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Gabapentin monotherapy for epilepsy

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ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To assess the effects of gabapentin monotherapy for people with epileptic partial seizures with and without secondary generalisation.

BACKGROUND

Description of the condition

Epilepsy is one of the most common chronic, non-contagious, neurological disorders, affecting more than 50 million people globally (Banerjee 2009; De Boer 2008; Goldenberg 2010; World Health Organization 2016). Epilepsy makes a 0.75% contribution to the global burden of disease, which shows years of life lost due to premature death and time spent living in less than full health (World Health Organization 2016). Brief recurrent episodes of involuntary movements and sensations or loss of consciousness, or both, characterise epilepsy. Recurrent seizures may be focal (partial), involving only a part of the body, or generalised, involving the entire body. Loss of consciousness and control of autonomic functions or involuntary actions, which are not under conscious control, in particular those of the bowel or bladder, or both, may accompany seizures. Epilepsy is a heterogeneous group of disorders, as classified by the International League Against Epilepsy (ILAE Commission 1998): excessive electrical discharges in epileptic fo-

cus (a group of damaged brain cells, located in various parts of the brain) may trigger most seizure episodes, while some may be generalised at onset (idiopathic generalised epilepsy) (Marson 2007b). The latter include generalised onset tonic-clonic seizures, absence seizures, and myoclonic seizures, which could be due to genetic predisposition, and are characterised by specific generalised spike-wave abnormalities in an electroencephalogram (Marson 2007b). Seizures vary substantially in their form, duration, frequency, and implications for the affected individual; they may be as short as the briefest lapses of attention or muscle jerks, but may be severe prolonged convulsions, from less than one episode per year to several per day. It is important to note that one seizure alone cannot result in diagnosis of epilepsy since up to 10% of the general population worldwide experience one seizure in their lifetime. Epilepsy is defined as having two or more unprovoked seizures (Fisher 2014). Despite massive research in the field of epilepsy and advances in its management, still, in many parts of the world, people with epilepsy and their families suffer from stigma and discrimination, with nearly 80% living in low- and middle-income countries (World Health Organization 2016). Epilepsy presents a significant burden

of disease with profound socioeconomic consequences both for the individual and for society as a whole (Jennum 2011; Megiddo 2016; World Health Organization 2016). A 2011 study found that in Europe, people with epilepsy had lower employment rates and lower income compared with people without epilepsy, with direct net annual healthcare and indirect costs of EURO14,575 (Jennum 2011). In a 1998 study conducted in India, the cost of treatment per person with epilepsy was 88.2% of the country's per capita gross national product (GNP), and epilepsy-related costs, including lost work time, exceeded \$2.6 billion per year (Megiddo 2016). According to the World Health Organization (WHO) fact sheet, approximately three fourths of people with epilepsy who live in low- and middle-income countries do not receive adequate treatment (World Health Organization 2016).

Description of the intervention

Pharmacotherapy is the mainstay in the management of epilepsy. Antiepileptic drugs (AEDs) can successfully treat epilepsy, with complete seizure control rates of up to 70% in children and adults (World Health Organization 2016), or 70% of people with epilepsy enter remission, which is defined as five or more years of seizure freedom while being on drug treatment (Goldenberg 2010). According to the WHO estimates, treatment with antiepileptic drugs is affordable, with daily medication costs of US\$5 per year (World Health Organization 2016). Complete treatment withdrawal can be successfully achieved in 75% of seizure-free people with epilepsy who have been on drug treatment for two to five years (Goldenberg 2010), or in about 70% of children and 60% of adults without subsequent relapse (World Health Organization 2016).

There is an expanding number of new antiepileptic drugs (AED) approved for epilepsy treatment either as monotherapy or as add-on treatment. Despite the diversity of chemical structures and variations in the mode of action of antiepileptic drugs, the problem of epilepsy resistant to pharmacotherapy remains a challenge. Approximately 30% of people with epilepsy may be resistant to antiepileptic medicines and experience seizures (Bazil 2005; Cockerell 1995; Kwan 2000; Walker 1997; World Health Organization 2016). The strategy to overcome resistance and to minimise adverse effects includes slow-dose titration of an AED, used as monotherapy until seizure control is achieved or side effects of AEDs preclude further dose increments, and combination therapy, i.e. addition of one antiepileptic agent to another, known as add-on therapy (Bazil 2005; Goldenberg 2010; St. Louis 2015). Gabapentin, 1- (aminomethyl)cyclohexaneacetic acid, which is structurally related to gamma-aminobutyric acid (GABA) (Goldenberg 2010; Marson 1997; Morris 1999), is a "newer" antiepileptic drug (Goldenberg 2010). It has been licensed in the UK as an add-on therapy for epilepsy since 1993 (Pitkanen 2005). Currently, the U.S. Food and Drug Administration (FDA) recommends gabapentin use for postherpetic neuralgia in adults, and

