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Strategies for improving adherence to antiepileptic drug treatment in people with epilepsy (Review)

Al-aqeel S, Gershuni O, Al-sabhan J, Hiligsmann M

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[Intervention Review]

Strategies for improving adherence to antiepileptic drug treatment in people with epilepsy

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ABSTRACT

Background

Poor adherence to antiepileptic medication is associated with increased mortality, morbidity and healthcare costs. In this review, we focus on interventions designed and tested in randomised controlled trials (RCTs) and quasi-RCTs to assist people with adherence to antiepileptic medication. This is an update of a Cochrane review first published in 2011, and last updated in 2017.

Objectives

To determine the effectiveness of interventions aimed at improving adherence to antiepileptic medication in adults and children with epilepsy.

Search methods

For the latest update, we searched the following databases on 18 February 2020: Cochrane Register of Studies (CRS Web), MEDLINE, CINAHL Plus and PsycINFO. CRS Web includes RCTs or quasi-RCTs from PubMed, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), CENTRAL, and the Specialized Registers of Cochrane Review Groups including Epilepsy. We also searched the reference lists of relevant articles.

Selection criteria

RCTs and quasi-RCTs of adherence-enhancing interventions aimed at people with a clinical diagnosis of epilepsy (as defined in individual studies), of any age and treated with antiepileptic drugs in a primary care, outpatient or other community setting.

Data collection and analysis

All review authors independently assessed lists of potentially relevant citations and abstracts. At least two review authors independently extracted data and performed a quality assessment of each study according to the Cochrane tool for assessing risk of bias. We graded the level of evidence for each outcome according to GRADE. The studies differed widely according to the type of intervention and measures of adherence; therefore combining data was not appropriate.

Main results

We included 20 studies reporting data on 2832 participants. Thirteen studies targeted adults with epilepsy, one study included participants of all ages, one study included participants older than two years, one recruited pediatric patients aged between 1 month to 15 years, one study targeted caregivers of children with epilepsy, one targeted adolescents and caregivers, and two studies targeted families

of children with epilepsy. We identified three ongoing studies. Follow-up time was generally short in most studies, ranging from 1 to 12 months. The studies examined three main types of interventions: educational interventions, behavioural interventions and mixed interventions. All but three studies compared treatment with usual care or 'no intervention'. Due to heterogeneity between studies in terms of interventions, methods used to measure adherence and the way the studies were reported, we did not pool the results and these findings were inappropriate to be included in a meta-analysis.

Education and counselling of participants with epilepsy had mixed success (moderate-certainty evidence). Behavioural interventions such as the use of intensive reminders provided more favourable effects on adherence (moderate-certainty evidence). The effect on adherence to antiepileptic drugs described by studies of mixed interventions showed improved adherence in the intervention groups compared to the control groups (high-certainty evidence).

Eleven studies described seizure frequency or seizure severity or both, with four of them, reporting improved adherence and decreased seizure frequency in the intervention groups (moderate-certainty evidence). Findings related to self-efficacy and quality of life were mixed, with no clear pattern across types of intervention.

Authors' conclusions

Behavioural interventions such as intensive reminders and the use of mixed interventions demonstrate some positive results, however, we need more reliable evidence on their efficacy, derived from carefully-designed RCTs before we can draw a firm conclusion. None of the newly included studies have provided additional information that would lead to significant changes in our conclusions.

PLAIN LANGUAGE SUMMARY

What is the best way to ensure people with epilepsy take their medication as prescribed?

Why is this question important?
Epilepsy is a very common condition that affects the brain. People with epilepsy experience seizures - or fits - that can affect their daily lives. They are often prescribed medicines to control or prevent seizures. People with epilepsy can find it difficult to take their medicines as prescribed, and this is thought to be a reason for poor control of seizures. This review of studies reports on ways of improving how they take their antiepileptic medication.

What we did
We searched medical databases for clinical studies looking at ways of improving adherence to medication in people with epilepsy. We limited our search to randomised controlled trials (RCTs) involving people with a clinical diagnosis of epilepsy of any age and treated with antiepileptic drugs in a primary care (for example, doctor's surgery), outpatient or other community setting. RCTs are medical studies where people are chosen at random to receive a treatment (called the intervention group) or to receive a different treatment or no treatment (called the control group). This type of study provides the most reliable evidence about whether different approaches to health care make a difference.

The results are up to date to February 2020.

What we found
We identified 20 studies (2832 participants). The studies were conducted in different countries with the majority from the USA. The studies examined three main types of interventions:

1. education and counselling of participants about topics such as epilepsy and medication used to control epilepsy (4 studies);

2. behavioural interventions, such as asking people with epilepsy to link the intention of taking their medication with a particular time, place and other routine activity (13 studies); and

3. mixed interventions, which is the use of more than one intervention (4 studies).

One study is counted twice because it compared a behavioural intervention with a mixed intervention.

Studies measured adherence to medication in various ways, for example, with questionnaires, blood samples or electronic bottle tops. Studies also measured reduction in frequency or severity of seizures to see if taking medication as prescribed made a difference. The studies were all very different from each other, so we could not combine their results.

Key results and reliability of the evidence
Education and counselling interventions may improve medication adherence. Two studies showed improvement, one study showed a small improvement and one no improvement.

Behavioural and mixed interventions probably improve adherence to medication. People in the intervention groups showed improved adherence compared to the control groups.

Four studies showed that when adherence improved in the intervention groups, seizure frequency or seizure severity was decreased.

We were unable to draw firm conclusions about the results because the studies were very different from each other and did not always use the best methods. This means we are not certain about their evidence.

What should happen next?

We need carefully-designed randomised controlled studies involving more people with longer follow-up periods to identify the best intervention to improve adherence to antiepileptic medication.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings table

Strategies for improving adherence to antiepileptic drug treatment in people with epilepsy

Patient or population: adults and children with epilepsy
Setting: all settings
Intervention: adherence-enhancing intervention
Comparison: no intervention or other intervention

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no intervention or other intervention	Risk with adherence-enhancing intervention				
Effects on adherence (behavioural interventions) Assessed with MEMS caps, self-reported Antiretroviral General Adherence Scale (AGAS), the serum level and the Medication Adherence Report Scale (MARS) Follow-up: range 1 month to 6 months	Not estimable See comments	Not estimable See comments	-	391 (4 RCTs)	⊕⊕⊕⊖[a,b] Moderate	2 studies showed significant improvement in adherence (see Summary of results for each included study Table 1). 1 study showed minimal adherence improvements by the end of the follow-up in combination with high levels of baseline adherence. Due to different interventions and assessment methods we are unable to draw further conclusions.
Effects on adherence (educational interventions) Assessed with serum or plasma concentration, Medication Adherence Scale (MAS), MEMS, TrackCap and a 10-item subscale from 'Epilepsy Self-management Scale', the Morisky Medication Adherence Scale (MMAS-8). Follow-up: range 4 weeks to 13 months	Not estimable See comments	Not estimable See comments	-	1938 (13 RCTs)	⊕⊕⊕⊖[a,b] Moderate	Only 5 studies presented significant results of improved adherence. 1 study included families (the information on the total number of people is not specifically mentioned). Due to different interventions and assessment methods, we are unable to draw further conclusions (see Summary of results for each included study Table 1).
Effects on adherence (mixed interventions)	Not estimable See comments	Not estimable See comments	-	612 (4 RCTs)	⊕⊕⊕⊕[b] High	Only 2 studies reported significant improvement in adherence. Due to hetero-

Assessed with serum or plasma concentration, Medication Adherence Scale (MAS), MEMS, and Medication Adherence Scale (MARS-5) Follow-up: range 6 months to 12 months						geneity of interventions and assessment methods, we are unable to draw further conclusions (see Summary of results for each included study Table 1).
Seizure frequency and/or seizure severity Assessed by National Hospital Seizure Severity Scale (NHS3), seizure diary and self-reporting Follow-up: range 4 months to 12 months	Not estimable See comments	Not estimable See comments	-	2147 (11 RCTs)	⊕⊕⊕⊖[a,b] Moderate	Decreased seizure frequency and/or seizure severity related to improved adherence to AEDs was described in 4 out of 11studies presenting this secondary outcome. 2 studies reported improvement, however, no significant difference between 2 groups was reported or showed any changes. In 1 study, the intervention was associated with a stronger impact on self-efficacy and seizure management (see Summary of results for each included study Table 1).
Self-efficacy Assessed with the Epilepsy Self-Efficacy Scale (ESES), General Self-Efficacy Scale (GSES) and Sherer's Self-Efficacy Scale Follow-up: range 3 months to 12 months	Not estimable See comments	Not estimable See comments	-	453 (5 RCTs)	⊕⊕⊖⊖[a,c] Low	Only 1 study presented significantly important results supporting improvement in self-efficacy skills. Other studies reporting positive effects as a result of an intervention with mixed reliability (see Summary of results for each included study Table 1)
Quality of life Assessed with Quality of Life in Epilepsy Scale (QOLIE-10, QOLIE-31-P) and health-related quality of life (HRQOL) Follow-up: range 4 months to 12 months	Not estimable See comments	Not estimable See comments	-	1027 (6 RCTs)	⊕⊕⊕⊖[a,b] Moderate	Only 1 study reported significant benefit in the intervention group. 3 studies showed that there were no statistically significant differences and another study failed to present results supporting the added value of an intervention. Another study tried to evaluate HRQoL and to discuss relationships with other related outcomes: patients with lower QoL values were reporting lower levels of general well being and satisfaction. (see Summary of results for each included study Table 1)

*__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).

AED: antiepileptic drug; **CI:** confidence interval; **HRQoL:** health-related quality of life; **MEMS:** Medication Event Monitoring System; **QoL:** quality of life; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]The certainty of the evidence of the studies measuring this outcome was downgraded due to the lack of precision or lack of consistency, or both.
[b]The majority of studies measuring this outcome were not at high risk of bias.
[c]The certainty of the evidence of the studies measuring this outcome was downgraded due to the lack directness.

BACKGROUND

This is an update of a Cochrane review first published in 2011, and last updated in 2017 (Al-aqeel 2017).

Description of the condition

The International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy define epilepsy as, "a disorder of the brain characterised by an enduring predisposition to generate epileptic seizures and by the neurobiological, cognitive, psychological and social consequences of this condition" (Fisher 2005). The definition of epilepsy requires the occurrence of at least one epileptic seizure. Epilepsy is one of the most common neurological disorders worldwide, with a prevalence estimated to be between 4 and 10 per 1000 people (Sander 2003). The systematic review by Ngugi 2011 presented the pooled incidence of epilepsy and included 33 relevant studies. The median incidence of epilepsy was 50.4 per 100,000 people per year and ranged from 30.3 to 66.7 per 100,000 people per year (median 45.0) in high-income countries, and from 28.0 to 239.5 cases per 100,000 people per year (median 81.7) generally quoted for middle-income countries.

The term 'adherence' describes the extent to which a person takes their medication as prescribed with respect to dosage and dosing intervals (Cramer 2008). Adherence is not the same as 'concordance', which includes a consensual agreement about treatment-taking that is established between patient and practitioner (Eatock 2007). However, both terms are quantifiable parameters and both describe the dose quantity and the medication intake in general (Vrijens 2012). Adherence, as a process, includes three stages according to Vrijens 2012: initiation, implementation and discontinuation.

Non-adherence can be intentional, with patients acting in a certain way according to their own expectations of treatment, side effects and lifestyle choice; or non-intentional, when patients do not adhere through forgetfulness, misunderstanding or uncertainty about clinicians' recommendations, which might result from a more passive behaviour. Non-adherence to medication is a prevalent and persistent healthcare problem, particularly for people with a chronic disorder (Lehane 2006).

A few older studies (Helgeson 1990; Peterson 1984; Pryse-Phillips 1982; Shope 1980), and one newer study (Li 2013), included in this review used the term 'medication compliance', although the description of the outcome by the study authors is comparable with the term 'adherence' according to the new taxonomy (Vrijens 2012).

Description of the intervention

Interventions designed to enhance medication adherence include a simplified dosage regimen, combinations of more thorough patient instruction and counselling, (intensive) reminders, close follow-up, supervised self-monitoring, rewards for success, family therapy, psychological therapy and telephone follow-up.

Why it is important to do this review

Of those people diagnosed with epilepsy, the vast majority are treated with antiepileptic drugs, and approximately 70% can become seizure-free once the most effective regimen is followed (Eatock 2007). Unfortunately, evidence suggests that adherence to medication among people with epilepsy is suboptimal (Briesacher 2008; Davis 2008; Ettinger 2009a; Malek 2017).

Poor adherence to antiepileptic drugs is associated with increased mortality, emergency department visits, hospitalisations, fractures and head injuries (Davis 2008; Ettinger 2009b; Faught 2008). Seizure risk is 21% higher among non-adherers than adherers (Manjunath 2009). Increased frequency of seizures can have serious repercussions on an individual's perceived quality of life (Baker 1997; Hovinga 2008). It appears also to be associated with increased utilisation and costs of inpatient and emergency services (Davis 2008; Ettinger 2009b; Faught 2008).

To tackle the problem of non-adherence, we need to identify the most effective adherence-enhancing interventions and find out how well they improve adherence in people with epilepsy. Several systematic reviews published in the Cochrane Library have looked at adherence-enhancing interventions. For instance, the Nieuwlaat 2014 review included unconfounded randomised controlled trials (RCTs) of interventions to improve adherence with prescribed medication, measuring both medication adherence and clinical outcome (such as seizure frequency), with at least 80% follow-up of each group studied and, for long-term treatments, at least six months' follow-up for studies with positive findings at earlier time points. Of all 182 RCTs identified, only 17 had the lowest risk of bias for study design features and their primary clinical outcome. Only five out of the 17 RCTs reported improvements in both adherence and clinical outcomes. The review identified one study looking at antiepileptic drugs, which reported improved medication adherence by combining a number of interventions such as counselling, a special medication container, self-recording of medication intake and seizures, and mailed reminders to collect prescription refills and attend clinic appointments (Peterson 1984). Another review of interventions to enhance antiepileptic drug adherence and clinical outcomes published in 2017 (da Mota Gomes 2017), identified four studies included in our review (Dash 2015; Pakpour 2015; Peterson 1984; Tang 2014).

Considering the burden of poor adherence to antiepileptic drugs, substantial efforts in adherence research and assessing whether these efforts have led to more effective interventions for epilepsy, an updated review is highly relevant. These gaps can be addressed by summarising new high-quality evidence from RCTs to date. We have therefore updated our comprehensive systematic review, last published in 2017, by searching for recent studies published up to February 2020.

OBJECTIVES

To determine the effectiveness of interventions aimed at improving adherence to antiepileptic medication in adults and children with epilepsy.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs and quasi-RCTs comparing adherence-enhancing interventions versus no intervention or other intervention.

Types of participants

The target population consisted of people with a clinical diagnosis of epilepsy (as defined in individual studies), of any age and of either gender, treated with antiepileptic drugs in a primary care, outpatient or other community setting. We examined interventions targeting all types of epilepsy. We excluded studies that examined people with epilepsy with neurological comorbidities, such as intellectual disabilities and behavioural problems.

Types of interventions

Interventions of any type intended to increase adherence to antiepileptic medication. We considered interventions that were aimed at patients as well as at parents and caregivers, including but not exclusive to the following.

- Simplification of drug regimen
- Patient education and information
- Intensified patient care (increasing follow-up, sending out reminders, etc.)
- Complex behavioural approach (increasing motivation by arranging group sessions, giving out rewards, etc.)

Control groups should have received no intervention, another intervention or 'usual care'.

Types of outcome measures

Primary outcomes

- Improved adherence to medication (including any definition of adherence and noting how this was defined and measured in each study)

Secondary outcomes

- Seizure frequency or seizure severity, as measured by the Liverpool Seizure Severity Scale or similar measure
- Treatment side effects
- Self-efficacy
- Quality of life
- Serious adverse events
- Costs or cost effectiveness of adherence-modifying interventions

Search methods for identification of studies

Electronic searches

We ran the original search in June 2010. We ran subsequent searches in July 2012, February 2013, September 2014, September 2015, February 2016, and June 2018.

For the latest update, we searched the following electronic databases on 18 February 2020:

- Cochrane Register of Studies (CRS Web), using the search strategy outlined in Appendix 1. CRS Web includes RCTs or quasi-RCTs 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 Specialized Registers of Cochrane Review Groups including Epilepsy;
- MEDLINE (Ovid 1946 to 14 February 2020), using the search strategy outlined in Appendix 2;
- CINAHL Plus (EBSCOhost 1937 onwards), using the search strategy outlined in Appendix 3;
- PsycINFO (EBSCOhost 1887 onwards), using the search strategy outlined in Appendix 4.

Previously, review authors searched Embase (Ovid 1980 to June 2012) using the search strategy outlined in Appendix 5; however, RCTs and quasi-RCTs published in Embase are now included in CRS Web, so there was no longer any need to search Embase separately.

Searching other resources

We screened the reference lists of all retrieved articles to identify additional publications.

Data collection and analysis

Selection of studies

All review authors independently assessed lists of potentially relevant citations and abstracts. Each review author indicated whether a citation was:

- relevant (meeting all prespecified inclusion criteria);
- possibly relevant (meeting some, but not all, inclusion criteria); or
- rejected (not relevant to the review; did not meet any of the inclusion criteria).

