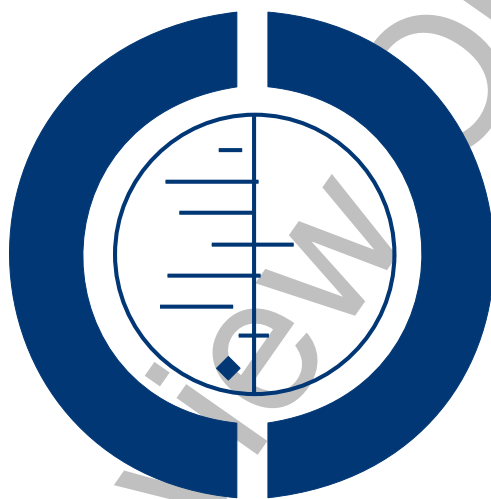


Antiepileptic drugs for the primary and secondary prevention of seizures in viral encephalitis (Review)

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Antiepileptic drugs for the primary and secondary prevention of seizures in viral encephalitis

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ABSTRACT

Background

Viral encephalitis is characterised by diverse clinical and epidemiological features. Seizures are an important clinical manifestation and associated with increased mortality and morbidity. Patients may have seizures during the acute illness or they may develop after recovery. There are no recommendations regarding the use of antiepileptic drugs for the primary or secondary prevention of seizures in patients with viral encephalitis.

Objectives

To assess the efficacy and safety of antiepileptic drugs for the primary and secondary prophylaxis of seizures in viral encephalitis. We intended to answer the following questions.

1. Do antiepileptic drugs used as primary prophylaxis routinely for all patients with suspected or proven viral encephalitis reduce the risk of seizures during the acute illness and reduce neurological morbidity and mortality?
2. Do antiepileptic drugs used as secondary prophylaxis routinely for all patients who have had at least one seizure due to suspected or proven viral encephalitis reduce the risk of further seizures during the acute illness and reduce neurological morbidity and mortality?

Search methods

We searched the Cochrane Epilepsy Group Specialised Register (13 May 2014), the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 4) (April 2014), MEDLINE (Ovid, 1946 to 13 May 2014), the WHO ICTRP search portal (13 May 2014) and ClinicalTrials.gov (13 May 2014). We did not impose any language restrictions.

Selection criteria

Randomised and quasi-randomised controlled trials in which patients were assigned to a treatment or control group (placebo or no drug).

Data collection and analysis

One author (SP) searched the publications by title, abstract and keywords and decided on their suitability for inclusion in the review. For any studies where it was unclear whether they would be suitable for inclusion, the co-authors (CR, BM) were consulted. The co-authors (CR, BM) evaluated the selected studies independently. Since there were no included studies, we carried out no data analysis.

Main results

We did not find any randomised or quasi-randomised controlled trials that compared the effects of antiepileptic drugs with placebo (or no drug) for the primary or secondary prevention of seizures in viral encephalitis. We identified two studies from the literature search where different antiepileptic drugs were used in patients with viral encephalitis, however both failed to meet the inclusion criteria. The first study included children with viral encephalitis where antiepileptic drugs were given. However, it is not clear how the diagnosis was established or the aetiologies. In addition, the randomisation and blinding method is not disclosed; the patients received a diverse and ill-defined range of antiepileptic drugs and adjunctive therapies, and none of the primary or secondary outcome measures was assessed. In the second study, adults with status epilepticus (of whom a proportion had viral encephalitis), who had failed to respond to two initial boluses of diazepam, were randomised to either valproate or diazepam. The study was open-label and the randomisation methodology was not disclosed; none of the primary or secondary outcomes were reported. Data on treatment response between the two arms for those patients with viral encephalitis are not presented for subgroup analysis; the Cochrane Epilepsy Group have contacted the authors for these data but have yet to receive a response.

Authors' conclusions

There is insufficient evidence to support the routine use of antiepileptic drugs for the primary or secondary prevention of seizures in viral encephalitis. There is a need for adequately powered randomised controlled trials in viral encephalitis patients to assess the efficacy and safety of antiepileptic drugs for the primary and secondary prophylaxis of seizures, which is an important clinical problem.

PLAIN LANGUAGE SUMMARY

Antiepileptic drugs for the primary and secondary prevention of seizures in viral encephalitis

Viral encephalitis is characterised by inflammation and swelling of the brain and is caused by viral infection. Seizures can occur both during viral encephalitis and as a later consequence following resolution of the infection. Patients who have seizures during encephalitis are more likely to die or have a disability; some may also develop prolonged or repeated seizures, which can be very difficult to treat. As not all patients will develop seizures, it is unclear whether the use of antiepileptic drugs in patients with viral encephalitis before they have seizures can prevent further seizures and improve their outcome. It is also not clear whether the use of these drugs after the first seizure can prevent the occurrence of further seizures and long-term epilepsy.

We carried out the searches for this Cochrane review on 13 May 2014, however we did not find any high-quality clinical trials that assessed whether the use of antiepileptic drugs in patients with no seizures or one seizure is more effective than placebo in preventing seizures and improving the outcome in viral encephalitis. We did identify two important studies where antiepileptic drugs were used in patients with viral encephalitis, but it is not clear how it was established that these patients had viral encephalitis, what sort of virus was responsible or exactly which drugs were given. Established outcome measures such as mortality, morbidity and seizure recurrence were also not used. These studies did not provide clear information regarding the use of antiepileptic drugs for the primary and secondary prevention of seizures in viral encephalitis. Further research is needed to assess the efficacy and safety of antiepileptic drugs for the primary and secondary prophylaxis of seizures.

