer, Johnson & Johnson, and GlaxoSmithKline. In previous years, he has served as a consultant to Abbott Laboratories, Pfizer, Johnson & Johnson (Janssen, McNeil Consumer Health), Novartis, Parke–Davis, GlaxoSmithKline, AstraZeneca, and Seaside Therapeutics; has been a speaker for Abbott Laboratories, Pfizer, Novartis, Bristol–Meyers Squibb; and has received grant support from Abbott Laboratories, Pfizer, Johnson & Johnson (Janssen, McNeil Consumer Health), Akzo-Nobel/Organon, and the NIMH. McNeil Consumer Health provided the active OROS methylphenidate and matching placebo for this study. In the past year, Dr. Stephen Faraone has received consulting fees and has been on advisory boards for Eli Lilly, McNeil, and Shire and has received research support from Eli Lilly, Pfizer, Shire, and the National

Gonzalez-Heydrich 2010 *(Continued)*

Institutes of Health. In previous years, Dr. Faraone has received consulting fees, has been on advisory boards, or has been a speaker for the following sources: Shire, McNeil, Janssen, Novartis, Pfizer, and Eli Lilly. In previous years he has received research support from Eli Lilly, Shire, Pfizer, and the National Institutes of Health.
Dr. Joseph Biederman is currently receiving research support from the following sources: Alza, AstraZeneca, Bristol–Myers Squibb, Eli Lilly,
Janssen Pharmaceuticals, McNeil, Merck, Organon, Otsuka, Shire, NIMH, and NICHD. In 2009, Dr. Joseph Biederman received a speaker's fee from the following sources: Fundacion Areces, Medice Pharmaceuticals, and the Spanish Child Psychiatry Association. In previous years, he received research support, consultation fees, or speaker's fees for/from the following additional sources: Abbott, AstraZeneca, Celltech, Cephalon, Eli Lilly, Esai, Forest, Glaxo, Gliatech, Janssen, McNeil, NARSAD, NIDA, New River, Novartis, Noven, Neurosearch, Pfizer, Pharmacia, The Prechter Foundation, Shire, The Stanley Foundation, UCB Pharma, and Wyeth.

Dr. Blaise Bourgeois has received grant/research support from Eisai, Ovation, and UCB Pharma. In the past 2 years, he also received consulting fees from Genzyme and Bayer Material Science."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study reported that participants were randomly allocated to either active or control arm for the first arm of the cross-over and that randomisation lists for each dose group were prepared by a statistician and maintained by the research pharmacist. However, the study did not report the method of randomisation.
Allocation concealment (selection bias)	Unclear risk	Study did not report how allocation was concealed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Study reported that the study personnel and the supervising organisations (the Data and Safety Monitoring Board and the Institutional Review Board of the Children Hospital Boston) were blind to medication status.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Study reported that the PI (the outcome assessor) was blind to medication status.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All 33 randomised participants were included in the data analyses.
Selective reporting (reporting bias)	Low risk	All outcomes reported.
Other bias	High risk	Funding bias: several authors received funding from McNeil Consumer Health, the provider of active OROS methylphenidate and matching placebo for this study.

ADHD = Attention Deficit Hyperactivity Disorder; ADHD-RS = ADHD Rating Scale; ASM = anti seizure medication; CGI-ADHD-I = Clinical Global Impression for ADH - Improvement Subscale; CGI-ADHD-S =Clinical Global Impressions for ADHD - Severity Subscale; DSM-IV-TR = Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Revised; ILAE = International League Against Epilepsy; ITT = intention-to-treat; IR-MPH = immediate-release methylphenidate; NR = not reported; OROS-MPH = osmotic-release oral system methylphenidate; PI = Principal Investigator

