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Clonazepam add-on therapy for refractory epilepsy in adults and children (Review)

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Clonazepam add-on therapy for refractory epilepsy in adults and children

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ABSTRACT

Background

Epilepsy affects about 50 million people worldwide, nearly a quarter of whom have drug-refractory epilepsy. People with drug-refractory epilepsy have increased risks of premature death, injuries, psychosocial dysfunction, and a reduced quality of life.

Objectives

To assess the efficacy and tolerability of clonazepam when used as an add-on therapy for adults and children with refractory focal onset or generalised onset epileptic seizures, when compared with placebo or another antiepileptic agent.

Search methods

We searched the following databases on 14 September 2017: Cochrane Epilepsy Group Specialized Register, Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO), MEDLINE (Ovid 1946 to 14 September 2017), ClinicalTrials.gov, and the WHO International Clinical Trials Registry Platform (ICTRP).

Selection criteria

Double-blind randomised controlled studies of add-on clonazepam in people with refractory focal or generalised onset seizures, with a minimum treatment period of eight weeks. The studies could be of parallel or cross-over design.

Data collection and analysis

Two review authors independently selected studies for inclusion, extracted relevant data, and assessed trial quality. We contacted study authors for additional information.

Main results

No double-blind randomised controlled trials met the inclusion criteria.

Authors' conclusions

There is no evidence from double-blind randomised controlled trials for or against the use of clonazepam as an add-on therapy for adults and children with refractory focal or generalised onset epileptic seizures.

PLAIN LANGUAGE SUMMARY

Clonazepam add-on therapy for refractory epilepsy in adults and children

Review question

This review aimed to evaluate the efficacy and tolerability of clonazepam when used as an add-on therapy for adults and children with refractory focal onset or generalised onset epileptic seizures, when compared with placebo or another antiepileptic agent.

Background

Epilepsy affects about 50 million people worldwide, nearly a quarter of whom have drug-refractory epilepsy. Clonazepam is one of the 1,4-benzodiazepine drugs commonly used in epilepsy management, and recommended for second-line adjunctive treatment for various types of seizures. Previous studies have shown that clonazepam is effective in comparison with placebo when used as a supplement to previous medication for people with an insufficient response to conventional antiepileptic treatment.

Review methods

We searched different databases that contain both published and unpublished results of medical studies. We included only randomised controlled studies (i.e. studies in which participants are randomly allocated to one or more treatments), which are considered the gold-standard of experimental studies in research literature. Two review authors independently selected studies for inclusion, extracted relevant data, and assessed trial quality.

Key results

We found no double-blind randomised controlled trials that considered clonazepam as an add-on therapy for adults and children with refractory focal or generalised onset epileptic seizures, thus its efficacy and safety could not be analysed in this review. There is a need for double-blind randomised controlled trials of clonazepam as an add-on therapy for refractory epilepsy.

The evidence is current to September 2017.

BACKGROUND

Description of the condition

Epilepsy is one of the most common serious disorders of the brain, affecting about 50 million people worldwide. Nearly a quarter of those affected have drug-refractory epilepsy (also known as drug-resistant epilepsy) (Kwan 2011). According to the International League Against Epilepsy (ILAE), drug-resistant epilepsy may be defined as the failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drugs (AEDs) (whether used as monotherapy or in combination) to achieve sustained seizure freedom (Kwan 2010). People with drug-refractory epilepsy have

increased risks of premature death, injuries, psychosocial dysfunction, and a reduced quality of life (Kwan 2011). The number of seizures of all types at presentation, presence of a neurological disorder, and an abnormal electroencephalogram may be the significant factors in indicating seizure recurrence, and individuals with two of these features, or more than three seizures, can be identified as a high-risk group (Kim 2006). Although a significant number of new AEDs have been introduced for people with epilepsy during the last two decades, providing more treatment options and improved ease of use and tolerability, none of these AEDs have been able to significantly prevent or reverse drug-refractory epilepsy (Simonato 2012). Some of the new AEDs used as adjunctive therapy can produce a 50% reduction in seizure frequency in

around 30% to 40% of refractory patients, but only about 5% of people with drug-refractory epilepsy attain seizure freedom per year (French 2007; Schuele 2008).

Description of the intervention

Clonazepam is one of the 1,4-benzodiazepine drugs commonly used in epilepsy management, and recommended for second-line adjunctive treatment for various types of seizures (NICE 2012; Riss 2008; Shorvon 2009). It is superior to diazepam due to its lower dosage, almost complete absence of side effects, and more favourable efficacy (Shorvon 2009). Studies have shown it to be used primarily as an adjunctive therapy in the treatment of people with different types of drug-resistant primarily and secondarily generalised seizures (Riss 2008). After oral administration, clonazepam is rapidly and completely absorbed with maximal plasma concentrations achieved within 1 to 4 hours, and the absolute bioavailability is about 90%. It is highly metabolised by cytochrome P450 (CYP450), and the elimination half-life is 30 to 40 hours. Propantheline and CYP450 inducers, such as phenytoin and carbamazepine, may decrease the plasma levels of clonazepam, and antipsychotic agents, antidepressants, and other anticonvulsant drugs may have an impact on the pharmacodynamic effects, resulting in related drug toxicity or treatment failure. The main adverse events are depression, somnolence, dizziness, nervousness, ataxia, and reduced intellectual ability (FDA 2010).

How the intervention might work

The precise mechanism by which clonazepam exerts its antiepileptic effect is unknown (FDA 2010), but as one of the benzodiazepine drugs, clonazepam behaves as a long-acting, high-potency GABA-A receptor agonist and then mimics the inhibitory effect of GABA in the central nervous system (Shangguan 2015). Furthermore, it is a serotonin agonist and appears to accelerate treatment response to panic disorder (Griffin 2013); an animal study showed that the antimyoclonic action of clonazepam was mediated by enhancement of serotonergic rather than GABAergic neurotransmission (Hwang 1979).

Why it is important to do this review

Data to guide the physician on how best to combine AEDs are insufficient (WHO 2005). As a broad-spectrum antiepileptic drug, clonazepam has been found to be effective in comparison with placebo when used as a supplement to previous medication for people with insufficient response to conventional antiepileptic treatment (Bang 1976; Birket-Smith 1973; Mikkelsen 1976). However, its efficacy, side effects, and tolerability have not been systematically assessed. Consequently there was good reason to conduct

a systematic review to assess the efficacy and tolerability of clonazepam when used as an add-on treatment in adults and children with refractory epilepsy. This review may provide high-quality evidence for policymakers and clinicians making treatment decisions for patients, and help patients and the general public make health-care decisions such as selecting one of several treatment alternatives.

OBJECTIVES

To assess the efficacy and tolerability of clonazepam when used as an add-on therapy for adults and children with refractory focal onset or generalised onset epileptic seizures, when compared with placebo or another antiepileptic agent.

METHODS

Criteria for considering studies for this review

Types of studies

1. Randomised controlled studies with adequate methods of concealment of randomisation, including quasi-randomised trials, cluster-randomised trials, and cross-over trials (results from first randomised period).
2. Double-blinded trials in which both participant and clinician treating or assessing the outcome were blinded to the treatment allocated.
3. A minimum treatment period of eight weeks.

Types of participants

Children (< 16 years) or adults with drug-resistant generalised or focal onset epileptic seizures (including simple focal, complex focal, or secondary generalised seizures). We defined drug resistance as failure of adequate trials of two tolerated and appropriately chosen and used antiepileptic drugs (whether as monotherapy or in combination) to achieve sustained seizure freedom (Kwan 2010). We excluded people with eclampsia, mood disorders, schizophrenia, disorders with psychotic features, and alcohol-related disorders.

Types of interventions

1. The treatment groups received clonazepam in addition to their regular antiepileptic drug therapy.
2. The control groups received placebo or another antiepileptic agent in addition to their regular antiepileptic drug therapy.

For the normal method of delivery of clonazepam, according to the label of Klonopin tablets (FDA 2010): for adults, the initial dose should not exceed 1.5 mg/day divided into three doses, the maintenance dosage must be individualised for each patient depending upon response, and the maximum recommended daily dose is 20 mg; for paediatric patients, the initial dose for infants and children (up to 10 years of age or 30 kg of body weight) should be between 0.01 and 0.03 mg/kg/day but not to exceed 0.05 mg/kg/day given in two or three divided doses, and a daily maintenance dose of 0.1 to 0.2 mg/kg of body weight is acceptable.

Types of outcome measures

We included studies that met the above inclusion criteria regardless of whether they reported on the following outcomes, and when studies reported the outcomes at various time points, we subdivided the treatment indices as follows: 1) short-term: less than 6 weeks post-treatment, 2) medium-term: 6 to 12 weeks post-treatment, 3) long-term: more than 12 weeks post-treatment. We assessed only primary outcomes at different time points, but for secondary outcomes, we also considered the longest follow-up.

Primary outcomes

1. The proportion of participants with a 50% or greater reduction in seizure frequency in comparison to the pre-randomisation baseline period (intention-to-treat analysis).
2. The proportion of participants achieving total cessation of seizures.
3. The proportion of participants having their treatment withdrawn during the course of the treatment period. The treatment might be withdrawn due to adverse effects, lack of efficacy, or a combination of both.

Secondary outcomes

Tolerability measures

1. The proportion of participants experiencing adverse events requiring medication withdrawal.
2. The proportion of participants experiencing any of the following adverse effects: ataxia (co-ordination problems); somnolence; dizziness; fatigue; drowsiness; nervousness; reduced intellectual ability.
3. The proportion of participants experiencing the 10 most common adverse effects if different from above.

Quality of life measures

There had been no agreement on how quality of life should be measured, therefore we decided to summarise data qualitatively.

Search methods for identification of studies

Electronic searches

We searched the following databases on 14 September 2017.

- Cochrane Epilepsy Group Specialized Register, using the search strategy shown in [Appendix 1](#).
- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO), using the search strategy shown in [Appendix 2](#).
- MEDLINE (Ovid 1946 to 14 September 2017), using the search strategy shown in [Appendix 3](#).
- ClinicalTrials.gov (clinicaltrials.gov), using the search strategy shown in [Appendix 4](#).
- World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch/), using the search strategy shown in [Appendix 5](#).

Searching other resources

We reviewed the reference lists of relevant retrieved studies to identify additional reports of relevant studies. We attempted to contact pharmaceutical manufacturers and original investigators of relevant trials to identify any additional published or unpublished data.

Data collection and analysis

Selection of studies

Two review authors (LS and YJ) independently screened titles and abstracts of all the studies identified as a result of the search and coded them as 'retrieve' (eligible or potentially eligible/unclear) or 'do not retrieve'. We retrieved the full-text study reports/publication, and two review authors (LS and YJ) independently screened these for inclusion, and identified and recorded reasons for exclusion of the ineligible studies. Any disagreements were resolved through discussion or by consulting a third review author (FL). We identified and excluded duplicate records and collated multiple reports that related to the same study so that each study, rather than each report, was the unit of interest in the review. We recorded the selection process in sufficient detail to complete a PRISMA flow diagram and 'Characteristics of excluded studies' table ([Liberati 2009](#)).

After selection of studies, we found that no double-blind randomised controlled trials met the inclusion criteria. Should any trials meet the inclusion criteria in the future, we will use the plan described in the protocol to assess their methodological quality, and extract and analyse data as below ([Song 2016](#)).

Data extraction and management

Should any studies be included in a future update of this review, we will extract study characteristics and outcome data from the published reports using a data collection form that has been piloted on at least one study in the review. Two review authors (LS and RZ) will extract study characteristics and outcome data from the included studies. We will extract the following study characteristics.

1. Methods: study design; method of randomisation, concealment of randomisation; method of blinding; duration of baseline period; duration of treatment period; number of study centres and location; study setting; withdrawals; date of study.
2. Participants: N; mean age; age range; gender; inclusion and exclusion criteria; seizure type(s); mean baseline seizure frequency; number of background drugs.
3. Interventions: dose(s) of clonazepam tested; comparison and dosage; concomitant medications.
4. Outcomes: primary and secondary outcomes specified and collected, and time points reported.
5. Notes: funding for trial, and notable conflicts of interest of trial authors.

We will note in the 'Characteristics of included studies' table if outcome data were not reported in a usable way. Any disagreements will be resolved by consensus or by involving a third review author (FL). One review author (HJ) will transfer data into the Review Manager 5 file (RevMan 2014). We will double-check that data are entered correctly by comparing the data presented in the systematic review with the study reports. A second review author (YJ) will spot-check study characteristics for accuracy against the trial report.

Assessment of risk of bias in included studies

Should any studies be included in a future update of this review, two review authors (LS and FL) will independently assess risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreements will be resolved by discussion or by involving another review author (YJ). We will assess the risk of bias according to the following domains.

1. Random sequence generation.
2. Allocation concealment.
3. Blinding of participants and personnel.
4. Blinding of outcome assessment.
5. Incomplete outcome data.
6. Selective outcome reporting.
7. Other bias.

We will judge each potential source of bias as high, low, or unclear and provide a supporting quotation from the study report together with a justification for our judgement in the 'Risk of bias' table. Where information on risk of bias relates to unpublished data or

correspondence with a trialist, we will note this in the 'Risk of bias' table.

We will also use the Evidence-Based Practice Centers GRADE approach, based on the standard GRADE system, to assess domain-specific and overall strength of evidence for relevant outcomes (GRADE Working Group 2004). Two review authors (LS and FL) will independently grade the body of evidence using adapted decision rules. We will explore the following domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. We will grade the overall strength of evidence as 'high', 'moderate', 'low', or 'very low', and will resolve any disagreements through discussion or by referral to an arbitrator (YJ).

Measures of treatment effect

Should any studies be included in a future update of this review, we will analyse dichotomous data as risk ratios (RR) with 95% confidence intervals (CIs), and mean differences (MD) or standardised mean differences (SMD) with 95% CIs for continuous data. We will interpret a P value of less than or equal to 0.05 as statistically significant.

Unit of analysis issues

Should any studies be included in a future update of this review, we will consider the unit of analysis issues as follows:

- For cross-over trials, we will only use data up to the point of the first cross-over. Where multiple trial arms are reported in a single trial, we will include only the relevant arms. If a study involves two or more appropriate dose groups of clonazepam or the comparator, we will pool the different dose arms and consider them as one.
- For cluster-randomised controlled trials (RCTs), we will assume that there is a 'unit of analysis' error if clustering is unaccounted for and if data from the RCTs are interpreted as though the group had been the individual participants (Divine 1992). For dichotomous data, the number of participants and the number experiencing the event will be divided by a 'design effect' calculated using the mean number of participants per cluster (m) and the intraclass correlation coefficient (ICC) [Design effect = $1 + (m - 1) * ICC$] (Donner 2002), and for continuous data, the sample size will be divided by the 'design effect'. We will contact the investigators or study sponsors to obtain an ICC value for their clustered data (Gulliford 1999), and if the ICC is unaccounted for, we will assume the value to be 0.1 (Ukoumunne 1999). We will present the data of the included cluster-RCTs as if from a non-cluster-RCT, but will adjust for the clustering effect by use of the ICC value. If ICC values are taken into account and relevant data are documented in the study report, synthesis with other trials will be possible.

Dealing with missing data

Should any studies be included in a future update of this review, we will contact investigators or study sponsors in order to verify key study characteristics and to obtain missing numerical outcome data where possible (e.g. when a study is identified as abstract only), and will document all correspondence with trialists and report which trialists responded in the full review. For dichotomous data, we will perform intention-to-treat (ITT) analyses, with dropouts being included. If participants left the study before the intended endpoint, we will assume that they would have experienced the negative outcome. For continuous data, we will perform loose ITT analyses, whereby all participants with at least one postbaseline measurement are represented by their last observations carried forward (LOCF), and only the data presented by the original authors will be used. If ITT data are available, they will be preferred to 'per-protocol analysis'.

Assessment of heterogeneity

Should any studies be included in a future update of this review, we will first evaluate the methodological and clinical heterogeneity by comparing the methods, types of participants, interventions, and outcomes of the included studies, and will not combine data from trials with considerable methodological and clinical heterogeneity, but describe them separately. We will evaluate statistical heterogeneity using the χ^2 test with a P value ≤ 0.1 indicating significant heterogeneity, and use the I^2 statistic to quantify statistical heterogeneity. We will interpret the I^2 statistic according to the *Cochrane Handbook* recommendations.

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

Moreover, we will consider the sample size, the magnitude and the direction of the treatment effects, and the strength of evidence to assess the importance of the I^2 statistic.

Assessment of reporting biases

Should any studies be included in a future update of this review and meta-analysis performed, we will assess reporting biases for the main comparisons and primary outcomes by visual interpretation of funnel plots and by testing for funnel plot asymmetry (Egger's test) if more than 10 studies are found (Higgins 2011).

Data synthesis

We will undertake meta-analysis only where this is meaningful, that is if the treatments, participants, and the underlying clinical question are similar enough for pooling to make sense. We will describe skewed data reported as medians and interquartile ranges. We will use Review Manager 5 to combine outcomes when

outcome data are available (RevMan 2014). Since heterogeneity will always exist whether or not it is detectable using a statistical test, we plan to use the random-effects model for combining trials regardless of the degree of heterogeneity. When there is no heterogeneity, both fixed-effect and random-effects models will give identical results; when there is heterogeneity, the random-effects model is more suitable as it incorporates the two possible sources of heterogeneity (caused by sampling error or substantive variability) among the studies. We will thus use the random-effects model, and utilise the fixed-effect model in a sensitivity analysis (Higgins 2011; Huedo-Medina 2006). We will conduct meta-analysis of dichotomous outcomes using Mantel-Haenszel methods, and continuous outcomes (e.g. quality of life measures) using inverse variance methods (Higgins 2011). We will report all results with 95% CIs. We will also use GRADEpro software to create a 'Summary of findings' table considering the main comparisons and primary outcomes (GRADEpro GDT 2015).

Subgroup analysis

As subgroup analyses should be kept to a minimum to avoid multiple testing issues, and are often exploratory in nature and should be interpreted very cautiously, if possible we will perform the following subgroup analyses for the main comparisons and primary outcomes.

1. Age groups (children less than 16 years versus adults).
2. Comparison (the control groups received placebo in addition to their regular antiepileptic therapy versus received another antiepileptic agent in addition to their regular antiepileptic therapy).
3. Doses of clonazepam (maintenance dosage of below 4 mg/d versus 4 to 8 mg/d versus above 8 mg/d).
4. Types of seizures (generalised versus focal versus other seizures).

Investigation of heterogeneity

If the inconsistency is high, we will first check again whether data have been entered correctly. If data are correct, we will inspect the graph visually and successively remove trials that are placed outside of the company of the rest on the graph, to see if homogeneity is restored. We will present both the analysis with all information, and that with the outlying studies removed, and if unanticipated clinical or methodological heterogeneity are discovered, we will state a hypothesis regarding these findings and not combine these data.

Sensitivity analysis

Should any studies be included in a future update of this review and meta-analysis performed, we plan the following sensitivity analyses to investigate the robustness of the meta-analysis.

1. Excluding trials that are of low methodological quality.

2. Excluding trials with large effect size.
3. Excluding all cross-over trials.
4. Excluding trials funded by pharmaceutical companies.
5. Examine potential differences when using the fixed-effect model compared to the random-effects model.
6. Excluding all quasi-randomised trials.
7. Excluding cluster trials in which we have to assume the ICC values.

RESULTS

Description of studies

Results of the search

The Information Specialist of the Cochrane Epilepsy Group performed the searches for this review on 14 September 2017, which identified 202 records, and we identified one other record through reviewing the reference lists of relevant retrieved studies. After screening the titles and abstracts, we retained 12 potentially relevant records for full-text assessment, of which we excluded nine studies with clear reasons (see [Characteristics of excluded studies](#)), and left three studies awaiting classification ([Miyasaka 1977](#); [Shakir 1979](#); [Suzuki 1978](#)), but as it was unlikely that we would be able to contact the study authors of the three studies given the age of the studies, we decided finally to exclude them (see [Characteristics of excluded studies](#)). We thus did not identify any suitable trials for inclusion ([Figure 1](#)); should such trials become available, we will update the review to include them.

Figure 1. Study flow diagram.

Included studies

We did not identify any suitable trials for inclusion.

Excluded studies

We excluded 12 studies for the following reasons: six studies were not randomised trials; two studies did not evaluate an eligible population or the treatment period was less than eight weeks; one study was a single-blinded randomised controlled study; two studies could not be obtained as full text and we were unable to contact the authors; and one cross-over study did not report the full characteristics of the study design and outcome data before cross-over, and we were unable to contact the authors. The details of these studies are given in the [Characteristics of excluded studies](#) table.

Risk of bias in included studies

No double-blind RCTs met the inclusion criteria. Should any studies be included in a future update of this review, we will assess the risk of bias of the studies as stated above.

Effects of interventions

No double-blind RCTs met the inclusion criteria. Should any studies be included in a future update of this review, we will assess their methodological quality, and extract and analyse data as stated above.

DISCUSSION

We did not identify any double-blind RCTs suitable for inclusion, and there are several limitations in the previous trials of clonazepam add-on therapy for refractory epilepsy, as follows.

1. Trials were mainly carried out and published in 1970s and 1980s and were mostly clinical experiences and observational studies, with limited RCTs ([Dahlin 2000](#); [Feldman 1981](#); [Shakir 1979](#); [Yamatogi 1997](#)). Four trials used a single-blind, cross-over design ([Birker-Smith 1973](#); [Edwards 1973](#); [Mikkelsen 1975](#); [Mikkelsen 1976](#)), with no randomisation, in which all participants were started on placebo and followed by clonazepam, to prevent participants with obvious benefit from clonazepam from leaving or being withdrawn from the trial during the subsequent placebo period.
2. Some trials stated that a double-blind method was used ([Bensch 1977](#); [Nanda 1977](#)), but did not specify who were blinded.

3. Duration of some trials might be not sufficiently long to allow evaluation of persistence of antiepileptic effect. In one cross-over trial ([Dahlin 2000](#)), each child was examined during two different 48-hour periods with an interval of one month, and saline or clonazepam was given as a single intramuscular injection in each period. In another cross-over trial ([Nanda 1977](#)), the first tablets were reduced slowly at the end of four to six weeks, while the second unknown tablet was introduced. In an RCT ([Feldman 1981](#)), the treatment period was six weeks. There are guidelines for clinical evaluation of antiepileptic drugs for add-on study ([EMA 2010](#); [Levy 1989](#)), that is that the study should include a baseline period, a titration period (when applicable), and a maintenance period, and the maintenance period should last at least 12 weeks in order to establish that efficacy is not short-lasting ([EMA 2010](#)).

4. All the trials stated that they included patients with poorly controlled epilepsy, or patients with insufficient response to conventional antiepileptic treatment, or patients for whom all available drugs had already been tried in adequate doses, or patients with refractory or drug-resistant epilepsy, but none of the trials provided their diagnostic criteria or definition of refractory epilepsy, and drugs that the participants used before the trials were unclear. The International League Against Epilepsy recently published a definition of refractory epilepsy ([Kwan 2010](#)), which was used in this review and will be used in subsequent updates of this review.

5. Sample sizes of the intervention trials ranged from 11 participants, in [Dahlin 2000](#), to 83 participants, in [Yamatogi 1997](#), with most studies including fewer than 50 participants, and whether the sample size calculation was performed was unknown.

There was a single-blinded, randomised, clonazepam-controlled, parallel-group trial of clobazam add-on therapy for refractory epilepsy ([Yamatogi 1997](#)), which was published in Japanese. We have contacted the author Yasuko Yamatogi, MD, and confirmed that all the participants were resistant to more than two AEDs suitable for each epilepsy type, most more than three AEDs, and sequentially numbered envelopes were used to conceal allocation, but the randomisation method was unclear. Participants were 1 to 15 years old, and the treatment period was 12 weeks. The initial dose of clobazam was 0.2 mg/kg/day, and was increased by 0.2 mg/kg every two - four weeks until the seizure was improved, with a maximum dose of 0.8 mg/kg/day. The initial dose of clonazepam was 0.025 mg/kg/day, and was increased by 0.025 mg/kg every two - four weeks, with a maximum dose of 0.1 mg/kg/day. Sixty-six participants were analysed for efficacy, and 76 for safety. The study showed a statistically significant difference in the proportion of participants with a 50% or greater reduction in seizure frequency (risk ratio 2.82, 95% confidence interval 1.39 to 5.72); the proportion of participants achieving total cessation of seizures was 7/34 for clobazam group, and 0/32 for clonazepam

group. Three of the 36 participants in the clobazam group were discontinued during the test, of whom two were due to side effects and one due to delayed administration of clobazam, and 14/40 participants in the clonazepam group were discontinued, of whom 10 were due to side effects, two due to lack of efficacy and two due to delayed administration of clonazepam. The proportion of participants with adverse effects was 15/36 for clobazam group and 23/40 for clonazepam group.

AUTHORS' CONCLUSIONS

Implications for practice

There is no evidence from double-blind randomised controlled trials for or against the use of clonazepam as an add-on therapy for adults and children with refractory epilepsy.

Implications for research

According to the guideline on clinical investigation of medicinal products in the treatment of epileptic disorders published by the European Medicines Agency (EMA 2010), the pivotal add-on studies should have a randomised, double-blind, controlled parallel-group study design, with a treatment period sufficiently long to allow evaluation of persistence of antiepileptic effect. Given the lack of evidence, trials evaluating the efficacy and tolerability of clonazepam when used as an add-on therapy for adults and children with refractory focal onset or generalised onset epilep-

tic seizures compared with placebo or other antiepileptic agent are warranted. Such studies should recruit a population with a well-defined diagnostic criteria or definition of refractory epilepsy, and well-defined seizure and epilepsy types to allow the identification of patient factors, pathology, seizure types, and baseline antiepilepsy drugs associated with the greatest benefit or harm. The following factors should also be taken into account in future studies: the sample size should be calculated before research; there should be an eligible randomisation procedure; the allocation concealment and blinding of both the participants or results assessors should be performed and reported in detail; dropouts or withdrawals should be recorded with an intention-to-treat analysis applied to analyse the outcomes; and finally reports of the studies should conform to the recommendations of the CONSORT statement (Schulz 2010).

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Song L, Liu F, Zhang R, Ji H, Jia Y. Clonazepam add-on therapy for refractory epilepsy in adults and children. *Cochrane Database of Systematic Reviews* 2016, Issue 6. DOI: 10.1002/14651858.CD012253

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Bacia 1980	Non-randomised controlled study
Bensch 1977	Claimed “Children were accepted for the study provided that all available drugs had already been tried in adequate doses...”, but it was stated that at least 2 of the included participants had not yet tried 2 antiepileptic drugs, and did not meet our inclusion criteria of participants. In addition, it is unclear if this study was randomised
Birket-Smith 1973	Non-randomised controlled study
Dahlin 2000	Only some of the participants had medically refractory epilepsy, and the treatment period was less than 8 weeks
Dincheva 1984	Non-randomised controlled study
Edwards 1973	Non-randomised controlled study
Mikkelsen 1976	Non-randomised controlled study
Miyasaka 1977	The full text of the study is unavailable, and unable to establish contact details at this time. Given the age of the study, it is unlikely that we will be able to contact the study authors in the future
Nanda 1977	Non-randomised controlled study
Shakir 1979	Full characteristics (randomisation process, blinding information, medication history of the participants, etc.) and outcome data before cross-over not reported. We attempted to contact the author. Given the age of the study, it is unlikely that we will be able to contact the study authors in the future
Suzuki 1978	The full text of the study is unavailable, and unable to establish contact details at this time. Given the age of the study, it is unlikely that we will be able to contact the study authors in the future
Yamatogi 1997	Single-blinded randomised controlled study

APPENDICES

Appendix 1. Cochrane Epilepsy Group Specialized Register search strategy

- 1 MeSH DESCRIPTOR Clonazepam Explode All AND INREGISTER
- 2 Antilepsin or Chlonazepam or Cloazepam or Clonazepam* or Clonex or Clonopin or Iktorivil or Klonopin or Kriadex or Landsen or Paxam or Petril or Ravotril or Rivatril AND INREGISTER
- 3 #1 OR #2 AND INREGISTER
- 4 (monotherap* NOT (adjunct* OR “add-on” OR “add on” OR adjuvant* OR combination* OR polytherap*)):TI AND INREGISTER
- 5 #3 NOT #4 AND INREGISTER

Appendix 2. CENTRAL via CRSO search strategy

- #1 MESH DESCRIPTOR Clonazepam EXPLODE ALL TREES
- #2 (antelepsin OR clonazepam* OR rivotril):TI,AB
- #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 #3 AND #7
- #9 (monotherap* not (adjunct* or “add-on” or “add on” or adjuvant* or combination* or polytherap*)):TI
- #10 #8 NOT #9
- #11 MESH DESCRIPTOR anxiety disorders EXPLODE ALL TREES
- #12 MESH DESCRIPTOR Mood Disorders EXPLODE ALL TREES
- #13 MESH DESCRIPTOR Schizophrenia Spectrum and Other Psychotic Disorders EXPLODE ALL TREES
- #14 MESH DESCRIPTOR Alcohol-Related Disorders EXPLODE ALL TREES
- #15 #11 OR #12 OR #13 OR #14
- #16 #10 NOT #15

Appendix 3. MEDLINE (Ovid) search strategy

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

- 1 exp Clonazepam/
- 2 (Antilepsin or Chlonazepam or Cloazepam or Clonazepam\$ or Clonex or Clonopin or Iktorivil or Klonopin or Kriadex or Landsen or Paxam or Petril or Ravotril or Rivatril).tw.
- 3 1 or 2
- 4 exp *anxiety disorders/ or exp *mood disorders/ or exp *Schizophrenia Spectrum and Other Psychotic Disorders/ or exp *Alcohol-Related Disorders/
- 5 3 not 4
- 6 exp Epilepsy/
- 7 exp Seizures/
- 8 (epilep\$ or seizure\$ or convuls\$).tw.
- 9 6 or 7 or 8
- 10 exp *Pre-Eclampsia/ or exp *Eclampsia/
- 11 9 not 10
- 12 (randomized controlled trial or controlled clinical trial or pragmatic clinical trial).pt. or (randomi?ed or placebo or randomly).ab.
- 13 clinical trials as topic.sh.
- 14 trial.ti.
- 15 12 or 13 or 14
- 16 exp animals/ not humans.sh.

17 15 not 16
18 5 and 11 and 17
19 (monotherap\$ not (adjunct\$ or “add-on” or “add on” or adjuvant\$ or combination\$ or polytherap\$)).ti.
20 18 not 19
21 remove duplicates from 20

Appendix 4. ClinicalTrials.gov search strategy

clonazepam | Epilepsy

Appendix 5. ICTRP search strategy

clonazepam AND epilepsy NOT NCT*

CONTRIBUTIONS OF AUTHORS

YJ and LS assessed studies for inclusion, contacted the authors, and managed and wrote the review. FL edited and advised on parts of the review, and participated in resolving disagreements between YJ and LS. RZ and HJ retrieved full-text study reports, collected data, and participated in the writing and editing of the review. YL advised on parts of the review, and made an intellectual contribution to the review.

DECLARATIONS OF INTEREST

Lin Song: None known.

Fang Liu: None known.

Yao Liu: None known.

Ruoqi Zhang: None known.

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- FL is employed at and receives salary from the First Affiliated Hospital of the Third Military Medical University, Chongqing, China.
- Chengdu University of Traditional Chinese Medicine, China.
- RZ is employed at and receives salary from the Chengdu University of Traditional Chinese Medicine, Chengdu, China.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We did not perform data collection and analysis because we did not identify any suitable trials for inclusion. Should any trials meet the inclusion criteria in the future, we will use the plan described in our protocol to assess their methodological quality and extract and analyse data ([Song 2016](#)).

Under subgroup analysis in our protocol, an age group analysis of children less than 17 years versus adults was described ([Song 2016](#)); however, children were defined as less than 16 years under 'Types of participants' earlier in the text. It was a lapse, and we changed "17 years" to "16 years" in the 'Subgroup analysis' in this review. Also in this section, we revised "Comparison (placebo versus other antiepileptic agents)" to "Comparison (the control groups received placebo in addition to their regular antiepileptic therapy versus received another antiepileptic agent in addition to their regular antiepileptic therapy)" in this review, for clarification.

INDEX TERMS

Medical Subject Headings (MeSH)

Anticonvulsants [administration & dosage; *therapeutic use]; Clonazepam [administration & dosage; *therapeutic use]; Drug Resistant Epilepsy [*drug therapy]

MeSH check words

Adult; Child; Humans