Description of the condition

Viral encephalitis is a broad group of rare and potentially fatal central nervous system infections, which can be caused by many

BACKGROUND

different viruses. Depending upon the underlying viral aetiology, it can occur either in a sporadic or epidemic manner, with the most common global causes being herpes simplex virus (HSV) and Japanese encephalitis virus (JEV), respectively (Michael 2012). The annual incidence of viral encephalitis has been reported as being between 3.5 and 7.4/100,000 patient-years (Johnson 1996; Koskiniemi 1997), with a relatively higher incidence in children aged between 1 and 15 years (10.5/100,000 child-years) and infants (18.4/100,000 child-years) (Granerod 2007). However, due to the low sensitivity of clinical and laboratory tests and the difficulty of obtaining virological confirmation for all patients, a viral aetiology is proven in only 30% to 60% of cases (Misra 2008). Seizures are a common clinical manifestation of viral encephalitis and their frequency in part depends upon the underlying viral aetiology (Michael 2012). Seizures may occur during the acute illness, with some patients developing subsequent symptomatic epilepsy after their recovery from this. A minority of patients will develop epilepsy at a later time point despite not having had seizures during the acute encephalitis, as a consequence of the brain damage caused. The incidence of seizures in the acute stage is high (perhaps up to 50%) in encephalitis due to HSV, and is reported variably in encephalitis due to JEV (7% to 46%) (Kalita 2003; Misra 2008). Status epilepticus has also been reported and control of seizures in this group may be particularly difficult (Misra 2008). In one study of 30 patients with status epilepticus due to encephalitis, the seizures continued even after a third antiepileptic drug in eight patients and nine patients died (Kalita 2008). Post-encephalitic epilepsy is also common and may lead to significant morbidity. In a prospective study of 144 patients with encephalitis due to JEV, a history of convulsions was present in 59 patients (41%) (Solomon 2002). A poor outcome, defined as death or severe neurological disability, was reported in 24 of 40 patients (62%) with witnessed seizures compared to 26 of 104 patients (14%) with no witnessed seizures (odds ratio (OR) 4.50; 95% confidence interval (CI) 1.94 to 10.52; P value < 0.0001). Moreover, patients with status epilepticus had higher risk of mortality compared to those with other seizures (P value = 0.003). In the same study, patients with seizures were more likely to have features of raised intracranial pressure and brain herniation. In a retrospective study of 103 patients with acute encephalitis, 28 of whom had a viral aetiology, those with status epilepticus were found to have a significantly increased risk of death (Thakur 2013). In a retrospective study of 45 children with encephalitis due to HSV, seizures occurred in 71% of 14 patients with poor outcome and in 56% of 26 patients with good outcome (Hsieh 2007). Patients with acute encephalitis who develop status epilepticus and multifocal spikes on electroencephalography (EEG) may also have an increased risk of developing intractable epilepsy (Chen 2006). Following viral encephalitis the risk of subsequent seizures is approximately 16 times that of the general population, and the risk may remain elevated for as long as 15 years following the acute episode. In one older study, patients who developed acute seizures

during the encephalitis had a 10% incidence of seizure by five years and a 22% incidence by 20 years, in comparison to 2% and 10%, respectively, in those without acute seizures (Annegers 1988). This is comparable to patients with severe head injury (Annegers 1980). There are important predictors of early seizure in viral encephalitis, including younger age, lower level of consciousness and cortical involvement on imaging (Misra 2008). High incidence of seizures in HSV encephalitis is thought to be mainly due to the involvement of the highly epileptogenic mesial temporal lobes, but it may also reflect other pathophysiological processes, such as haemorrhage, necrosis and neuroimmunological processes. This may also partly explain the reportedly low incidence of seizures in encephalitis due to JEV. In Nipah encephalitis early seizures have been reported in 24% of patients and late-onset seizures in 50% of patients (Tan 2002). Late seizures in viral encephalitis may be due to cortical injury, which may possibly be greatest in the parietal and temporal lobes. In a retrospective study of seizure characteristics of patients with intractable epilepsy following encephalitis, it was found that the majority of these patients had neocortical foci (Marks 1992). In patients with La Crosse encephalitis, the incidence of later seizures is only 10% to 12% (Misra 2008). There is therefore a marked difference in the incidence of late seizures in different types of viral encephalitis.

Description of the intervention

Despite the high rate of seizures in some cases of viral encephalitis, and some evidence suggesting an association with poor outcome, there are no recommendations available regarding the use of antiepileptic drugs, as primary or secondary prophylaxis, in patients with viral encephalitis (Michael 2012; Solomon 2012; Steiner 2010; Tunkel 2008). The majority of the current guidelines primarily focus on specific treatment for targeting the suspected or confirmed aetiology, with little emphasis on seizure management. It is unclear why patients with viral encephalitis who develop seizures have a worse prognosis. It may be that the development of seizures is a proxy marker for those patients with the greatest brain injury, reflecting both viral cytopathy and neuro-inflammatory processes. Alternatively, it may be that the seizures themselves cause additional brain damage resulting in poorer outcomes, perhaps through excitotoxic injury, metabolic disturbances, cerebral oedema, raised intracranial pressure and metabolic disturbances, such as hypoxia and hypoglycaemia (Solomon 2002). If the latter is the case then routine antiepileptic drug prophylaxis may potentially improve outcomes.