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adams 2017	Participants do not have a diagnosis of both epilepsy and attention-deficit hyperactivity disorder (according to the DSM/ICD).
Dave 1993	Participants do not have a diagnosis of both epilepsy and attention-deficit hyperactivity disorder (according to the DSM/ICD).
Eapen 2005	Study is not a randomised controlled trial, or does not describe a process of random allocation into intervention groups.
Feldman 1989	Study is not a randomised controlled trial, or does not describe a process of random allocation into intervention groups.
Frank 1993	Participants do not have a diagnosis of both epilepsy and attention-deficit hyperactivity disorder (according to the DSM/ICD).
Ghose 1983	Participants do not have a diagnosis of both epilepsy and attention-deficit hyperactivity disorder (according to the DSM/ICD).
Gross-Tsur 1997	Study is not a randomised controlled trial, or does not describe a process of random allocation into intervention groups.
Gunning 2004	Study is not a randomised controlled trial, or does not describe a process of random allocation into intervention groups.
Ikeda 1996	Participants do not have a diagnosis of both epilepsy and attention-deficit hyperactivity disorder (according to the DSM/ICD).
Moorthy 2018	Study is not a randomised controlled trial, or does not describe a process of random allocation into intervention groups.
Swanson 2008	Participants do not have a diagnosis of both epilepsy and attention-deficit hyperactivity disorder (according to the DSM/ICD).
van der Feltz-Cornelis 2006	Study is not a randomised controlled trial, or does not describe a process of random allocation into intervention groups.
Villanueva 2016	Participants do not have a diagnosis of both epilepsy and attention-deficit hyperactivity disorder (according to the DSM/ICD).
Wernicke 2007	Literature review

DSM = Diagnostic and Statistical Manual; ICD = International Classification of Disease

Characteristics of ongoing studies *[ordered by study ID]*

NCT02348073 2015

Study name	Efficacy of Phosphatidylserine Enriched With n-3 PUFA Supplementation on ADHD in Children With Epilepsy (AGPIn3)
Methods	**Treatment allocation:** randomised Controlled Trial **Study design:** triple-blind parallel group **Intervention period:** 24 weeks

NCT02348073 2015 *(Continued)*

	Assessment period: 12 to 36 weeks, depending on outcome
Participants	**Country:** France **Participants recruited from:** 12 clinical sites across France **Number of participants randomised:** NR; 77 enrolled **Number of participants included in the analysis:** NR; 77 enrolled **Age of participants:** range 6 years to 15 years 11 months **Gender of participants:** either sex (male/female) **Diagnosis of epilepsy:** NR **Duration of epilepsy:** NR; however, please refer to inclusion criteria — participants on a stable dose of AEDs for a minimum of one month prior to inclusion. **Type of epilepsy:** epilepsy, regardless of syndrome classification **Type of seizures:** NR **Baseline seizure frequency (monthly):** NR **Diagnosis of ADHD:** diagnosed according to DSM V criteria; inattentive or mixed type **Duration of ADHD:** NR **Severity of ADHD:** NR **Comorbid conditions and developmental status:** see exclusion criteria — participants with intellectual disability and comorbid psychiatric and neurodevelopmental disorders were excluded. **Medication use:** See inclusion and exclusion criteria — on a stable dose of AEDs for a minimum of 1 month prior to enrolment. Participants using psychoactive drugs and any dietary supplementation other than vitamins were excluded. **Inclusion criteria** 1. Children and adolescents aged between 6 years and 15 years and 11 months. 2. Children and adolescents of either sex (male/female) with epilepsy (any syndrome classification). 3. Children and adolescents on a stable dose of antiepileptic drugs (AED) for a minimum of 1 month prior to inclusion, and participants for whom no change is considered a priori for the 3 months following inclusion. 4. Diagnosis of ADHD according to the DSM V criteria; inattentive or mixed type. 5. Children and adolescents who agreed to take part, with their parents or legal guardian providing written informed consent. **Exclusion criteria** 1. Children and adolescents aged less than 6 years or older than 16 years 2. AED use not stable for a minimum of 1 month and/or a change in AED was expected in the 3 months following inclusion. 3. Diagnosis of ADHD hyperactivity type (exclusive), according to DSM-V criteria. 4. Presence of intellectual disability, defined as a score < 70 on the verbal comprehension and perceptual reasoning of the WISC-IV, performed within 18 months prior to inclusion or at visit 1. 5. Diagnosis of a psychiatric comorbidity other than ADHD according to the DSM-V criteria, including: pervasive developmental disorders including autism disorders; bipolar disorders and psychotic disorders. 6. Children and adolescents with any type of diabetes