as an adjunctive therapy in the treatment of partial onset seizures with and without secondary generalisation in adults and paediatric patients three years of age or older with epilepsy (U.S. Food and Drug Administration 2016), while the European Medicines Agency (EMA) in its harmonisation documents of the summaries of product characteristics (SmPCs) labelling and package leaflet for gabapentin (Neurontin) and associated names included uses of gabapentin as adjunctive therapy in the treatment of partial seizures with and without secondary generalisation in adults and children aged six years and above; as monotherapy in the treatment of partial seizures with and without secondary generalisation in adults and adolescents aged 12 years and above; and as treatment of peripheral neuropathic pain, such as painful diabetic neuropathy and postherpetic neuralgia in adults (European Medicines Agency 2006). The Russian regulator, the Ministry of Health of the Russian Federation, recommends its use both as an add-on therapy and as monotherapy for epilepsy, as well as for neuropathic pain (MoH 2016).

Like other antiepileptic medicines, multiple adverse effects, which regulatory and manufacturer's documents describe, characterise gabapentin (MoH 2016; Pfizer 2016; U.S. Food and Drug Administration 2016). Among them are suicidal thoughts or actions. On the basis of the analysis of reports of suicidal behaviour or ideation from placebo-controlled trials of drugs used to treat epilepsy, the FDA require that all manufacturers of antiepileptic drugs included a warning in their labelling and developed a medication guide for people to inform them of the risk of suicidal thoughts or actions while taking antiepileptic drugs. The requirement was based on the finding that the increased risk of suicidal behaviour or thoughts was consistent among 11 drugs with varying mechanisms of action and across a range of indications, including epilepsy. Gabapentin was on the list of the 11 drugs (U.S. Food and Drug Administration 2008). The latest instruction for gabapentin (Neurontin) use in the Russian Federation, approved by the national regulator (the Ministry of Health of the Russian Federation), describes its adverse effects: gabapentin causes serious, life-threatening allergic reactions; severe withdrawal syndrome - rebound seizures with abrupt cessation of treatment; acute pancreatitis; myopathy; hepatitis; jaundice; renal failure; sleepiness and dizziness; lack of co-ordination resulting in injuries and falls; whole body swelling; acute increase in body mass; laboratory test changes; sexual dysfunction; swelling of breasts; and many other adverse effects - of particular note are pains in various parts of the body, including acute chest pain. Cases of the sudden deaths of people on gabapentin were reported (MoH 2016). The manufacturer lists the following among the most common side effects: lack of or difficulty with co-ordination; viral infections; feeling drowsy; nausea and vomiting; difficulty with speaking; tremors; swelling (usually of legs and feet); feeling tired; fever; jerky movements; double vision; and unusual eye movement (Pfizer 2016).

Direct comparison of gabapentin versus other antiepileptic drugs used for treatment of partial epilepsy showed that it was most likely

to be associated with treatment failure due to inadequate seizure control and that carbamazepine was the least likely to be associated with treatment failure (gabapentin verus carbamazepine: hazard ratio (HR) 2.45, 95% confidence interval (CI) 1.81 to 3.32). At the same time, gabapentin was the least likely to result in treatment failure due to unacceptable adverse events (gabapentin versus carbamazepine: HR 0.60, 95% CI 0.44 to 0.81) (Marson 2007a). Likewise, the recent Cochrane Review looking at monotherapy treatment of epilepsy in pregnancy and congenital malformation outcomes in the child found that there was no increased risk of major malformation for gabapentin, along with a few other antiepileptic medicines (lamotrigine, levetiracetam, oxcarbazepine, primidone, zonisamide), though the authors noted that there were substantially fewer data for these medicines (Weston 2016).

Obviously, the trade-off between effectiveness and safety of gabapentin in monotherapy of epilepsy needs to be systematically evaluated, for example, it might be an acceptable alternative for some fraction of pregnant women with partial epilepsy.

