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[Intervention Review]

Immediate-release versus controlled-release carbamazepine in the treatment of epilepsy

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ABSTRACT

Background

Carbamazepine (CBZ) is a commonly used drug for epilepsy that is associated with troublesome adverse events including dizziness, double vision, drowsiness, poor co-ordination and unsteadiness. These adverse events often occur during peaks in drug plasma concentration. These adverse events may limit the daily dose of CBZ that can be tolerated and reduce the chances of seizure control in patients who require high doses. A controlled-release formulation of CBZ delivers the same dose over a longer period of time when compared to a standard immediate-release formulation, thereby reducing post-dose peaks in CBZ plasma concentration and potentially reducing adverse events.

This is an updated version of the original Cochrane review published in Issue 12, 2014.

Objectives

To determine the efficacy of immediate-release CBZ (IR CBZ) versus controlled-release CBZ (CR CBZ) in patients diagnosed with epilepsy.

The following review questions were investigated.

- (1) For newly diagnosed patients commencing CBZ, how do IR and CR formulations compare for efficacy and tolerability?
- (2) For patients on established treatment with IR CBZ but experiencing unacceptable adverse events, what is the effect on seizure control and the tolerability of a switch to a CR formulation versus remaining on the IR formulation?

Search methods

We searched the Cochrane Epilepsy Group Specialized Register, CENTRAL, and MEDLINE (Ovid) from inception to 30 August 2016.

Selection criteria

Randomised controlled trials comparing IR CBZ to CR CBZ in patients commencing monotherapy and patients presently treated with IR CBZ but experiencing unacceptable adverse events.

Primary outcome measures included measures of seizure frequency, incidence of adverse events, proportion of patients with treatment failure and quality of life measures.

Data collection and analysis

Two review authors independently assessed trials for inclusion, extracted the data and recorded relevant information on a standardised data extraction form. We used the Cochrane risk of bias tool to assess the methodological quality of included studies.

The heterogeneity of the included trials with respect to the reporting of outcomes resulted in only a narrative, descriptive analysis being possible for both the categorical and time-to-event data.

Main results

Ten trials (296 participants) fulfilled the criteria for inclusion in this review. Only one study had a low risk of bias. Two studies had a high risk of bias and the rest of the studies were rated as unclear risk of bias. One trial included patients with newly diagnosed epilepsy and nine included patients on treatment with IR CBZ.

Eight trials reported heterogeneous measures of seizure frequency with conflicting results. A statistically significant difference was observed in only one trial, with patients prescribed CR CBZ experiencing fewer seizures than patients prescribed IR CBZ.

Nine trials reported measures of adverse events. There was a trend in favour of CR CBZ with four trials reporting a statistically significant reduction in adverse events compared to IR CBZ. A further two trials reported fewer adverse events with CR CBZ but the reduction was not statistically significant. One trial found no difference in adverse events, and another trial reported more adverse events in the CR CBZ group than the IR CBZ group, although the increase was not statistically significant.

Authors' conclusions

For this update no new eligible studies were identified and the conclusions drawn from the initial review remain unchanged.

At present, data from trials do not confirm or refute an advantage for CR CBZ over IR CBZ for seizure frequency or adverse events in patients with newly diagnosed epilepsy.

For trials involving epilepsy patients already prescribed IR CBZ, no conclusions can be drawn concerning the superiority of CR CBZ with respect to seizure frequency.

There is a trend for CR CBZ to be associated with fewer adverse events when compared to IR CBZ. A change to CR CBZ may therefore be a worthwhile strategy in patients with acceptable seizure control on IR CBZ but experiencing unacceptable adverse events. The included trials were of small size and of poor methodological quality limiting the validity of this conclusion.

Randomised controlled trials comparing CR CBZ to IR CBZ and using clinically relevant outcomes are required to inform the choice of CBZ preparation for patients with newly diagnosed epilepsy.

PLAIN LANGUAGE SUMMARY

Fast-release versus slow-release carbamazepine as medication for patients with epilepsy

Background

Epilepsy is a common brain disorder that is often treated with carbamazepine. With treatment, people often have fewer seizures but many people experience side effects. When carbamazepine is swallowed it is taken into the blood stream quickly and there is a sharp rise of drug levels in the blood. These 'peaks' may be associated with side effects such as dizziness, double vision, drowsiness, unsteadiness and poor co-ordination. A type of carbamazepine that releases the medication into the body slowly may lessen these 'peaks' in the blood levels, possibly meaning fewer side effects.

This review compared studies looking at the differences between a 'fast-release' carbamazepine and a 'slow-release' carbamazepine.

Participants

To be included in this review, all participants had to be diagnosed with epilepsy and be either just starting carbamazepine treatment or be already on it but with intolerable side effects. The participants could be of any age or gender.

Studies

Ten trials with a total of 296 people with epilepsy were included in the review. All 10 trials were randomised controlled trials (patients were compared in randomly assigned groups). All of the studies had at least two groups, one group taking fast-release carbamazepine and one group taking slow-release carbamazepine, and some also had a control group (a group of non-epileptic people). The evidence is current to August 2016.

Results

Just one of 10 studies found a significant difference between the two carbamazepine types in the number of seizures experienced, with patients prescribed the slow-release carbamazepine experiencing fewer seizures than patients prescribed the fast-release drug. Patients taking slow-release carbamazepine tended to experience fewer side effects.

Quality of the evidence

Out of the 10 trials in the review, only one study was judged to be of 'good' quality, and so the evidence in this review was rated as low quality. It must be stressed that there are not many studies assessing the differences between these two carbamazepine types and more studies are needed before we can make a definitive conclusion about one over the other.

BACKGROUND

Description of the condition

Epilepsy is defined as the tendency to spontaneous, excessive neuronal discharge manifesting as seizures. It is a common disorder with an incidence of 50 per 100,000 per year and a prevalence of 0.5% to 1% in the developed world (Hauser 1993).

Description of the intervention

In the treatment of epilepsy, carbamazepine (CBZ) is a first-line antiepileptic drug of proven efficacy when compared to other standard drugs such as valproate (Marson 2000; NICE 2012). However, CBZ is associated with a number of adverse events including dose-related events such as dizziness, double vision and unsteadiness.

How the intervention might work

Adverse events can occur during peaks in plasma concentration of CBZ following ingestion of a dose. The occurrence of such events may limit the daily dose that can be tolerated and reduce the chances of seizure control for patients requiring higher doses (Vojvodic 2002). This problem may be compounded by unpredictable fluctuations of CBZ serum concentrations due to its poor water solubility, which causes slow and irregular absorption. Such problems might be alleviated by prescribing a controlled-release formulation, which delivers the same dose over a longer period of time when compared to a standard formulation, thereby reducing post-dose peaks and potentially reducing adverse events.

CBZ has numerous qualities that may make it a good candidate for a controlled-release preparation. These qualities include a short half-life, lack of first-pass metabolism, a narrow therapeutic index and efficient absorption throughout the gastrointestinal tract (Collins 2000). Several controlled-release preparations are currently available.

Why it is important to do this review

In this review we have summarised evidence from randomised controlled trials assessing immediate-release and controlled-release CBZ in patients with epilepsy. Through assessing the intended effects, including reduction in seizure frequency, and unintended effects, including adverse drug reactions, we aimed to inform clinical decision making in this population. This review is an update of a previously published Cochrane review on immediate-release versus controlled-release carbamazepine for the treatment of epilepsy (Powell 2010; Powell 2014a; Powell 2014b).

OBJECTIVES

To determine the efficacy of immediate-release CBZ (IR CBZ) versus controlled-release CBZ (CR CBZ) in patients diagnosed with epilepsy.

The following review questions were investigated.

- (1) For newly diagnosed patients commencing CBZ, how do IR and CR formulations compare for efficacy and tolerability?
- (2) For patients on established treatment with IR CBZ but experiencing unacceptable adverse events, what is the effect on seizure control and tolerability of a switch to a CR formulation versus remaining on the IR formulation?

METHODS

Criteria for considering studies for this review

Types of studies

(1) Randomised controlled trials (RCTs) comparing IR CBZ to CR CBZ. Our initial intention was to only include studies with an adequate method of allocation concealment. However, due to the small number of studies identified by the literature searches, studies where the method of randomisation was not clearly stated have also been included.

(2) Studies could be double blind, single blind or unblinded.

Types of participants

Patients of any age and either gender with a diagnosis of epilepsy who were either:

- (1) commencing monotherapy with IR CBZ or commencing monotherapy with CR CBZ; or
- (2) currently prescribed monotherapy with IR CBZ but experiencing unacceptable adverse events and were being switched to a CR CBZ formulation.

Types of interventions

The intervention group should have received a CR formulation of CBZ and the control group a standard, IR formulation of CBZ.

Types of outcome measures

The outcome measures of interest to this review are listed below for studies addressing each objective.

Primary outcomes

Objective 1: analysis of newly diagnosed patients

- (1) Time to 12-month remission

Objective 2: analysis of patients with established epilepsy

- (1) Proportion seizure free at six months

Secondary outcomes

For objective 1: analysis of newly diagnosed patients

- (1) Proportion seizure free at six months;
- (2) Proportion seizure free at 12 months;
- (3) A 50% or greater reduction in seizure frequency;
- (4) Proportion with treatment failure (inadequate seizure control, adverse events, or both) at six months;
- (5) Proportion with treatment failure (inadequate seizure control, adverse events, or both) at 12 months;
- (6) Incidence of adverse events; and
- (7) Quality of life measures.