NCT02348073 2015 *(Continued)*

	7. Children and adolescents who used psychoactive drugs in ADHD within the previous month: methylphenidate, amphetamine, atomoxetine, modafinil and antidepressants, whatever the class. 8. Children and adolescents who used dietary supplements, other than vitamins, within the last 3 months 9. Children and adolescents who used a ketogenic diet within the last 3 months 10. Children and adolescents with an allergy to fish or other sea products 11. Children and adolescents with a soy allergy 12. Absence of coverage by social security
Interventions	Each day, participants in the active arm received 2 capsules of Vayarin, supplementation of n-3 polyunsaturated fatty acid (PUFA): each capsule contains 8.5 mg of docosahexaenoic acid (DHA), 21.5 mg of eicosapentaenoic acid (EPA) and 75 mg of phosphatidylserine. Capsules were administered 20 to 30 minutes prior to breakfast and dinner over a 12-week period (between visit 1 and visit 2). Participants in the control arm took a placebo: 2 daily capsules, each made of cellulose and a small amount of fish power (added to maintain the double-blind in odour and taste). Capsules were administered 20 to 30 minutes prior to break and dinner over a 12-week period (between visit 1 and visit 2). After this initial 12-week period, participants in both arms took Vayarin (same dose) over a subsequent 12-week open-label period.
Outcomes	1. Comparison of the reduction of the ADHD-rating scale IV inattentive sub-score between participants in the active and control arms, after 12 weeks of treatment. 2. Comparison of the reduction of the ADHD Rating Scale-IV total score between participants in the active and control arms, after 12 weeks of treatment. 3. Comparison of the reduction in the TOVA score (Test of Variables of Attention) between participants in the active and control arms, after 12 weeks of treatment 4. Comparison of the proportion of participants with a normalized TOVA score between the active and control arms, after 12 weeks of treatment 5. Comparison of the change in quality of life score (EFIQUACEE questionnaire — a quality of life scale for children with epilepsy) between the active and control groups, after 12 weeks of treatment. 6. Adverse events reported throughout the study; timeframe 36 weeks. 7. Comparison of the number participants with a reduction in the frequency of seizures ≥ 50% between the active and control groups, after 12 weeks of treatment.
Starting date	March 2015
Contact information	Sylvain Rheims, MD Hospices Civils de Lyon sylvain.rheims@chu-lyon.fr
Notes	This study was completed in 2018. We contacted the study authors, who are preparing the manuscript for publication

ADHD = Attention Deficit Hyperactivity Disorder; AED = antiepileptic drug; DHA = docosahexaenoic acid; DSM V = Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; EPA = eicosapentaenoic acid; NR = not reported; TOVA = Test of Variables of Attention

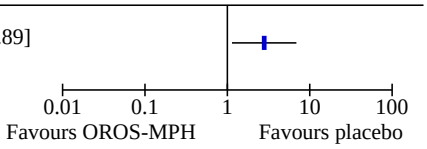
DATA AND ANALYSES

Comparison 1. OROS-MPH versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Proportion of people withdrawing from treatment - primary outcome	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.2 Individual adverse drug events - secondary outcome	1		Risk Ratio (M-H, Fixed, 99% CI)	Totals not selected
1.2.1 Worsened emotional lability	1		Risk Ratio (M-H, Fixed, 99% CI)	Totals not selected
1.2.2 Seizures	1		Risk Ratio (M-H, Fixed, 99% CI)	Totals not selected

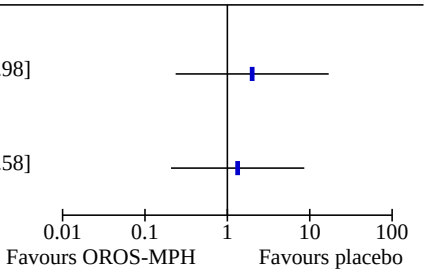
Analysis 1.1. Comparison 1: OROS-MPH versus placebo, Outcome 1: Proportion of people withdrawing from treatment - primary outcome

Study or Subgroup	OROS-MPH Events	OROS-MPH Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 95% CI
Gonzalez-Heydrich 2010	14	33	5	33	2.80 [1.14 , 6.89]
Test for subgroup differences: Not applicable					



Analysis 1.2. Comparison 1: OROS-MPH versus placebo, Outcome 2: Individual adverse drug events - secondary outcome