We obtained articles classified in categories 1 and 2 in full, and at least two of the review authors reviewed them independently. The review authors reached their final decision by consensus, with disagreements resolved by discussion.

Data extraction and management

At least two review authors independently extracted data from the full papers, with disagreements handled in the same way as for study selection. Extracted information included details of randomisation methods, demographics and clinical characteristics of each group, entry and exclusion criteria, number of participants excluded or lost to follow-up, details of the intervention, baseline and post-intervention results and methods of analysis.

We kept records in the form of a 'Quality of reporting of meta-analyses', or QUOROM, statement (Moher 1999).

Assessment of risk of bias in included studies

We assessed the methodological quality of studies using the Cochrane 'Risk of bias' guidelines (Higgins 2017). We examined the following sources of bias.

- Selection bias: systematic differences between baseline characteristics of the groups compared
- Performance bias: systematic differences between groups in the care provided, or in exposure to factors other than the interventions of interest
- Attrition bias: systematic differences between groups in withdrawal from a study
- Detection bias: systematic differences between groups in how outcomes are determined

- Reporting bias: systematic differences between reported and unreported findings

Measures of treatment effect

We analysed interventions for adults independently from those aimed at children. We grouped studies according to types of interventions and compared outcomes independently of each other.

For dichotomous outcomes (proportions of participants with improved adherence per group), we used the risk ratio (RR) as the summary statistic. For continuous data, we used the mean difference (MD) (when all studies reported the outcome using the same scale) or the standardised mean difference (SMD) (when studies used different scales). For all data, we computed 95% confidence intervals (CIs).

If in the original reports participants were not analysed within the group to which they were randomly assigned, but information in the study report was sufficient, we attempted to restore participants to their correct group to allow an intention-to-treat analysis.

Dealing with missing data

We contacted study authors to ask for missing information and data.

Assessment of heterogeneity

We assessed clinical (age, gender, epilepsy type and duration of epilepsy) and methodological (randomisation concealment, losses to follow-up, adherence measurement and reporting) differences between studies. If a group of studies seemed to be similar enough to be pooled in meta-analysis, we planned to assess statistical heterogeneity of pooled results by using the I^2 statistic (Deeks 2019; Higgins 2003). However, due to clinical and methodological heterogeneity between identified studies, we did not perform statistical heterogeneity tests.

Data synthesis

We undertook a quantitative analysis of all included studies. We summarised data statistically if they were available, were of sufficient quality and were sufficiently similar, and if we observed no important clinical and methodological heterogeneity. If no significant heterogeneity was present, we had planned to synthesise the data using a fixed-effect model; otherwise we used a random-effects model. We performed statistical analysis using Review Manager 5 (Review Manager 2014).

Included studies were heterogeneous in terms of types of adherence-enhancing interventions and methods used to measure and report adherence. This did not allow pooling of data.

Subgroup analysis and investigation of heterogeneity

We planned to analyse interventions and results in children and adults as separate subgroups throughout the review (results, analysis, discussion, implications for practice and research sections).

We planned to conduct subgroup analyses of the primary outcomes, classifying the studies by interventions used, numbers of interventions, types of adherence measurement used, duration of follow-up and epilepsy type, if the data permitted.

Sensitivity analysis

We planned to undertake sensitivity analyses to explore the influence of factors such as the quality of included studies on the results.

Summary of findings and assessment of the certainty of the evidence

We created a Summary of findings table using the browser-based GRADEpro software, available to Cochrane review authors (GRADEpro GDT) for the primary outcome (improved adherence to medication) and secondary outcomes (seizure frequency or seizure severity, self-efficacy, and quality of life). For each outcome we summarised the following information.

- Risk in the intervention group and its 95% confidence interval based on the assumed risk in the comparison group and the relative effect of the intervention.
- Relative magnitude of effect and its 95% confidence interval.
- Numbers of participants and studies addressing these outcomes.
- A grade of the overall quality of the body of evidence for each outcome as described in Assessment of risk of bias in included studies.
- Any relevant comments.

We evaluated the overall certainty of evidence for outcomes identified as critical or important for clinical decision-making using the GRADE approach (Schünemann 2013). These outcomes included: effects on adherence (behavioural interventions), effects on adherence (educational interventions), effects on adherence (mixed interventions), seizure frequency and severity, self-efficacy, and quality of life. The GRADE approach considers evidence from RCTs as high certainty, which may be downgraded based on consideration of any of five areas: design (risk of bias), consistency across studies, directness of the evidence, precision of estimates and presence of publication bias.

RESULTS

Description of studies

Results of the search

The search of the databases resulted in 1040 'hits', from which we obtained 506 articles from MEDLINE, 317 from CENTRAL, 86 from PsycINFO, 25 from the Cochrane Epilepsy Group Specialised Register, 20 from ClinicalTrials.gov, 31 from CINAHL, and 14 from ICTRP. The search of CRS Web yielded 41 new hits (see Figure 1). In previous versions of this review, searching Embase (Ovid 1980 to June 2012) contributed 2913 citations. However, the citations did not yield any new studies other than those identified in other databases.

Figure 1. Study flow diagram (PRISMA Template)

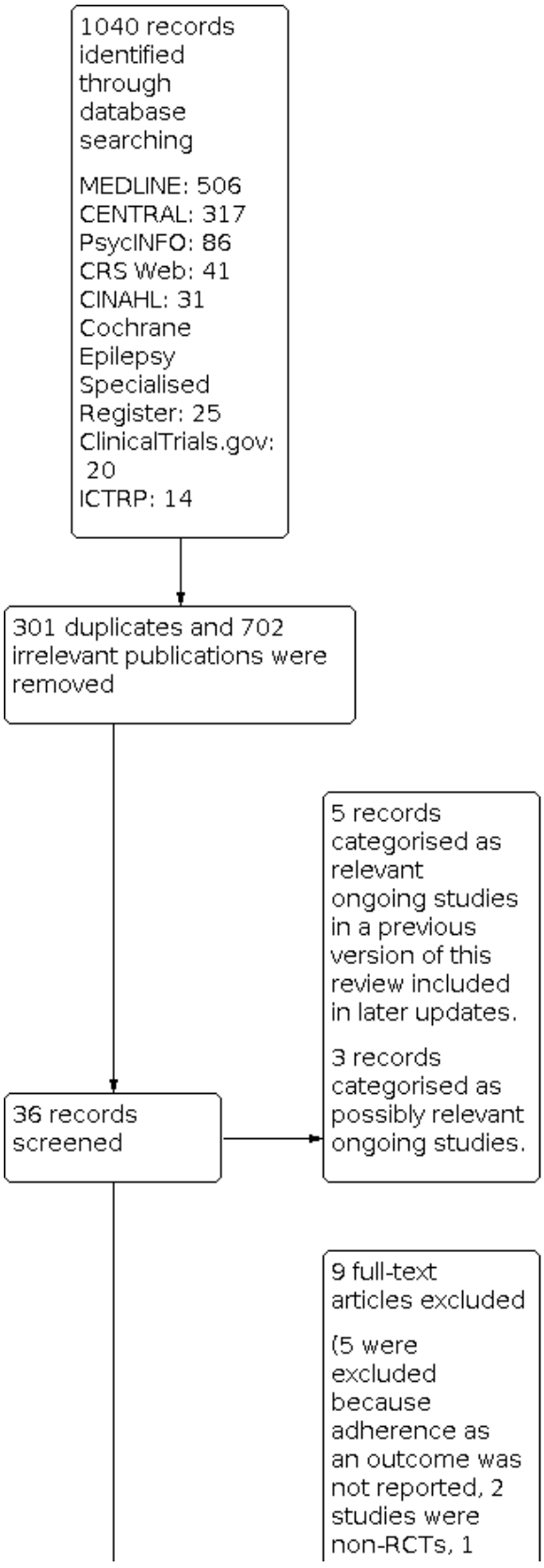
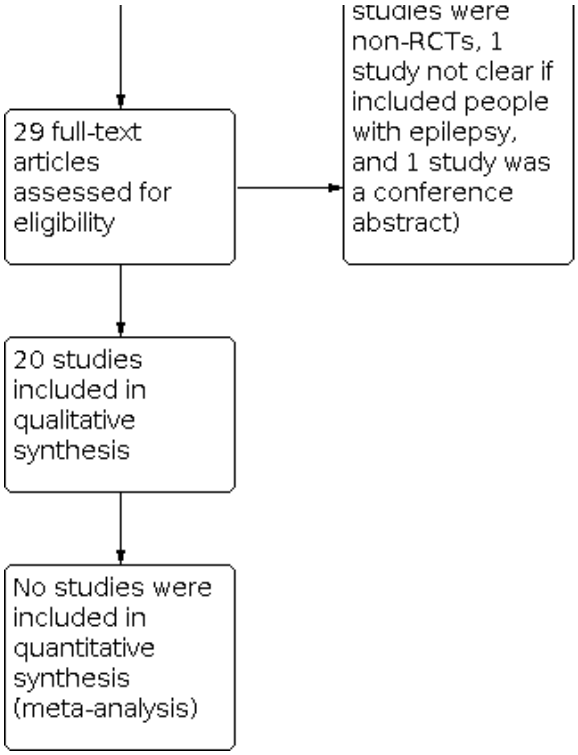


Figure 1. (Continued)



We screened titles and abstracts and excluded 301 duplicates and 702 irrelevant publications. The most common reason for exclusion at this stage was that studies did not perform any adherence-enhancing intervention, or did not measure changes in adherence to medication, or both. The other common reason for exclusion was that the study population did not consist of participants with a clinical diagnosis of epilepsy; this was expected, as antiepileptic medications have many other clinical uses. The total number of citations after irrelevant and duplicate references were removed was 36. Two review authors reviewed these independently. We had categorised five records as relevant ongoing studies in a previous version of this review and included them in a later update. Three studies are possibly relevant ongoing studies (see Characteristics of ongoing studies table).

We excluded nine studies (see Characteristics of excluded studies table). The reasons for exclusion are as follows: five because adherence as an outcome was not reported, two were not designed as RCTs, one was not clear if any people with epilepsy were included and, one where we were unable to obtain sufficient information to make a sound decision. We therefore included 20 studies in the current update, reporting data on 2832 participants. Thirteen of the 20 studies targeted adults with epilepsy (Brown 2009; Dash 2015; DiIorio 2009; Dilorio 2011; Edward 2019; Helgeson 1990; Leenen 2018; Pakpour 2015; Peterson 1984; Pryse-Phillips 1982; Ridsdale 2018; Tang 2014; Zheng 2019), one included participants of all ages (Ibinda 2014), one included participants ≥ 13 years (Li 2013), one targeted caregivers of children with epilepsy (Shope 1980), one targeted adolescents and caregivers (Modi 2016a), one recruited pediatric patients aged between 1 month to 15 years (Saengow 2018), and two targeted families of children with epilepsy (Modi 2013; Modi 2016b; see Characteristics of included studies table).

Included studies

See Characteristics of included studies table.

Seven studies were conducted in the USA (DiIorio 2009; Dilorio 2011; Helgeson 1990; Modi 2013; Modi 2016a; Modi 2016b; Shope 1980), three in China (Li 2013; Tang 2014; Zheng 2019), two in the UK (Brown 2009; Ridsdale 2018), and Australia (Peterson 1984; Edward 2019), and one each in Canada (Pryse-Phillips 1982), India (Dash 2015), Iran (Pakpour 2015); Kenya (Ibinda 2014), the Netherlands (Leenen 2018), and Thailand (Saengow 2018). All but three studies compared treatment versus 'usual care' or 'no intervention': Modi 2016a compared different formats of text messaging; Pryse-Phillips 1982 compared an educational intervention presented in different formats (oral form, oral and written, and by telephone contact only); and Tang 2014 compared educational versus behavioural interventions. Follow-up times ranged from four weeks to one year. All included studies were RCTs, or described the randomisation procedure if 'RCT' was not specifically mentioned.

Type of interventions

Interventions that the studies examined could be grouped into behavioural, educational and mixed interventions.

Behavioural interventions

- Reminder text messaging or application ('app') for the adolescent and caregiver (Modi 2016a).
- Three, weekly face-to-face motivational interviewing sessions each lasting for 40 to 60 minutes. Patients then created a personal action plan by specifying where, when, how, and how often they would take medications and use a drug diary calendar to help them stick to their plans. Patients were encouraged to identify the barriers that might interfere with

the implementation of their medication adherence plans and to specify how to overcome it (Pakpour 2015).

- Implementation intention interventions, which involved the completion of a simple worksheet by participants and linking of the intention of taking medication with a particular time, place and other routine activity (Brown 2009). For instance, the participant could write, "If it is 8 am and I am in the bathroom and have finished brushing my teeth, then I will take my first dose".
- Face-to-face introductory motivational interviews followed by four telephone-based motivational interviews over 12 weeks. This intervention was provided by a specially-trained nurse and was aimed at enhancing self-management practices in the following areas: medication, information, seizures, safety and lifestyle (DiIorio 2009).

Educational interventions

- A multidisciplinary management programme including face-to-face interviews with an epileptologist, online consultations by epilepsy specialist nurses; and group education by the multidisciplinary team twice a year (Zheng 2019).
- One 120-minute self-management and lifestyle education session delivered face-to-face by a clinical nurse specialist in neurosciences (Edward 2019).
- Self-management education for people with poorly controlled epilepsy (SMILE [UK]) is a group-based education course with nine modules delivered for 16 hours over two consecutive days. The premise of the course was to communicate information and to encourage participants to share their own experiences with others. A workbook containing course content was given to participants (Ridsdale 2018).
- An 8.52 min video animation on: diagnosis of epilepsy, aetiology of epilepsy, treatment of epilepsy, first aid seizure care, prognosis of epilepsy and safe activity for epilepsy (Saengow 2018).
- Four face-to-face sessions and two telephone problem-solving sessions over eight weeks. Session one addressed deficit in epilepsy knowledge. Sessions two through four aimed to teach families a problem-solving approach for their identified antiepileptic drug-adherence barriers (Modi 2016b).
- One-on-one teaching in a structured format, covering aspects such as treatment modalities was administered by an epilepsy nurse in four sessions lasting at least 30 minutes; also pamphlets were provided, mostly with animations, to explain the different aspects of the disease (Dash 2015).
- A one-day educational programme providing epilepsy-related information such as types of seizures, causes of epilepsy, effects of epilepsy on child development, treatment of epilepsy, side effects of drugs and what to do during a seizure. A brochure detailing all of the topics discussed was given to each participant (Ibinda 2014).
- Medication education in the form of oral education and written materials, reinforced by monthly calls from the pharmacist over the next six months (Tang 2014).
- The first component of the intervention (session one) provided education on epilepsy treatment, antiepileptic drug adherence and the family's specific epilepsy treatment regimen (i.e. dosing schedule). Sessions two through four aimed to teach families a problem-solving approach for their identified antiepileptic drug adherence barriers (Modi 2013).
- An online epilepsy self-management programme, Web Epilepsy Awareness, Support, and Education (WebEase), that assists people with taking medication, managing stress and improving sleep quality (Dilorio 2011).
- A two-day Seizures and Epilepsy Education programme designed to provide medical education and psychosocial therapy to participants and families (Helgeson 1990).
- Three groups were given oral information about the name of the drug; its colour, shape and strength; the therapeutic effect; and dosage, precautions and possible unwanted effects; the same information supplemented by its presentation in written form; and the same information by telephone contact only (Pryse-Phillips 1982).
- Two mothers' discussion group meetings, each lasting 1.5 hours. The aim of these meetings was to provide mothers with information that would enable them to know what they should do for their children and why, and would allow them to increase their sense of responsibility while making their commitment (Shope 1980).

Mixed interventions

- The multicomponent self-management intervention consisted of five weekly group sessions of two hours each, followed by a two-hour booster session after three weeks. All group sessions consisted of two components: education and practicing goal-setting skills (Leenen 2018).
- Medication education (see description above) was combined with a behavioural intervention: a modified medication schedule, which was presented in the form of a table that illustrated the daily medication therapy of participants with pictures of antiepileptic drugs, and providing them with cues to take their medication (Tang 2014).
- A programme with four components: (1) intensive education, (2) consultation services to ensure that clinical providers and telephone support were available for participants at any time, (3) reminders provided by keeping a simple record with specifically designed cards, and (4) repeated participant reminders about medical adherence sent every month (Li 2013).
- Patient counselling on the goals of antiepileptic drugs and the importance of sufficient adherence and intensive reminders: diary of medication use and seizures, Dosett medication container (pill organiser), and prescription refill and appointment-keeping reminders (Peterson 1984).

Adherence assessment and reporting

Studies measured adherence to antiepileptic drugs both directly and indirectly. Six studies used serum or plasma concentration of the antiepileptic drug (Helgeson 1990; Ibinda 2014; Pakpour 2015; Peterson 1984; Pryse-Phillips 1982; Shope 1980). Indirect measurement techniques included use of the Medication Event Monitoring System (MEMS), an electronic monitoring cap that recorded the number and timing of bottle openings (Brown 2009; DiIorio 2009; Leenen 2018; Modi 2013; Modi 2016a; Modi 2016b); assessment of participant-reported adherence using the Antiretroviral General Adherence Scale (AGAS; DiIorio 2009), Epilepsy Self-Management Scale (Ridsdale 2018), or the Medication Adherence Scale (MAS, MARS or Morisky MAS; Dash 2015; Dilorio 2011; Edward 2019; Ibinda 2014; Leenen 2018; Li 2013; Pakpour 2015; Saengow 2018; Tang 2014; Zheng 2019); and tracking of

prescription refill frequency and appointment keeping (Peterson 1984).