How the intervention might work

The precise mechanism of action of gabapentin is not fully understood (McClean 1995; Morris 1999; Pfizer 2016). By its chemical structure, gabapentin is related to the neurotransmitter gamma-aminobutyric acid (GABA). However, in vivo and in human body gabapentin is not metabolised into GABA or a GABA agonist; it does not inhibit GABA re-uptake or degradation. Gabapentin does not modify GABA_A or GABA_B radioligand binding (Goldenberg 2010; Pfizer 2016). According to the manufacturer, gabapentin binds with high affinity to the $\alpha 2\delta$ subunit of voltage-activated calcium channels in *in vitro* studies; however, the relationship of this binding to the therapeutic effects of gabapentin is unknown (Pfizer 2016).

Why it is important to do this review

This review is needed to clarify whether gabapentin is of any benefit for epilepsy treatment as monotherapy. This is particularly important and timely since gabapentin is heavily promoted in Russia and other post Soviet countries for various neurologic and psychiatric disorders, including epilepsy. The pattern of off-label illegal promotion of gabapentin in the US in the 1990s for a wide range of unapproved conditions, all of which were off-label uses according to the FDA labelling at that time, became a classical example in drug promotion literature (Steinman 2006; Steinman 2007). For these promoted uses, gabapentin has not been adequately tested, and its potential benefits may not outweigh its potential harm (Steinman 2006). The Study of Neurontin: Titrate to Effect, Profile of Safety (STEPS) trial without a control group provided an example of inadequate testing of gabapentin in a low-quality trial

with high risk of bias, which had the marketing objective to increase its dose and market share, involving 772 physicians who treated four participants each on average (Krumholz 2011). In this study, gabapentin salespeople collected data and were directly involved in suggesting to the doctors which people to enrol while being present in the doctors' offices. The participants of this study were not informed about its true marketing purpose, while the actual study subjects were the doctors, since the effect of their participation in the study on gabapentin sales was closely monitored (Götzsche 2013; Krumholz 2011).

There is discrepancy between FDA-approved uses and those approved by the EMA and Russian drug regulator. The FDA recommends gabapentin use only as an adjunctive therapy in the treatment of partial seizures with and without secondary generalisation in people over three years of age with epilepsy (U.S. Food and Drug Administration 2016), while the EMA (European Medicines Agency 2006) and Russian regulator, the Ministry of Health of the Russian Federation (MoH 2016) recommend it both as adjunctive therapy and as monotherapy for epilepsy.

Guidelines are not completely unanimous in their recommendations of gabapentin as monotherapy for epilepsy. For example, the Scottish Intercollegiate Guidelines Network (SIGN) recommends gabapentin as an adjunctive treatment of drug-resistant focal epilepsy, drug-resistant generalised or unclassified epilepsy, and as an alternative monotherapy or adjunctive therapy option in older people with epilepsy (Scottish Intercollegiate Guidelines Network 2015). The National Institute for Health and Care Excellence (NICE) recommends gabapentin only as adjunctive treatment for refractory focal seizures in children, young people, and adults and for treatment of children and young people with benign epilepsy with centrotemporal spikes, Panayiotopoulos syndrome, or late-onset childhood occipital epilepsy (Gastaut type). NICE specifically emphasises that gabapentin should not be used in people who have generalised tonic-clonic seizures (GTC); if absence or myoclonic seizures or juvenile myoclonic epilepsy is suspected; in people with tonic or atonic seizures; in people with Dravet syndrome and Lennox-Gastaut syndrome; and in children, young people, and adults with idiopathic generalised epilepsy (IGE) syndromes (NICE 2016). The International League Against Epilepsy (ILAE) recommended gabapentin as initial monotherapy of newly diagnosed, not yet treated focal seizures in adults; for focal seizures in the elderly; and for idiopathic focal epilepsy in children (Glauser 2006; Glauser 2013). The American Academy of Neurology (AAN) recommends gabapentin only as adjunctive treatment for epilepsy, referring to insufficient evidence to recommend gabapentin as monotherapy for refractory partial epilepsy (American Academy of Neurology 2016). Russian Federal guidance on the use of medicines recommends gabapentin as monotherapy for partial seizures with or without secondary generalisation in adults and adolescents aged 12 years and above (Federal guideline 2016).