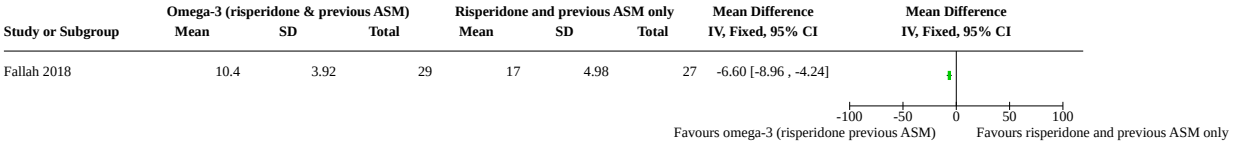
Study or Subgroup	OROS-MPH Events	OROS-MPH Total	Placebo Events	Placebo Total	Risk Ratio M-H, Fixed, 99% CI
1.2.1 Worsened emotional lability					
Gonzalez-Heydrich 2010	4	33	2	33	2.00 [0.24 , 16.98]
1.2.2 Seizures					
Gonzalez-Heydrich 2010	4	33	3	33	1.33 [0.21 , 8.58]



Comparison 2. Omega-3 (risperidone & previous ASM) versus risperidone and previous ASM only

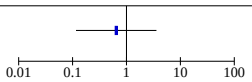
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Seizure frequency (monthly, postintervention) - primary outcome	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.2 Proportion of individuals withdrawing from treatment - primary outcome	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.3 Proportion of people achieving 50% or greater reduction in monthly seizure frequency (change from baseline) - secondary outcome	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.4 Best-case scenario: proportion of people achieving 50% or more reduction in seizure frequency	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.5 Worst-case scenario: proportion of people achieving 50% reduction in seizure frequency	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.6 Proportion of people experiencing adverse drug events - secondary outcome	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2.7 Individual adverse effects	1		Risk Ratio (M-H, Fixed, 99% CI)	Totals not selected
2.7.1 Sleepiness	1		Risk Ratio (M-H, Fixed, 99% CI)	Totals not selected
2.7.2 Diarrhoea	1		Risk Ratio (M-H, Fixed, 99% CI)	Totals not selected
2.7.3 Nausea & vomiting	1		Risk Ratio (M-H, Fixed, 99% CI)	Totals not selected
2.7.4 Anorexia	1		Risk Ratio (M-H, Fixed, 99% CI)	Totals not selected
2.7.5 Constipation	1		Risk Ratio (M-H, Fixed, 99% CI)	Totals not selected

Analysis 2.1. Comparison 2: Omega-3 (risperidone & previous ASM) versus risperidone and previous ASM only, Outcome 1: Seizure frequency (monthly, postintervention) - primary outcome



Analysis 2.2. Comparison 2: Omega-3 (risperidone & previous ASM) versus risperidone and previous ASM only, Outcome 2: Proportion of individuals withdrawing from treatment - primary outcome

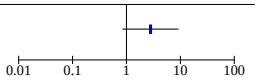
Study or Subgroup	Omega-3 (risperidone & previous ASM) Events	Total	Risperidone and previous ASM only Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F G
Fallah 2018	2	31	3	30	0.65 [0.12 , 3.59]		+ + - + - + +



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

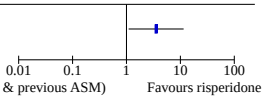
Analysis 2.3. Comparison 2: Omega-3 (risperidone & previous ASM) versus risperidone and previous ASM only, Outcome 3: Proportion of people achieving 50% or greater reduction in monthly seizure frequency (change from baseline) - secondary outcome

Study or Subgroup	Omega-3 (risperidone & previous ASM) Events	Total	Risperidone and previous ASM only Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Fallah 2018	9	29	3	27	2.79 [0.84 , 9.24]	



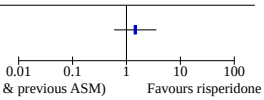
Analysis 2.4. Comparison 2: Omega-3 (risperidone & previous ASM) versus risperidone and previous ASM only, Outcome 4: Best-case scenario: proportion of people achieving 50% or more reduction in seizure frequency

Study or Subgroup	Omega-3 (risperidone & previous ASM) Events	Total	Risperidone and previous ASM only Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Fallah 2018	11	31	3	30	3.55 [1.10 , 11.48]	