For objective 2: analysis of patients with established epilepsy

- (1) Proportion seizure free at 12 months;
- (2) A 50% or greater reduction in seizure frequency;
- (3) Proportion with treatment failure (inadequate seizure control, adverse events, or both) at six months;
- (4) Proportion with treatment failure (inadequate seizure control, adverse events, or both) at 12 months;
- (5) Incidence of adverse events; and
- (6) Quality of life measures.

Search methods for identification of studies

We carried out searches as follows.

Electronic searches

Searches were run for the original review in September 2009 and subsequent searches were run in July 2011, September 2013, and November 2014. For the latest update we searched the following databases. There were no language restrictions.

(a) Cochrane Epilepsy Group Specialized Register (30 August 2016) using the search strategy outlined in [Appendix 1](#).

(b) Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO), 30 August 2016, using the search strategy outlined in [Appendix 2](#).

(c) MEDLINE (Ovid, 1946 to 30 August 2016) using the strategy outlined in [Appendix 3](#).

Searching other resources

We did not contact pharmaceutical companies or researchers in the field as a result of the time period the majority of studies were published. However, contact may be made prior to a future update of this review.

Data collection and analysis

Selection of studies

Two review authors (GP, MS) screened all the titles, abstracts and keywords of publications identified by the searches to assess eligibility for inclusion. Publications that clearly did not meet the inclusion criteria were excluded at this stage. A paper copy of the full publication of each relevant study was obtained. Both review authors assessed these studies according to pre-specified selection criteria. Any disagreement concerning eligibility for inclusion was resolved by discussion and a consensus decision was made.

Data extraction and management

Two review authors (GP, MS) independently extracted the data and recorded relevant information on a standardised data extraction form. The extracted results were compared to assess agreement. The data reported by published sources were used for analysis in this review. Both review authors pilot tested the data collection form on a sample study and found it to be suitable. Disagreement or uncertainty concerning extracted data was resolved by discussion and a consensus decision was made.

Assessment of risk of bias in included studies

Three review authors (GP, MS and AR) independently assessed the risk of bias for each trial using the Cochrane risk of bias tool ([Higgins 2011](#)). We discussed and resolved any disagreements. We rated studies as high, low or unclear for six domains applicable to RCTs: randomisation method, allocation concealment, blinding methods, incomplete outcome data, selective outcome reporting and other sources of bias.

We intended to create 'summary of findings' tables and use the GRADE approach for assessing quality of evidence. However, this was not appropriate due to the discrepancy between the outcomes of interest in the protocol and the reviewed studies.

Measures of treatment effect

For categorical outcomes, we planned to express relative treatment effects as the risk ratio with corresponding 95% confidence intervals (CI). For time-to-event data we did not plan to undertake a meta-analysis using aggregate data, rather we planned to summarise the trial results in text tables. Due to the small number of trials identified, we did not explore the possibility of obtaining individual patient data to include in a meta-analysis using inverse variance methods. This may be considered in an update of the review. Similarly, quality of life data were summarised in the text and tables.

Unit of analysis issues

We included crossover trials as well as parallel group trials in the review. However, there were no unit of analysis issues as we could not combine any of the data from the included studies in a meta-analysis. All findings from the included studies were reported narratively.

Dealing with missing data

We did not seek missing data from the study authors due to the time period during which the majority of studies were published (i.e. from 1987 through 1998). However, contact may be made prior to an update of this review.

Assessment of heterogeneity

Clinical heterogeneity was assessed by comparing study designs and the recruited patient populations among the trials. Where appropriate, the degree of heterogeneity was to be assessed using the I^2 statistic. A value of 25% would indicate low heterogeneity, 50% moderate heterogeneity and 75% high heterogeneity. If heterogeneity was present, its significance was considered and a decision made as to whether meta-analysis was appropriate. If so, a random-effects model would be used.

Assessment of reporting biases

Due to the age of the included studies (published between 1987 and 1998), protocols were not requested from the authors. To assess outcome reporting bias we used the ORBIT tool ([Kirkham 2010](#)). We originally intended to examine funnel plots to investigate potential publication bias, however this was not possible.

Data synthesis

No meta-analyses were carried out, all results were discussed narratively. Comparisons we expected to investigate included:

1. IR versus CR on time to 12-month remission;
2. IR versus CR on proportion seizure free at six months.

Other comparisons included IR versus CR for all secondary outcomes (see [Types of outcome measures](#)).

Subgroup analysis and investigation of heterogeneity

We stratified the comparisons made by type of participant, that is newly diagnosed patients and established epilepsy patients.

Sensitivity analysis

No sensitivity analyses were planned.

RESULTS

Description of studies

Results of the search

Searching of the databases as described in [Search methods for identification of studies](#) yielded 1973 records, and two additional records were identified from other sources. After the removal

of duplicates (865), the remaining 1110 records were screened for potential inclusion: 1087 were excluded for irrelevance. The following assessment for eligibility excluded another 13 studies (see [Figure 1](#) and [Characteristics of excluded studies](#) for reasons of exclusion) leaving a total of 10 studies to be included in the review. None of these studies were included in a meta-analysis. No new studies were identified by the current literature search carried out on 30 August 2016.

Figure 1. Study flow diagram.

Included studies

Ten trials fulfilled the criteria for inclusion in this review. One trial concerned patients with newly diagnosed epilepsy and was included under the first objective (Nag 1998); 20 patients with ages ranging from 16 to 35 years were recruited. The remaining nine trials included patients currently treated with IR CBZ and were included under the second objective. In total, 296 patients with ages ranging from 6 to 69 year were recruited into these 10 trials. One trial included children in addition to adult patients (Kaski 1991). Summary information on the trials included in this review can be found in the [Characteristics of included studies](#) table. In addition, more detailed information, particularly concerning interventions and the results of each study, can be found in [Appendix 4](#).

Included trials were primarily concerned with the pharmacokinetic parameters of both CBZ and its predominant metabolite, CBZ epoxide. The clinical parameters that were of interest in this review were generally considered as secondary outcomes within the included studies and there was significant heterogeneity with respect to the outcomes reported. The clinical outcomes that were reported included mean seizure frequency, total number of seizures experienced in each study arm, mean total number of seizures per patient in each study arm, total incidence of adverse events reported in each study arm, total number of patients reporting adverse events, and total scores of inventories designed to quantify adverse event occurrence.

Excluded studies

Two trials were not published in English and could not be included due to restrictions that prevented translation (Dam 1980; Remy 1990). It is likely one study (Dam 1980) is subsequently included (Dam 1981). The remaining study may be included in an update of this review. Thirteen trials were excluded as they did not meet the eligibility criteria. Four trials did not include CR formulations of CBZ (Dam 1981; Ghose 1983; Monaco 1984; Thakker 1991), two of which were concerned with the dose frequency of IR CBZ (Ghose 1983; Monaco 1984). Three trials did not make the required treatment comparison: two trials involved a comparison of two CR CBZ formulations (Jensen 1990; Scheuch 1992), and one trial compared CR CBZ to sodium valproate (Sobaniec 2004). There was no mention of randomisation in two trials (Bojinova 1997; Pieters 1992). One trial was observational in design, involving a treatment cohort with no control group (Mirza 1998), and a further trial did not report any relevant outcome measures (Ramsay 1989). Additional details can be found in the table [Characteristics of excluded studies](#).

Risk of bias in included studies

See [Figure 2](#) for a summary of the risk of bias in each included study. For each study, we allocated an overall rating for the risk of bias. One study was rated as low risk of bias (Persson 1990), two as high risk of bias (Nag 1998; Sivenius 1988) and the remainder as unclear risk of bias. See below for specific domain ratings. Across all studies we rated the evidence as unclear risk of bias.

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

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Aldenkamp 1987	?	?	-	-	+	+	+
Anonymous 1995	?	?	+	?	+	+	?
Canger 1990	?	?	+	?	+	+	+
Garnett 1998	?	?	+	?	+	+	?
Kaski 1991	?	?	+	?	+	+	+
McKee 1991	?	?	+	+	+	+	?
Nag 1998	?	?	-	-	+	+	?
Persson 1990	+	?	+	?	+	+	+
Reunanen 1990	?	?	+	-	+	+	+
Sivenius 1988	?	?	-	-	+	-	+

Allocation

We rated allocation concealment as unclear risk of bias for all of the studies as the trials did not report the methods used for allocation concealment. Persson 1990 was rated as low risk of bias for sequence generation due to the use of a computer program for patient randomisation. All of the other studies were rated as unclear risk of bias for sequence generation as the method used for randomisation was not described, although all stated that randomisation had been performed.

Blinding

Four studies were rated as high risk of bias for the blinding domain due to the fact that they were open label trials (Nag 1998; Sivenius 1988) or single-blind (Aldenkamp 1987; Reunanen 1990). The remaining eight trials were adequately blinded, involving identical tablets and packaging.

Incomplete outcome data

All of the studies in this review were rated as low risk of attrition bias because the proportion of patients who did not complete the studies was low in each study. Thus the number of patients randomised but not included in the analysis was determined not to be significant. Therefore, despite some studies not reporting missing data, or not carrying out intention-to-treat analysis, there were deemed to be no issues with attrition bias.

Selective reporting

Study protocols were not requested due to the time period in which the majority of the studies were published. All but one study (Sivenius 1988), was rated as low risk of bias for this domain. We applied the ORBIT classification system to this study and rated it 'A'

due to its lack of reporting analysed adverse effect data; therefore this study was rated as high risk of bias for selective reporting.

Other potential sources of bias

Four studies were rated as unclear risk of bias in this category due to quoting financial support from Ciba-Geigy Pharmaceuticals, Intas Pharmaceuticals, Shire Pharmaceuticals, all of which produce CR carbamazepine based medications (Anonymous 1995; Garnett 1998; McKee 1991; Nag 1998).