Adherence was reported as mean score, percentage change in adherence score from baseline to post-intervention, percentage of doses taken, percentage of days correct doses were taken, percentage of doses taken on schedule, percentage of mean change from baseline to post-intervention and percentage of change from the initial level towards the mean of the accepted therapeutic range (see Summary of results for each included study, Table 1).

Excluded studies

See the Characteristics of excluded studies table.

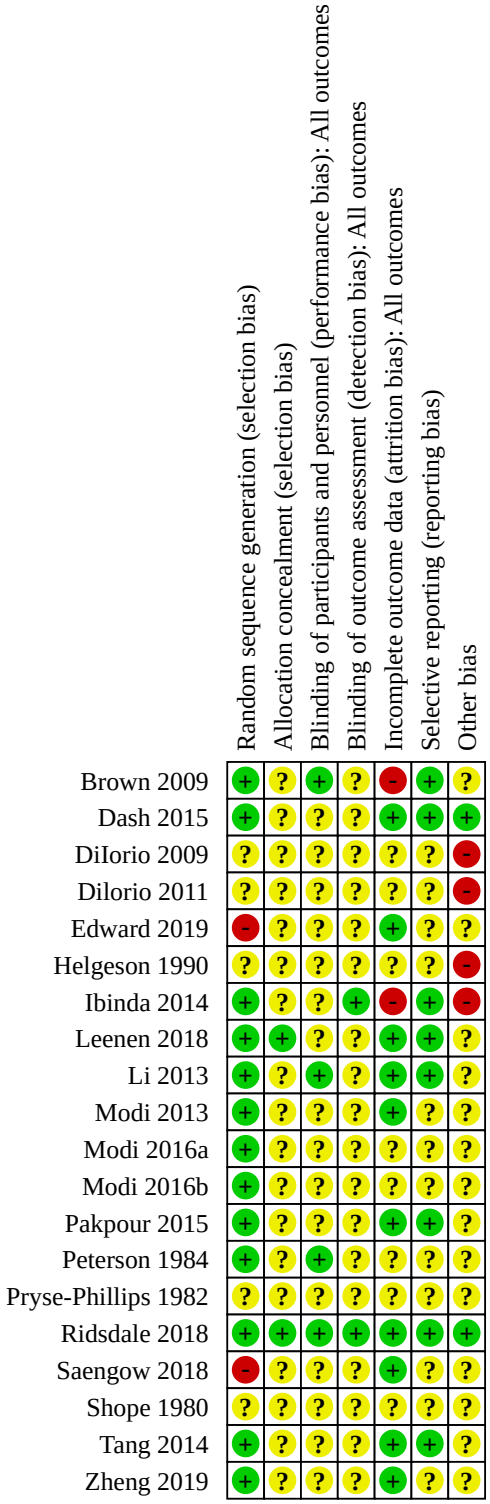
We defined a list of the most common characteristics for the exclusion criteria.

- Inappropriateness of the study design: not a RCT or no randomisation procedure performed, or both
- Adherence as an outcome is not reported or no adherence-enhancing intervention, or both
- Not an original publication
- The study was not performed in the field of epilepsy

Risk of bias in included studies

We applied the full version of Cochrane's tool for assessing risk of bias (Higgins 2017). Descriptions by domain are provided below (see 'Risk of bias' summary for each included study, Figure 2).

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Random sequence generation (selection bias)

Seven studies used computer-generated randomisation, which we considered to be an adequate randomisation procedure (Brown 2009; Dash 2015; Ibinda 2014; Pakpour 2015; Ridsdale 2018; Tang 2014; Zheng 2019). Three studies reported the use of block randomisation (Leenen 2018; Modi 2013; Modi 2016b). One study used stratified block randomisation with type of phone (Modi 2016a). Another study (Li 2013), stated that they used a simple randomisation method but did not describe it further. One study used the toss of a coin (Peterson 1984). The risk of bias for random sequence generation was high in two studies - one study used day of the week (Saengow 2018) and one study reported that random allocation to groups was used; however, if a participant was unable to attend the intervention face-to-face session, they were placed into the control group (Edward 2019). Data on the method of randomisation were missing from the other study reports, so we cannot properly judge the adequacy of randomisation.

Allocation

Only one study reported that the randomisation scheme was distributed to the researcher in sealed envelopes during the first visit, prior to baseline assessment (Leenen 2018). None of the remaining 19 studies properly reported this domain, thus we cannot evaluate it.

Sixteen studies provided comparative baseline information on the intervention and control groups (Brown 2009; Dash 2015; Dilorio 2011; Edward 2019; Helgeson 1990; Ibinda 2014; Leenen 2018; Li 2013; Modi 2016a; Modi 2016b; Pakpour 2015; Peterson 1984; Ridsdale 2018; Saengow 2018 Tang 2014, Zheng 2019). Dilorio 2009 and Shope 1980 provided demographic characteristics for the whole study sample but did not present the characteristics of each group. In Modi 2013 the authors provided the characteristics for the two groups and stated that the statistical comparison was not conducted owing to small sample sizes. Ten studies provided baseline adherence levels for both groups (Dash 2015; Dilorio 2011; Edward 2019; Ibinda 2014; Li 2013; Modi 2013; Ridsdale 2018; Saengow 2018; Tang 2014; Zheng 2019).

Blinding

None of the studies reported blinding of participants to the intervention they were receiving, as it was not possible in this particular setting. Only five studies reported blinding of healthcare providers or outcome assessors or both and we judged the risk of performance bias as low. Ridsdale 2018 reported that researchers who completed follow-up assessments and the patients ' healthcare providers were blind, staff organising the courses were not involved in data collection and not blind, and the statistician remained blind until the end of the analysis. Laboratory technicians determining drug levels in the blood assays were blinded to randomisation in Ibinda 2014, although the blinding procedure is incomplete and we therefore judged the study to have a high risk of bias. Li 2013 reported that study designers, local physicians and the data analyst were blinded to the intervention. Brown 2009 blinded the neurologist and clinic and pharmacy staff to group participation. Peterson 1984 blinded physicians treating study participants. Although blinding of healthcare providers should avoid systematic differences in the care provided (performance bias), this approach is vulnerable to disclosure by participants. In all studies it was unclear whether blinding of outcome assessors was maintained, and we therefore cannot determine the risk of detection bias.

Incomplete outcome data

Thirteen studies reported losses to follow-up (Brown 2009; Dash 2015; Dilorio 2009; Edward 2019; Helgeson 1990; Ibinda 2014; Leenen 2018; Li 2013; Pakpour 2015; Peterson 1984; Ridsdale 2018; Tang 2014; Zheng 2019). However, it was apparent that participants lost to follow-up were excluded from the analysis in only six studies (Dash 2015; Edward 2019; Li 2013; Modi 2013; Tang 2014; Zheng 2019). Three studies reported using intention-to-treat analysis (Leenen 2018; Pakpour 2015; Ridsdale 2018). In 7 studies we judged risk of attrition bias as low because missing outcome data were balanced in numbers across groups with similar reasons for missing data. Missing outcome data detected in Brown 2009 and Ibinda 2014 were likely to be related to true outcome, and to cause high risk of bias. The number of participants lost to follow-up ranged from 2 to 157.

Selective reporting

Selective outcome reporting bias could occur, for instance, if seizure frequency was measured and analysed but was not reported in the study results. The study protocol or details were available only for four studies (Ibinda 2014; Leenen 2018; Pakpour 2015; Ridsdale 2018), and all outcomes reported in the protocol were reported either in the same paper or somewhere else. For studies with no protocols we cannot confirm or exclude this type of bias in the other seven studies as we did not contact study authors. Five studies (Brown 2009; Dash 2015; Ibinda 2014; Li 2013; Tang 2014), published all expected outcomes.

Other potential sources of bias

Nine studies (Brown 2009; Li 2013; Modi 2013; Modi 2016a; Modi 2016b; Peterson 1984; Pryse-Phillips 1982; Shope 1980; Tang 2014), reported insufficient information to judge whether or not other risks of bias might have been introduced. Four studies discussed possible threats to validity:Dilorio 2011 argued that self-reported responses might be affected by social desirability biases, including the tendency to overemphasise behaviour in favour of the desired outcomes; Helgeson 1990 reported many statistically non-significant results; Ibinda 2014 reported that improved adherence in both groups could be explained by the sharing of knowledge between groups and participants who did not provide blood samples to assess AED drug levels held significantly more traditional religious and cultural beliefs; Zheng 2019 discussed the impact of recall bias on the study findings. Only five studies (Ibinda 2014; Leenen 2018; Li 2013; Pakpour 2015; Ridsdale 2018), performed appropriate sample size calculations.

One study met all seven quality criteria (Ridsdale 2018), one study met five criteria (Leenen 2018), three studies (Dash 2015; Li 2013;Leenen 2018), met four quality criteria, four studies (Brown 2009; Ibinda 2014; Tang 2014; Pakpour 2015), met three quality criteria, three studies (Modi 2013; Peterson 1984; Zheng 2019), met two quality criteria for risks of bias, and four studies met one quality criteria (Edward 2019; Modi 2016a; Modi 2016b; Saengow 2018).

Effects of interventions

See: **Summary of findings 1** Summary of findings table

The effects of interventions on identified outcomes can be found in Summary of findings 1, and the results by study are described in Table 1.

Effects on adherence

Behavioural interventions

Four studies examined behavioural interventions.

Brown 2009: the implementation intention intervention (69 participants) showed improved adherence relative to control. The percentage of doses taken in the intervention group was 93.4% (standard deviation (SD) 12.3%) versus 79.1% (SD 28.1%) in the control group (P = 0.01). The percentage of days on which correct doses were taken in the intervention group was 88.7% (SD 15.1%), versus 65.3% (SD 35.6%) in the control group (P = 0.01). The percentage of doses taken on schedule in the intervention group was 78.8% (SD 23.5%), versus 55.3% (SD 34.8%) in the control group (P = 0.001). The overall adherence scores were generated by standardising and then averaging the three percentage measures. The mean overall adherence score in the intervention group was 0.35 (SD 0.55), versus 0.40 (SD 1.15) in the control group (P < 0.01).

DiIorio 2009: use of motivational interviewing to enhance self-management practices had no effect on adherence (20 participants). The percentage of doses taken in the intervention group was 81.29% (SD 13.48%) versus 82.19% (SD 21.76%) in the control group (P = 0.912). The percentage of doses taken on schedule in the intervention group was 53.27% (SD 17.74%) versus 66.01% (SD 29.61%) in the control group (P = 0.258). The mean AGAS score in the intervention group was 4.28 (SD 0.74) versus 4.46 (SD 0.58) in the control group (P = 0.523).

Modi 2016a: text messaging and phone applications targeting teenagers with and without caregivers resulted in minimal adherence improvements due to high levels of baseline adherence. A trend indicated that parental involvement decreased adherence and text messaging improved adherence compared to applications.

Pakpour 2015: the motivational interviewing group (138 participants) reported significantly higher medication adherence compared with the control group (137 participants) at three-month (β = 4.6; P = 0.001) and six-month (β = 1.73; P = 0.001) follow-up. The odds ratios (OR) of serum level increased by 1.35 in participants in the intervention group (OR 1.35, 95% CI 1.07 to 1.71; P = 0.03) compared with those in the active comparator group at three months' follow-up.

Educational interventions

Thirteen studies assessed the added value of educational interventions.

Dash 2015: in the epilepsy health education group, the pretest mean adherence score was 6.58, whereas the post-test mean score was 7.53 (P = 0.001). The mean adherence scores for the control group's pretest and post-test were 6.46 and 6.58 respectively (P = 0.224).

Dilorio 2011: use of the online epilepsy self-management programme WebEase was found to be an effective means of enhancing adherence (148 participants). The mean adherence score after 12 weeks was 7.33 in the intervention group (SD 1.833), versus 6.90 (SD 2.33) in the control group (P = 0.049), with a mean difference of 0.43 (95% CI -0.24 to 1.10).

Edward 2019: the difference in mean change adherence scores between control and intervention was −0.388 (95% CI −1.27 to 0.493; P = 0.376).

Helgeson 1990: the intervention group showed a significant and sustained increase in blood serum concentrations of antiepileptic medication from baseline to four-month follow-up (a mean increase of 70%). Over the same period, the control group showed a mean decline in blood serum levels of 18% (P < 0.05).

Ibinda 2014: one year after an educational intervention was provided, there was no significant difference in adherence to antiepileptic drugs based on detectable drug levels (OR 1.46, 95% CI 0.74 to 2.90; P = 0.28) or by self-reports (OR 1.00, 95% CI 0.71 to 1.40; P = 1.00) between the intervention and nonintervention groups.

Modi 2013: in the group of children and their caregivers who received educational interventions, the mean percentage change in adherence from baseline to post-intervention was 31.5 (SD 52.9), versus 9.3 (SD 8.7) in the no-intervention group. The authors reported that the statistical comparison was not conducted, owing to small sample sizes.

Modi 2016b: adherence scores after session 4 were 15.3 in the intervention group versus 9.7 in the nonintervention group (P value < 0.05). There were no significant group differences on antiepileptic drug adherence during the three-month follow-up period.

Pryse-Phillips 1982 reported that whether information was given in oral form alone or both orally and in written form, it produced no significant rise or fall in the mean serum level of prescribed antiepileptic medication.

Ridsdale 2018: at 12 months, the medication adherence score median for the intervention group was 47.8 (interquartile range (IQR) 45.6 to 48.9; range 27.8 to 50.0) versus 47.8 (IQR 45.6 to 48.9; range 35.6 to 50.0) in the nonintervention group (P = 0.964).

Saengow 2018: the proportion of participants with improved adherence after three months was higher in the intervention group (54 (42.9%)) versus the control group (141 (5.9%); P value < 0.001).

Shope 1980 reported that the mean adherence score derived from serum level for children of parents who received the intervention was 2.9 versus 2.2 in the control group (P = 0.015).

Tang 2014 reported that adherence improved in both the medication education group (62.3%) and the medication education with behavioural intervention group (64.3%); P value = 0.827.

Zheng 2019: at 12-month follow-up compared with baseline, there was an increase in number of participants with moderate to high antiepileptic drug adherence was observed in the intervention group (65 (60.9%) versus 71 (77.2%); P = 0.006) and in the control group (55 (59.8%) versus 63 (68.5%); P = 0.096).

Mixed interventions

Four studies focused on mixed interventions, with one study (Tang 2014), comparing an educational intervention plus a behavioural component to a single educational intervention (described in the 'Educational intervention' section).

Leenen 2018: at six months the adherence rates were 63.7% and 75.9% and the adherence scores were 23.7 (SD 1.3) and 23.9 (SD 0.9) for the non-intervention and the intervention groups respectively; the difference was not statistically significant.

Li 2013 reported no statistically significant differences at baseline between the numbers of participants in intervention and non-intervention groups who rated their adherence as excellent or very good (12.6% versus 9.1% respectively; P = 0.579). One year after the intervention was provided, 77.6% of intervention group members rated their adherence as excellent or very good, versus 9.6% in the non-intervention group (P < 0.001).

Peterson 1984: use of patient prompts, such as mailed reminders for prescription refills and appointments, together with a counselling leaflet, produced positive effects on adherence. At follow-up, mean serum levels of phenytoin, carbamazepine and sodium valproate were higher in the intervention group than in the control group, and this was accompanied by a greater shift from subtherapeutic to therapeutic plasma levels in the intervention group than in the control group (P < 0.005). The high serum level can be explained by participants taking more medication rather than higher doses, as no significant changes in antiepileptic drug dosages were reported within treatment groups. The proportion of compliant participants, as judged by prescription refill frequencies, was higher in the intervention group than in the control group (88% versus 50%; P > 0.01). There was no difference between the intervention and control groups for appointment-keeping (59% versus 65%; P > 0.5).

Tang 2014: after intervention adherence increased greatly in all participants and the number who missed antiepileptic drugs decreased to 45.0% from 64.3% (P = 0.988). Adherence improved in 62.3% of education group versus 64.3% of education/behavioural group participants (P = 0.827).

Effects on seizure frequency or seizure severity

Eleven studies described seizure frequency or seizure severity or both, with four of them (Dash 2015; Li 2013; Peterson 1984; Saengow 2018), presenting improved adherence and decreased seizure frequency in the intervention groups.

Dash 2015 reported a higher proportion of participants with decreased seizure frequency in the intervention compared to the control group (34.1% versus 18.6%; P = 0.043) six months after the intervention. The rest of the participants either had increased seizure frequency (12.3% versus 14.3%; P = 0.811), or unchanged (53.6% versus 67.1%; P = 0.099).

Edward 2019 reported the mean seizure occurrences between the control (12.71, SD 24.55) and intervention (6.76, SD 13.40) groups.