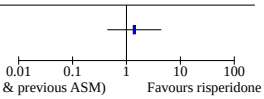
Analysis 2.5. Comparison 2: Omega-3 (risperidone & previous ASM) versus risperidone and previous ASM only, Outcome 5: Worst-case scenario: proportion of people achieving 50% reduction in seizure frequency

Study or Subgroup	Omega-3 (risperidone & previous ASM) Events	Total	Risperidone and previous ASM only Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Fallah 2018	9	31	6	30	1.45 [0.59 , 3.58]	

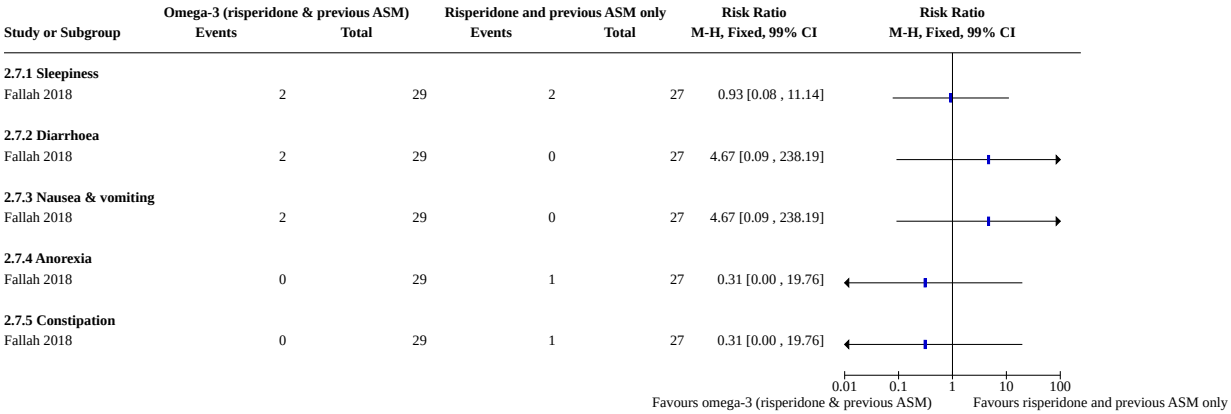


Analysis 2.6. Comparison 2: Omega-3 (risperidone & previous ASM) versus risperidone and previous ASM only, Outcome 6: Proportion of people experiencing adverse drug events - secondary outcome

Study or Subgroup	Omega-3 (risperidone & previous ASM) Events	Total	Risperidone and previous ASM only Events	Total	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI
Fallah 2018	6	29	4	27	1.40 [0.44 , 4.42]	



Analysis 2.7. Comparison 2: Omega-3 (risperidone & previous ASM) versus risperidone and previous ASM only, Outcome 7: Individual adverse effects



APPENDICES

Appendix 1. CRS Web search strategy

1. MESH DESCRIPTOR Attention Deficit Disorder with Hyperactivity EXPLODE ALL WITH QUALIFIER DT AND CENTRAL:TARGET

2. (ADHD or ADDH or (hyperactiv* ADJ4 disorder*)):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

3. (attention ADJ3 deficit*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

4. (attention ADJ3 disorder*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

5. #2 OR #3 OR #4 AND CENTRAL:TARGET

6. MESH DESCRIPTOR Drug Therapy EXPLODE ALL AND CENTRAL:TARGET

7. (drug* or stimulant* or pharmacol* or medicat* or chemotherap*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

8. MESH DESCRIPTOR Central Nervous System Stimulants EXPLODE ALL AND CENTRAL:TARGET

9. (amphetamin* or amfetamin* or dexamphetamin* or dexamfetamin* or dextroamphetamin* or dextroamfetamin* or lisdexamphetamin* or lisdexamfetamin*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

10. (Adderall or Adzenys or Dexedrine or Dyanavel or Evekeo or ProCentra or Vyvanse or Zenzedi):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

11. (methylphenidat* or methylfenidat* or Ritalin or Concerta or Aptensio or Biphentin or Daytrana or Equasym or Medikinet or Metadate or Methylin or QuilliChew or Quillivant):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