Effects of interventions

With the exception of adverse events, none of the included studies reported on our pre-specified primary and secondary outcomes. A narrative summary follows concerning the results for each relevant outcome. More detailed results can be found in the Additional tables section.

Objective 1: analysis of newly diagnosed patients

Seizure frequency

No data relating to seizure frequency were reported in the one trial involving patients with newly diagnosed epilepsy (Nag 1998).

Incidence of adverse events

One unblinded parallel trial was identified that involved 20 adult patients with newly diagnosed epilepsy (Nag 1998). During the 20-day study period, a total of four adverse events were reported in patients prescribed IR CBZ: diplopia, rash, and two reports of sedation. Two adverse events, sedation and diplopia, were reported in patients prescribed CR CBZ. The data is presented in a forest plot, together with other studies where this is possible (Figure 3) The statistical significance of the difference between groups was not reported.

Figure 3. Forest plot of comparison: 1 Adverse Events, outcome: 1.1 Adverse Events.

Objective 2: analysis of patients with established epilepsy

Seizure frequency

The occurrence of seizures during each treatment period was reported heterogeneously. The majority of studies where seizures were recorded reported the mean number of seizures per patient during each study period.

- Garnett 1998 reported an increased mean number of seizures per patient during CR CBZ treatment. A mean 2.8 seizures per patient (range 0 to 29) occurred in patients prescribed CR CBZ compared to 1.6 (range 0 to 18) in patients prescribed IR CBZ in each two-week treatment arm. This difference was not statistically significant. The CBZ dose remained stable throughout the study period.
- Persson 1990 reported an increased mean number of seizures per patient for the IR CBZ treatment group: 2.2 compared to 1.2 during CR CBZ treatment. These figures were only derived from the first month of the three-month treatment period. This was not statistically significant. There were no statistically significant differences between the mean number of seizures per month per patient for IR CBZ (1.34) and CR CBZ (1.24). The CBZ dosage remained the same throughout the study period.
- McKee 1991 reported an increased mean number of seizures per patient during treatment with CR CBZ: 3.8 (SD 0.9) compared to 2.8 (SD 1.2) during treatment with IR CBZ (95% CI -0.7 to 2.8). The CBZ dose remained stable during the four-week study period. Seizure frequency was not statistically significantly different for either CBZ formulation when compared to baseline.

- [Anonymous 1995](#) reported a lower mean monthly seizure rate during IR CBZ treatment: 0.41 compared to 0.53 during treatment with CR CBZ. SDs or CIs were not given for these estimates. The CBZ dose remained stable during each 56-day study arm. The difference was not statistically significant.

Seizure frequency was reported in the following studies.

- [Canger 1990](#) reported a statistically significant reduction in mean monthly seizure frequency during treatment with CR CBZ: 6.3 (SD 9.8) compared to 9.3 (SD 15.6) during treatment with IR CBZ. The CBZ dose remained stable during the one-month study period.
- [Kaski 1991](#) reported the total number of seizures during the 10-week study period: 44 (range 9 to 133) in patients prescribed CR CBZ compared to 42.7 (range 4 to 107) in patients prescribed IR CBZ. This difference was not statistically significant. The CBZ dose remained stable throughout the study period.

The total numbers of seizures that occurred in each study group was reported in the following studies.

- [Reunanen 1990](#) reported an increased total number of seizures during treatment with IR CBZ: 56 seizures compared to 31 during treatment with CR CBZ in each two-week treatment arm. The CBZ dose remained stable throughout the study period. This difference was not statistically significant.
- [Sivenius 1988](#) reported identical total numbers of seizures during each treatment period. Nine seizures occurred during treatment with both CBZ formulations in each two-week study period. The CBZ dose remained stable throughout the study period.

Incidence of adverse events

Adverse events were reported heterogeneously in the studies included in this review. The following studies used various inventories designed to assess adverse events as a result of antiepileptic drugs. Total scale scores were calculated following completion of the studies to allow the comparison of these psychometric outcomes between groups.

- [McKee 1991](#) reported significantly lower cognitive adverse event scores at one hour with CR CBZ compared to IR CBZ. In addition, reaction times were significantly shorter at one and four hours with CR CBZ compared to IR CBZ.
- [Aldenkamp 1987](#) reported increased performance in various tests of cognitive function in patients taking CR CBZ. The statistical significance of this result was not reported.
- [Persson 1990](#) reported lower scores on a combined systemic toxicity and neurotoxicity scale in patients taking CR CBZ compared to those on IR CBZ. The difference was statistically significant.

Numerous studies reported the individual numbers of adverse events reported.

- [Anonymous 1995](#) reported that four patients experienced six adverse events when prescribed CR CBZ: dizziness (2 patients), diplopia (1), headache (1), nausea (1) and vomiting (1). Five patients experienced five adverse events when prescribed IR CBZ: dizziness, drowsiness, hand tremor, stomach cramps and vomiting. These differences were not statistically significant.

- [Reunanen 1990](#) reported 19 adverse events during IR CBZ treatment compared to 12 with CR CBZ. Dizziness (7 patients), fatigue (4), visual disturbance (4), headache (1) and difficulty with co-ordination (3) were experienced during IR CBZ treatment. Dizziness (1), fatigue (4), visual disturbance (2), headache (2), difficulty with co-ordination (1), nausea (1) and gastric discomfort (1) were experienced during CR CBZ treatment. The difference was statistically significant for dizziness, reported seven times during IR CBZ treatment and just once during CR CBZ treatment.
- [Garnett 1998](#) reported one adverse event: somnolence during IR CBZ treatment.

The following studies reported the number of patients experiencing adverse events.

- [Sivenius 1988](#) reported that four patients in each treatment group experienced adverse events. No further details concerning the individual adverse events were reported.
- [Canger 1990](#) stated that 26 patients reported intermittent adverse events with IR CBZ whereas six patients reported adverse events with CR CBZ. No further details concerning the individual adverse events were reported. The difference was statistically significant.

DISCUSSION

Summary of main results

Ten trials were included in this review. All were primarily concerned with comparisons of the pharmacokinetic parameters of IR CBZ and CR CBZ.

Only one trial involving patients with newly diagnosed epilepsy was identified ([Nag 1998](#)). This trial involved only 20 patients and reported a total of six adverse events, four occurring during IR CBZ treatment. Given the small number of patients and low number of events, no conclusions can be drawn regarding the comparative tolerability of IR CBZ and CR CBZ in patients with newly diagnosed epilepsy. Measures of seizure frequency, quality of life measures and time-to-event data were not reported.

Eight of the included trials reported measures of seizure frequency in patients with an established diagnosis of epilepsy and currently treated with IR CBZ. The reported outcome measures were heterogeneous and we have described general trends. Three trials reported a reduced occurrence of seizures in patients taking CR CBZ, which was statistically significant in one trial. In addition, three trials reported a reduced occurrence of seizures in patients taking IR CBZ, which was statistically significant in one trial. The remaining two trials reported no difference in seizure occurrence between the two formulations. There appears to be no difference between formulations in controlling the occurrence of seizures. However, the absence of further statistical analyses, methodological limitations and risk of bias limit the accuracy of these narrative conclusions.

Eight of the included trials reported data concerning adverse events in patients with an established diagnosis of epilepsy and already prescribed IR CBZ. Although methods of reporting differed greatly, and outcomes could not be statistically combined, four of the trials found a significantly reduced incidence of adverse events in patients taking CR CBZ compared to IR CBZ. A further two trials

reported a lower incidence of adverse events with CR CBZ, which was not statistically significant. Of the remaining two trials, one found no difference in adverse event rates between the two CBZ formulations and one reported a reduced incidence of adverse events in patients taking IR CBZ (Anonymous 1995). Interestingly this crossover trial included the largest study sample, 101 patients, and had one of the longest study periods, with 56 days in each treatment arm. Our narrative analysis suggests a reduced incidence of adverse events and therefore superiority of CR CBZ compared to IR CBZ when considering adverse events. These results do not, however, provide robust evidence due to the heterogeneous methods of reporting that prevented further statistical analysis of the results, inherent limitations in methodological quality, and the risk of bias present in many of the trials included in this review.

Overall completeness and applicability of evidence

For the first objective of this review, the comparison in newly diagnosed patients, only one study met the inclusion criteria specified in our protocol. Therefore, the evidence for this conclusion is lacking without other studies to support it.

For the second objective, the comparison in patients with established epilepsy, only one study showed any significant difference in seizure frequency between the two groups, with patients in the CR group experiencing a lower mean monthly seizure frequency. In the remaining seven studies that reported seizure frequency there was no significant difference between the two groups. For adverse events, however, five studies reported a significant reduction in named or all adverse events for those patients on CR CBZ, with a further two studies reporting similar results but without reporting statistical significance. The remaining three studies noted no significant differences in adverse events between the two groups.

Quality of the evidence

Few of the clinical outcomes pre-specified in the protocol of this review were measured in these trials. The overall methodological quality of the trials included in this review was poor, as was the reporting of important methodological factors. The risk of bias was low in only one of the 10 trials included in this review (Persson

1990). The methods of randomisation and allocation concealment were unclear in the remaining nine trials, whilst eight trials were adequately blinded.

AUTHORS' CONCLUSIONS

Implications for practice

Existing randomised controlled trials comparing IR CBZ to CR CBZ have not focused on clinical outcomes. At present, data from trials do not confirm or refute an advantage for CR CBZ over IR CBZ concerning seizure frequency or adverse events in patients with newly diagnosed epilepsy.

Trials involving patients with an established diagnosis of epilepsy and already prescribed IR CBZ were more numerous. No conclusions can be drawn concerning superiority with respect to seizure frequency.