Helgeson 1990 reported that seizure frequencies did not change significantly from baseline to follow-up in either intervention or control groups.

Ibinda 2014 reported no difference in seizure frequency between the groups (P = 0.58).

Leenen 2018 reported no difference in seizure severity measured using the National Hospital Seizure Severity Scale (NHS3) between intervention (6.2 (SD 7.3)) and control (8.7 (SD 10.0)).

Li 2013 reported that before the intervention, baseline numbers of participants with more than a 50% seizure reduction were similar in the two groups (50.9% versus 45.8%; P = 0.337). After the intervention, the proportion of participants with more than a 50% seizure reduction rose to 79.8% in the intervention group, compared with 61.0% in the non-intervention group (P < 0.05).

Peterson 1984 compared the number of seizures between intervention and control groups at follow-up and found no statistically significant differences (median 2.5 versus 3.5; P > 0.5). The reduction in seizure frequency from baseline was more observed for the intervention group (median from 6 to 2.5; P < 0.01) versus the control group (median from 4 to 3.5; P > 0.1).

Ridsdale 2018 reported a difference between the two study arms in a number of participants with ≥1 seizure per month as − 0.02 (95% CI −0.63 to 0.58; P = 0.939).

Saengow 2018 reported a higher proportion of participants with improved severity of seizure in the intervention group 47 (37.3%) than control group 22 (25.0%) (P = 0.14).

Tang 2014 reported no difference in seizure control between the medication education group and the behavioural intervention group (64.2% versus 64.3%; P = 0.988).

Zheng 2019 reported an increase in the proportion of participants with a low seizure frequency in both the intervention group (70 (76.1%) versus 41 (44.6%); P= 0.001) and the control group (74 (80.4%) versus 50 (54.3%); P = 0.001) however, the difference between the two groups, is not significant (80.5% versus 76.1%; P = 0.475).

Effects on self-efficacy

Five studies (Dash 2015; DiIorio 2009; Dilorio 2011; Helgeson 1990; Leenen 2018), reported self-efficacy effects and one study reported self-mastery (Ridsdale 2018). Four studies used the Epilepsy Self-Efficacy Scale (ESES), which measures different aspects of efficacy in people with epilepsy, rating the items on an 11-point (Likert) rating scale covering personal levels of confidence regarding the ability to manage epilepsy. One study (Helgeson 1990), presented self-efficacy using the Sherer's Self-Efficacy Scale.

Dash 2015 used continuous variables to represent a total score and the assessment was administered by a specialised epilepsy nurse. The intervention, however, did not improve the overall self-efficacy score in participants with epilepsy.

DiIorio 2009 reports a positive effect of self-efficacy on understanding ability for self-management practices. Much higher levels of self-efficacy (mean intervention group 8.63 (SD 1.23) compared to the mean in the control group of 7.51 (SD 1.53)) were shown in the intervention group, resulting in better seizure management and epilepsy knowledge (T = 1.757, P = 0.097).

Dilorio 2011 showed higher levels of self-efficacy at post-intervention measurement in participants receiving the intervention compared to the control group. The trend testing was significant, with a post-intervention mean of 188.02 (SD 32.88) versus 171.17 (SD 40.21) in the intervention group versus the control group respectively (F = 6.49, P = 0.0130).

Helgeson 1990 reported general and social self-efficacy using Sherer's Self-Efficacy scale. Both mean scores, however, were higher in the control group compared to the intervention group at pre-assessment and at four months' follow-up.

Leenen 2018 reported no significant difference in self-efficacy between the intervention and control (263.2 (SD 26.3) versus 252.3 (SD 32.8)).

Ridsdale 2018 reported that self-mastery changed little at the 12-month follow-up with no statistically significant difference between study arms.

Effects on quality of life

Seven studies reported quality of life as an outcome.

Edward 2019 measured quality of life using the SF-12 (Short-Form 12 question) health survey. The difference in mean change scores between control and intervention for physical health quality-of-life score was −4.60 (95% CI −10.6 to 1.42; P = 0.129) and for the mental health quality-of-life score it was −1.97 (95% CI −7.67 to 3.74; P value = 0.487).

Leenen 2018 reported that the difference in total Quality of Life in Epilepsy Scale (QOLIE-31P) scores between the intervention and control groups was not significant but three subscales 'Emotional well-being' (P = 0.01), 'Social functioning' (P = 0.001), and 'Distress' (P = 0.01) had a significantly better result in the intervention group.

Modi 2013 measured the impact on quality of life using a feasibility and acceptability questionnaire. The questionnaire included one item, "Treatment helped improve my child's quality of life" rated on a 7-point Likert scale by four families who received the intervention. A mean benefit of 6.75 (SD 0.6) was reported.

Pakpour 2015 assessed quality of life using the QOLIE-31. At six months, no significant changes from baseline in any domain were evident in the control group (from 52.85 (SD 17.98) to 52.25 (SD 17.21)). In participants receiving intervention, the mean changes from baseline to six months after intervention were significant (from 53.75 (SD 19.52) to 62.67 (SD 14.51).

Ridsdale 2018 measured quality of life as main outcome using Quality of Life in Epilepsy-31 with added Patient-specific weightings (QOLIE-31-P). The analysis did not detect any difference at 12-month follow-up between the mean scores for intervention (67.4,SD 13.5) and nonintervention (69.5, SD 14.8); P value = 0.564.

Tang 2014 presented the overall quality of life using the Quality of Life in Epilepsy Scale-10 (QOLIE-10), with each of the 10 items rated on a five-point scale. The difference in scores between the two groups was not clear (P = 0.9475).

Zheng 2019 assessed the quality of life using the Quality of life in Epilepsy-31(QOLIE-31). After 12 months, the intervention group showed improvements in five of the seven subscales in QOLIE-31, while the control group showed improvements in only in three aspects.

Effects on side effects, serious adverse events

Two studies examined the effects of interventions on treatment side effects and serious adverse events.

Leenen 2018: at six months, there was a significant difference on the side-effect scale (SIDAED) between intervention 19.1 (SD 15.3) and control 25.5 (SD 19.1; P value = 0.04).

Ridsdale 2018 reported insignificant differences in median adverse effects of medications between intervention and control (7 (range 2 to 10) versus 8 (range 2 to 10); P = 0.151).

Costs and cost effectiveness

Two studies (Leenen 2018; Ridsdale 2018), measured costs and estimated cost effectiveness of the intervention (the results are reported in the secondary references).

Leenen 2018: the self-management intervention for adults with epilepsy (ZMILE study) intervention costs were EUR 648 at 12 months' follow-up. For the control group the costs were EUR 95, which were mainly protocol-driven costs attributable to the MEMS bottle. At 12 months, total costs were EUR 9314 for the intervention group and EUR 8189 for the control group. The intervention resulted in an incremental cost-effectiveness ratio of EUR 88 per percentage of adherence increase at six months. When looking at the quality adjusted life years (QALYs; Dutch tariff), an incremental cost-utility ratio of EUR 15,144 per QALY was gained at 12-month follow-up. All costs were indexed for the year 2015.

Ridsdale 2018: a complete course of the self-management education for adults with poorly controlled epilepsy (SMILE (UK)), with four sessions, was estimated to be GBP 224.00. At 12 months follow up, health and social care costs and total societal costs were GBP 3453 and GBP 30,732 for the SMILE (UK) intervention group compared to GBP 4608 and GBP 30,675 for treatment as usual group, respectively. The associated incremental cost-effectiveness ratio from a health and social care perspective is GBP 5548 per one extra QALY. Costs are reported at 2014 to 2015 prices.

Dilorio 2011 argues that the intervention will be more cost-effective, mainly because it is an online product that will save working hours and require less administration in comparison with usual care. However they did not present any further information on cost effectiveness. No further reports described costs associated with adherence-modifying interventions.

DISCUSSION

Summary of main results

We identified 20 studies examining the effects on adherence to antiepileptic drugs using different interventions. Among these, four studies used behavioural interventions, 13 studies used educational interventions and four studies used mixed interventions. One study (Tang 2014), compared an educational intervention plus a behavioural component to a single educational intervention, and we have therefore presented the study results in both the educational intervention and in the mixed intervention categories.

The aim of this review was to assess the effectiveness of interventions aimed at improving adherence to antiepileptic medication. Education and counselling of people with epilepsy showed mixed success. Behavioural interventions, such as the use of intensive reminders and implementation intention interventions, demonstrated more favourable effects on

adherence. Mixed interventions were shown to improve adherence in the intervention groups compared to the control groups.

The impact of these interventions on secondary outcomes such as seizure frequency, self-efficacy, and quality of life were reported by a limited number of studies with mixed results and no clear pattern across types of intervention..

Due to very limited number of studies and the small sample sizes, further studies are needed to confirm the initial indications that adherence to antiepileptic drugs can be improved by these means.

Overall completeness and applicability of evidence

Applicability of the findings to everyday practice is uncertain for many reasons. Firstly, translation of education, counselling and motivation from the study setting to everyday practice is not necessarily feasible. Secondly, improving medication adherence will not necessarily translate into clinical benefits for the patient (Nieuwlaat 2014; Roter 1998). The effects of adherence-enhancing interventions must therefore be judged by their clinical outcomes. Outcomes such as reduced seizure frequency, quality of life and side effects were not always reported by the included studies. Out of 11 studies that reported seizure frequency, four showed a statistically significant decrease in seizure frequency when adherence was also improved. Thirdly, the value of adherence research to clinical practice is enriched by studying the relationship between adherence and factors known to influence adherence (DiMatteo 2004). Only two studies examined the relationship between adherence and patient-related factors (Brown 2009; Ibinda 2014), and found no statistically significant relationship between them. Fourthly, short-term follow-up makes it difficult to ascertain whether interventions with promising adherence-improving effects can maintain their effects over time. Finally, adherence-enhancing interventions require utilisation of healthcare resources, meaning that cost-effectiveness information is required for informed decision-making about their implementation. Two of the identified studies discussed the cost implications of these interventions.

Quality of the evidence

Twenty studies met our inclusion criteria. Insufficient reporting of what happened in these studies has hindered our ability to ascertain all risks of bias. For instance, we were unable to establish for all the studies the adequacy of the generation of the allocation sequence and of allocation concealment, and differences between baseline characteristics of the groups that were compared. Information on calculation of the statistical power of the sample size was provided in only five studies (Ibinda 2014; Leenen 2018; Li 2013; Pakpour 2015; Ridsdale 2018). Inadequate sample size could increase the likelihood of a type II error, and other biases.

In adherence-enhancing intervention studies, the validity and reliability of adherence measurement and reporting are central. Among the different measures of adherence, no single intervention can be regarded as a gold standard, and use of multiple measures of adherence is recommended (DiMatteo 2004; Eatock 2007; Nichol 1999; Paschal 2008; Vermeire 2001). Only four studies used more than one adherence measure (DiIorio 2009; Ibinda 2014; Pakpour 2015; Peterson 1984).

We examined the overall certainty of evidence for selected outcomes. This was high for effects on adherence with mixed interventions and quality of life; moderate for effects on adherence with behavioural interventions, effects on adherence with educational interventions, and seizure frequency and severity; and low for self-efficacy.

Potential biases in the review process

We did not contact authors of excluded studies to enquire whether adherence was measured but not reported, and therefore cannot exclude outcome reporting bias from our review (Kirkham 2010).

Agreements and disagreements with other studies or reviews

One review (da Mota Gomes 2017), of RCTs of interventions to enhance adherence with antiepileptic drugs, which also measured clinical outcomes with at least 80% follow-up of participants for at least six months, identified four studies and concluded that evidence is limited concerning enhancement of adherence among people with epilepsy. Several systematic reviews have examined the issues of adherence-enhancing interventions in general (Nieuwlaat 2014; Peterson 2003; Roter 1998); others have focused on adherence in older people (Higgins 2004), adherence to lipid-lowering medication (Schedlbauer 2010), to type 2 diabetes treatment recommendations (Vermeire 2005), and to antihypertensive medication (Schroeder 2004). Remarks on internal and external validity of the adherence literature in previous reviews are concordant with those in our review. Reviews looking at the methodological rigour of the literature on patient compliance with medication have similarly emphasised the importance of reliability and validity of adherence measurement (Cramer 2008; DiMatteo 2004; Nichol 1999; Vermeire 2001).

AUTHORS' CONCLUSIONS

Implications for practice

Despite the increasing number of studies indicating that poor adherence to antiepileptic medication is common and is associated with increased morbidity and mortality, the literature concerning interventions to improve medication adherence in epilepsy is still limited in quantity and quality. Behavioural interventions and mixed interventions demonstrate some positive results; however, we are unable to draw firm conclusions regarding the long-term effects of these interventions.

Implications for research

The results of our review highlight gaps in research on the effectiveness of interventions aimed at improving adherence to antiepileptic medication. Our findings emphasise the need for further adequately-powered randomised controlled trials (RCTs) that use a combination of adherence measurement techniques and that provide participant follow-up for a longer period. The differences between subjective self-reporting and objective blood tests are difficult to resolve in order to report firm conclusions. Studies should investigate the effects of interventions on adherence, as well as important clinical outcomes such as seizures. Researchers should minimise the risks of bias by using suitable randomisation techniques, concealment of allocation and blinding of both healthcare providers and outcome assessors. Differences in medical systems between countries are another

implication, as low- and middle-income countries face many difficulties and limited possibilities to apply hospital-based results to the general population, even within the same country.

Patients' beliefs and preferences are prevalent influences on the medicine-taking process (Rand 2000; Sieber 2000). One of the studies included in this review describes major limitations introduced by negative stereotypes about the medication treatment, and strong beliefs in traditional healing. Qualitative research involving people with epilepsy is of value in developing adherence-enhancing interventions, in evaluating the validity of the content of these interventions, and in assessing their feasibility. This can be regarded as a foundational step before these interventions are tested in RCTs.

Finally, the impact of adherence-enhancing interventions on resource utilisation and its cost effectiveness merit further research.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Brown 2009

Study characteristics	
Methods	**Study design:** RCT Methods of randomisation: a computerised, random-number generator Follow-up: 4 weeks Setting: 5 outpatient clinics at 1 hospital in the UK Date it was conducted: participants were recruited between January and June 2007 Source of funding: Janssen Cilag, Epilepsy Action, and the University of Sheffield Conflict of interest: not reported
Participants	**Inclusion/exclusion criteria:** people > 16 years of age. Patients were excluded if they were already using an adherence-enhancing method that could be compromised if they took part in the study, if they were receiving a diagnosis of epilepsy for the first time or if they had learning difficulty. Sample size: 81 participants were recruited; 12 participants did not complete follow-up measures, as they did not return their MEMS medication monitor bottles. Gender: 27 (40%) were men. Age: mean age was 41 years (SD 15.4) in the IG and 44 years (SD 16.4) in the CG.
Interventions	**Type of intervention:** behavioural All participants completed a 14-page packet of self-report measures. The IG group participants were given an additional worksheet on which they specified the environmental cues for tablet taking, using the format of an "if/then" plan. This means participants would write when and where they intended to take their medication every day, and what they would be doing at the moment of taking it.

Brown 2009 *(Continued)*

Outcomes	**Primary outcome measured:** adherence It was measured via MEMS, an electronic monitoring cap that recorded the number and timing of bottle openings. From this information, the percentage of prescribed doses taken and the percentage of doses taken on time were calculated. Overall adherence scores were generated by standardising and then averaging the 3 percentage measures. **Secondary outcome(s) measured:** the number of missed doses during the preceding month, the Brief Illness Perception Questionnaire and the Liverpool Seizure Severity Scale were administered at baseline and at follow-up.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised random-number generator was reported
Allocation concealment (selection bias)	Unclear risk	No information on concealment was reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The doctors and clinic and pharmacy staff were blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Information on blinding of other parties (e.g. outcome assessor) was not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing outcome data were reported and likely to be related to true outcome
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes
Other bias	Unclear risk	Insufficient rationale or evidence to permit judgement

Dash 2015

Study characteristics

Methods	**Study design:** RCT Method of randomisation: computer-generated table of random numbers Setting: outpatient clinic of a referral teaching institute in India Date it was conducted: June-December 2012 Follow-up: 6 months Source of funding: this study received no support in the form of grants, equipment, or drugs. Printing and publishing educational material funded by Center of Excellence Epilepsy, Department of Biotechnology, Ministry of Science and Technology, India.