How the intervention might work

Theoretically there is a case for primary and secondary prophylaxis with antiepileptic drugs in viral encephalitis. Antiepileptic drugs work by modifying different structures and processes involved in

seizure development, such as ion channels, neurons, glia and inhibitory and excitatory synapses. As seizures are associated with a worse outcome in viral encephalitis, reducing the frequency of seizures may improve the outcome. However, it remains unclear whether the use of prophylactic antiepileptic drugs can prevent the subsequent occurrence of seizures and influence immediate and long-term outcome without compromising safety. Moreover, it is unclear which antiepileptic drugs should be used and at what dosage. There is relative lack of evidence-based information on this subject and it requires further study. Present treatment plans are based on clinical experience and on the data extrapolated from other acute neurological disorders.

Why it is important to do this review

This review intends to summarise the available information. For primary prevention, we aim to review whether the prophylactic administration of antiepileptic drugs in all patients with proven or suspected viral encephalitis is safe and effective in preventing seizures, improving outcome and reducing the risk of subsequent symptomatic epilepsy. For secondary prevention, we aim to review whether the use of antiepileptic drugs after a seizure in patients with proven or suspected viral encephalitis is safe and effective in preventing further seizures, improving outcome and reducing the risk of subsequent symptomatic epilepsy. Using antiepileptic drugs for any indication carries a significant risk of side effects. Therefore, we also need to know whether antiepileptic drugs do more harm than good in order to inform treatment policy. Moreover, blanket use of antiepileptic drugs may result in a worse outcome overall, as was identified when phenobarbital was used in children with cerebral malaria (Crawley 2000). Physicians are therefore not clear whether or not to treat a single seizure following viral encephalitis. Furthermore, intractable epilepsy following viral encephalitis often requires more than one antiepileptic drug. A favourable risk-benefit ratio needs to be established before recommending the use of antiepileptic drugs for the primary prophylaxis of seizures in viral encephalitis. In addition, even if antiepileptic drug prophylaxis can improve outcomes, the best regimen and how long the antiepileptic drugs should be continued after the acute stage is unknown.

OBJECTIVES

To assess the efficacy and safety of antiepileptic drugs for the primary and secondary prophylaxis of seizures in viral encephalitis. We intended to answer the following questions.

1. Do antiepileptic drugs used as primary prophylaxis routinely for all patients with suspected or proven viral encephalitis reduce the risk of seizures during the acute illness and reduce neurological morbidity and mortality?

2. Do antiepileptic drugs used as secondary prophylaxis routinely for all patients who have had at least one seizure due to suspected or proven viral encephalitis reduce the risk of further seizures during the acute illness and reduce neurological morbidity and mortality?

METHODS

Criteria for considering studies for this review

Types of studies

We considered all double-blind, randomised and quasi-randomised controlled trials in which patients were assigned to a 'treatment' or 'control' group (that is, placebo or no drug).

Types of participants

We used the World Health Organization (WHO) definition for viral encephalitis, as a person of any age, at any time of year, with an acute onset of fever and a change in mental status (including symptoms such as confusion, disorientation, coma or inability to talk) and/or a new onset of seizures (excluding simple febrile seizures) (WHO 2006). We included studies where the diagnosis of viral encephalitis was made using the Health Protection Agency criteria: cerebrospinal fluid (CSF) examination documenting slightly raised protein levels, with a raised lymphocyte count (> 5 but $< 500 \times 10^6$ cells/L) and normal glucose level with exception of mumps infection, advanced HSV and lymphocytic choriomeningitis virus infection where CSF glucose may be low (HPA 2011). We included only those studies where the diagnosis of viral aetiology was confirmed by methods such as polymerase chain reaction assays for HSV types 1 and 2, enteroviruses, varicella-zoster, Epstein-Barr virus, human herpes virus 6, cytomegalovirus, lymphocytic choriomeningitis and arboviruses (HPA 2011). We excluded studies in which patients had undergone a neurosurgical intervention for any indication. We considered all types of seizures including simple and complex partial, with or without secondary generalisation.

Types of interventions

We intended to include all trials where antiepileptic drugs were used in viral encephalitis and compared with placebo or no treatment. We only considered those drugs that appear in the list of antiepileptic drugs in the glossary section of the Cochrane Epilepsy Group module in *The Cochrane Library* (<http://onlinelibrary.wiley.com/doi/cochrane/about/articles/EPILEPSY/frame.html>). We defined primary prophylaxis as the use of antiepileptic drugs to reduce the likelihood of seizures in patients who have viral encephalitis but have

not had a seizure. We defined secondary prophylaxis as the use of antiepileptic drugs to reduce further seizures in viral encephalitis patients who have had at least one seizure.

Types of outcome measures

We intended to assess all primary and secondary outcomes in studies of both primary and secondary prophylaxis. We also intended to perform an intention-to-treat (ITT) analysis.

Primary outcomes

1. Proportion of patients having a documented seizure during the admission.
2. Average number of seizures per patient during the admission.
3. Proportion of patients needing intensive care support for seizures during admission.
4. Change in outcome score from admission to discharge (Glasgow Outcome Scale score, Modified Rankin Scale score, Liverpool Outcome Score).
5. Proportion of patients remaining seizure-free throughout the course of the follow-up period.

Secondary outcomes

1. Proportion of patients achieving seizure freedom at a defined follow-up period after discharge.
2. Proportion of patients achieving 50% seizure reduction in comparison to controls with acute encephalitis syndrome, who did not receive antiepileptic drugs during the acute period.
3. Proportion of patients requiring one further antiepileptic drug at a defined follow-up period after discharge.
4. Proportion of patients requiring two further antiepileptic drugs over two years after discharge.
5. Average disability score at one year and two years after discharge.
6. Proportion of deaths after two years of discharge.
7. Quality of life as measured by a validated scale (e.g. SF-36) at discharge and at one and two-year follow-up.
8. Proportion of patients experiencing at least one side effect (skin rash, ataxia, cognitive/behavioural, sedation, weight gain, sleep disturbance).
9. Any other adverse events or sequelae and tolerability.

Search methods for identification of studies

Electronic searches

We searched the following databases:

1. Cochrane Epilepsy Group Specialised Register (13 May 2014), using the search strategy outlined in [Appendix 1](#);
2. Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 4) (April 2014), using the search strategy outlined in [Appendix 2](#);
3. MEDLINE (Ovid, 1946 to 13 May 2014), using the search strategy outlined in [Appendix 3](#);
4. World Health Organization International Clinical Trials Registry Platform search portal ([ICTRP](#)) (searched on 13 May 2014), using the search string 'encephalitis AND seizures';
5. [ClinicalTrials.gov](#) (searched on 13 May 2014), using the search terms 'encephalitis' in the condition field and 'seizures' in the outcomes field.

We did not impose any language restrictions.

Searching other resources

We checked the reference lists of the reports identified in our searches for additional reports of relevant studies. We also contacted the authors and experts in the related field. We also searched conference proceedings (International Epilepsy Congress, European Congress on Epileptology and the American Epilepsy Society's Annual Meeting).

Data collection and analysis

Selection of studies

One author (SP) searched the publications retrieved by title, abstract and keywords and decided on the suitability for inclusion in the review. For any studies where it was unclear whether they would be suitable for inclusion, the co-authors (CR, BM) were consulted.

Two co-authors (CR, BM) independently evaluated the selected studies. Three authors (SP, CR, BM) discussed the likely included and excluded studies and resolved any differences during mutual discussion.

Data extraction and management

We determined patient factors such as age, sex, seizure type(s), number of seizures prior to randomisation, presence of neurological deficits/signs at baseline, co-morbidities, number and generic names of antiepileptic drugs, EEG and neuroimaging (computerised tomography (CT) or magnetic resonance imaging (MRI)) results at baseline. We considered the following trial design aspects: sampling method, inclusion and exclusion criteria, method of diagnosis of encephalitis and epilepsy, method of randomisation, concealment of randomisation, blinding, drug aesthetics matching, stratification factors, treatment period and description of withdrawals, drop-outs and adverse events. Three authors (SP,

CR, BM) independently assessed all trials for inclusion as outlined in [Appendix 4](#).

Measures of treatment effect

We did not include any studies for this review so we were unable to calculate measures of treatment effect. We had planned to assess treatment effect for the primary and secondary outcomes by reporting the odds ratio (with 95% confidence interval) for binary outcomes and the Mann-Whitney U test or t test for continuous non-parametric and parametric data, respectively.

Dealing with missing data

The Cochrane Epilepsy Group has approached the corresponding author of one excluded study for the raw data to undertake a subgroup analysis ([Chen 2011](#)), however we have not received any reply to date.

Data synthesis

We were unable to perform meta-analysis as no studies were included in the review. However, we assessed measures of treatment

effect in two excluded studies with the limited information available. We performed a post hoc Chi² test to measure response to therapy in one of the excluded studies ([Huang 2007](#)), using SPSS (version 21 for Mac).

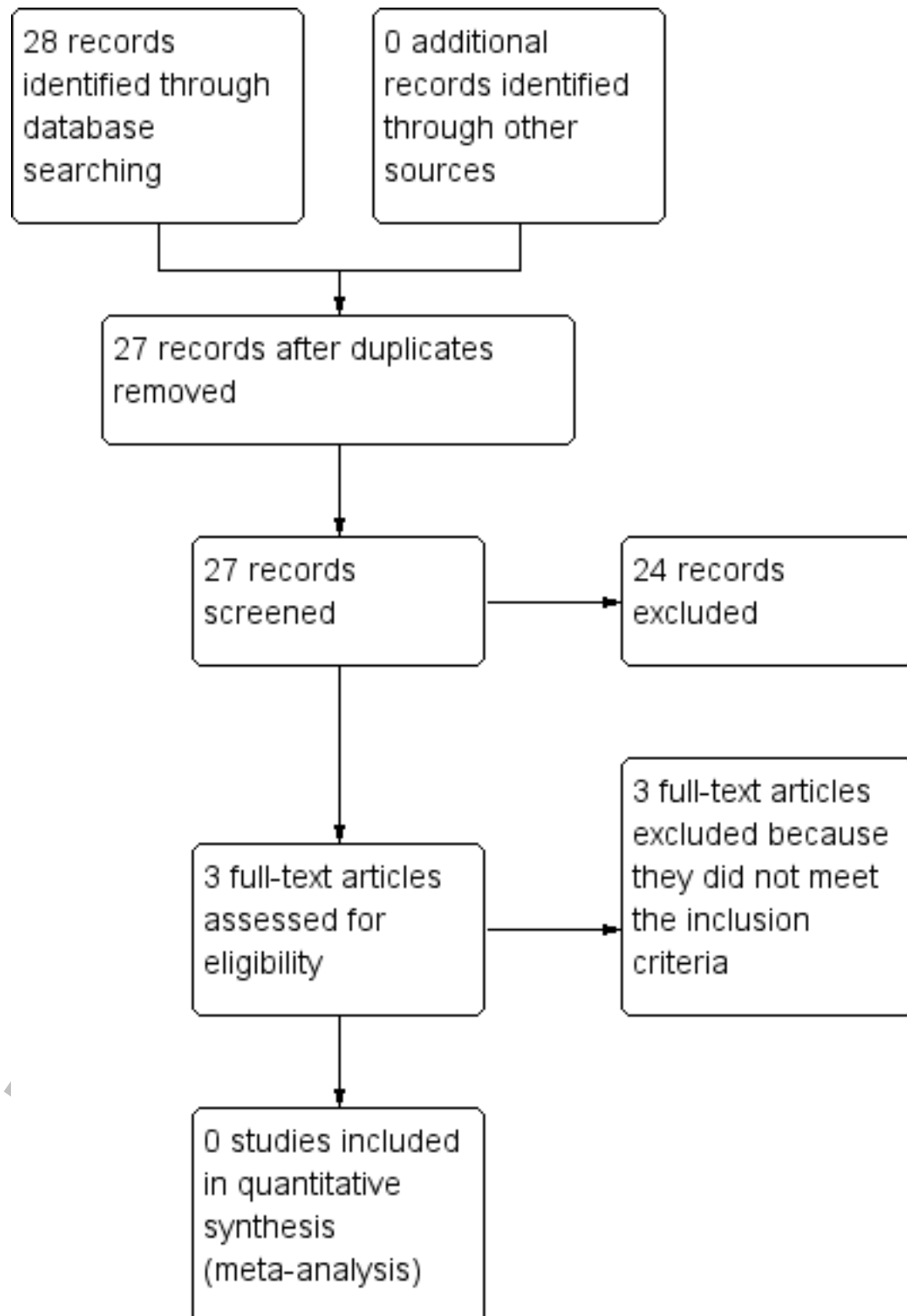
RESULTS

Description of studies

Results of the search

[Figure 1](#) summarises the results of the searches and the process of screening and selecting studies for inclusion in the review. We screened 27 publications identified by the searches. We identified three publications that were relevant to our review and obtained the full papers ([Chen 2011](#); [Huang 2007](#); [Zhang 2009](#)). None of them fulfilled our inclusion criteria therefore we excluded them (see [Excluded studies](#)). [Huang 2007](#) and [Zhang 2009](#) appear to report the same study and it is not clear why they have been published twice so we have discussed only [Huang 2007](#) ([Table 1](#)).

Figure 1. Study flow diagram.



Included studies

No studies are included in the review.

Excluded studies

We identified three publications (Chen 2011; Huang 2007; Zhang 2009) but none of them fulfilled our inclusion criteria therefore we excluded them.

Study I

The first excluded study, conducted by Huang et al, was initially reported in 2007. It was again described in a separate report published in 2009, although this did not provide any additional information and it is unclear why this study has been published twice (Huang 2007; Zhang 2009).

This study reports 96 children (under 16 years old) with encephalitis identified between 2000 and 2006. It is unclear whether these were consecutive admissions or which patients were excluded from the study. In addition, the cases are described as 'severe' encephalitis, however no definition is provided. All patients had an extra-central nervous system prodromal infection two weeks prior to the encephalitic presentation, however neuroimaging data are not presented to establish what proportion of cases had post-infectious acute disseminated encephalomyelitis and all were febrile on admission. Seventy-four cases were described as 'acute-onset' and 22 as 'sub-acute onset', although no definitions for this are given. Moreover, only 88 patients had a cerebrospinal fluid (CSF) pleocytosis, therefore it is unclear how the diagnosis of encephalitis was made. For none of the cases was the aetiology of the encephalitis described. All cases included had developed convulsive status epilepticus; it is unclear what proportion had antiepileptic treatment before the development of status epilepticus, therefore no clear conclusions about primary or secondary prophylaxis can be made.

Patients were randomly allocated to the control (n = 40) or treatment groups (n = 56), however neither the method of randomisation nor blinding are described. Both groups received antiviral medication, ice-compress and treatments to control intracranial hypertension; some also received an undisclosed 'hormone therapy' and some received some form of trophic nerve intervention. The distribution of these myriad therapies between the groups is not described. The control group also received chlorpromazine (Wintermin) and promethazine (Phenergan) (each 0.5 mg/kg intramuscular to a maximum of 25 mg); 100 g/L chloral hydrate (0.5 mg/kg enema to a maximum of 15 mL); phenobarbital (Luminal) (5 mg/kg intramuscular to a maximum of 150 mg) and diazepam (0.3 mg/kg intramuscular to a maximum of 10 mg). These drugs

were alternately delivered when convulsions occurred. The exact drugs received by the patients in the control group are not described. Patients in the intervention group received 'large' doses (not specified) of chlorpromazine and promethazine to keep the patient in 'lethargy' (not specified) for few (not specified) days. Some of the intervention patients also then received chloral hydrate, phenobarbital and diazepam every four to six hours according to their half-life. The administration of anticonvulsants lasted two days, even when no convulsions had occurred. The exact details of the distribution of these drugs between the intervention and control groups is not given. A blanket and unsupported statement that the "usage was the same as the control group" is included.

Response to therapy was defined as follows.