There was a trend for CR CBZ to be associated with fewer adverse events when compared to IR CBZ. This difference was statistically significant in four of the eight trials. However, the included trials were small, had poor methodological quality, and possessed a high risk of bias. In addition, this conclusion has been reached following a narrative analysis, which is inherently less reliable and less accurate than using statistical techniques. Nevertheless, in patients currently prescribed IR CBZ and experiencing unacceptable dose-related adverse events, changing to CR CBZ may be worthwhile and should be considered by the clinician when faced with this scenario.

Implications for research

Randomised controlled trials comparing CR CBZ to IR CBZ and using clinically relevant outcomes are required to provide evidence to inform the choice of CBZ preparation for patients with newly diagnosed epilepsy.

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McKee 1991 {published data only}

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CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Aldenkamp 1987

Methods	Single-blind, cross over study
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Kirkham 2010

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Aldenkamp 1987 (Continued)

3-armed study: 1 non-medication non-epileptic, 1 IR CBZ, 1 CR CBZ

Post-randomisation baseline period with all patients on conventional CBZ - length of time unclear

Treatment period: at least 1 month

Participants	<p>Patients with a diagnosis of partial or generalised epilepsy</p> <p>11 patients were enrolled and completed both study periods, number in each group not reported</p> <p>11 patients with no epilepsy and no treatment completed the period as control in the third arm</p> <p>Mean age: 32.1 (16-58) years</p>
Interventions	<p>Both CR and IR CBZ administered as 400 mg tablets twice daily</p> <p>Order determined by randomisation</p>
Outcomes	Incidence of cognitive adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "assigned randomly"</p> <p>Comment: insufficient information provided to determine judgement for sequence generation</p>
Allocation concealment (selection bias)	Unclear risk	Comment: details regarding allocation concealment were not provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	<p>Quote: "single-blind"</p> <p>Comment: identical tablets and dose frequency were administered</p>
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "single-blind"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants were included in the analysis
Selective reporting (reporting bias)	Low risk	Comment: protocol unavailable, but appears all expected and pre-specified outcomes are reported
Other bias	Low risk	Comment: the study appears to be free of other sources of bias

Anonymous 1995

Methods	<p>Double-blind, controlled, crossover study</p> <p>2 treatment arms: 1 IR CBZ, 1 CR CBZ</p>
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Anonymous 1995 (Continued)

Pre-randomisation retrospective baseline period: 3 months

Treatment period: 56 days per arm

Participants	<p>Patients diagnosed with partial or generalised epilepsy prescribed monotherapy with CBZ 200 mg tablets either 3 or 4 times daily as a stable regimen for at least 3 months</p> <p>Participants must not have had more than 3 seizures in each of the 3 months prior to enrolment</p> <p>101 patients enrolled, 87 completed both study arms (44 in group 1, 43 in group 2)</p> <p>Mean age for group 1 was 34 years, group 2 was 32 years</p>
Interventions	<p>Monotherapy at usual daily dose with IR and CR CBZ, order determined by randomisation</p> <p>Mean daily dose: 1084 mg (range 400 to 2000 mg)</p>
Outcomes	<p>Seizure frequency</p> <p>Incidence of adverse events</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "randomised"</p> <p>Comment: insufficient information provided to determine judgement for sequence generation</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: details regarding allocation concealment were not provided</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "placebo identical in appearance"</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>Quote: "double-blind"</p> <p>Comment: details of outcome assessment blinding not provided</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Comment: 86 patients were included in the analysis out of 96 randomised, and study attrition has been reported</p> <p>Therefore, despite no ITT analysis, there are no concerns about missing data</p>
Selective reporting (reporting bias)	Low risk	<p>Comment: protocol unavailable, but appears all expected and pre-specified outcomes are reported</p>
Other bias	Unclear risk	<p>Comment: financial support provided by Ciba-Geigy Corporation</p>

Canger 1990

Methods	Double-blind, controlled, crossover study
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Canger 1990 (Continued)

2 treatment arms: 1 IR CBZ, 1 CR CBZ

Optimal dose-finding phase: up to 2 months (per arm)

Maintenance phase (used for statistical analysis): 1 month

Participants	<p>Adult patients with epilepsy treated with CBZ monotherapy for at least 3 months with either inadequate seizure control or intermittent adverse events</p> <p>48 patients were enrolled and completed both study arms, number in each group not reported</p> <p>Mean age: 34.2 (range 18 to 64) years</p>
Interventions	<p>Monotherapy with either CR or IR CBZ during each study arm</p> <p>Optimal doses and frequencies of administration were determined over the initial 2 months of each study period</p> <p>Mean daily dose: 1.125 mg (range 400 to 2400 mg)</p>
Outcomes	<p>Seizure frequency</p> <p>Incidence of adverse events</p>

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "treatments were administered in randomised sequence"</p> <p>Comment: insufficient information provided to determine judgement for sequence generation</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: details regarding allocation concealment were not provided</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "the two CBZ formulations were indistinguishable in taste or physical appearance"</p> <p>Comment: double-blind</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>Comment: details of outcome assessment blinding not provided</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Quote: "a total of 48 patients (...) were enrolled in the study and none of them were withdrawn from it"</p> <p>Comment: All 48 patients are included in the results</p>
Selective reporting (reporting bias)	Low risk	<p>Comment: protocol unavailable, but appears all expected and pre-specified outcomes are reported</p>
Other bias	Low risk	<p>Comment: the study appears to be free of other sources of bias</p>

Garnett 1998

Methods	<p>Double-blind, controlled, crossover study</p> <p>2 treatment arms: 1 IR CBZ, 1 CR CBZ</p> <p>Pre-randomisation baseline period: 30 days</p> <p>Treatment period: 2 weeks (per arm)</p>
Participants	<p>Adult patients with a diagnosis of epilepsy prescribed IR CBZ at a stable and therapeutic dose for at least 30 days</p> <p>24 patients were enrolled, 23 were included in the analysis, number in each group not reported</p> <p>Mean age: 36.1 (range 21 to 54) years</p>
Interventions	<p>CBZ dose was determined according to pre-study dose</p> <p>If a change was required the dose remained the same for 30 days prior to commencing the study</p> <p>9 patients were prescribed 800 mg, 9 patients 1200 mg and 6 patients 1600 mg daily</p> <p>IR CBZ was administered four times daily, CR CBZ twice daily with 2 placebo tablets</p>
Outcomes	<p>Seizure frequency</p> <p>Incidence of adverse events</p>

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "the order of the sequence was randomised"</p> <p>Comment: insufficient information provided to determine judgement for sequence generation</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: details regarding allocation concealment were not provided</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "All active drugs and placebos were formulated in identical capsules, which in turn were packaged in blister packs."</p> <p>Comment: double-blind</p>
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	<p>Comment: details of outcome assessment blinding not provided</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Quote: "An additional patient was enrolled but did not complete the study for reasons related to difficulties in proper blood sampling"</p> <p>Comment: Only missing data for one patient, and study attrition has been reported - therefore, no concerns about missing data</p>
Selective reporting (reporting bias)	Low risk	<p>Comment: protocol unavailable, but appears all expected and pre-specified outcomes are reported</p>
Other bias	Unclear risk	<p>Comment: support provided by Shire Laboratories</p>

Kaski 1991

Methods	Double-blind, controlled, crossover study 2 treatment arms: 1 IR CBZ, 1 CR CBZ Pre-randomisation baseline period: 2 months Treatment period: 10 weeks (per arm)
Participants	Mentally retarded patients prescribed CBZ at a therapeutic serum level for at least 2 months and with at least 4 seizures per month despite treatment 21 patients enrolled, 20 patients completed both arms, number in each group not reported Mean age 24.9 (6 to 38) years
Interventions	Usual daily CBZ dose divided into three times daily for IR CBZ and twice daily with placebo tablet for CR CBZ Order determined by randomisation Mean daily dose: 780 mg
Outcomes	Seizure frequency
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: insufficient information provided to provide judgement for sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: details regarding allocation concealment were not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "the conventional CBZ, slow-release CBZ, and placebo tablets all looked identical" Comment: double blind
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: details of outcome assessment blinding not provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "one of them was withdrawn because of appendicitis" Comment: Only one withdrawal, and study attrition reported
Selective reporting (reporting bias)	Low risk	Comment: protocol unavailable, but appears all expected and pre-specified outcomes are reported
Other bias	Low risk	Comment: the study appears to be free of other bias

McKee 1991

Methods	<p>Double-blind, controlled, crossover study</p> <p>2 treatment arms: 1 IR CBZ, 1 CR CBZ</p> <p>Pre-randomisation baseline period: 3 months</p> <p>Treatment period: 4 weeks (per arm)</p>
Participants	<p>Adult patients with an existing diagnosis of partial or generalised epilepsy prescribed CBZ at a stable dose</p> <p>25 patients enrolled, 21 included in the final analysis, number in each group not reported</p> <p>Age range: 18 to 53 years</p>
Interventions	<p>IR CBZ either 2,3 or 4 times daily</p> <p>CR CBZ twice daily</p> <p>In all cases placebo tablets were included where necessary to total 4 tablets taken per day</p> <p>Mean CBZ dose: 1076 mg (range 600 to 2000 mg)</p>
Outcomes	<p>Seizure frequency</p> <p>Incidence of cognitive adverse events</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "random order"</p> <p>Comment: insufficient information provided to determine judgement for sequence generation</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: details regarding allocation concealment were not provided</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: "A double-dummy technique was employed to control the study"</p> <p>Comment: patients received an identical number of tablets daily throughout both arms of the study- either active conventional CBZ with CBZ-CR placebo or conventional CBZ placebo with active CBZ-CR</p>
Blinding of outcome assessment (detection bias) All outcomes	Low risk	<p>Quote: "investigator who was also unaware of the order of therapy"</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Quote: "Four of the 25 patients entering the study were excluded from analysis."</p> <p>Comment: 21 patients were included in the analysis out of 25 randomised, and study attrition has been reported. Therefore, despite no ITT analysis, there are no concerns about missing data</p>
Selective reporting (reporting bias)	Low risk	<p>Comment: protocol unavailable, but appears all expected and pre-specified outcomes are reported</p>