Dash 2015 *(Continued)*

	Conflict of interest: the authors declare no conflict of interest
Participants	**Includion/exclusion criteria:** people diagnosed with epilepsy at least 1 month prior to the date of the study, ≥ 15 years of age, ability to understand Hindi/English, and willingness to participate in the study. Sample size: 180 participants were recruited. After a follow-up of 6 months, 82 participants in IG and 70 in the CG completed the questionnaires. Gender: male 52 (63%) in IG and 44 (63%) in CG Age: mean age was 34 years (SD 10.65) in IG and 35 years (SD 11.61) in CG.
Interventions	**Type of intervention:** educational A one-on-one, structured format teaching administered by an epilepsy nurse in 4 sessions each lasting at least 30 min. The teaching sessions covered the following domains: basic knowledge regarding epilepsy, myths and truths regarding epilepsy, diagnosis, treatment modalities (emphasis on compliance), living with epilepsy, and employment issues. Pamphlets written in Hindi and supplemented with illustrations and animations were also provided. The programme was developed by a group that included 3 epilepsy nurses, 2 epileptologists and 2 social workers.
Outcomes	**Primary outcome(s) measured:** adherence and self-care Adherence was assessed using the modified MMAS. **Secondary outcome(s) measured:** the change in seizure frequency
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was done using a computer-generated table of random numbers
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding was reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding was reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data were reported
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes
Other bias	Low risk	The study seems to be free of other sources of bias

Dilorio 2009

Study characteristics	
Methods	**Study design:** RCT Method of randomisation: not reported Setting: 3 clinics in a large south-eastern metropolitan area of the USA Date it was conducted: not reported Follow-up: 12 weeks Source of funding: Emory University Research Committee Conflict of interest: not reported
Participants	**Inclusion/exclusion criteria:** ≥ 18 years, were able to understand and speak English, had telephone access and were mentally stable Sample size: 22 Gender: 15 were men (68.2%) Age: mean age was 43 years (SD 13.51)
Interventions	**Type of intervention:** behavioural 5 motivational intervention sessions were conducted: 1 face-to-face and 4 telephone-based. For each session, a specially trained nurse used a script that included key aspects of self-management and discussed medication management with the participant. The nurse began by asking a general question about medication-taking practices.Those who reported problems with medication were provided support. A goal and action plan of at least one strategy to improve adherence was developed. Participants were encouraged to develop their own solutions and to devise an action plan. Then, the nurse asked the participant to select 1 or 2 other self-management components (information, seizure, safety and lifestyle issues) that were important to him or her. The rest of discussion aimed at identifying barriers and facilitators of desired behaviours, eliciting change strategies and building confidence.
Outcomes	**Primary outcome(s) measured:** adherence It was measured via MEMS cap (presented as percentage of doses taken and percentage of doses taken on time), and self-reported adherence by using AGAS. **Secondary outcome(s) measured:** outcome expectancy (a judgement of the likely consequences of practising self-management strategies and epilepsy self-management), self-efficacy and knowledge of epilepsy (medical and social aspects).
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	No information on concealment was reported

Dilorio 2009 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding was reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding was reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	High risk	Inadequate sample size could increase the likelihood of a type II error and other bias

Dilorio 2011

Study characteristics	
Methods	**Study design:** RCT Method of randomisation: not reported. However, authors reported that after a random start for the first participant, participants were assigned alternatively to the intervention or CG. Date it was conducted: not reported Setting: USA Follow-up: 12 weeks Source of funding: the CDC Epilepsy Program in the National Center for Chronic Disease Prevention and Health Promotion Conflict of interest: not reported
Participants	**Inclusion/exclusion criteria: ≥** 18 years of age, had been diagnosed with epilepsy, had been taking AEDs for at least 3 months, could speak and read English, had access to the Internet, were willing to participate in WebEase and had not participated in WebEase in the past Sample size: 148 participants Age: mean 41 years (SD 12.9) in IG and 40 years (SD 13.6) in CG Gender: female 48 (68.6%) in IG and 61 (78.2%) in CG
Interventions	**Type of intervention:** educational In the WebEase (Web Epilepsy Awareness, Support, and Education) programme, participants spent 2 weeks in each of the 3 modules that constitute the core of WebEase: medication, stress and sleep management. After logging into the WebEase site, participants were first required to complete the MyLog section to record information about seizures, medication taking, stress and sleep quality ratings. Then, they were given access to the other components of WebEase, including the modules. Weekly reminders to continue working through the modules and exploring the site resources were sent to participants. At the end of 6 weeks, access to the programme was ended for participants.

Dilorio 2011 *(Continued)*

Outcomes	**Primary outcome(s) measured:** adherence It was measured using the MAS. **Secondary outcome(s) measured:** perceived stress, sleep quality, epilepsy self-management, self-efficacy, knowledge about epilepsy and quality of life
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	No information on concealment was reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding was reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding was reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	High risk	Self-reported responses can be affected by social desirability biases

Edward 2019

Study characteristics

Methods	**Study design:** RCT Method of randomisation: allocation by ability of the participant to attend intervention Setting: 2 large hospitals in Melbourne, Australia Follow-up: 6 months Date it was conducted: 2015 Source of funding: St Vincent's Private Hospital Melbourne Conflict of interest: the authors declare no conflict of interest
Participants	**Inclusion criteria:** include: 1. adults (> 18 years)

Edward 2019 *(Continued)*

	2. diagnosed with epilepsy. Exclude: 1. people with a history of seizures from causes other than epilepsy, such as acute trauma 2. people with limited English comprehension 3. unable to give informed consent Sample size: 60 (CG 37 and IG 23) only 35 were analysed (18 CG, 17 IG) Age: mean 26 (median 22.3) in IG and 28 (median 23.3) in CG Gender: female 40 (43.5%) in IG and 44 (47.8%) in CG
Interventions	**Type of intervention:** educational The Self-Management and Lifestyle Education for Adults Living with Epilepsy education package consist of one 120-min session delivered face-to-face by a clinical nurse specialist in neurosciences. A booklet of the programme's content was given to each participant. The education package was divided into 4 education modules: Managing epilepsy and medical care; Socialising on a budget; Leading a healthy lifestyle; and Emotional self-management.
Outcomes	Frequency of seizures Psychological morbidity and HRQoL Subjective well-being Resilience Adherence measured using MMAS-8
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Allocation by ability of the participant to attend intervention
Allocation concealment (selection bias)	Unclear risk	No information on concealment was reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding was reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding was reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	50% loss to follow-up in CG and 26% in IG. Little's 'Missing Completely at Random' test showed no evidence that data were not missing at random
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Edward 2019 *(Continued)*

Other bias	Unclear risk	Insufficient information to permit judgement

Helgeson 1990

Study characteristics	
Methods	**Study design:** RCT Method of randomisation: not reported Setting: an outpatient clinic in the USA Date it was conducted: not reported Follow-up: 4 months Source of funding: partial financial support from the Epilepsy Foundation of America Conflict of interest: not reported
Participants	**Inclusion/exclusion criteria:** mentally retarded, demented, or psychotic patients Sample size: 120 people were recruited, and 100 agreed to participate. Of the 50 in the IG, only 23 completed a pre-assessment questionnaire and 3 were excluded because they did not attend the whole 2-day programme. Of the 50 in the CG, only 20 completed the pre-assessment questionnaire and 18 returned the follow-up questionnaire. Thus, the final sample included 38 participants: 20 in the IG and 18 in the CG. Gender: 14 (70%) in both groups were women Age: mean age was 36.15 years (SD 12.81) in the IG and 38.56 years (SD 10.67) in the CG Other characteristics: mean duration of seizure disorders was 17.40 years (SD 10.78) in the IG and 15.44 years (SD 11.14) in the CG
Interventions	**Type of intervention:** educational A 2-day programme designed to provide medical education and psychosocial therapy for participants and families. No more information were given on the programme.
Outcomes	**Primary outcome(s) measured:** adherence It was measured using serum drug level and expressed as percentage of mean change from baseline to 4 months. **Secondary outcome(s) measured:** anxiety and depression, coping with epilepsy, self-efficacy, psychosocial seizure inventory and epilepsy knowledge and medical management.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	No information on concealment was reported

Helgeson 1990 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding was reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding was reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	High risk	The risk may be explained by small sample size and limited follow-up (4 months)

Ibinda 2014

Study characteristics	
Methods	**Study design:** RCT Method of randomisation: via computer Setting: Kenya Date it was conducted: recruitment started August 2009 Follow-up: 1 year Source of funding: Wellcome Trust Conflict of interest: the study authors declare no conflict of interest
Participants	**Inclusion/exclusion criteria:** included people of all ages who had active convulsive epilepsy, defined as at least 2 unprovoked convulsions, with 1 in the 12 months prior to being assessed. Sample size: 738 participants; IG = 370; CG = 368. Analysis was done for 303 participants in the IG and for 278 participants in the CG who were observed at both the beginning and the end of the study. Assays of AEDs were done on 105 in the IG and 86 in the CG who provided blood samples. Age: mean age in IG 19 years (SD 17.4) and 19.5 (SD 15.6) in CG Gender: female 47.2 % of IG and 49.6% in CG
Interventions	**Type of intervention:** educational A 1-day educational programme on epilepsy, types of seizures, causes of epilepsy, effects of epilepsy on child development, treatment of epilepsy, side effects of drugs, drug safety, what to do during a seizure, when to take a person with epilepsy to hospital, prevention of epilepsy, what a person with epilepsy can and cannot do and advice for families. In addition, a brochure detailing all of the topics discussed was given to each participant. The intervention was designed and delivered by a team of epilepsy researchers and field staff.
Outcomes	**Primary outcome(s) measured:** adherence

Ibinda 2014 *(Continued)*

	It was assessed by plasma drug concentrations and self-report using the 4-item MMAS. Both measurements were compared between the baseline and the end of the study. **Secondary outcome(s) measured:** seizure frequency and KEBAS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation was reported
Allocation concealment (selection bias)	Unclear risk	No information on concealment was reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Insufficient information to permit clear judgement
Blinding of outcome assessment (detection bias) All outcomes	Low risk	The laboratory technicians conducting the assays were blinded to the randomisation
Incomplete outcome data (attrition bias) All outcomes	High risk	Missing outcome data are reported and are likely to be related to true outcome
Selective reporting (reporting bias)	Low risk	The study protocol is available and all prespecified outcomes of interest have been reported
Other bias	High risk	Authors indicated that improved adherence in both groups could be explained by the sharing of knowledge between groups.Also, those who did not give blood samples to assess drug levels held significantly more traditional religious and cultural beliefs, and believed that AEDs caused epilepsy than those who provided blood samples.

Leenen 2018

Study characteristics

Methods	**Study design:** RCT Method of randomisation: patients with epilepsy were assigned to the IG or the TAU group by means of block randomisation. Setting: Academic Centre for Epileptology. Sessions were conducted at several locations in the southern part of the Netherlands (Heeze, Maastricht, and Nijmegen) Date it was conducted: between March 2014 and December 2015 Source of funding: this study was funded by the Netherlands Organization for Health Research and Development (ZonMw) Conflict of interest: the study authors declare no conflict of interest

Leenen 2018 *(Continued)*

Participants	**Inclusion/exclusion criteria:** adults who were ≥ 18 years, living at home, diagnosed with epilepsy, and using AED; who understood the Dutch language; and who were willing and able to use health devices belonging to the multicomponent self-management intervention. Sample size: 102 people with epilepsy were included in the study (52 were in the IG), of whom 86 completed the study. In total, 49/52 of the intervention and 44/50 of the TAU group were included in the analysis. Age: mean 41.7 years (14.7) Gender: 50 (49.0%) male
Interventions	**Type of intervention:** mixed The multicomponent self-management intervention consisted of 5 weekly group sessions of 2 h each, followed by a 2-h booster session after 3 weeks. The groups comprised 3-5 participants with possibly a relative, if present and willing to participate. Sessions led by 2 nurse practitioners were conducted at several locations in the southern part of the Netherlands. All group sessions consisted of 2 components: education and practicing goal-setting skills. In the educational part, participants were sharing and discussing strategies about three topics: 1) self-monitoring and self-monitoring using (e-Health) tools; 2) risk-evaluation and management; and 3) shared decision-making/ concordance. The goal-setting component of the intervention is based on Aspinwall and Taylors' 5 stages of proactive coping, namely: resource accumulation; recognition of potential stressors; initial appraisal; preliminary coping efforts; and elicitation and use of feedback concerning initial efforts.
Outcomes	**Primary outcome measure:** disease-specific self-efficacy **Secondary outcome measure:** general self-efficacy, adherence, seizure severity, emotional functioning, quality of life, proactive coping, and side-effects of AED
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed by means of block randomisation using an online randomisation program
Allocation concealment (selection bias)	Low risk	The randomisation scheme was distributed to the researcher in sealed envelopes during the first visit, prior to baseline assessment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding was reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding was reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Number of missing data is reported and is balanced
Selective reporting (reporting bias)	Low risk	The study protocol is published including similar outcome (EURQoL5D, societal costs data reported in a separate publication)
Other bias	Unclear risk	Insufficient rationale or evidence to permit judgement

Li 2013

Study characteristics	
Methods	**Study design:** RCT Method of randomisation: simple randomisation (random selection software) Setting: 2 rural communities of western China Date it was conducted: between September 2009 and December 2012 Follow-up: 1 year Source of funding: not reported Conflict of interest: the study authors declare no conflict of interest.
Participants	**Inclusion exclusion criteria:** age ≥ 13 and < 65 years and constant receipt of phenobarbital monotherapy The exclusion criteria: patients with severe mental retardation or neurologic diseases or psychosis; and patients receiving another 1 or 2 AEDs in addition to phenobarbital as additional therapy. Sample size: the study included a sample of 200 participants with epilepsy for each group (IG and CG). After a 12-month follow-up, 183 cases were retained in IG and 177 in CG. Gender: 105 male in IG and 99 male in CG. Age: mean age was 36.6 years (median 38) in the IG and 39.4 years (median 40) in the CG Other characteristics: mean duration since diagnosis was 12.3 years (median 14) in the IG and 10.6 years (median 12) in the CG
Interventions	**Type of intervention:** mixed A 4-component programme. First, intensive education that included explanation of epilepsy, emphasising the importance of receiving appropriate AED treatment and taking medication regularly. Second, consultation services where clinical providers and telephone support were available for participants at any time. Third, reminders in the form of keeping a simple record with a specifically-designed card. Fourth, participants received repeated (> 3 times at each attending clinic) reminders about medical adherence every month.
Outcomes	**Primary outcome(s) measured:** adherence, seizure control and avoiding lifestyle-precipitated seizures. Adherence and lifestyle were each graded on a 6-point scale with possible scores and measured and compared between the groups before and after the intervention.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Simple randomisation was reported
Allocation concealment (selection bias)	Unclear risk	No information on concealment was reported

Li 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	The study designers, local physicians and data analyst were blinded to the intervention
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Insufficient information to permit clear judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data are reported
Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes
Other bias	Unclear risk	Insufficient rationale or evidence to permit judgement

Modi 2013

Study characteristics	
Methods	**Study design:** RCT Method of randomisation: via a permuted block randomisation method with block size of 2 Setting: a new-onset seizure clinic at a pediatric children's hospital in the USA Date it was conducted: not reported Follow-up: 4 months Source of funding: National Institute of Health Conflict of interest: the study authors declare no conflict of interest.
Participants	**Inclusion/exclusion criteria:** diagnosis of a non-epilepsy medical disorder requiring daily medication, a significant developmental disorder (e.g. autism), or the family living > 90 miles (145 km) away from the hospital. Families had to read/speak English. Sample size: 40 families were approached for study participation; 30 agreed to participate and 3 withdrew before randomisation or did not return. After a 1-month run-in period, participants with near perfect adherence (> 90%) were monitored (n = 19). Participants with adherence < 90% (n = 8) were randomly assigned to IG or to the CG group. Age: mean age was 8.0 years (SD 5.6) in the IG and 7.1 years (SD 2.3) in the CG. Gender: 50% male Other characteristics: mean duration since diagnosis was 3.2 months (SD 1.2) in the IG group and 1.5 months (SD 0.88) in the CG
Interventions	Type of intervention: educational The IG received 4 sessions over > 2 months. The first component of the intervention (session 1) provided education on epilepsy treatment, AED adherence and the family's specific epilepsy treatment regimen (i.e. dosing schedule). Sessions 2 through 4 aimed to teach families a problem-solving approach for their identified AED-adherence barriers.

Modi 2013 *(Continued)*

Outcomes	**Primary outcome(s) measured:** adherence It was measured by an electronic monitoring system that measures the time and date a pill bottle and cap were opened. **Secondary outcome(s) measured:** assessment of feasibility and acceptability of the adherence Intervention.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Permuted block randomisation with block size of 2 was described
Allocation concealment (selection bias)	Unclear risk	No information on concealment was reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding was reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding was reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing data
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient rationale or evidence to permit judgement

Modi 2016a

Study characteristics

Methods	**Study design:** RCT feasibility and acceptability Method of randomisation: stratified block randomisation with type of phone (text-enabled only vs smart phone) as the blocking variable Setting: Cincinnati Children's Hospital Medical Center Date it was conducted: not reported Source of funding: the Fifth Third Bank/Charlotte R. Schmidlapp Women Scholars Program Conflict of interest: the study authors declare no conflict of interest
Participants	**Inclusion/exclusion criteria:** patients 13–17 years old, live within 75 miles of the hospital, no chronic medical disorders requiring daily medications, no significant parent-reported developmental disorders, no liquid AED formulation, and no AED weaning plans in the 3 months following enrolment

Modi 2016a *(Continued)*

	Sample size: 25 adolescents and caregivers. Not clear form the paper how many participant in each group. Missing data were observed for 4% of the baseline adherence data and 14.6% of the 'active intervention' and 'post-intervention' phases Age: 15.7 years (SD 1.5) Gender: 48% were female
Interventions	**Type of intervention:** behavioural The IGs received reminder text messaging as follows. Group 1: text messaging received by adolescent only; Group 2: text messaging received by adolescent and their caregiver, as well as a single-family communication session; Group 3: application for the adolescent only; Group 4: application for both the adolescent and caregiver, with the single-family communication sessions; Group 5: the Epilepsy Tool Kit application created by the National Society for Epilepsy (CG)
Outcomes	Adherence, treatment acceptability and feasibility
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Stratified block randomisation with type of phone (text-enabled only versus smart phone) as the blocking variable was described
Allocation concealment (selection bias)	Unclear risk	No information on concealment was reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding was reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding was reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No reporting of attrition/exclusions
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient rationale or evidence to permit judgement

Modi 2016b

Study characteristics

Methods	**Study design:** pilot RCT Method of randomisation: permuted block randomisation with block size 2 Setting: new-onset seizure clinic in a Midwestern children's hospital

Modi 2016b *(Continued)*

	Date it was conducted: January 2011-October 2012 Source of funding: National Institutes of Health Conflict of interest: the study authors declare no conflict of interest
Participants	**Inclusion/exclusion criteria:** patients with recent diagnosis of epilepsy (within 7 months), aged 2–12 years, no comorbid chronic illnesses requiring routine medications (e.g., diabetes), AED medication in pill or sprinkle form, family residing within 75 miles of the hospital, no significant parent-reported developmental disorders (e.g. autism), and no prior AED treatment. Children with major developmental disorders were excluded. Sample size: 50 families. STAR intervention (n = 11) versus TAU (n = 12). Families with high adherence at baseline (n = 22) were not randomised. Of those randomised to the STAR intervention, 2 withdrew prior to treatment initiation and 1 family completed the intervention sessions but was lost to follow-up. Age: 7.6 years (SD 3.0) Gender: 66.0% male
Interventions	**Type of intervention:** educational Participants involved in 4 face-to-face sessions and 2 telephone problem-solving sessions over 8 weeks Session 1 addressed deficit in epilepsy knowledge and provided feedback on each family AED adherence over the last 2 weeks. Sessions 2 through 4 aimed to teach families a problem-solving approach for their identified AED-adherence barriers.
Outcomes	**Primary outcome:** adherence **Secondary outcomes:** epilepsy knowledge; medication self-management; problem-solving skills
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	permuted block randomisation with block size 2
Allocation concealment (selection bias)	Unclear risk	No information on concealment was reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding was reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding was reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Of those randomised to the STAR intervention, 2 withdrew prior to treatment initiation and 1 family completed the intervention sessions but was lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement

Modi 2016b *(Continued)*

Other bias	Unclear risk	Insufficient rationale or evidence to permit judgement

Pakpour 2015

Study characteristics	
Methods	**Study design:** randomised multi-centre study Method of randomisation: 1:1, double-blind Setting: neurologic clinics in Iran Date it was conducted: June 2014-February 2015 Source of funding: NR Conflict of interest: the study authors declare no conflict of interest
Participants	**Inclusion criteria:** 1. have a diagnosis of epilepsy according to the International League Against Epilepsy criteria 2. be aged ≥ 18 years 3. have independence in daily living activities or be responsible for taking their medications 4. be prescribed AEDs. **Exclusion criteria:** 1. presence of a rapidly progressing neurological or medical disorder 2. not prescribed AEDs 3. diagnosis of an intellectual disability 4. major cognitive impairment (as assessed by the mini–mental state examination b23) 5. unable to read and write Persian Sample size: 275 participants enrolled in the study. 138 in the active comparator (lost to follow-up = 1 and dropout = 1) and 137 in the IG (lost to follow-up = 3 and dropout = 3). Age: CG 39.86 (SD 15.01); IG 41.37 (SD 16.25) Gender: CG 89 (67.2%) male; IG 92 (67.2%) male
Interventions	3 weekly face-to-face sessions were performed to improve medication adherence [24,30,31]. The MI sessions were delivered individually by a male health psychologist with 10 years of experience working with medication adherence in patients with chronic diseases and 60 h of training of MI in Qazvin and Tehran. During the sessions, the participants were encouraged to express their experiences, values, readiness, and confidence for the behaviour change. All sessions were held in a private and quiet setting within a neurologic clinic. Each session lasted for 40-60 min. Patients then created a personal action plan by specifying where, when, how, and how often they would take medications and use drug diary calendar to help them stick to their plans. Patients were encouraged to identify the barriers that might interfere with the implementation of their medication adherence plans and to specify how to overcome them.
Outcomes	**Primary outcome measures:** adherence to prescribed AEDs, assessed with serum level and MARS **Secondary outcome measures:** QoL and several psychosocial variables were also measured.
Notes	
Risk of bias	

Pakpour 2015 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a computer-generated code based on random number sequence with stratification by the study sites.
Allocation concealment (selection bias)	Unclear risk	No information on concealment was reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Double-blind trial was mentioned
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind trial was mentioned
Incomplete outcome data (attrition bias) All outcomes	Low risk	Numbers of missing data reported and are balanced
Selective reporting (reporting bias)	Low risk	The study protocol is published, including similar outcomes
Other bias	Unclear risk	Insufficient rationale or evidence to permit judgement

Peterson 1984

Study characteristics	
Methods	**Study design:** RCT Method of randomisation: coin-toss randomisation Setting: outpatient clinic at a hospital in Australia Date it was conducted: not reported Follow-up: 4 weeks and 6 months Source of funding: Astra Pharmaceuticals (Pty) Ltd supplied Dosetts Conflict of interest: not reported
Participants	**Inclusion/exclusion criteria:** people who were consecutive attenders at outpatient clinics during the study period, who were responsible for their own medication and who possessed a hospital pharmacy prescription book. Sample size: 53 participants were recruited. At follow-up, 2 participants from the CG and 1 from the IG had not returned to the clinic and were excluded from the analysis. Gender: 15 (58%) men were included in the IG and 15 (56%) in the CG. Age: median age was 35 years (range 19-74) in the IG and 28 years (range 18-64) in the CG. Gender: female 44% in the IG and 42% in CG
Interventions	**Type of intervention:** mixed

Peterson 1984 *(Continued)*

	IG participants were counselled on the goals of anticonvulsant therapy and the importance of good adherence in achieving these goals; a schedule of medication-taking was devised that corresponded with participants' everyday habits; participants were given a copy of an educational leaflet; each participant was provided with a 'Dosett' medication container (pill organiser) and was counselled on its use; participants were instructed to use a medication/seizure diary; and participants were reminded by mail of upcoming appointments and of missed prescription refills.
Outcomes	**Primary outcome(s) measured:** adherence It was assessed by 1. changes in plasma anticonvulsant levels (provided that the participant's medication regimen had not been altered in the preceding 2 weeks) 2. a check of the participant's prescription record book to determine prescription refill frequency (if refill frequency was 1 or more weeks later than expected at least once during the previous 6 months, the participant was considered non-adherent) 3. participant appointment-keeping frequency (those who had attended all scheduled appointments in the previous 6 months were considered compliant).
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Coin toss was reported
Allocation concealment (selection bias)	Unclear risk	No information on concealment was reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The physicians were blinded to the allocated interventions
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	The information on blinding of other parties (e.g. outcome assessors) was not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient rationale or evidence to permit judgement

Pryse-Phillips 1982

Study characteristics

Methods	**Study design:** RCT Method of randomisation: not reported

Pryse-Phillips 1982 *(Continued)*

	Setting: 2 outpatient clinics in Canada Date it was conducted: Follow-up time: 4 weeks Source of funding: Conflict of interest:
Participants	**Inclusion/exclusion criteria:** people with psychotic and severe neurotic disorders were excluded. 50 participants were accepted into the study. No loss to follow-up was reported. No further details on participants were provided
Interventions	**Type of intervention:** educational 2 structured interviews separated by 4 weeks were conducted in the clinic or by telephone. At each interview, the participant described his/her seizure, the medication given and general background information. An information pamphlet containing details on the name of the drug; its colour, shape and strength; the therapeutic effect; and dosage, precautions and possible unwanted effects was read and explained or was read, explained and given to the participant to take home.
Outcomes	**Primary outcome(s) measured:** adherence It was assessed by measurement of serum drug level and expressed as percentage of change from the initial level towards the mean of the accepted therapeutic range. **Secondary outcome(s) measured:** alteration in knowledge about epilepsy and alteration in insightful behaviour such as a request for advice from the physician due to loss of hair.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	No information on concealment was reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding was reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding was reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient rationale or evidence to permit judgement

Ridsdale 2018

Study characteristics	
Methods	**Study design:** multicenter RCT Method of randomisation: online randomisation system. Randomisation occurred in blocks of 2 (1:1 IG: CG) and stratified by treatment centre. Setting: London and South East England Date it was conducted: between December 2013 and August 2016. Source of funding: the National Institute for Health Research Conflict of interest: the study authors declare no conflict of interest.
Participants	**Inclusion/exclusion criteria:** patients aged ≥ 16 years, epilepsy for ≥ 1 year, prescribed AEDs, reporting at least 2 seizures (of any type) in the previous year, able to give informed consent, answer questionnaires in English, and attend a 2-day course. Excluded patients with psychogenic nonepileptic seizures or due to acute illness or substance misuse, serious psychiatric illness or a terminal condition, or if they were currently participating in other epilepsy-related research. Sample size: The SMILE training programme plus TAU (n = 205) versus TAU only (n = 199) At 12 months, 81.9% of participants remained in the study (IG: 79.5% (n = 163); TAU: 84.4% (n = 168)) Age: 41.7 years (SD 14.1) Gender: 219 (54.2%) female
Interventions	**Type of intervention:** educational Self-management education for people with poorly controlled epilepsy (SMILE [UK]) is a group-based education course. There are 9 modules in the course, such as living with epilepsy;and basic knowledge about seizures. The course was delivered by an epilepsy nurse specialist and an EEG technician for 16 h over 2 consecutive days. The premise of the course was to communicate information and to encourage participants (people with poorly controlled epilepsy, with carers also invited) to share their own experiences with others through the use of interactive discussion, presentation slides, the use of flip-chart. Participants were given a workbook containing course content to use during the sessions and to take home.
Outcomes	**Primary outcome:** epilepsy-specific QoL **Secondary outcomes:** seizure frequency scales, seizure recency (number of days since last seizure), HADS for psychological distress (anxiety and depression), Impact of Epilepsy, Stigma of Epilepsy, Medication Adherence, medication adverse effects extracted from the QOLIE-31-P, and self-mastery and control
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Online system

Ridsdale 2018 *(Continued)*

Allocation concealment (selection bias)	Low risk	No information on concealment was reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The participants' healthcare providers were blind. Staff organising the courses were not involved in data collection and not blind.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Researcher who completed follow-up assessments were blind. The statistician remained blind until the end of the analysis
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data balanced in numbers across groups with similar reasons for missing data
Selective reporting (reporting bias)	Low risk	The study protocol is published, including similar outcomes
Other bias	Low risk	The study seems to be free of other sources of bias

Saengow 2018

Study characteristics	
Methods	**Study design:** RCT Method of randomisation: day of the week Setting: pediatric neurology clinic in Thailand Follow-up: 3 months Date it was conducted: June 2016-September 2016 Source of funding: not reported Conflict of interest: nothing reported
Participants	**Inclusion criteria:** pediatric patients aged between 1 month-15 years, diagnosed with epilepsy, visited routine service pediatric neurology clinic. Sample size: 214 patients were recruited (IG: 126, CG: 88) Age: mean 7.6 (mean 4.5) in IG and 7.6 (mean 4.8) in CG Gender: female 53 (42.1%) in IG and 36 (40.9%) in CG
Interventions	**Type of intervention:** educational An 8.52-min video animation on: diagnosis of epilepsy, etiology of epilepsy, treatment of epilepsy, first aid seizure care, prognosis of epilepsy and safe activity for epilepsy
Outcomes	**Primary outcomes:** adherence measured using the 8-item MMAS Epilepsy knowledge measured using 10 questions on epilepsy knowledge **Secondary outcomes:** severity of seizure

Saengow 2018 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Days of the week
Allocation concealment (selection bias)	Unclear risk	No information on concealment was reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding was reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding was reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Apparently, no incomplete outcome data
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient rationale or evidence to permit judgement

Shope 1980

Study characteristics

Methods	**Study design:** RCT Method of randomisation: not reported Setting: 1 paediatric seizure clinic in the USA Date it was conducted: March 1977- April 1978 Follow-up: 11 weeks following the intervention Source of funding: Epilepsy Foundation of America, Epilepsy Center of Michigan Conflict of interest: not reported
Participants	**Inclusion/exclusion criteria:** children were eligible if they were prescribed a continuing dosage of phenobarbital and/or phenytoin; < 16 years of age; the only child of the family; accompanied by the person who took primary care of the child Sample size: 211 children were recruited. 70 children were judged non-compliant because serum levels were below predicted levels for individual age and dosage. 3 children were dropped from the study because their physician discontinued their medication. Parents of the 67 children remaining in the study were allocated to IG (28 parents) and CG (37 parents). Of the 28 parents invited to the discussion meeting, only 14 attended the discussion.

Shope 1980 *(Continued)*

	Age: mean age was 9 years and ranged from 1-15 years. Mean age of children in the CG was significantly higher than children assigned to the IG. Gender: half of children were girls and 67% were black. Other characteristics: half of the parents had < 11th grade education and income < USD 8330.
Interventions	**Type of intervention:** educational 2 mothers' discussion group meetings, each lasting 1.5 h. The aim of these meetings was to provide mothers with information to enable them to know what to do for their children and why, increasing their sense of responsibility and obtaining their commitment. Follow-up and interview and laboratory results were obtained at regularly-scheduled visits, a mean of 11 weeks following the discussion session.
Outcomes	**Primary outcome(s) measured:** adherence It was assessed by measurement of serum drug levels and expressed as a score ranging from 1-4. 1 indicated zero level of medication in the serum, 2 indicated > 30% less than predicted, 3 indicated within predicted mean and 4 indicated 30% more than predicted mean. **Secondary outcome(s) measured:** knowledge of seizure disorder, locus of control and dependency
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Method of randomisation was not reported
Allocation concealment (selection bias)	Unclear risk	No information on concealment was reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding was reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding was reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Insufficient reporting of attrition/exclusions to permit judgement
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient rationale or evidence to permit judgement

Tang 2014

Study characteristics

Methods	**Study design:** RCT

Tang 2014 *(Continued)*

	Method of randomisation: random-number table Setting: an outpatient clinic of a hospital in China Date it was conducted: September 2011- March 2013 Follow-up: 1 year Souce of funding: not reported Conflict of interest: the study authors declare no conflict of interest
Participants	**Inclusion/exclusion criteria:** people diagnosed with epilepsy, > 16 years of age, took AEDs for > 6 months, and did not take their AEDs at least once over the past 6 months. Sample size: 124 were assigned to education intervention (n = 59) and education and behavioural intervention (n = 65). 56 and 53 participants completed the last assessment of all measures in education and behavioural IG and education only respectively. Age: mean age was 31 years (SD 13.0) in education and behavioural IG and 30 years (SD 11.6) in education only group Gender: men 49% in education and behavioural IG and 59% in education only group
Interventions	**Type of intervention:** mixed Study defines 2 IGs: the medication education group (group 1) and the medication education with behavioural IG (group 2). Group 1 was initially provided with medication education in the form of oral education and written materials, and this education was reinforced by monthly calls from the pharmacist over the next 6 months. The behavioural intervention provided to group II consisted of a modified medication schedule which was based on cue–dose training therapy
Outcomes	**Primary outcome(s) measured:** adherence It was assessed by using MMAS-4 **Secondary outcome(s) measured:** seizure control, knowledge of AEDs, QoL, number of participants who missed a dose of their AEDs
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomisation was performed using a random-number table
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding was reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding was reported
Incomplete outcome data (attrition bias)	Low risk	Similar reasons for missing outcome data were reported between groups

Tang 2014 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	The study protocol is not available but it is clear that the published reports include all expected outcomes
Other bias	Unclear risk	Insufficient rationale or evidence to permit judgement

Zheng 2019

Study characteristics	
Methods	**Study design:** RCT Method of randomisation: a computer-generated table Setting: tertiary referral hospital in China Follow-up: 12 months Date it was conducted: June 2014-January 2016 Source of funding: the National Natural Science Foundation of China, the Zhejiang Provincial Administration of Traditional, and the Major Program of Science and Technology Department of Zhejiang Province, China Conflict of interest: the study authors declare no conflict of interest
Participants	**Inclusion criteria:** 1. ≥ 18 years of age 2. diagnosis of epilepsy according to the 2001 International League Against Epilepsy (ILAE) diagnostic scheme 3. AED treatment for at least 3 months 4. the ability to read and write 5. absence of major cognitive impairment Sample size: in total, 194 patients met the study criteria and agreed to participate, 184 completed the programme (IG 92, CG 92), with a dropout rate of 5.15% (lost to follow-up or discontinued intervention) in both the IG and CG. Age: mean 26 (median 22.3) in IG and 28 (median 23.3) in CG Gender: female 40 (43.5%) in IG and 44 (47.8%) in CG
Interventions	**Type of intervention:** educational A multidisciplinary management programme included 3 items: 1. face-to-face interviews with an epileptologist to answer questions regarding epilepsy and self-management skills, and to evaluate depression, anxiety, and AED adherence. Patients with low adherence would be referred to the pharmacist for education and to receive an epilepsy tracking card for reminder 2. online consultations by epilepsy specialist nurse to answer participant's questions daily, monthly release the educational information, and remind participants to visit in time 3. group education by the multidisciplinary team twice a year
Outcomes	**Primary outcomes:** proportion of participants with moderate to severe depression, moderate to severe anxiety, and proportion of participants with low AED adherence

Zheng 2019 *(Continued)*

	Secondary outcomes: QoL and self-reported seizure frequency in the last 6 months
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A computer-generated table
Allocation concealment (selection bias)	Unclear risk	It was reported that concealed random allocation was used. No information on method of concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	No information on blinding was reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No information on blinding was reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Similar dropout rate between 2 groups with dropouts excluded from analysis
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement
Other bias	Unclear risk	Insufficient rationale or evidence to permit judgement

AED: antiepileptic drug; **AGAS:** Antiretroviral General Adherence Scale; **CG:** control group; **EEG:** electroencephalography; **HADS:** Hospital Anxiety and Depression Scale; **HRQoL:** health-related quality of life; **IG:** intervention group; **KEBAS:** Kilifi Epilepsy Beliefs and Attitudes Scores; **MAS:** Medication Adherence Scale; **MARS:** Medication Adherence Report Scale; **MEMS:** Medication Event Monitoring System; **MI:** motivational interviewing; **MMAS:** Morisky Medication Adherence Scale; **QoL:** quality of life; **RCT:** randomised controlled trial; **SD:** standard deviation; **TAU:** treatment as usual

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

Study	Reason for exclusion
Adamolekun 1999	Not a RCT; the 24 health facilities were consecutively allocated to intervention or control.
Boggs 2007	There is insufficient information to make a sound decision.
Choudhry 2017	The study examined the effect of 3 low-cost reminder devices on medication adherence. Results are presented for cardiovascular or other nondepression chronic conditions (the chronic disease stratum) but not clear if any epileptic patients were included.
Cramer 1995	A placebo-controlled trial of vigabatrin; during the trial, the utility of an electronic monitoring device in evaluating what dose was actually received by participants was examined. However, randomisation was to receiving vigabatrin or placebo, not to any adherence-enhancing intervention
Lewis 1990	Effect of educational programme on parents' knowledge, dealing with anger and anxiety and decision-making skills; adherence as an outcome is not reported.

Study	Reason for exclusion
May 2002	Effect of educational programme on QoL, knowledge and seizure frequency, but adherence as outcome is not reported.
McLaughlin 2011	Examined the effectiveness of CBT to manage seizures and improve psychosocial functioning in older adults with epilepsy. Adherence as an outcome is not reported.
Ridsdale 1997	Effect of nurse intervention on knowledge, emotional state and seizure frequency, but no adherence outcome reported.
Ridsdale 1999	Effect of nurse intervention on knowledge, emotional state and seizure frequency, but no adherence outcome reported.

CBT: cognitive behavioural therapy; **QoL:** quality of life; **RCT:** randomised controlled trial

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

NCT02646631

Study name	Behavioural and educational tools to improve epilepsy care
Methods	A parallel-group, single-blind (participant), randomised trial. Participants will be followed for 3 months
Participants	Individuals ≥ 18 years of both genders, who are suffering from epilepsy
Interventions	Smartphone-based self-management intervention called Management of Risks in Epilepsy (MORE), or MORE + telephone-based MI
Outcomes	Primary outcome measures: percent adherence to AED schedule (pill counts) Secondary outcome measures: number of participants who complete the study, percentage of MI sessions completed, percentage of diary entries completed, adherence to AED schedule (self-reported) as measured by the MMAS, seizure frequency, and QoL
Starting date	January 2016
Contact information	Tanya Spruill, New York University School of Medicine, USA
Notes	

NCT03484039

Study name	Incorporating multidimensional psychosocial interventions improves the well-being of individuals with epilepsy
Methods	Parallel assignment, randomised
Participants	568 participants
Interventions	Patients will be enrolled in 1 module of own choice. Except for Module 3 Submodule 2, every module will consist of a particular intervention, as well as its accompanying set of assessments. Prior to being given the intervention, participants assigned to a given module will be randomly assigned to either an Immediate Intervention (II) or a Delayed Intervention (DI) group. Although every participant will receive the intervention, the timing of the intervention and assessments will distinguish

NCT03484039 *(Continued)*

	the II and DI group. The II group will receive the module (a 1-2-h course on either medication adherence, seizure documentation, memory improvement or stress management) right after a baseline assessment. A post-assessment and delayed post-assessment will be conducted after the module is administered. The DI group will receive a baseline assessment. 6 weeks-3 months later (average 2 months) a pre-intervention assessment will be conducted just prior to administering the modules (a 1-2-h course on either medication adherence, seizure documentation, memory improvement or stress management). A post-intervention assessment will then be administered.
Outcomes	Changes in Quality of Life in Epilepsy-10 scores (time frame: to be administered at baseline (upon participant screening), pre-intervention (with 2 weeks prior to intervention), post-intervention (between 6 weeks to 3 months post-intervention), and delayed post-intervention (within 4.5-6 months post-intervention)) This is a well-validated measure of quality of life for people with epilepsy. The unit of measure is a composite score ranging from 0-100 with higher scores indicating better QoL. Adherence was mentioned in the introduction as an outcome but not listed under primary outcomes.
Starting date	6 June 2018
Contact information	Ramon E Bautista, MD 904-244-9190 ramon.bautista@jax.ufl.edu
Notes	

Singh 2019

Study name	A home-based, primary-care model for epilepsy care in India: basis and design
Methods	The experimental group will be compared to a routine clinic-based care group using a cluster-randomised design in which the unit of analysis is a cluster of 10 people with epilepsy residing in an area cared for by a single accredited government grass-roots healthcare worker
Participants	People > 1 year old with active epilepsy were invited to enrol in the trial regardless of prior treatment status. People with febrile seizures, neonatal seizures, single seizures not fulfilling the current operational definition for epilepsy, and acute symptomatic seizures associated with head injury, stroke, and toxic, metabolic, and acute infective conditions were excluded
Interventions	A home-based intervention comprises epilepsy medication provision, adherence reinforcement, and epilepsy self-management and stigma management guidance provided by an auxiliary nurse-midwife equivalent.
Outcomes	The primary outcome is treatment adherence as measured by monthly tablet counts supplemented by 2 self-completed questionnaires. The secondary outcomes include monthly seizure frequency, time to first seizure (in days) after enrolment, proportion of participants experiencing seizure freedom for the duration of the study, and QoL measured by the 'Personal Impact of Epilepsy Scale', all assessed by an independent study nurse.
Starting date	The screening phase and neurologic evaluations and randomisations have been recently completed and follow-up is underway.
Contact information	
Notes	

AED: antiepileptic drug; **MI:** motivational interviewing; **MMAS:** Morisky Medication Adherence Scale; **QoL:** quality of life

ADDITIONAL TABLES

Table 1. Summary of results for each included study

Behavioural interventions

References	Assessment methods	Statistical analysis	Study results
Brown 2009	All participants completed a 14-page packet of self-report measures. Adherence was measured with MEMS cap. To assess the equivalence of control and intervention groups, and to identify factors that could moderate the impact of the intervention, a collection of self-report measures was applied (methods such as a single-item self-estimate of the number of missed doses during the preceding month, BIPQ, TPB, MASQ, HADS, PRMQ, LSSS were administered at baseline and at follow-up.	ANOVA and Chi2 test	Intervention participants showed improved adherence relative to controls on all 3 outcomes: doses taken in total (93.4% vs 79.1%), days on which correct dose was taken (88.7% vs 65.3%), and doses taken on schedule (78.8% vs 55.3%); P < 0.01
DiIorio 2009	Adherence was measured using MEMS cap and self-reported medication adherence via AGAS (at baseline and follow-up assessment). The following scales were also used: ESMS (follow-up assessment only), ESES, and knowledge about epilepsy measured by EKQ.	Independent t-test used to compare treatment and control group on variables assessed at follow-up	Prescribed doses taken overall in the intervention group was 81.29% (SD 13.48) and doses taken on schedule 53.27% SD (17.74). The results for adherence and self-efficacy were in the correct direction and statistically significant only at the 0.10 level, suggesting that the intervention may also improve confidence in self-management
Modi 2016a	MEMS TrackCap (Aardex Corporation). The cap contains a microchip to register the dates and times the bottle is opened and closed. For families using a pill box, adolescents were asked to use a The SimpleMed + to administer AED. When a compartment is opened a date/time stamp is sent wirelessly to a secure website, which was accessed by study staff.	Hierarchical linear modelling (HLM)	The results are not reported clearly, but it appears that there were high levels of baseline adherence and minimal adherence improvements among all groups. Group 4 demonstrated lower overall adherence compared to all groups.
Pakpour 2015	The primary outcomes were adherence to prescribed AEDs, assessed with serum level and the MARS. QoL and several psychosocial variables were also measured.	The linear mixed models (PROCMIXED) for continuous outcome variables. As serum level was a binary outcome, a logistic mixed model was conducted	There was a progressive increase in average MARS in the intervention group, but no change was observed in the standard care group. Patients in the intervention group reported significantly higher medication adherence compared with those in the active comparator group at 3-month (β = 4.6, p b 0.001) and 6-month (β = 1.73, p b 0.001) follow-up.

Table 1. Summary of results for each included study *(Continued)*

		to assess the intervention effects on the serum level in patient groups between the two arms.	The ORs of serum level were increased by 1.35 in participants in the intervention group (OR 1.35, 95% CI 1.07 to 1.71; P = 0.03) compared with those in the active comparator group at 3 months' follow-up.

Educational interventions

References	Assessment methods	Statistical analysis	Study results
Dash 2015	Drug adherence and self-care were measured respectively using the modified MMAS and the ESES.	Statistical analysis was carried out using SPSS software (version 16 for Windows), a paired t-test was applied.	In the intervention group, the pre-test mean MMAS score was 6.58, whereas the post-test mean MMAS score was 7.53; the difference was significant (P = 0.001). The mean MMAS scores for the control group's pre-test and post-test were 6.46 and 6.58 respectively, which were not significantly different (P = 0.224).
Dilorio 2011	Medication adherence was measured using the MAS 8-item measurement of self-reported medication-taking behaviours; perceived stress was measured by PSS and the ESI-R. PSQI, ESMS, ESES, EKP and QOLIE-10 measurements were also assessed	Repeated ANOVA measures were conducted using SPSS version 18.	Trends toward statistical significance were noted for medication adherence (P = 0.118), stress (P = 0.098), self-management (P = 0.098), and knowledge (P = 0.077). Participants who completed WebEase modules (intervention group) reported an increase in self-efficacy (P = 0.013), meaning that they were more positive about their ability to manage medication, stress, or sleep issues.
Edward 2019	Seizure frequency: seizure diary Psychological morbidity and HRQoL: SF-12 Subjective well-being: SWLS Resilience: CD-RISC Adherence: MMAS-8	Before and after scores were compared using repeated ANOVA measures. Analyses of covariances were conducted on each of the outcomes, measured at time point 2, using groups as the controlling variable and controlling for baseline values recorded at time point 1.	The baseline versus after the intervention adherence score was 2.05 (SD 1.45) versus 1.72 (SD 1.99) in CG and 1.65 (SD 1.80) versus 1.76 (SD 1.64) in IG; P= 0.376. The difference in mean change scores (95% CI) was reported as –0.388 (–1.27, 0.493); P= 0.376. The mean seizure occurrences between the control and intervention groups were 12.71 (SD 24.55) and 6.76 (SD 13.40).
Helgeson 1990	Blood test measuring serum drug level was used to assess adherence with medication. The following measurements were also performed: level of anxiety was assessed by STAI, WPSI, AD scale, Sherer's Self-Efficacy Scale and epilepsy knowledge and medical management 50-item true-false questionnaire	Repeated ANOVa measures and a series of paired t-tests	Percentage change scores in blood AED levels (adherence) in the intervention group increased significantly $F(1,24) = 4.18$, $P < 0.05$. The treatment group showed a significant decrease in level of fear of death and brain damage due to seizures, $F(1,36) = 7.49$ (P = 0.009) and a significant decrease in hazardous medical self-management practices, $F(1,36) = 29.67$ (P = 0.0001).
Ibinda 2014	Improvement in adherence to AEDs was assessed by self-report	Pearson's Chi^2 test, modified Poisson	No significant difference in adherence to AEDs was noted between the 2 groups based on self-

Table 1. Summary of results for each included study *(Continued)*

	using the 4-item MMAS. Plasma drug concentrations were measured using a fluorescence polarisation immunoassay analyser (TDxFLx Abbott Laboratories) Epilepsy beliefs were measured using KEBAS	regression t-tests and logistic regression. All statistical analyses were performed using STATA (version 12)	reports (OR 1.00, 95% CI 0.71 to 1.40; P = 1.00) or in detectable drug levels (OR 1.46, 95% CI 0.74 to 2.90; P = 0.28). No difference in seizure frequency was found between groups.
Modi 2013	Caregivers completed baseline questionnaires and all families were provided with MEMS-6 Track-Cap to monitor adherence. Caregivers (intervention group) also completed several questionnaires: psychosocial (e.g. QoL), epilepsy knowledge, social problem-solving skills, epilepsy medication management, feasibility-acceptability questionnaire, medical chart review and background information form	Means, SDs and frequencies were measured using IBM SPSS statistics software (version 20)	Mean percentage change in adherence from baseline to post-intervention was 31.5 (SD 52.9) for the intervention group and 9.3 (SD 8.7) for the control group (no significance levels were reported). The impact on quality of life due to the implementation of the intervention reported a significant benefit (mean 6.75 (SD 0.6)). Other outcomes measured included assessment of feasibility and acceptability of the adherence intervention.
Modi 2016b	For adherence, MEMS TrackCap (Aardex Corporation) For secondary outcomes: EKQ; Social Problem-Solving Inventory-Revised; Parent response to child illness	A repeated-measures model based on maximum likelihood estimation	Adherence score (weeks 4–6; TAU = 12.0 vs STAR (intervention group) = 18.1, P < 0.01; and weeks 6–8: TAU = 9.7 vs STAR = 15.3, P < 0.05). During the 3-month follow-up period, no significant group differences were found on AED adherence.
Pryse-Phillips 1982	Serum drug levels of phenobarbitone, phenytoin, carbamazepine, sodium valproate, and ethosuximide were performed using a gas liquid chromatograph or by the EMIT method on each occasion where relevant.	Comparisons of means in paired samples, Student's t-test, correlation coefficients, and linear regressions were performed using an IBM computer	The results show whether information was given in oral form alone or both orally and in written form; adherence to drug treatment as measured by serum levels was not improved.
Ridsdale 2018	For QoL: QOLIE-31-P with added patient-specific weightings. For adherence, Medication Adherence, a 10-item subscale from ESMS Other outcomes assessed using seizure frequency scales, seizure recency (number of days since last seizure), HADS for psychological distress (anxiety and depression), Impact of Epilepsy, Stigma of Epilepsy, medication adverse effects extracted from the QOLIE-31-P, and self-mastery and control	All outcomes were analysed using the ITT approach. Linear mixed regression model was used for analysis of primary and secondary outcomes.	At 12-month follow-up, the medication adherence score median (IQR) for intervention was 47.8 (IQR 45.6 to 48.9; range 27.8 to 50.0) versus 47.8 (IQR 45.6 to 48.9; range 35.6 to 50.0) in the TAU group. There were no statistically significant differences between trial arms in QOLIE-31-P (intervention mean 67.4, SD 13.5; control mean 69.5, SD 14.8).
Saengow 2018	Adherence was measured using the MMAS-8	Pearson's correlation, t-test, Fisher Exact test	At baseline, the mean scores of knowledge questionnaire