1. Markedly effective (later described as "excellence"):
 - i) temperature reduced to normal, convulsions and other major symptoms and vital signs improved "markedly" 24 to 48 hours after treatment.
2. Effective (later described as "utility"):
 - i) temperature reduced to normal, convulsions and other major symptoms and signs improved "markedly" 48 to 96 hours after treatment.
3. Ineffective:
 - i) temperature, symptoms and signs did not improve within 96 hours.

The "total efficiency rate" was then calculated as being equal to the number of cases defined as markedly effective plus the number of cases defined as effective, divided by the total number of cases, then expressed as a percentage.

Markedly effective response was seen in 31 patients (55%) and 15 patients (38%) in the intervention and control groups respectively; no P values are given. A post hoc Chi² test we conducted was not significant (Yates-corrected 2.31, P value = 0.129; odds ratio (OR) 2.067; 95% confidence interval (CI) 0.84 to 5.16, two-sided P value = 0.1001).

An effective response was seen in 21 patients (38%) and 14 patients (35%) in the intervention and control groups, respectively; no P values are given. A post hoc Chi² test we conducted was not significant (Yates-corrected 0.0013, P value = 0.971; OR 1.114; 95% CI 0.44 to 2.85, two-sided P value = 0.833).

A markedly effective or effective response was seen in 52 patients (93%) and 29 patients (72%) in the intervention and control arms, respectively; the Chi² value is reported as statistically significant (Chi² = 5.871, P value < 0.05) and we have confirmed this.

The control group had status epilepticus for an average four days, and the intervention group had status epilepticus for an average of two days. However, it is not clear whether this represents ongoing tonic-clonic activity or recurrent seizures between which the patient did not regain consciousness, nor at what point the sta-

tus epilepticus was confirmed as having resolved. In addition, it is not clear if status epilepticus and response to treatment were confirmed electrophysiologically. Five cases (13%) in the control group died and two patients (4%) in the intervention group died (P value = 0.097, not significant). Moreover, the follow-up duration is not given and these may represent in-hospital mortalities. No longitudinal follow-up is reported.

The duration of fever, headache, vomiting, convulsions, paralysis, coma and aphasia are reported as statistically significantly shorter in the treatment group than the control group. However, the definition and methodology used to establish the symptom or sign are not described, nor is the proportion suffering with the symptom or sign.

No patients are reported to have dropped out or been lost to follow-up.

There are many methodological flaws in this study. In brief, it is not clear that all the patients had encephalitis and the aetiology is also unknown. It is not clear what proportion were treated with primary or secondary prophylaxis. There is significant heterogeneity in the management of patients in this study and the details of this are not presented. The outcome only reaches statistical significance when an arbitrary outcome score is generated. The 'subhibernation' therapy approach needs examination in a formal, standardised, double-blind, randomised controlled trial with adequate establishment of the diagnosis of encephalitis, determination of the aetiology, standardised drug regimens and use of validated clinical and electrophysiological outcomes.

Study 2

The second excluded study was conducted by Chen et al (Chen 2011). This was an open-label randomised controlled trial that recruited adults (over 14 years) consecutively admitted to the emergency room and neurological intensive care unit with clinically diagnosed generalised convulsive status epilepticus (GCSE) between 2007 and 2010. However, treatment was commenced for presumed GCSE after five minutes of seizures or if there had been two seizures or more between which there had not been a full recovery of consciousness. Patients were enrolled if they failed to respond to intravenous diazepam (0.2 mg/kg) given twice with a 10-minute interval. Patients were randomised to either a 'diazepam group' or a 'valproate group'. The former consisted of a 3rd bolus of diazepam (0.2 mg/kg at 5 mg per minute) followed by an infusion at 4 mg per hour; this was increased every three minutes by 1 µg/kg until seizures were controlled or for a maximum of one hour. The latter consisted of intravenous sodium valproate loading (30 mg/kg at 6 mg/minute) followed by a continuous infusion at 1 mg to 2 mg/kg/hour until the seizures were controlled, and for a minimum of six hours; following cessation of clinical seizure activity, the dose was gradually tapered over 24 hours.

Patients with hypotension, bradycardia, hypoxia, hepatic dysfunction and those thought to require neurosurgery or who were

pregnant or breast-feeding were excluded. Every patient underwent EEG monitoring for a minimum of six hours and control of seizures was defined electrophysiologically by two electroencephalographers. However, it is not stated that these individuals were blinded to the treatment group allocation.

One hundred and twenty-one patients with GCSE were screened; 67 were not controlled with first-line therapy, one dropped out; 36 cases were assigned to the diazepam group and 30 to the valproate group; 10 cases (28%) and 12 cases (40%) were due to viral encephalitis, respectively. However, the diagnostic definition is not given and nor is the aetiology.

Overall there was no significant difference in the proportion of patients who had resolution of seizures within one hour or the proportion who had a recurrence of status epilepticus within 24 hours. Control of seizures in patients described as having viral encephalitis was low (4 (18%)); this was significantly lower than the other causes combined ($\chi^2 = 18.089$, P value < 0.01, OR 0.09; 95% CI 0.026 to 0.329). No other data are presented for subgroup analysis of drug effectiveness between the treatment groups.

The Cochrane Epilepsy Group has approached the study authors for the raw data to undertake a subgroup analysis of the relative effectiveness of the two drug regimens in patients with viral encephalitis and also for clarification of the diagnostic definition of 'encephalitis' in this study and the aetiology of these cases. To date we have not received a response to this data request. We will add subgroup analysis to an update of this review if the data are received at a later date.

Risk of bias in included studies

Assessment of risk of bias was to be performed for the following domains:

- selection bias (sequence generation, allocation concealment)
- performance bias (blinding of study participants and personnel)
- detection bias
- reporting bias
- attrition bias

We also planned to assess the potential impact of outcome reporting bias by inputting an ORBIT table.

Since there are no included studies we were unable to make any 'Risk of bias' assessments.

Effects of interventions

We did not include any studies in this review and therefore could not make an assessment of the effects of interventions.

DISCUSSION

Summary of main results

The aim of this review was to assess the effects of antiepileptic drugs for the primary and secondary prophylaxis of seizures in viral encephalitis. No randomised or quasi-randomised controlled trials with a placebo or no drug arm were identified.

However, we identified two articles where different antiepileptic drugs were used in patients with viral encephalitis. The first study reported 96 children with viral encephalitis who were randomly allocated to the control ($n = 40$) or treatment groups ($n = 56$), however neither the method of randomisation nor blinding were described. It is also not clear from the study whether all patients had viral encephalitis, what the aetiology was, how many received antiepileptic drugs as primary or secondary prophylaxis or exactly which antiepileptic drugs were received by patients in each arm in addition to undisclosed adjunctive therapies (Huang 2007). The second study was an open-label randomised controlled trial in 67 adults with a clinical diagnosis of generalised convulsive status epilepticus refractory to two doses of diazepam (Chen 2011). Patients were randomised to either further diazepam or valproate. Overall there were no differences in the outcome between the two groups. Twenty-two cases were due to viral encephalitis, although neither how the diagnosis was established nor the aetiology are disclosed. Moreover, the outcome data for this group are not presented for subgroup analysis. The Cochrane Epilepsy Group have contacted the authors for these data but to date have not received a response.

Overall completeness and applicability of evidence

In the absence of any randomised or quasi-randomised trials no conclusions can be drawn regarding the overall completeness and applicability of the evidence.

Quality of the evidence

There is insufficient evidence for the use of antiepileptic drugs for the primary or secondary prevention of seizures in viral encephalitis as there are no randomised or quasi-randomised trials.

Agreements and disagreements with other studies or reviews

Seizure is an important cause of mortality and morbidity in patients with viral encephalitis. Treatment of seizures in patients with viral encephalitis has been challenging and controversial

(Michael 2012). There are no guidelines regarding use of different antiepileptic drugs (Michael 2012; Solomon 2012). In a recent guideline published by the European Federation of Neurological Societies (EFNS) the only recommendation was to use phenytoin for the control of seizures in patients with viral encephalitis (Steiner 2010). It is not clear whether antiepileptic drugs reduce the risk of seizures during the acute illness or decrease morbidity and mortality when used as primary prophylaxis. It is also not clear whether antiepileptic drugs reduce the risk of further seizures when used as secondary prophylaxis. Use of antiepileptic drugs carries an inherent risk of adverse events.

In the absence of any data in the form of randomised or quasi-randomised controlled trials no recommendation can be made regarding use of antiepileptic drugs as primary or secondary prophylaxis for seizures in viral encephalitis patients.

AUTHORS' CONCLUSIONS

Implications for practice

There is insufficient evidence to support the use of antiepileptic drugs for the primary or secondary prophylaxis of seizures in viral encephalitis.

Implications for research

There is a need for well-designed, randomised, double-blind, placebo-controlled trials of antiepileptic drugs as primary and secondary prophylaxis for the prevention of seizures in viral encephalitis. Such studies should clearly establish the diagnosis of viral encephalitis and the aetiology. Drug regimens should be clearly described and there should be adequate follow-up using established outcome measures. This research is desperately needed if we are to ascertain the efficacy and tolerability of antiepileptic drugs for the primary and secondary prophylaxis of seizures in viral encephalitis, to guide clinical practice in the treatment of this often devastating condition.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Study	Reason for exclusion
Chen 2011	No other data are presented for subgroup analysis comparing drug effectiveness between the treatment groups; longitudinal follow-up and outcome scores are not provided
Huang 2007	Study has many methodological flaws: it is not clear that all the patients had encephalitis and the aetiology is unknown; it is not clear what proportion were treated with primary or secondary prophylaxis; there is significant heterogeneity in the management and details are not presented; outcome is only significant with an arbitrary outcome score
Zhang 2009	The studies reported by Huang 2007 and Zhang 2009 were similar and it is not clear why they have been published twice, so we have only discussed Huang 2007 as one of the excluded studies

Details of the excluded studies are provided in [Table 1](#).

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Excluded studies

Reference	Type of study	Type of participants	Types of intervention	Types of outcome measures	Conclusion
Huang 2007	Randomisation and blinding methodology not disclosed	Only 88/96 had a CSF pleocytosis and no neuroimaging data are provided to establish the WHO criteria for encephalitis. Aetiology is unknown for all patients. 74 'acute' and 22 'sub-acute' but no definitions given. All convulsive SE; unclear who was treated before/after development. Control (n = 40) or treatment (n = 56)	Control: chlorpromazine (Wintermin) and promethazine (Phenergan) (0.5 mg/kg intramuscular < 25 mg); 100 g/L chloral hydrate (0.5 mg/kg enema < 15 mL); phenobarbital (Luminal) (5 mg/kg intramuscular < 150 mg); diazepam (0.3 mg/kg intramuscular < 10 mg), alternately delivered with convulsions. Exact drugs received not described Intervention: 'large' doses (not specified) of chlorpromazine and promethazine to keep patient in 'lethargy' (not specified) for a few days (not specified). Some also received chloral hydrate, phenobarbital and diazepam every 4 to 6 hours according to their half-life. The exact details of the distribution of these drugs between groups are not given. A blanket and unsupported statement that the	None of our primary or secondary outcome measures is assessed	Study has many methodological flaws: it is not clear that all the patients had encephalitis and the aetiology is unknown; it is not clear what proportion were treated with primary or secondary prophylaxis; there is significant heterogeneity in the management and details are not presented; outcome is only significant with an arbitrary outcome score

Table 1. Excluded studies (Continued)

			“usage was the same as the control group” is included. Anticonvulsants were given for 2 days, even when no convulsions occurred		
Chen 2011	Open-label randomised controlled trial of secondary prophylaxis. Randomisation methodology not disclosed	Adults (> 14 years) with clinically diagnosed convulsive SE, who failed intravenous diazepam (0.2 mg/kg) twice with a 10-minute interval. 121 screened, 67 failed diazepam, 1 dropped out. 36 in diazepam group and 30 in valproate group; 10 (28%) and 12 (40%) due to 'viral encephalitis'. Data to establish WHO criteria and aetiology are not provided	Group 1: 3rd bolus of diazepam (0.2 mg/kg, 5 mg/minute) then infusion (4 mg/hour; increased every 3 minutes by 1 µg/kg until seizures controlled or max < 1 hour) Group 2: sodium valproate bolus (intravenous 30 mg/kg, 6 mg/minute) then infusion (1 to 2 mg/kg/hour until seizures controlled, and > 6 hours)	None of our primary or secondary outcomes are reported. EEG (> 6 hours), control of seizures defined by 2 electroencephalographers; blinding not stated. No significant difference in resolution of seizures < 1 hour or recurrence < 24 hours. Control in 'viral encephalitis' was lower 4 (18%) than for the other causes ($\chi^2 = 18.089$, $P < 0.01$, OR 0.009; 95% CI 0.026 to 0.329)	No other data are presented for subgroup analysis comparing drug effectiveness between the treatment groups; longitudinal follow-up and outcome scores are not provided

CI: confidence interval

CSF: cerebrospinal fluid

EEG: electroencephalography

OR: odds ratio

SE: status epilepticus

WHO: World Health Organization

APPENDICES

Appendix 1. Cochrane Epilepsy Group Specialised Register search strategy

#1 MeSH DESCRIPTOR Encephalitis, Viral Explode All WITH BL CF CI CL CO CN DI DH DT EC EM EN EP EH ET GE HI IM ME MI MO NU PS PA PP PC PX RA RI RT RH SU TH TM US UR VE VI

#2 “viral encephalitis” or “viral meningoencephalitis”

#3 #1 OR #2

Appendix 2. CENTRAL search strategy

#1 (epilep* or seizure* or convuls*):ti,ab,kw (Word variations have been searched)

#2 MeSH descriptor: [Epilepsy] explode all trees

#3 MeSH descriptor: [Seizures] explode all trees

#4 (#1 or #2 or #3) in Trials

#5 MeSH descriptor: [Encephalitis, Viral] explode all trees

#6 “viral encephalitis” or “viral meningoencephalitis”

#7 #5 or #6

#8 #4 and #7

Appendix 3. MEDLINE search strategy

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

1. (randomized controlled trial or controlled clinical trial).pt. or (randomized 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 Encephalitis, Viral/

12. (viral encephalitis or viral meningoencephalitis).tw.

13. 11 or 12

14. 6 and 10 and 13

Appendix 4. Checklist of items considered in data collection or data extraction

For Preview Only

Source

- Study ID (created by review author)
- Report ID (created by review author)
- Review author ID (created by review author)
- Citation and contact details

Eligibility

- Confirm eligibility for review
- Reason for exclusion

Methods

- Study design
- Total study duration
- Sequence generation
- Allocation sequence concealment
- Blinding
- Other concerns about bias

Participants

- Total number
- Setting
- Diagnostic criteria
- Age
- Sex
- Country
- Co-morbidity
- Socio-demographics
- Ethnicity
- Date of study

Interventions

- Total number of intervention groups
- Specific intervention

Outcomes

- Outcomes and time points (i) collected; (ii) reported

For each outcome of interest:

- outcome definition (with diagnostic criteria if relevant);
- unit of measurement (if relevant);
- scales: upper and lower limits, and whether high or low score is good.

Results

- Number of participants allocated to each intervention group

For each outcome of interest:

- sample size;
- missing participants.;
- summary data for each intervention group (e.g. 2×2 table for dichotomous data; means and standard deviations for continuous data);
- estimates of effect with confidence intervals and P values;
- subgroup analyses.

Miscellaneous

- Funding source
- Key conclusions of the study authors
- Miscellaneous comments from the study authors
- References to other relevant studies
- Correspondence required

- Miscellaneous comments by the review authors

CONTRIBUTIONS OF AUTHORS

The first author (SP) searched the retrieved publications by title, abstract and keywords and decided their suitability for inclusion in review; where this was unclear the co-authors (CR, BM) reviewed this. The co-authors (CR, BM) evaluated the selected studies independently. Authors SP, CR and BM discussed the likely included and excluded studies. All the authors (SP, CR, BM) jointly wrote the first draft and resolved disagreements by mutual discussion.

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Dr. Sanjay Pandey: none

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