McKee 1991 (Continued)

Other bias	Unclear risk	Comment: financial support provided by Ciba-Geigy Pharmaceuticals
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Nag 1998

Methods	Open, controlled, parallel group study 2 treatment arms: 1 IR CBZ, 1 CR CBZ No pre-randomisation baseline period Treatment period: 20 days
Participants	Adult patients with a new diagnosis of partial seizures with no previous history of antiepileptic drug treatment 20 patients were enrolled and completed the study period, 10 in each group IR CBZ group mean age: 20.32 (16 to 34) years CR CBZ group mean age: 22.48 (18 to 35) years
Interventions	Either CR or IR CBZ treatment initiated in dose increments to a maximum of 200 mg 3 times daily
Outcomes	Incidence of adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "patients were randomly assigned" Comment: insufficient information provided to determine judgement for sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: details regarding allocation concealment were not provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open trial"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open trial"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: no participants were excluded from analysis
Selective reporting (reporting bias)	Low risk	Comment: protocol unavailable, but appears all expected and pre-specified outcomes are reported
Other bias	Unclear risk	Comment: support provided by Intas Pharmaceuticals

Persson 1990

Methods	Double-blind, controlled, crossover study 2 treatment arms: 1 IR CBZ, 1 CR CBZ Pre-randomisation baseline period: 2 months Treatment period: 3 months (per arm)
Participants	Adult patients with epilepsy with few or no seizures treated with IR CBZ and experiencing moderate to severe adverse events 21 patients were enrolled, 20 completed both study arms, number in each group not reported Mean age: 43.35 (20 to 69) years
Interventions	Participants continued to take their usual dose at the same dose frequency throughout study period and in both study arms Treatment with IR and CR CBZ as monotherapy, order determined by randomisation Mean CBZ dose: 682 mg (range 300 to 1100 mg)
Outcomes	Seizure frequency Incidence of adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomised by a computer program"
Allocation concealment (selection bias)	Unclear risk	Comment: details regarding allocation concealment were not provided
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Both tablets looked identical and were supplied in identical containers with appropriate labels"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: details of outcome assessment blinding not provided
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "One withdrew during the trial of the first drug (C) due to ataxia and did not wish to participate further" Comment: Only 1 withdrawal, and study attrition was reported
Selective reporting (reporting bias)	Low risk	Comment: protocol unavailable, but appears all expected and pre-specified outcomes are reported
Other bias	Low risk	Comment: the study appears to be free of other bias

Reunanen 1990

Methods	<p>Single-blind, controlled, crossover study</p> <p>2 treatment arms: 1 IR CBZ, 1 CR CBZ</p> <p>Pre-randomisation baseline period: 3 months</p> <p>Treatment period: 2 weeks (per arm)</p>
Participants	<p>Patients diagnosed with partial epilepsy and experiencing seizures prescribed a stable CBZ dose for at least 3 months</p> <p>21 patients enrolled, 18 completed both treatment arms, number in each group not reported</p> <p>Mean age: 42 years</p>
Interventions	<p>Both IR and CR CBZ were administered twice daily</p> <p>Order determined by randomisation</p> <p>Dose remained same as prior to study</p> <p>Mean dose: 644 mg</p>
Outcomes	<p>Total number of seizures</p> <p>Total incidence of adverse events</p>
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	<p>Quote: "randomised"</p> <p>Comment: insufficient information provided to determine judgement for sequence generation</p>
Allocation concealment (selection bias)	Unclear risk	<p>Comment: details regarding allocation concealment were not provided</p>
Blinding of participants and personnel (performance bias) All outcomes	Low risk	<p>Quote: given in identical containers for 2 weeks during each study period, and the observer did not know which drug was being administered"</p>
Blinding of outcome assessment (detection bias) All outcomes	High risk	<p>Quote: "single-blind"</p> <p>Comment: details of outcome assessment blinding not provided</p>
Incomplete outcome data (attrition bias) All outcomes	Low risk	<p>Quote: "The study comprised 21 epileptic patients (...) 18 patients could be evaluated"</p> <p>Comment: Missing data, although study attrition reported. Therefore, no concerns about missing data</p>
Selective reporting (reporting bias)	Low risk	<p>Comment: protocol unavailable, but appears all expected and pre-specified outcomes are reported</p>

Reunanen 1990 (Continued)

Other bias	Low risk	Comment: the study appears to be free of other bias
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Sivenius 1988

Methods	Open, controlled, crossover study 2 treatment arms: 1 IR CBZ, 1 CR CBZ Pre-randomisation baseline period: 6 months Treatment period: 2 weeks (per arm)
Participants	Adult patients with a diagnosis of epilepsy prescribed CBZ monotherapy at a stable, therapeutic dose for at least 6 months 24 patients enrolled and 22 completed both study arms, number in each group not reported Mean age: 36.9 (range 18 to 62) years
Interventions	CBZ dose remained same as prior to study IR CBZ divided into 3 daily doses CR CBZ divided into 2 daily doses Mean daily dose: 615 mg (range 300 to 1100 mg)
Outcomes	Seizure frequency Incidence of adverse events
Notes	Unclear how many participants were randomised to each group

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomised" Comment: insufficient information provided to determine judgement for sequence generation
Allocation concealment (selection bias)	Unclear risk	Comment: details regarding allocation concealment were not provided
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open" Comment: study was not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open" Comment: study was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "24 patients started the study. Four patients had to be excluded" Comment: Although there is missing data, study attrition has been reported - there is no ITT analysis

Sivenius 1988 *(Continued)*

Selective reporting (reporting bias)	High risk	Quote: "practically no difference in side effects between the 2 treatment periods" Comment: Using the ORBIT tool we rated the study as 'A', as specific side effect outcomes were analysed, but only reported that the results are not significant. Dizziness, disturbances of vision, and any other side effects were not reported individually. It is also unclear how many participants were randomised to each group, therefore this study has been rated as high risk of bias for selective outcome reporting
Other bias	Low risk	Comment: the study appears to be free of other bias

IR CBZ: Immediate-release carbamazepine

CR CBZ: Controlled-release carbamazepine

ITT: Intention-to-treat

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

Study	Reason for exclusion
Bojinova 1997	There was no mention of randomisation
Dam 1980	Study not published in English Translation will be sought for an update of this review
Dam 1981	It is unclear whether a controlled-release preparation of CBZ was used Further information will be sought and this study will be included in an update of this review, if eligible
Ghose 1983	This study concerned dose frequency of IR CBZ
Jensen 1990	This study involved a comparison of two CR CBZ preparations
Mirza 1998	Observational study involving one treatment cohort without comparison group
Monaco 1984	This study concerned dose frequency of IR CBZ
Pieters 1992	There was no mention of randomisation
Ramsay 1989	No relevant outcome measures were reported
Remy 1990	Study not published in English Translation will be sought for an update of this review
Scheuch 1992	This study involved a comparison of two CR CBZ formulations
Sobaniec 2004	This study compared CR CBZ to sodium valproate
Thakker 1991	It is unclear whether a controlled-release preparation of CBZ was used Further information will be sought and this study will be included in an update of this review, if eligible

DATA AND ANALYSES

Comparison 1. Adverse Events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse Events	2	107	Odds Ratio (M-H, Fixed, 95% CI)	0.85 [0.30, 2.43]

Analysis 1.1. Comparison 1 Adverse Events, Outcome 1 Adverse Events.

APPENDICES

Appendix 1. Cochrane Epilepsy Group specialized register search strategy

#1 MeSH DESCRIPTOR Carbamazepine Explode All

#2 Carbamazepin* OR Carbamezepin* OR CBZ OR SPD417 OR Apo-Carbamazepine OR Atretol OR Biston OR Calepsin OR Carbagen OR Carbamazepen OR Carbatrol OR Carbazepine OR Carbelan OR Epitol OR Equetro OR Finlepsin OR Karbamazepin OR Lexin OR Neurotol OR Novo-Carbamaz OR Nu-Carbamazepine OR Sirtal OR Stazepin OR Stazepine OR Taro-Carbamazepine OR Tegretal OR Tegretol OR Telesmin OR Teril OR Timonil

#3 #1 OR #2

#4 MeSH DESCRIPTOR Delayed-Action Preparations Explode All

#5 (control* or delay* or prolong* or sustain* or timed) ADJ3 (release* or action*)

#6 #4 OR #5

#7 INREGISTER AND >10/11/2014:CRSCREATED

#8 #3 AND #6 AND #7

Appendix 2. CENTRAL via CRSO search strategy

The following search strategy was used for the latest update.

#1 MESH DESCRIPTOR Carbamazepine EXPLODE ALL TREES

#2 (biston OR carbamazepin* OR carbatrol OR cbz OR epitol OR equetro OR neurotop OR tegretol OR teril OR timonil):TI,AB,KY

#3 #1 OR #2

#4 (epilep* OR seizure* OR convuls*):TI,AB,KY

#5 MESH DESCRIPTOR Epilepsy EXPLODE ALL TREES

#6 MESH DESCRIPTOR Seizures EXPLODE ALL TREES

#7 #4 OR #5 OR #6

#8 MESH DESCRIPTOR Delayed-Action Preparations EXPLODE ALL TREES

#9 ((control* or delay* or prolong* or sustain* or timed) ADJ3 (release* or action*)):TI,AB,KY

#10 #8 OR #9

#11 #3 AND #7 AND #10

#12 ("Conference Abstract"):PT AND INEMBASE

#13 #11 NOT #12

#14 11/11/2014 TO 30/08/2016:CD

#15 #13 AND #14

The following was the original search strategy used to search CENTRAL in *The Cochrane Library*.