Table 1. Summary of results for each included study *(Continued)*

			was lower in intervention (6.73) compared with control (7.48). After the video animation, intervention group mean score increased (7.42; P < 0.001) and at the 3-month follow-up (7.47). There were slight score changes at 3-time point in control group (7.48,7.53, 7.44). The proportion of participants with improved adherence was 54 (42.9%) in intervention versus 14 (15.9%) in control group P < 0.001 Proportion of participants with improved severity of seizure higher in intervention 47 (37.3%) than control group 22 (25.0%) in CG, P = 0.14.
Shope 1980	Adherence was assessed by measurement of serum drug levels using blood tests	ANOVA, ANCOVA and Chi^2 tests were performed	The mean score of the intervention group on the combined adherence score was 2.9, which is significantly higher than the mean score in the control group 2.2 (F(1,48) = 6.36, P = 0.015).
Zheng 2019	Adherence was assessed using MMAS-8, other measures included Beck Depression Inventory, Beck Anxiety Inventory, QOLIE-31	t-test and Mann-Whitney test	Increased number of participants with moderate-to-high AED adherence (71 (77.2%) vs 56 (60.9%); P =0.006). The intervention group showed improvements in 5 of the 7 subscales in QOLIE-31, overall QoL (74.1 ± 15.0 vs 63.2 ± 14.6; P = 0.010), emotional well-being (81.3 ± 16.2 vs 69.0 ± 15.5; P = 0.006), energy (74.8 ± 18.2 vs 63.4 ± 17.0; P = 0.013), cognitive function (77.7 ± 20.4 vs 66.5 ± 19.3; P = 0.011), and social function (72.0 ± 22.7 vs 61.8 ± 21.6; P = 0.015). The control group showed improvements in only 3 aspects; seizure worry (51.0 ± 32.7 vs 46.1 ± 30.0; P = 0.038), emotional well-being (68.7 ± 22.1 vs 67.8 ± 21.1; P = 0.007), and medication effect (52.1 ± 36.3 vs 47.8 ± 34.4; P = 0.015). Proportion of participants with a low seizure frequency increased in both the intervention group (70 (76.1%) vs 41 (44.6%); (P= 0.001) and the control group (74 (80.4%) vs 50 (54.3%); P = 0.001) however, the difference between the 2 groups, is not significant (80.5% vs 76.1%; P = 0.475). A reduction of number of participants with severe depression and anxiety.
Mixed interventions			
References	**Assessment methods**	**Statistical analysis**	**Study results**
Leenen 2018	For adherence, MEMS (Aardex) and MARS-5. Other outcomes were self-efficacy and general self-efficacy (disease-specific self-efficacy (ESES and GSES), seizure severity NHS3); emotional well-being (HADS); QoL (QOLIE-31P); proactive coping (Utrecht Proactive	The baseline differences between the multicomponent self-management intervention group and TAU group were analysed using independent t-tests	Participants with epilepsy lost to follow-up or who did not use the cap at all, were considered nonadherent. Adherence rates of those included in the MEMS analysis over 6 months were 63.7% for the CAU group and 75.9% for the intervention group; the difference was not statistically significant. Adherence score over 6 months were 23.7 (1.3) for the CAU group and 23.9(0.9) for the intervention

Table 1. Summary of results for each included study *(Continued)*

	Coping Competence); and side-effects of antiepileptic drugs.		group; the difference was not statistically significant.
Li 2013	To assess drug adherence, 6-response-option rating scales were applied. With regard to lifestyle or habits, 6 similar ratings were used to measure frequency of seizure-provoking events. The subsequent seizure assessment for intervention group was obtained from the epilepsy tracking card. In control group medical adherence ratings were derived from self-reported data and calculated AED adherence by counting the remaining pills to count the number of missed doses	Chi^2 test, or correlated Chi^2 test or Fisher's exact test and one-way ANOVA were used to conduct statistical analyses with SPSS (version 17.0)	Adherence improved in the intervention group, as most members (142 (77.6%) compared to 17 (9.6%)) rated their adherence as excellent or very good, but it remained nearly unchanged in the control group. A moderate correlation was found between the changes in AED adherence and seizure control ($r = 0.4$, $P < 0.05$), and a weaker correlation was found between lifestyle and seizure control ($r = 0.328$, $P < 0.05$). The percentage of participants reported a reduction in seizures in at least 50% (including those who were seizure-free) rose to 79.8% in the intervention group, compared to 61.0% in the control group ($P < 0.05$).
Peterson 1984	Adherence was assessed by changes in plasma anticonvulsant levels (provided that the participant's medication regimen had not been altered in the preceding 2 weeks), a check of the participant's prescription record book to determine prescription refill frequency, medication seizure diary (to record Dosett container check) and participant appointment-keeping frequency (those who had attended all scheduled appointments in the previous 6 months were considered compliant)	McNemar tests for related samples, Wilcoxon matched-pair tests, Stuart-Maxwell tests, and Student's paired t-tests, Chi^2 tests, Mann-Whitney tests, and Student's unpaired t-tests	Study shows that adherence (mean plasma levels) can be improved and seizure frequency lessened by compliance-improving intervention. Although the differences between the 2 groups in mean anticonvulsant dosages were not statistically significant, they might be clinically important.
Tang 2014 (This study is presented in this review as both educational and mixed interventions)	Adherence was measured using the MMAS-4; seizure control was reported according to the participants' records and telephone follow-ups by the pharmacist; a questionnaire was developed to evaluate the level of each participant's knowledge of AEDs; QOLIE-31 was used to measure QoL. Adherence, knowledge of AEDs, number of seizures and other measures were evaluated at the beginning and at the end of follow-up. QoL was only measured after intervention	All analyses were performed using the IBM SPSS statistics (version 19). Tests such as Pearson's Chi^2 tests, student's t-tests and Mann–Whitney U test were performed	The adherence and knowledge of AEDs increased greatly after intervention in all participants, the number of seizures and missed dosages also decreased. However, no significant differences were observed between 2 groups: increased adherence (62.3% vs 64.3%, $P = 0.827$); increased knowledge of AEDs (88.7% vs 80.4%, $P = 0.231$) and improved seizure control (64.2% vs 64.3%, $P = 0.988$).

AD: Acceptance of Disability; **AED:** antiepileptic drug; **AGAS:** Antiretrovial General Adherence Scale; **ANCOVA:** analyses of co-variance; **ANOVA:** analysis of variance; **BIPQ:** Brief Illness Perception Questionnaire; **CD-RISC:** Connor-Davidson resilience scale; **CI:** confidence interval; **EKQ:** Epilepsy Knowledge Questionnaire; **EKP:** Epilepsy Knowledge Profile; **EMIT:** enzyme-multiplied immunoassay technique; **ESES:** Epilepsy Self-Efficacy Scale; **ESI-R:** Revised Epilepsy Stressor Inventory; **ESMS:** Epilepsy Self-Management Scale;

Table 1. Summary of results for each included study *(Continued)*

GSES: General Self-Efficacy Scale; **HADS:** Hospital Anxiety and Depression Scale; **HRQoL:** health-related quality of life; **KEBAS:** Kilifi Epilepsy Beliefs and Attitudes Scores; **LSSS:** Liverpool Seizure Severity Scale; **MARS:** Medication Adherence Report Scale; **MAS:** Medication Adherence Scale; **MASQ:** Multiple Ability Self Report Questionnaire; **MEMS:** Medication Event Monitoring Systems; **MMAS:** Morisky Medication Adherence Scale; **NHS3:** National Hospital Seizure Severity Scale; **OR:** odds ratio; **PRMQ:** Prospective and Retrospective Memory Questionnaire; **PSQI:** Pittsburgh Sleep Quality Index; **PSS:** Perceived Stress Scale; **QoL:** quality of life; **QOLIE:** Quality of Life in Epilepsy Scale; **SD:** standard deviation; **SF-12:** Short-Form 12-question health survey; **STAI:** State-Trait Anxiety Inventory, State Annxiety Scale; **SWLS:** Satisfaction with Life Scale; **TAU:** treatment as usual; **TPB:** Theory of Planned Behaviour; **WPSI:** Washington Psychosocial Seizure Inventory

APPENDICES

Appendix 1. Cochrane Register of Studies (CRS Web) search strategy

1. MeSH DESCRIPTOR Patient Compliance Explode All AND CENTRAL:TARGET

2. MeSH DESCRIPTOR Medication Adherence Explode All AND CENTRAL:TARGET

3. MeSH DESCRIPTOR Health Behavior Explode All AND CENTRAL:TARGET

4. MeSH DESCRIPTOR Health Education Explode All AND CENTRAL:TARGET

5. MeSH DESCRIPTOR Patient Education as Topic Explode All AND CENTRAL:TARGET

6. MeSH DESCRIPTOR Behavior Therapy Explode All AND CENTRAL:TARGET

7. MeSH DESCRIPTOR Treatment Refusal Explode All AND CENTRAL:TARGET

8. MeSH DESCRIPTOR Patient Dropouts Explode All AND CENTRAL:TARGET

9. patient NEXT complian* AND CENTRAL:TARGET

10. patient NEXT adheren* AND CENTRAL:TARGET

11. #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 AND CENTRAL:TARGET

12. MESH DESCRIPTOR Epilepsy EXPLODE ALL WITH QUALIFIER DT AND CENTRAL:TARGET

13. MESH DESCRIPTOR Seizures EXPLODE ALL WITH QUALIFIER DT AND CENTRAL:TARGET

14. MESH DESCRIPTOR Anticonvulsants EXPLODE ALL AND CENTRAL:TARGET

15. (antiepilep* or anticonvuls*):AB,KW,MC,MH,TI AND CENTRAL:TARGET

16. #12 OR #13 OR #14 OR #15

17. #11 AND #16

18. >04/06/2018:CRSCREATED AND CENTRAL:TARGET

19. #17 AND #18

Appendix 2. MEDLINE search strategy

This strategy includes the Cochrane Highly Sensitive Search Strategy for identifying randomised trials (Lefebvre 2019).

1. exp Patient Compliance/

2. (patient adj complian$).tw.

3. (patient adj adheren$).tw.

4. exp Medication Adherence/ or (medication adj adheren$).tw.

5. exp Health Behavior/

6. exp Health Education/

7. exp Patient Education as Topic/

8. exp Behavior Therapy/

9. exp Treatment Refusal/

10. exp Patient Dropouts/

11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10

12. (epilep$ or seizure$ or convulsion$).ti,ab.

13. exp Epilepsy/dt

14. exp Seizures/dt

15. exp Anticonvulsants/

16. (antiepilep$ or anticonvuls$).ti,ab.

17. 12 or 13 or 14 or 15 or 16

18. (randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or placebo or randomly).ab.

19. clinical trials as topic.sh.

20. trial.ti.

21. 18 or 19 or 20

22. exp animals/ not humans.sh.

23. 21 not 22

24. 11 and 17 and 23

25. limit 24 to ed=20180604-20200218

26. 24 not (1$ or 2$).ed.

27. 26 and (2018$ or 2019$ or 2020$).dt.

28. 25 or 27

29. remove duplicates from 28

Appendix 3. CINAHL search strategy

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

S39	S8 AND S14 AND S37 Publication Year: 2016-
S38	S8 AND S14 AND S37
S37	S36 NOT S35
S36	S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29

(Continued)

S35	S33 NOT S34
S34	MH human
S33	S30 OR S31 OR S32
S32	TI animal model*
S31	MH animal studies
S30	MH animals+
S29	AB cluster W3 RCT
S28	MH crossover design OR MH comparative studies
S27	AB control W5 group
S26	PT randomized controlled trial
S25	MH placebos
S24	MH sample size AND AB (assigned OR allocated OR control)
S23	TI trial
S22	AB random*
S21	TI randomised OR randomized
S20	MH cluster sample
S19	MH pretest-posttest design
S18	MH random assignment
S17	MH single-blind studies
S16	MH double-blind studies
S15	MH randomized controlled trials
S14	S9 or S10 or S11 or S12 or S13
S13	TI antiepilep* or AB antiepilep*
S12	TI (epilep* OR seizure* OR convulsi*) or AB (epilep* OR seizure* OR convulsi*)
S11	(MM "Anticonvulsants")
S10	(MM "Seizures")
S9	(MM "Epilepsy")
S8	(S1 or S2 or S3 or S4 or S5 or S6 or S7)

(Continued)

S7	TI patient N1 adheren* or AB patient N1 adheren*
S6	TI patient N1 complian* or AB patient N1 complian*
S5	(MM "Patient Dropouts")
S4	(MM "Treatment Refusal")
S3	(MM "Patient Education")
S2	(MM "Health Behavior")
S1	(MM "Patient Compliance") or (MM "Medication Compliance")

Appendix 4. PsycINFO search strategy

S14	S4 AND S11 AND S12 Publication Year: 2016-
S13	S4 AND S11 AND S12
S12	S9 OR S10
S11	S5 OR S6 OR S7 OR S8
S10	AB randomized OR AB placebo OR AB randomly
S9	DE "clinical trials" OR TI clin* trial* OR AB clin* trial* OR AB trial
S8	DE "carbamazepine" OR DE "chloral hydrate" OR DE "clonazepam" OR DE "diphenylhydantoin" OR DE "nitrazepam" OR DE "oxazepam" OR DE "pentobarbital" OR DE "phenobarbital" OR DE "primidone" OR DE "valproic acid"
S7	DE "epilepsy" OR DE "seizures" OR DE "anticonvulsive drugs"
S6	AB epilep* OR AB seizure* OR AB convulsi*
S5	TI epilep* OR TI seizure* OR TI convulsi*
S4	S1 OR S2 OR S3
S3	AB patient complian* OR AB patient adheren*
S2	TI patient complian* OR TI patient adheren*
S1	DE "treatment refusal" OR DE "treatment compliance" OR DE "treatment dropouts" OR DE "client education" OR DE "behavior therapy"

Appendix 5. Embase search strategy

1 patient compliance/

2 (patient adj complian$).ti,ab.

3 (patient adj adheren$).ti,ab.

4 exp health behavior/

5 patient education/

6 health education/

7 behavior therapy/

8 treatment refusal/

9 treatment withdrawal/

10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9

11 (epilep$ or seizure$ or convulsion$).ti,ab.

12 exp epilepsy/

13 exp seizure/

14 exp anticonvulsive agent/

15 antiepilep$.ti,ab.

16 11 or 12 or 13 or 14 or 15

17 exp animal/

18 animal experiment/

19 nonhuman/

20 17 or 18 or 19

21 human/

22 human experiment/

23 21 or 22

24 23 not 20

25 Clinical trial/

26 Randomized controlled trial/

27 Randomization/

28 Single blind procedure/

29 Double blind procedure/

30 Crossover procedure/

31 Placebo/

32 Randomi?ed controlled trial$.tw.

33 RCT.tw.

34 Random allocation.tw.

35 Randomly allocated.tw.

36 Allocated randomly.tw.

37 (allocated adj2 random).tw.

38 Single blind$.tw.

39 Double blind$.tw.

40 ((treble or triple) adj blind$).tw.

41 Placebo$.tw.

42 Prospective study.tw.

43 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42

44 Case study/

45 Case report.tw.

46 Abstract report/ or letter/

47 44 or 45 or 46

48 43 not 47

49 24 and 48

50 10 and 16 and 49

WHAT'S NEW

Date	Event	Description
15 July 2020	New citation required but conclusions have not changed	Conclusions are unchanged.
18 February 2020	New search has been performed	Searches updated 18 February 2020; eight new studies have been included.

HISTORY

Protocol first published: Issue 1, 2010
Review first published: Issue 1, 2011

Date	Event	Description
4 June 2018	New citation required but conclusions have not changed	Conclusions are unchanged
4 June 2018	New search has been performed	Searches updated 4 June 2018; 5 new studies have been included
10 May 2016	New citation required but conclusions have not changed	Conclusions remain the same.
4 February 2016	New search has been performed	Searches updated on 4 February 2016. Six new studies have been included.
24 September 2015	New search has been performed	searches updated

Date	Event	Description
4 September 2014	New citation required but conclusions have not changed	4 new studies have been included (Dilorio 2011; Ibinda 2014; Li 2013; Modi 2013). Conclusions remain unchanged
4 September 2014	New search has been performed	Searches updated on 4 September 2014

CONTRIBUTIONS OF AUTHORS

2020 update

Sinaa Al-Aqeel: involved in reviewing articles for eligibility, abstracting articles, assessing risk of bias, preparation of study characteristics tables, and text preparation for 2020 update.

Olga Gershuni: involved in reviewing articles for eligibility, abstracting articles, assessing risk of bias, and preparation of summary of findings tables.

Jawza Al-Sabhan: involved in reviewing articles for eligibility, abstracting articles, and assessing risk of bias.

Mickael Hiligsmann: involved in reviewing articles for eligibility, abstracting articles, and assessing risk of bias.

All authors have approved the final version of this manuscript.

2015 update

Sinaa Al-aqeel: involved in reviewing articles for eligibility, abstracting articles, preparation of tables, assessing risk of bias of all included studies and text preparation for 2015 update.

Olga Gershuni: involved in reviewing articles for eligibility, abstracting articles, preparation of tables assessing risk of bias of all included studies and text preparation for 2015 update.

Jawza Al-sabhan: involved in reviewing articles for eligibility.

Mickael Hiligsmann: involved in reviewing articles for eligibility, abstracting articles, preparation of tables assessing risk of bias of all included studies, and text preparation for 2015 update.

2012 update

Sinaa Al-aqeel: involved in reviewing articles for eligibility, abstracting articles, and text preparation for 2012 update.

Jawza Al-sabhan: involved in reviewing articles for eligibility.

2010 review

Sinaa Al-aqeel developed the search strategy, performed the bibliographic searches and produced the first draft of the review.

Sinaa Al-aqeel and Jawza Al-sabhan reviewed articles for eligibility, assessed their methodological quality and extracted the data.

DECLARATIONS OF INTEREST

Alaqeel S: none known

Olga Gershuni: none known

Jawza Al-sabhan: none known

Mickael Hiligsmann has received research grants through his institution from Amgen, Bayer and Radius Health.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Changes have been made to the format and content of the methods and the review from the protocol and from the last update to this version of the review, in line with current MECIR standards and the Cochrane Style Manual.

We added the effect of interventions on self efficacy and quality of life to our secondary outcomes.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [*therapeutic use]; Bias; Cost-Benefit Analysis; Epilepsy [*drug therapy] [psychology]; Medication Adherence [*psychology]; Quality of Life; Randomized Controlled Trials as Topic; Self Efficacy

MeSH check words

Adult; Child; Humans