12. MESH DESCRIPTOR Atomoxetine Hydrochloride EXPLODE ALL AND CENTRAL:TARGET

13. (atomoxetin* or tomoxetin* or Strattera):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

14. MESH DESCRIPTOR Clonidine EXPLODE ALL AND CENTRAL:TARGET

15. (Clonidine* or Catapres or Kapvay or Nexiclon or Clophelin):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

16. MESH DESCRIPTOR Guanfacine EXPLODE ALL AND CENTRAL:TARGET

17. (guanfacin* or Afken or Estulic or Intuniv or Tenex):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

18. MESH DESCRIPTOR Bupropion EXPLODE ALL AND CENTRAL:TARGET

19. (buproprion* or bupropion* or amfebutamone or aplenzin or elontril or wellbutrin or zyban):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

20. (lofexadin* or lofexidin* or britlofex or "Kai Er Ding"):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

21. #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20

22. #5 AND #21

23. #1 OR #22

24. MESH DESCRIPTOR Epilepsy EXPLODE ALL AND CENTRAL:TARGET

25. MESH DESCRIPTOR Seizures EXPLODE ALL AND CENTRAL:TARGET

26. (epilep* OR seizure* OR convuls*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

27. #24 OR #25 OR #26 AND CENTRAL:TARGET

28. #23 AND #27

Appendix 2. MEDLINE search strategy

This strategy includes a modification of the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (Lefebvre 2021).

1. exp Attention Deficit Disorder with Hyperactivity/dt [Drug Therapy]

2. (ADHD or ADDH or (hyperactiv$ adj4 disorder$)).tw.

3. (attention adj3 deficit$).tw.

4. (attention adj3 disorder$).tw.

5. 2 or 3 or 4

6. exp Drug Therapy/

7. (drug$ or stimulant$ or pharmacol$ or medicat$ or chemotherap$).tw.

8. exp Central Nervous System Stimulants/

9. (amphetamin$ or amfetamin$ or dexamphetamin$ or dexamfetamin$ or dextroamphetamin$ or dextroamfetamin$ or lisdexamphetamin$ or lisdexamfetamin$).tw.

10. (Adderall or Adzenys or Dexedrine or Dyanavel or Evekeo or ProCentra or Vyvanse or Zenzedi).tw.

11. (methylphenidat$ or methylfenidat$ or Ritalin or Concerta or Aptensio or Biphentin or Daytrana or Equasym or Medikinet or Metadate or Methylin or QuilliChew or Quillivant).tw.

12. exp Atomoxetine Hydrochloride/

13. (atomoxetin$ or tomoxetin$ or Strattera).tw.

14. exp Clonidine/

15. (clonidin$ or Catapres or Kapvay or Nexiclon or Clophelin).tw.

16. exp Guanfacine/

17. (guanfacin$ or Afken or Estulic or Intuniv or Tenex).tw.

18. exp Bupropion/ or (buproprion$ or bupropion$ or amfebutamone or aplenzin or elontril or wellbutrin or zyban).tw.

19. (lofexadin$ or lofexidin$ or britlofex or "Kai Er Ding").tw.

20. or/6-19

21. 5 and 20

22. 1 or 21

23. exp Epilepsy/

24. exp Seizures/

25. (epilep$ or seizure$ or convuls$).tw.

26. 23 or 24 or 25

27. exp *Pre-Eclampsia/ or exp *Eclampsia/

28. 26 not 27

29. 22 and 28

30. exp controlled clinical trial/ or (randomi?ed or placebo or randomly).ab.

31. clinical trials as topic.sh.

32. trial.ti.

33. 30 or 31 or 32

34. exp animals/ not humans.sh.

35. 33 not 34

36. 29 and 35

37. remove duplicates from 36

Appendix 3. CINAHL search strategy

This strategy includes a modification of the Cochrane CINAHL Plus search filter (Glanville 2019).