#1 (carbamazepine or tegretol)

#2 MeSH descriptor Carbamazepine explode all trees

#3 (#1 OR #2)

#4 MeSH descriptor Epilepsy explode all trees

#5 MeSH descriptor Seizures explode all trees

#6 epilep* or seizure* or convulsion*

#7 (#4 OR #5 OR #6)

#8 (#3 AND #7)

Appendix 3. MEDLINE search strategy

The following search strategy was used for the latest update.

This strategy is based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials ([Lefebvre 2011](#)).

1. (randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or placebo or randomly).ab.
2. clinical trials as topic.sh.
3. trial.ti.
4. 1 or 2 or 3
5. exp animals/ not humans.sh.
6. 4 not 5
7. exp Epilepsy/
8. exp Seizures/
9. (epilep\$ or seizure\$ or convuls\$).tw.
10. 7 or 8 or 9
11. exp Pre-Eclampsia/ or exp Eclampsia/
12. 10 not 11

13. (Carbamazepine or CBZ or SPD417 or Apo-Carbamazepine or Atretol or Biston or Calepsin or Carbagen or Carbamazepin or Carbatrol or Carbazepine or Carbelan or Epitol or Equetro or Finlepsin or Karbamazepin or Lexin or Neurotol or Novo-Carbamaz or Nu-Carbamazepine or Sirtal or Stazepin or Stazepine or Taro-Carbamazepine or Tegretol or Tegretol or Telesmin or Teril or Timonil).tw.

14. exp Carbamazepine/

15. 13 or 14

16. 6 and 12 and 15

17. limit 16 to ed=20141111-20160830

18. remove duplicates from 17

19. exp Delayed-Action Preparations/

20. ((control\$ or delay\$ or prolong\$ or sustain\$ or timed) adj3 (release\$ or action\$)).tw.

21. 19 or 20

22. 18 and 21

The following was the original search strategy.

The filter to identify randomised controlled trials was taken from the Cochrane highly sensitive search strategy for MEDLINE as set out in Appendix 5b of the Cochrane Handbook for Systematic Reviews of Interventions (version 4.2.4, updated March 2005) ([Higgins 2011](#)).

1. randomized controlled trial.pt.

2. controlled clinical trial.pt.

3. exp Randomized Controlled Trials/

4. exp Random Allocation/

5. exp Double-Blind Method/

6. exp Single-Blind Method/

7. clinical trial.pt.

8. Clinical Trial/

9. (clin\$ adj trial\$).ab,ti.

10. ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$ or mask\$)).ab,ti.

11. exp PLACEBOS/

12. placebo\$.ab,ti.

13. random\$.ab,ti.

14. exp Research Design/

15. or/1-14

16. (animals not humans).sh.

17. 15 not 16

18. (carbamazepine or tegretol).tw.

19. exp Carbamazepine/

20. 18 or 19

21. exp Epilepsy/

22. exp Seizures/

23. (epilep\$ or seizure\$ or convuls\$).tw.

24. 21 or 22 or 23

25. 17 and 20 and 24

Appendix 4. Summary tables of included studies

Aldenkamp 1987

Objective	Method	Quality assessment	Participants
2	<p>RCT, cross over, single blind, participants blinded</p> <p>Each arm of at least 1 month duration IR CBZ versus CR CBZ</p> <p>Outcome measures to assess cognitive side effects:</p> <ul style="list-style-type: none"> - 15-word Test: Verbal memory - Complex Figure Test: Nonverbal memory - Stroop Word Colour Test: Attention - WISC-R maze: Concentration - Perceptual Speed: Visual scanning ability <p>Tests to assess performance related to fluctuations in serum CBZ level:</p> <ul style="list-style-type: none"> - Tapping Task: Motor speed - Corsi's Block Tapping Test: Memory span - Computerised Visual Searching Task: Visual-spatial information processing <p>No follow up beyond completion</p> <p>Compliance not assessed</p>	<p>Randomisation stated but method unclear</p> <p>Concealment of allocation unclear</p> <p>Blinding: tablets administered in same tablet form and dose frequency</p> <p>Not analysed as intention-to-treat</p>	<p>11 patients with a diagnosis of epilepsy: Partial in 8, generalised in 2, multifocal in 1</p> <p>5 male, 6 female</p> <p>Age (mean) 32.1 years</p> <p>Age (range) 16 to 58 years</p> <p>Mean age of onset of epilepsy 11.6 years (range birth to 25 years)</p> <p>Patients treated with CBZ for at least 1 year</p> <p>Non-medication control group for cognitive testing standards was matched to epilepsy group for sex, age, educational level</p>

Interventions/protocol	Results	Other
<p>Patients randomised to receive either CR or IR CBZ in same tablet form and dose frequency</p> <p>400 mg CBZ given twice daily at 9.00 AM and 7.00 PM</p>	<p>Summary:</p> <p>CR CBZ produced overall increases in performance over IR in the following tests:</p> <ul style="list-style-type: none"> - 15 word test (direct and delayed recall) for verbal memory - Complex figure test (recall) for non-verbal memory - Stroop Colour Word Test for attention 	

(Continued)

At a non-specified day during the study period, the psychological tests were administered 6 hourly

The non-medication control group followed the same test scheme for 1 day

- Perceptual speed for visual scanning ability

CR CBZ produced superior results in all tests assessing differences in performance relating to fluctuations in serum level:

- Tapping task (dominant and non-dominant hands) for motor speed

- Corsi's Block Tapping Test for memory span

- Computerised Visual Searching Task for visual-spatial information processing

Anonymous 1985

Objective	Method	Quality assessment	Participants
2	<p>RCT crossover</p> <p>56-day treatment arms, no washout period</p> <p>Double blind including participant, but unclear whether outcome assessor or the clinician responsible for patients care is blinded</p> <p>Relevant outcomes include seizure frequency recorded continuously in a diary and adverse events assessed periodically during interim follow-up appointments</p> <p>No follow up beyond study completion reported</p> <p>Compliance was assessed</p>	<p>Randomisation stated, method unclear</p> <p>Concealment of allocation unclear</p> <p>Participants blinded</p> <p>Study is double blind but unclear whether outcome assessor or the clinician responsible for patients care is blinded</p> <p>Not analysed as 'intention to treat'</p>	<p>Patients diagnosed with partial or generalised epilepsy prescribed monotherapy with CBZ 200 mg tablets either tds or qds in a stable regimen for at least 3 months</p> <p>No more than 3 seizures in each of the 3 months prior to enrolment</p> <p>101 patients enrolled, 87 completed both arms</p> <p>Both groups were statistically comparable</p> <p>Mean age group 1 was 34 years, group 2 was 32 years</p>

Interventions/protocol	Results	Other
During the 21-day run-in period patients continued their usual regimen of IR CBZ	No change in pattern of seizure frequency observed overall during both arms. 74% during CR and 77% during IR, the seizure rate did not exceed that at baseline	
Day 22: patients were randomised to receive either IR or CR CBZ at their usual daily dose. Group 1: IR CBZ given every 12 hours plus placebo. Group 2: CR given every 12 hours plus placebo	Mean monthly seizure rate 0.53 during CR, 0.41 during IR. Not statistically significant	
	Adverse events:	
Day 78: patients were crossed over to alternate arm, no washout period mentioned	- CR: 4 patients reported 6 adverse events, dizziness, (2) diplopia, headache, nausea and vomiting	

(Continued)

Mean CBZ dose 1084 mg (range 400 to 2000 mg)

- IR: 5 patients reported 5 adverse events, dizziness, drowsiness, hand tremor, stomach cramps and vomiting

No adverse events were clinically significant or required discontinuation of therapy

96% of patients were compliant at any study visit

Canger 1990

Objective	Method	Quality assessment	Participants
2	<p>RCT double blind, crossover</p> <p>CBZ monotherapy at individualised doses for 1-month study period following 2-month dose finding phase</p> <p>No washout period stated</p> <p>Compliance was assessed prior to the study and non-compliant patients excluded</p> <p>Relevant outcomes include seizure frequency recorded continuously in a seizure diary, and side effects assessed by direct enquiry according to a form</p>	<p>Randomised, method unclear</p> <p>Concealment of allocation unclear</p> <p>CBZ formulations were indistinguishable in taste and physical appearance</p> <p>Outcome assessor blinded to treatment</p> <p>Not analysed as intention to treat</p>	<p>48 patients, 21 male, 27 female</p> <p>Treated with CBZ monotherapy for 3 months or greater with inadequate seizure control or intermittent side effects</p> <p>Exclusion criteria: oto-vestibular disease or poor pre-study compliance</p> <p>Age: mean 34.2, range 18 to 64 years</p> <p>No withdrawals</p> <p>2 generalised, 46 partial seizures</p> <p>Duration of epilepsy mean: 17.7 range: 1.5-44</p> <p>CBZ daily dose (mg) mean: 1.125, range: 400-2.400</p>

Interventions/protocol	Results	Other
Each period of cross over consisted of a 2-month optimal dose finding phase	CBZ total daily dose (mg) significantly ($P=0.001$) higher with CR CBZ: $1558.3 \text{ mg} \pm 735.7$ versus IR CBZ: $1310.4 \text{ mg} \pm 481.7$	
The dose was altered to reach the highest best tolerated in patients with seizures or lowest effective dose in patients with side effects	CR CBZ had significantly reduced number of administrations	
The 1-month maintenance phase was used for statistical analysis during which the dose was not altered	38 patients managed a twice daily regimen compared to 15 on IR ($P=0.001$)	
Seizure frequency was recorded throughout the maintenance phase in a seizure diary	Mean monthly seizure frequency was significantly reduced with CR: 6.3 ± 9.8 versus 9.3 ± 15.6 ($P=0.013$)	
Side effects were checked by direct enquiry according to a form assessing the most common effects	6 patients reported intermittent side effects with CR whereas 26 reported with IR ($P=0.001$)	

(Continued)

At the end of each period a global evaluation of tolerability was assessed

Global evaluation of tolerability significantly better in CR CBZ group ($P = 0.001$).