There is a Cochrane Review of gabapentin as an add-on treat-

ment for drug-resistant partial epilepsy (Al-Bachari 2013), which concluded that gabapentin was effective as an add-on treatment versus placebo. However, the studies included in the review were of relatively short duration and provided no evidence for the long-term effects of gabapentin beyond three months of follow up. The results of this review cannot be extrapolated to gabapentin monotherapy. Furthermore, the authors did not find any difference between gabapentin and placebo in global effectiveness; treatment withdrawal rates during the course of treatment, used as the secondary outcome measure, were the same in gabapentin and placebo add-on groups. Treatment withdrawal is an outcome to which participants make their contribution; it is the primary outcome measure recommended by the Commission on Antiepileptic Drugs of the International League Against Epilepsy (Glauzer 2013). The Cochrane Review found that adverse effects were significantly associated with gabapentin compared with placebo, with risk ratios at around two for ataxia, dizziness, fatigue, and somnolence (Al-Bachari 2013). A systematic review needs to assess the use of gabapentin as a monotherapy treatment.

OBJECTIVES

To assess the effects of gabapentin monotherapy for people with epileptic partial seizures with and without secondary generalisation.

METHODS

Criteria for considering studies for this review

Types of studies

We will search for and include randomised controlled trials comparing the following:

- gabapentin with placebo or any other antiepileptic drug; and
- differing dose of gabapentin as monotherapy for partial seizures with and without secondary generalisation.

We will exclude quasi-randomised controlled trials, in which allocation to treatment or control may not be concealed (e.g. allocation by alteration, open random number list, date of birth, day of the week, or hospital number), or uncontrolled studies.

Types of participants

We will include people of any age and sex, diagnosed with epileptic partial seizures with and without secondary generalisation.

Types of interventions

We will include gabapentin as monotherapy, compared with alternative antiepileptic drugs as monotherapy, different dose of gabapentin as monotherapy, or placebo.

Types of outcome measures

Primary outcomes

1. Treatment withdrawal rates (i.e. the number of people withdrawing from the trials for any cause).
2. Seizure freedom (i.e. the number of people completely free of seizures during the maintenance phase of treatment).

Secondary outcomes

1. Fifty per cent or greater reduction in seizure frequency (i.e. the number of people with 50% or greater reduction in seizures).
2. Time to withdrawal (retention time). The Commission on Antiepileptic Drugs of the International League Against Epilepsy recommends this outcome as the primary outcome measure in monotherapy trials (ILAE Commission 1998), because it is thought to reflect both efficacy and tolerability as treatment may be withdrawn due to continued seizures, adverse effects, or a combination of both. We will try to look at withdrawals due to adverse effects and withdrawals due to lack of efficacy separately.
3. Quality of life if measured by standardised validated self reported tools, like Quality of Life in Epilepsy (QOLIE), Seizure Severity Questionnaire (SSQ), the World Health Organization Quality of Life-BREF (WHOQOL-BREF), etc.

Adverse events and effects

1. Serious adverse events: fatal; life-threatening; requiring hospitalisation, prolongation of existing hospitalisation, or change of treatment regimen; resulting in persistent or significant disability/incapacity; or presenting as a congenital anomaly/birth defect, as defined according to the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guideline (ICH 2003).
2. Total number of people with any adverse event; we will provide descriptive information from the trials on adverse events.

Search methods for identification of studies

We will identify all relevant trials regardless of language or publication status (published, unpublished, in press, and in progress).

Electronic searches

We will search the following databases.

- the Cochrane Epilepsy Specialised Register;
- the Cochrane Central Register of Controlled Trials (CENTRAL; current issue) in the Cochrane Library;
- MEDLINE Ovid (from 1946);
- Embase Ovid (from 1974);
- Web of Science Core Collection, which includes Science Citation Index (from 1940);
- LILACS (Latin American and Caribbean Health Science Information database; from 1982);
- OpenGrey (System for Information on Grey Literature in Europe) (www.opengrey.eu) (from 1980);
- the Russian Databases: e-library (www.elibrary.ru) (from 1998); and
- East View (www.online.ebiblioteka.ru/index.jsp) (from 2006).

We will also search the following ongoing trials and research registers: US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov), ISRCTN registry (www.isrctn.com), and the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch). The proposed search strategy for MEDLINE is set out in [Appendix 1](#). This strategy will be modified for use with the other databases.

Searching other resources

We also will search the reference lists of all trials identified by the above methods for additional reports of relevant studies. We will search the relevant conference proceedings and contact the manufacturer of gabapentin (Neurontin), pharmaceutical company Pfizer.

Data collection and analysis

Selection of studies

At least two of the review authors will independently examine titles and abstracts of records from the results of the electronic searches identified by the aforementioned search strategy for inclusion. We will use Covidence software to allow speedy detection and resolution of conflicts between the reviewers ([Covidence 2016](#)). We will obtain the full texts of the remaining papers, and the same two authors will independently select studies for inclusion based on the aforementioned inclusion criteria, again using Covidence software. We will compare the resulting independent assessments of trials eligible for inclusion and resolve any disagreements through discussion. We will exclude studies that do not meet the eligibility criteria and give the reasons for exclusion (for the studies where

is isn't obvious why they were excluded) in the 'Characteristics of excluded studies' table/s.

Data extraction and management

We will independently extract data using Covidence software ([Covidence 2016](#)), with at least two authors extracting and inputting data. We will extract data on the methods of the studies, participants, interventions, and outcomes. We will resolve any differences in the extracted data by referring to the original articles and through discussion. We will extract data to allow an intention-to-treat (ITT) analysis (including all of the participants in the groups to which they were originally randomly allocated), and we will present the data in the 'Characteristics of included studies' table/s. We will calculate the percentage loss to follow-up and present it in a 'Risk of bias' table. For binary outcomes, we will extract the number of participants with the event in each group. For continuous outcomes, we will use arithmetic means and standard deviations for each group, converting reported data when needed and appropriate using statistical conversions ([Higgins 2011a](#)). If studies report medians and interquartile ranges and if the data are skewed rather than normally distributed, we will attempt to collect appropriate data summaries from the trialists or acquire individual participant data. We will decide on appropriate data summaries and analysis strategies for the individual participant data depending on the situation, based on consultation with a statistician from Cochrane Epilepsy ([Higgins 2011a](#)).

Assessment of risk of bias in included studies

We will independently evaluate methodological quality in terms of generation of allocation sequence, allocation concealment, blinding, loss to follow-up of participants, and other risks of bias using Cochrane's tool for assessing risk of bias, [Higgins 2011](#), in Covidence. At least two authors will assess risk of bias. We will follow the guidance to assess whether adequate steps have been taken to reduce the risk of bias across seven domains: generation of allocation sequence; allocation concealment; blinding (of participants and personnel); blinding of outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. We will categorise these judgments as 'low', 'high', or 'unclear' risk of bias. Where we judge risk of bias as unclear, we will attempt to contact the trial authors for clarification. We will consider loss to follow-up as acceptable if it is less than 10% ([Higgins 2011](#)). We will resolve any disagreements arising at any stage by discussion, and when needed, by asking Cochrane Epilepsy for advice.

Measures of treatment effect

We will present dichotomous data and combine them using risk ratios (RRs). We will cite RRs accompanied by 95% confidence intervals (CIs). We will present and combine continuous data as the standardised mean difference (SMD). We will present time-

to-event data using hazard ratios (HRs). We will combine them using the generic inverse-variance method. A hazard ratio will describe how many times more (or less) likely a participant is to suffer withdrawal at a particular point in time if participants receive gabapentin rather than an alternative antiepileptic drug as monotherapy, different dose of gabapentin as monotherapy, or placebo.

Unit of analysis issues

We will address unit of analysis issues if we include randomised controlled trials that are a non-standard design using Cochrane methods, as detailed in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

Dealing with missing data

We will ask for any missing data from the study authors. If the missing data are still unavailable, we will undertake analysis according to the ITT principle, assuming 'missing at random'. At the same time, we will test the assumption of 'not missing at random'. For this, we will perform sensitivity analyses to assess how sensitive results may be to changes in our assumptions: we will assume and impute all missing data as poor outcomes to generate the worst-case scenario, and we will assume and impute all missing data as favourable outcomes to generate the best-case scenario then we will compare the results.

We will address the potential impact of missing data on the findings of the review in the Discussion section.

Assessment of heterogeneity

We will assess clinical heterogeneity looking at important individual participant factors and comparing their distribution among trials (e.g. age, seizure type, duration of epilepsy), gabapentin doses used, and duration of follow-up among the trials. We will assess methodological heterogeneity by looking at trial design factors, including risk of bias (e.g. methods of randomisation and blinding, missing data, selective reporting).

We will test for statistical homogeneity or heterogeneity of effect sizes between studies using a Chi² test ($P > 0.10$) and the I² statistic, with a value of 30% to 60% used to denote moderate levels of heterogeneity.

Assessment of reporting biases

If the number of included trials is 10 or more, we will use funnel plots to examine asymmetry that publication bias or heterogeneity may have caused. We will request the protocols from trial authors to enable comparison of planned and reported outcome measures. If we do not get the protocols upon request, we will incorporate this fact into our assessments of reporting bias as evidence towards a higher risk of bias. We will examine reporting biases through

determining potential risks of bias in each study (e.g. sponsors of research, research teams involved).

Data synthesis

We will undertake analysis according to the ITT principle. We will use Review Manager (RevMan) to analyse the data (RevMan 2014). We will use RR as a measure of effect for binary outcomes. For continuous data, we plan to use the difference in means (MD). If appropriate, we plan to calculate a summary statistic for each outcome. When no significant clinical or statistical heterogeneity is present, we will synthesise data using a fixed-effect model, the Mantel-Haenszel method (Mantel 1959), as set by default in RevMan. Where we detect heterogeneity and it is still appropriate to pool data, we will use the random-effects (DerSimonian and Laird) method for meta-analysis (DerSimonian 1986).

Subgroup analysis and investigation of heterogeneity

We plan to investigate potential sources of heterogeneity using the following subgroups, if the number of studies permits:

1. gabapentin dose; and
2. length of treatment.

Sensitivity analysis

We will investigate the effect of methodological study quality (low, moderate, or high risk of bias) using a sensitivity analysis to test the robustness of the results.

Summarising and interpreting results

We will use the GRADE approach to interpret findings (Schunemann 2011). We will use GRADEprofiler software, GRADEpro 2004, and import data from Review Manager to create 'Summary of findings' tables for each comparison included in the review for the primary outcomes.

The 'Summary of findings' table for each comparison will include information on overall quality of the evidence from the trials and information of importance for healthcare decision-making. The GRADE approach determines the quality of evidence on the basis of an evaluation of eight criteria (risk of bias, inconsistency, indirectness, imprecision, publication bias, effect size, presence of plausible confounding that will change effect, and dose-response gradient). We will use these to guide our conclusions and recommendations.

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Chan, Information Specialist, and Ellen Dougan, Editorial Assistant. We would like to acknowledge Cochrane Stroke as we used some texts of methods description originally published in our review with their group (Ziganshina 2015).

The background and methods section of this protocol are based on a standard template used by Cochrane Epilepsy Review Group.

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Gabapentin monotherapy for epilepsy (Protocol)

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* Indicates the major publication for the study

APPENDICES**Appendix I. MEDLINE search strategy**

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

1. (gabapentin or neurontin).tw.
2. exp Epilepsy/
3. exp Seizures/
4. (epileps\$ or seizure\$ or convuls\$).tw.
5. 2 or 3 or 4
6. exp *Pre-Eclampsia/ or exp *Eclampsia/
7. 5 not 6
8. (randomized controlled trial or controlled clinical trial).pt. or (randomized or placebo or randomly).ab.

9. clinical trials as topic.sh.
10. trial.ti.
11. 8 or 9 or 10
12. exp animals/ not humans.sh.
13. 11 not 12
14. 1 and 7 and 13
15. ((adjunct\$ or “add-on” or “add on” or adjuvant\$ or combination\$ or polytherap\$) not (monotherap\$ or alone or singl\$)).ti.
16. 14 not 15
17. remove duplicates from 16

CONTRIBUTIONS OF AUTHORS

Liliya-Eugenevna Ziganshina (LEZ) prepared the protocol. Rimma G Gamirova contributed her epileptology expertise to discussions and performed initial literature searches. Tatyana R Abakumova (TRA) contributed with neurology expertise and performed literature searches of guidelines and the Russian language studies. LEZ, RGG, and TRA agreed on the text of the protocol.

DECLARATIONS OF INTEREST

Liliya Eugenevna Ziganshina: nothing to declare.

Rimma Gamirova: nothing to declare.

Tatyana Abakumova: nothing to declare.

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