S44 S38 NOT S43

S43 S41 NOT S42

S42 MH Human

S41 S39 OR S40

S40 MH animals+ OR MH (animal studies)

S39 TI animal model*

S38 S26 AND S37

S37 S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36

S36 MH (randomized controlled trials) OR MH (double-blind studies) OR MH (single-blind studies) OR MH (random assignment) OR MH (pretest-posttest design) OR MH (cluster sample) OR MH (placebos) OR MH (crossover design) OR MH (comparative studies)

S35 TI (randomised OR randomized OR trial)

S34 AB (random*)

S33 TI (trial)

S32 MH (sample size) AND AB (assigned OR allocated OR control)

S31 MH (placebos)

S30 PT (randomized controlled trial)

S29 AB (control W5 group)

S28 MH (crossover design) OR MH (comparative studies)

S27 AB (cluster W3 RCT)

S26 S22 AND S25

S25 S23 OR S24

S24 MM ("Epilepsy+") OR (MM "Seizures")

S23 epilep* OR seizure*

S22 S1 OR S21

S21 S5 AND S20

S20 S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19

S19 lofexadin* or lofexidin* or britlofex or "Kai Er Ding"

S18 buproprion* or bupropion* or amfebutamone or aplenzin or elontril or wellbutrin or zyban

S17 (MH "Bupropion")

S16 guanfacin* or Afken or Estulic or Intuniv or Tenex

S15 Clonidine* or Catapres or Kapvay or Nexiclon or Clophelin

S14 (MH "Clonidine")

S13 atomoxetin* or tomoxetin* or Strattera

S12 (MH "Atomoxetine")

S11 methylphenidat* or methylfenidat* or Ritalin or Concerta or Aptensio or Biphentin or Daytrana or Equasym or Medikinet or Metadate or Methylin or QuilliChew or Quillivant

S10 Adderall or Adzenys or Dexedrine or Dyanavel or Evekeo or ProCentra or Vyvanse or Zenzedi

S9 amphetamin* or amfetamin* or dexamphetamin* or dexamfetamin* or dextroamphetamin* or dextroamfetamin* or lisdexamphetamin* or lisdexamfetamin*

S8 (MH "Central Nervous System Stimulants+")

S7 TI (drug* or stimulant* or pharmacol* or medicat* or chemotherap*) OR AB (drug* or stimulant* or pharmacol* or medicat* or chemotherap*)

S6 (MH "Drug Therapy+")

S5 S2 OR S3 OR S4

S4 TX attention N3 disorder*

S3 TX attention N3 deficit*

S2 TX ADHD or ADDH or (hyperactiv* N4 disorder*)

S1 (MH "Attention Deficit Hyperactivity Disorder/DT")

HISTORY

Protocol first published: Issue 9, 2018

CONTRIBUTIONS OF AUTHORS

CE: selection of trials to include/exclude, data extraction, risk of bias assessment, data analysis, write-up of the review

KY: selection of trials to include/exclude, data extraction, risk of bias assessment, data analysis, write-up of the review

VW: drafting the protocol, developing the search strategy

GM: drafting the protocol, developing the search strategy, providing feedback and edits for the review

SR: providing feedback and edits for the review

RC: conceptualisation of the review, drafting the protocol, developing the search strategy, selection of trials to include/exclude, providing feedback and edits for the review

DECLARATIONS OF INTEREST

CE: none to declare

KY: none to declare

VW: none to declare

GM: none to declare

SR: none to declare

RC: has provided consultancy for Eisai, GW Pharma, Zogenix. He has received payment for lectures from GW Pharma, Zogenix and has received support for attendance to a conference to present results of a separate Eisai sponsored study. RC has shares in RIZE Medical Cannabis and Life Sciences. RC monies are paid to his institution.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- National Institute for Health and Care Research (NIHR), UK

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The following authors were added to the review: Kenneith Yong, Christopher Eaton and Sinead Rhodes.

The diversity of stimulant/non-stimulant drugs measured, study design and reported outcomes meant that we were unable to pool data from the two studies included in our review. We therefore did not conduct analyses of statistical heterogeneity or any of the subgroup analyses (see items 1 to 9 in Subgroup analysis and investigation of heterogeneity).

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [adverse effects]; *Attention Deficit Disorder with Hyperactivity [drug therapy]; *Central Nervous System Stimulants [adverse effects]; *Drug Resistant Epilepsy [drug therapy]; *Drug-Related Side Effects and Adverse Reactions; *Epilepsy [complications] [drug therapy]; Iran; Quality of Life; Risperidone [therapeutic use]

MeSH check words

Adolescent; Adult; Child; Humans