Garnett 1998

Objective	Method	Quality assessment	Participants
2	<p>RCT crossover, double blind</p> <p>2 weeks each arm</p> <p>Dose was according to existing CBZ therapy. Patients were assigned to 800, 1200 or 1600 mg/day</p> <p>Relevant outcomes:</p> <p>Incidence of adverse events</p> <p>Seizure frequency</p> <p>No follow up beyond study completion</p> <p>Compliance was assessed</p>	<p>Randomisation stated, method unclear</p> <p>Concealment of allocation: Identical capsules used and covered in powder and packaged in identical blister packs. Placebo tablets appeared the same and were packaged in the same blister packs</p> <p>Double blind: participant and outcome assessor</p> <p>Not analysed as intention to treat</p>	<p>Adult patients with a diagnosis of epilepsy prescribed IR CBZ at a stable and therapeutic dose for at least 30 days</p> <p>24 patients were included. 1 patient was excluded from pharmacokinetic analysis due to blood sampling problems</p> <p>Mean age: 36.1 ± 8.1 (range 21 to 54) years</p> <p>13 females 11 males</p> <p>CBZ dose (mg)</p> <p>800: 9 patients</p> <p>1200: 9 patients</p> <p>1600: 6 patients</p>

Interventions/protocol	Results	Other
<p>CBZ dose was determined according to patients pre-study dose: either 800, 1200 or 1600 mg was administered. If a change was required the dose was kept the same for 30 days prior to starting the study</p> <p>IR CBZ was divided into 4 doses/day</p> <p>CR CBZ was divided into 2 doses/day</p> <p>Placebo tablets were used during the CR CBZ arm</p> <p>The occurrence of seizures and adverse events was recorded throughout the study periods - method not stated</p>	<p>No patient was withdrawn from the study because of increased seizure frequency or adverse events</p> <p>Mean number of seizures during the study periods:</p> <p>CR CBZ: 2.8 ± 6.2</p> <p>IR CBZ: 1.6 ± 3.9</p> <p>However, 2 patients reported over half the total number of seizures</p> <p>1 adverse event, somnolence, was reported during the IR CBZ treatment period</p> <p>Compliance was assessed by pill counts and was of a high level and similar for both groups</p>	<p>Concomitant use of additional Antiepileptic Drugs (AEDs) was allowed but the dosing remained constant.</p> <p>9 patients received concomitant AEDs</p>

Kaski 1991

Objective	Method	Quality assessment	Participants
2	<p>RCT crossover</p> <p>Baseline period for 2 months, each treatment arm 10 weeks long</p> <p>Daily CBZ dose kept the same as prior to study</p> <p>Seizure frequency is the single relevant outcome, recorded by experienced nurses both day and night. Participants remained in the institution for the duration of the study</p> <p>No follow up beyond study completion</p>	<p>Randomisation stated but method unclear</p> <p>Concealment of allocation: IR CBZ, CR CBZ and placebo tablets looked identical</p> <p>Participants blinded but unclear whether outcome assessor or clinician responsible for participants care is blinded</p>	<p>Mentally retarded patients px CBZ at a therapeutic serum level for at least 2 months and with at least 4 seizures per month despite therapy were eligible</p> <p>21 patients enrolled, 1 withdrawn</p> <p>Mean age: 24.9 ± 10.3 (range 6 to 38) years</p> <p>11 females, 9 males</p> <p>18 patients experienced secondary generalised, and 2 primary generalised seizures</p> <p>Mean CBZ dose: 780.0 ± 370.8 mg</p>

Interventions/protocol	Results	Other
<p>2 10-week arms followed 2-month baseline period where usual CBZ treatment was given: IR was divided into 3 daily doses, CR was divided into 2 daily dosages with 1 placebo tablet</p> <p>Tablets were taken at the same times during both arms</p> <p>No washout period</p> <p>Seizure frequency was recorded by experienced nurses both day and night</p> <p>Participants remained in the institution for the duration of the study</p>	<p>1 patient was withdrawn due to appendicitis</p> <p>Mean total number of epileptic seizures were equivalent:</p> <p>CR: 44.0</p> <p>IR: 42.7</p> <p>Over time there was a significant trend for less seizures during CR CBZ ($P = 0.01$)</p> <p>During last 2 weeks of therapy, seizure frequency was significantly lower during CR CBZ ($P = 0.02$)</p> <p>There were no significant differences between the mean totals for different types of seizure</p>	<p>This trial involved mentally retarded patients, only 2 of which were prescribed CBZ monotherapy</p> <p>Many patients were prescribed additional non-antiepileptic medications</p>

McKee 1991

Objective	Method	Quality assessment	Participants
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(Continued)

1	<p>RCT, crossover</p> <p>Study period: 8 weeks, 4 weeks in each arm</p> <p>Patients stabilised on maximally tolerated doses of CBZ monotherapy for 3 months minimum. Previous attempts at increasing the dose resulted in neurotoxic adverse events</p> <p>Relevant outcomes:</p> <p>Seizure frequency</p> <p>Incidence of cognitive adverse effects</p> <p>No follow up beyond study completion</p> <p>Compliance was assessed by a tablet count following the study</p>	<p>Randomisation stated, method unclear</p> <p>Participant and outcome assessor blinded</p> <p>Concealment of allocation is unclear</p> <p>Not analysed as intention to treat</p>	<p>Adult patients with an existing diagnosis of epilepsy</p> <p>25 patients were included. 9 reported generalised seizures, 16 complex partial</p> <p>12 males, 13 females</p> <p>Age range: 18 to 53 years</p> <p>4 patients were excluded from analysis: 3 did not comply with the protocol and 1 experienced inadequate seizure control during the IR CBZ phase</p> <p>Mean CBZ dose: 1076 mg</p> <p>Range: 600 to 2000 mg</p>
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Interventions/protocol	Results	Other
Patients continued to take their usual CBZ dose for 3-month baseline period during which seizure frequency was recorded	There were no differences in cognitive function between baseline and after 4 weeks treatment with IR CBZ. Reaction times using Leeds Psychomotor Tester were shorter after CR CBZ:	Patients were pre-scribed CBZ monotherapy
CR CBZ: taken twice daily with 2 placebo tablets in all patients	Mean time $\pm$ SD after 1 hour:	Concomitant medication is not stated
IR CBZ: 4 times daily in 4, three times daily in 8 and twice daily in 1	IR CBZ: $0.51 \pm 0.19s$	
Placebo tablets were given if required	CR CBZ: $0.46 \pm 0.15s$ ($P < 0.01$)	
No mention of appearance of tablets	Mean time $\pm$ SD after 4 hours:	
Seizure frequency charts were completed throughout the trial	IR CBZ: $0.49 \pm 0.15s$	
Compliance was assessed following each treatment arm	CR CBZ: $0.45 \pm 0.1s$ ($P < 0.05$)	
Cognitive function tests were performed at 1, 4 and 8 hours following the morning dose at baseline and following each treatment arm	Adverse event scores were lower with CR CBZ at 1 hour: 8.7 ± 7 with IR CBZ compared to 6.6 ± 6.3 with CR CBZ ($P < 0.05$) Seizure frequency was higher with CR CBZ: 2.8 ± 1.2 with IR CBZ compared to 3.8 ± 0.9 with CR CBZ ($P < 0.01$) However, control was not statistically worse than baseline Compliance was good following tablet counts	

Nag 1998

Objective	Method	Quality assessment	Participants
1	<p>RCT, parallel</p> <p>The length of the study period is not stated but final measurements are taken on the 20th day. It can be assumed this is the length of the study period</p> <p>For both CR and IR CBZ, the target dose administered was 200 mg three times daily</p> <p>Relevant outcomes:</p> <p>Incidence of adverse effects</p> <p>No follow up beyond study completion</p> <p>Compliance is mentioned in the method but has not been reported in the results</p>	<p>Randomisation stated, method unclear</p> <p>Concealment of allocation: drugs given in plastic containers to ensure compliance but no mention of drug appearance</p> <p>This study can be considered unblinded</p> <p>Not analysed as intention to treat</p>	<p>Adult patients with a new diagnosis of partial seizures with no previous prescription of AED therapy</p> <p>20 patients were included. No withdrawals are mentioned</p> <p>IR CBZ group:</p> <p>Mean age: 20.32 ± 8.28 (range 16-34) years</p> <p>3 females, 7 males</p> <p>CR CBZ group:</p> <p>Mean age: 22.48 ± 9.23 (range 18 to 35) years</p> <p>2 F, 8 M</p>

Interventions/protocol	Results	Other
<p>CBZ doses in both groups given in increments:</p> <p>100 mg twice daily for 2 days</p> <p>200 mg twice daily for 2 days</p> <p>200 mg three times per day</p> <p>The drugs were given in plastic containers to ensure compliance</p> <p>There is no mention of placebo tablets or the appearance of the tablets themselves</p> <p>The occurrence of adverse events has been reported but there is no mention of how they were assessed</p>	<p>4 patients reported adverse events in the IR CBZ group:</p> <p>Sedation was present in 2</p> <p>Diplopia/ataxia in 1</p> <p>Skin rash in 1</p> <p>2 patients reported adverse events in the CR CBZ group:</p> <p>Sedation in 1</p> <p>Diplopia/ataxia in 1</p>	<p>This study is unblinded and of small sample size</p> <p>Patients were not prescribed any other concurrent medication</p> <p>Discrepancies between results reported in text and that stated in tables</p>

Persson 1990

Objective	Method	Quality assessment	Participants
1	RCT, crossover	Randomisation performed by a computer program	21 adult patients with epilepsy with few or no seizures and with subjectively moderate to severe adverse events caused by IR CBZ. 1 withdrew due to ataxia

(Continued)

Study period: 2 month baseline followed by 3 months in each arm	Participant and outcome assessor blinded	9 males, 11 females
Adult patients with epilepsy with few or no seizures and with subjectively moderate to severe adverse events caused by IR CBZ were entered into the trial	Concealment of allocation was adequate: IR CBZ and CR CBZ tablets looked identical and were supplied in identical containers with appropriate labels	Age: Mean: 43.35 ± 15.7 (range 20 to 69) years
Relevant outcomes:	Not analysed as intention to treat	Duration of epilepsy: Mean: 17.7 ± 14.4 (range 0.5 to 47) years
Seizure frequency		4 patients interrupted treatment during IR CBZ due to adverse events but tolerated SR CBZ. 1 patient interrupted treatment during both arms due to adverse events
Incidence of adverse effects		Mean CBZ dose: 682 mg (range 300 to 1100 mg)
No follow up beyond study completion		
Compliance was not assessed		

Interventions/protocol	Results	Other
Patients continued to take their usual CBZ dose for 2-month baseline period	1 patient withdrew during IR CBZ due to ataxia and did not continue	9 patients were prescribed additional AEDs, the dose of which was unaltered throughout
Total daily dose and dosing frequency was kept unchanged throughout study. There was no mention of placebo tablets	STRS mean total scores: IR CBZ: 12.1 ± 19.0 CR CBZ: 8.3 ± 18.6 ($P = 0.09$)	Concomitant medication is not stated
Adverse events were assessed at monthly visits by the study investigators using the Questionnaire on Systemic Toxicity (STRS) and Neurotoxicity Rating Scales (NTRS). Mean values for each arm were used in the analysis	NTRS mean total scores: IR CBZ: 80.3 ± 66.2 CR CBZ: 47.2 ± 39.5 ($P = 0.04$)	
Seizure frequency charts were completed throughout the trial and registered at each monthly visit	NTRS + STRS mean total scores: IR CBZ: 92.5 ± 68.8 CR CBZ: 55.5 ± 46.4 ($P = 0.04$) Statistically significant reductions in subscores for the occurrence of GI problems, disturbance of vision, speech and motor function, dizziness and headache Seizure frequency: 2.2 per patient during first month of IR CBZ 1.2 per patient during first month of CR CBZ No significant differences in mean seizure frequency per month	

(Continued)

11 patients preferred CR CBZ, 3 preferred IR CBZ, and 6 had no preference. ($P = 0.0176$)

Reunanen 1990

Obj	Method	Quality assessment	Participants
2	<p>RCT, crossover</p> <p>2 weeks in each treatment arm with no washout period. IR CBZ versus CR CBZ</p> <p>Single blind: outcome assessor blinded</p> <p>Outcomes include clinical parameters such as total seizure incidence and total incidence of reported adverse effects. Data was recorded for these parameters throughout the study period</p> <p>No follow up beyond study completion reported</p> <p>Compliance not assessed</p>	<p>Randomised, method unclear</p> <p>Concealment of allocation unclear</p> <p>Observer blinded to treatment, drugs were given in identical containers</p> <p>Not analysed as intention to treat</p>	<p>21 patients diagnosed with epilepsy and experiencing simple or complex partial seizures, on stable CBZ therapy for at least 3 months</p> <p>3 withdrawals</p> <p>18 evaluated: 10 females, 8 males</p> <p>Mean age: 42 ± 10 years</p>

Interventions/protocol	Results	Other
<p>CBZ given in identical containers during each 2-week study period</p> <p>Both controlled and immediate release were given at 12 hourly intervals</p> <p>Dose was kept the same as before the study. Mean: 644 ± 200 mg</p> <p>Throughout study period seizures and subjective adverse effects reported by patients were recorded. Dizziness, fatigue, movement disorders and visual disturbance received 'special attention'</p> <p>Patient preference was sought at the end of the study</p> <p>Wilcoxon's signed rank and McNemar's tests were used to test the significance of differences between the treatment periods</p>	<p>During immediate-release CBZ 12 generalised, 25 complex partial and 8 simple partial, totaling 56 seizures were recorded</p> <p>During controlled release CBZ, 2 generalised, 18 complex partial and 11 simple partial, totaling 31 seizures were recorded. The difference did not reach significance $P=0.093$</p> <p>Adverse effects were reported 12 times during CR and 19 times during IR CBZ</p> <p>Dizziness was reported 7 times during IR and once during CR, $P=0.034$.</p> <p>12 patients reported no adverse effects during CR compared to 9 during IR</p>	<p>Only 11 patients prescribed monotherapy</p>

Sivenius 1988

Objective	Method	Quality assessment	Participants
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(Continued)

2	<p>RCT, crossover, 2 weeks each arm</p> <p>Dose remained the same as prior to study</p> <p>Relevant outcomes:</p> <p>Incidence of adverse effects</p> <p>Seizure frequency</p> <p>No follow up beyond study completion</p> <p>Compliance was assessed</p>	<p>Randomisation stated, method unclear</p> <p>Concealment of allocation: drugs given in identical containers, no mention of appearance of drugs or inclusion of placebo tablets</p> <p>This study can be considered unblinded</p> <p>Analysed as intention to treat</p>	<p>Adult patients with a diagnosis of epilepsy prescribed CBZ monotherapy at a stable and therapeutic dose for 6 months minimum were eligible</p> <p>24 patients were included. 2 excluded due to compliance issues, 1 due to protocol violation and 1 due to difficulties in analysis</p> <p>Mean age: 36.9 (range 18 to 62) years</p> <p>Mean CBZ dose (mg) 615.0 (range 300 to 1100)</p> <p>9 females, 11 males</p>
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Interventions/protocol	Results	Other
<p>CBZ dose remained the same as prior to study</p> <p>IR CBZ was divided into 3 doses</p> <p>CR CBZ was divided into 2 doses</p> <p>The drugs were given in identical containers</p> <p>There is no mention of placebo tablets or the appearance of the tablets themselves</p> <p>The occurrence of seizures and adverse effects was recorded during the study periods. Method not stated. Special attention was paid to dizziness, fatigue and visual disturbance</p> <p>Patient preference was determined following study completion</p>	<p>9 seizures during each treatment arm</p> <p>Fatigue was the most common adverse effect, occurring in 4 patients in each group. There was 'practically no difference in adverse effects between the 2 treatment periods'</p> <p>50% of patients preferred CR CBZ</p> <p>20% preferred IR CBZ</p> <p>30% had no preference</p>	<p>3 patients were prescribed other non-antiepileptic medication</p> <p>This study is unblinded and of small sample size</p>

WHAT'S NEW

Date	Event	Description
26 April 2017	Amended	Declarations of interest text updated.

HISTORY

Protocol first published: Issue 2, 2008

Review first published: Issue 1, 2010

Date	Event	Description
30 August 2016	New citation required but conclusions have not changed	No new studies identified; conclusions remain the same.
30 August 2016	New search has been performed	Searches updated on 30 August 2016.
10 November 2014	New search has been performed	Searches were updated on 10 November 2014.
10 November 2014	New citation required but conclusions have not changed	No new trials identified. Conclusions remain the same.
5 September 2013	New search has been performed	Searches updated 5 September 2013.
21 July 2011	New search has been performed	Searches updated 21 July 2011; no new trials identified.

CONTRIBUTIONS OF AUTHORS

Graham Powell identified the studies, assessed their methodological quality, extracted the data and composed the review.

Matthew Saunders identified the studies, assessed their methodological quality and extracted the data.

Alexandra Rigby assisted with the assessment of risk of bias for included studies.

Tony Marson provided support and supervision during the review.

DECLARATIONS OF INTEREST

GP: None known.

MS: None known.

AR: None known.

AGM: A consortium of pharmaceutical companies (GSK, Eisai, UCB Pharma) funded the National Audit of Seizure Management in Hospitals (NASH) through grants paid to the University of Liverpool. Professor Tony Marson is Theme Leader for Managing Complex Needs at NIHR CLAHRC NWC.

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Internal sources

- No sources of support supplied

External sources

- National Institute for Health Research (NIHR), UK.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Many of the outcomes specified in the protocol of this review were not measured. The studies were predominantly designed as randomised crossover trials. The duration of treatment in each arm ranged from two weeks to three months. No trial reported follow-up beyond study completion. Categorical data including the proportion that were seizure free and the proportion with treatment failure, both at six and 12 months, were therefore not reported. In addition, time-to-event data were not reported.

Detailed statistical analysis, including meta-analysis, was not appropriate. Therefore, a narrative analysis was used in this review.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [adverse effects] [*therapeutic use]; Carbamazepine [adverse effects] [*therapeutic use]; Delayed-Action Preparations [adverse effects] [therapeutic use]; Epilepsy [*drug therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans