Antiepileptic drug add-on therapy for focal epilepsy: a network meta-analysis (Protocol)

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[Intervention Protocol]

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ABSTRACT

Objectives

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

To compare the efficacy and tolerability of antiepileptic drugs (AEDs) taken as add-on treatment for drug-resistant, focal-onset epilepsy, and to generate a clinically useful ranking of available AEDs.

BACKGROUND

This is a protocol for a systematic review and individual participant data (IPD) network meta-analysis (NMA) of randomised controlled trials of add-on treatment for people with drug-resistant focal-onset epilepsy, uncontrolled by one or more concomitant antiepileptic drugs (AEDs). In the majority of these trials, participants are randomised to have either active AED or placebo added to their existing AED treatment. This is in keeping with international guidelines on the development of AEDs (EMA 2018). Once a drug has confirmed efficacy and tolerability as an add-on therapy, it is usually then tested as monotherapy and in other epilepsy syndromes. An individual participant data network meta-analysis of AEDs taken as monotherapy is the subject of a separate Cochrane review (Nevitt 2017).

Description of the condition

Epilepsy is a common neurological condition, with between 4 and 10 per 1000 people estimated to have active epilepsy at any given time; In high-income countries, an estimated 49 per 100,000 people are diagnosed with epilepsy each year (WHO 2020). Between 2% and 3% of the population will be given a diagnosis of epilepsy at some time in their lives, the majority of whom will go into remission. However, up to 30% will fail to respond to monotherapy, often requiring treatment with combinations of AEDs (Cockerell 1995; Hauser 1993). These individuals will often experience significant adverse psychological and quality of life outcomes, due to continued and unpredictable seizures, side effects of drugs, and reduced educational and employment prospects.

Description of the intervention

In the majority of cases, epilepsy is treated with AEDs. These AEDs have varying mechanisms of action, and certain AEDs may be more effective at treating specific epilepsy syndromes or seizure types. For example, carbamazepine is more effective for focal seizures (Marson 2000), and valproate is more effective for generalised onset seizures (Marson 2007). Conventional first-line drugs include carbamazepine, lamotrigine, and sodium valproate, which have a broad therapeutic effect, but are associated with a number of adverse effects. In cases where monotherapy fails to induce seizure remission, AED 'add-on therapy' may be used in an attempt to improve seizure control.

In this network meta-analysis review, we will focus on 14 AEDs that are currently being commonly used in clinical practice as add-on treatments: brivaracetam; clobazam; eslicarbazepine acetate; gabapentin; lacosamide; lamotrigine; levetiracetam; oxcarbazepine; perampanel; pregabalin; topiramate; valproate; vigabatrin; zonisamide.

How the intervention might work

Clobazam has long been used as an add-on therapy to reduce seizure frequency, because with its broader spectrum of antiepileptic activity, it can inhibit the spread of seizures and increase the seizure threshold (Gastaut 1979).

The primary mechanism of action for valproate is probably GABAergic; it has been shown to raise cerebral GABA levels in animals (Turner 1980).

Lamotrigine, eslicarbazepine acetate (ESL), and oxcarbazepine act on voltage gated sodium channels; the latter two are derivatives of carbamazepine, which has the same mechanism of action. In contrast, lacosamide enhances the inactivation of slow sodium channels (Doty 2007).

Gabapentin is a structural analogue of the neurotransmitter gamma-aminobutyric acid (GABA), however, its mechanism of action is not via the GABA system, and remains poorly understood (McLean 1995).

Levetiracetam binds to, and modulates, the synaptic vesicle protein 2A (SV2A); a protein that has some controlling effect on neurotransmitter release from presynaptic vesicles (Gillard 2006; Lynch 2004). It also selectively inhibits N-type Ca^{2+} channels, and decreases intracellular calcium-ion increase (both of which negatively impact neurotransmitter release; (Lukyanetz 2002; Niespodziany 2001)).

Brivaracetam is a derivative of levetiracetam, with a similar mechanism of action.

Perampanel is a highly selective, non-competitive AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor antagonist that may exert its antiepileptic effect through selective inhibition of AMPA receptors (Ceolin 2012; Hanada 2011).

Pregabalin acts by binding to an auxiliary protein (alpha 2 delta) of the voltage-gated calcium channels; it has been shown to reduce calcium influx into nerve terminals, resulting in reduced presynaptic release of glutamate(Ben-Menachem 2004).

Topiramate has multiple mechanisms of action, including an effect on voltage-dependent sodium channels (Coulter 1993), and enhancement of gamma-aminobutyric acid-A (GABAA) mediated chloride flux (Brown 1993).

Vigabatrin is a structural analogue of GABA, which irreversibly inhibits GABA-transaminase (Grant 1991), and increases brain levels of the inhibitory transmitter GABA (Schechter 1984).

Zonisamide has multiple mechanisms of action, including via blockade of voltage-gated sodium channels, voltage-dependent T-type calcium channels, and potassium-evoked glutamate response, reduced glutamate-mediated synaptic excitation, and increased synaptic concentration of GABA (Leppik 2004; Ueda 2003).

Why it is important to do this review

Around 30% of people with epilepsy fail to achieve seizure control, and they usually require treatment with multiple antiepileptic drugs in an attempt to maximise seizure control. In addition, a significant proportion of those who do achieve seizure control require two or more antiepileptic drugs to do so. This might lead to a poor quality of life for people with epilepsy, and major drug costs (Strzelczyk 2008).

Whilst add-on therapy is common practice in epilepsy practice, the evidence that informs a choice among drugs has some important limitations. One major limitation is the fact that during drug development, drugs are tested against placebo. These trials generate evidence of efficacy to inform regulatory and licensing decisions, but they do not inform clinical practice, where a

choice needs to be made among a number of alternatives. We have published a series of Cochrane Reviews investigating the efficacy and tolerability of individual add-on AEDs, each of which evaluated the efficacy and tolerability of individual AEDs compared to placebo. (Bresnahan 2019; Bresnahan 2019a; Bresnahan 2019b; Bresnahan 2020; Bresnahan 2020a; Brigo 2020; Chang 2017; Mbizvo 2020; Panebianco 2019; Panebianco 2020; Panebianco 2021; Weston 2015).

However, in a network meta-analysis, it is possible to estimate the comparative effects of different AEDs if they have been compared against a common comparator (in this case, placebo). This 'indirect' evidence can be combined with 'direct' evidence in a network meta-analysis (NMA) to increase precision, and estimate the comparative effects of AEDS that would otherwise not be possible. Previous NMAs have been conducted to investigate the efficacy and tolerability of AEDs for focal epilepsy (Bodalia 2013; Costa 2011; Hu 2018). Whilst there are some similarities between the previous NMAs, with the two of them suggesting that levetiracetam, vigabatrin, and valproate are best for overall short-term efficacy and tolerability, there are some important limitations. All analyses were based on aggregate data extracted from published trial reports, and therefore, analyses were restricted by data availability in publications, and none of the NMAs explored the effect of dose. In addition, the NMAs either excluded children (Hu 2018), or combined children with adults in analyses (Bodalia 2013; Costa 2011); none of the reviews thoroughly explored the potential that treatment effects might be modified by participant characteristics. This can only be examined reliably by using individual participant data, from the included trials, to overcome the potential for ecological bias (Lambert 2002). Furthermore, AEDs (included in this review) have been licensed at different time points over the past 50 years, and the randomised controlled trials (RCT) included in the NMAs were conducted across a time period that spans 29 years. During this time, there have been inevitable changes to clinical management, options from which to choose, and the number of concurrent AEDs to trial. This could potentially mean that people recruited into more recently completed trials are more drug resistant than those recruited to earlier trials (Bodalia 2013; Costa 2011); this could have important implications on the underlying assumption of transitivity that we make in a NMA. The availability of IPD from RCTs will enable this to be thoroughly examined, and the analyses adjusted wherever possible.

OBJECTIVES

To compare the efficacy and tolerability of antiepileptic drugs (AEDs) taken as add-on treatment for drug-resistant, focal-onset epilepsy, and to generate a clinically useful ranking of available AEDs.

METHODS

Criteria for considering studies for this review

Types of studies

To be included in the review, studies must meet the following criteria:

- randomised controlled trials (RCTs), including quasi-randomised trials, in which the method of allocation concealment is adequate;

- double, single, or un-blinded trials;
- placebo-controlled or active-controlled studies;
- parallel group or cross-over studies.

Types of participants

Adults and children with drug-resistant focal epilepsy, as defined by the International League Against Epilepsy (Kwan 2010). We will include participants who had undergone other interventions to treat epilepsy, such as surgery, vagal nerve stimulation, or ketogenic diet.

Types of interventions

We will include RCTs that randomised participants to at least one of the following AEDs: brivaracetam, clobazam, eslicarbazepine acetate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, pregabalin, topiramate, valproate, vigabatrin, zonisamide, administered as add-on treatment for focal epilepsy.

RCTs that include one of these AEDs of 'direct' interest should have included a comparison with either the same AED at a different dose, a different AED (either from this list of interventions of direct interest, or any other AED), or with placebo. In principle, participants in the network could be randomised to any of the interventions being compared.

Types of outcome measures

We will investigate the following outcomes.

Primary outcomes

50% or greater reduction in seizure frequency

- 50% or greater reduction in seizure frequency in the treatment period compared to the pre-randomisation baseline period

Treatment withdrawal

- Premature withdrawal from the treatment during the course of the treatment period as a measure of 'global measure of tolerability'. In studies of relatively short duration, treatment is unlikely to be withdrawn due to lack of efficacy, and any treatment withdrawal is likely due to side effects.

Secondary outcomes

Seizure rate

- The monthly seizure rate during the treatment period

Percentage change in seizure rate

- The percentage change in monthly seizure rate during the treatment period compared to the pre-randomisation baseline period

Seizure freedom

- Complete cessation of seizures during the treatment period compared to the pre-randomisation baseline period

Adverse effects

- As different AEDs have different adverse effect profiles, we will only include descriptive summaries.

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Search methods for identification of studies

Electronic searches

We will update the searches carried out for the individual add-on AED reviews by searching the following databases:

1. Cochrane Register of Studies (CRS Web)
2. MEDLINE Ovid (1946-search date)

CRS Web includes randomised or quasi-randomised, controlled trials from PubMed, Embase, ClinicalTrials.gov, the World Health Organization International Clinical Trials Registry Platform (ICTRP), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Specialized Registers of Cochrane Review Groups, including Epilepsy. We will not impose any language restrictions.

The proposed search strategies for CRS Web and MEDLINE are set out in Appendix 1 and Appendix 2.

We will not impose any language restrictions.

Searching other resources

We will review the reference lists of retrieved studies to check for additional reports of relevant studies. We will also search the register of trials that individual pharmaceutical companies, which manufacture the drugs of direct interest, may hold.

Data collection and analysis

Selection of studies

Two of the review authors (MG and RH) will independently assess all identified trials for inclusion. Any disagreements will be resolved by mutual discussion. We will summarise the results of the screening process, including reasons for study exclusion, using a PRISMA flow diagram.

Data extraction and management

We will summarise information about trial design, setting, treatment, dose, participant inclusion criteria, risk of bias, and other relevant data in tables.

We will contact the trial author or sponsoring organisation of each eligible trial, and request anonymised individual participant data for all randomised participants and outcomes of interest for this review, along with metadata and relevant documentation (e.g. protocol and CDISC data dictionary) from the respective trial. If individual participant data (IPD) are not available, we will record the reason for this, and will extract the relevant summary data from published reports (journal articles, clinical study reports, conference abstracts) to allow as complete an analysis as possible. We already extracted data from several included RCTs for our previously published Cochrane Reviews; we will use these data wherever possible. For each trial, we will request at least the following data (recognising there may be differences in format necessary to anonymise the data):

- Age
- Gender
- Race
- AEDs before study start (number, timing, and type)

- Other interventions used for epilepsy (e.g. ketogenic diet) before study start
- Seizure types
- Dates of entry, randomisation, follow-up, withdrawal from treatment
- Reason for withdrawal from treatment
- Co-interventions
- Adverse events
- Dose seizure data (Number and timing of seizures during follow-up and baseline, if recorded)
- Duration of baseline period
- Duration of titration period
- Duration of maintenance treatment period

We will store the anonymised IPD on a secure password-protected server at the University of Liverpool; we will only grant access to the project statistical team. We will make no attempt to re-identify participants within datasets; copying or transferring data to local computers, or data storage devices, will be strictly prohibited. We will conduct a range of standard quality and consistency checks of the data; we will cross-check the re-analysed IPD against previously published results to discover inconsistencies or possible errors. We will raise any queries with the original trialists or sponsors wherever possible. We will clean and standardise the data to allow pooling and subsequent analyses of the data. We will also extract aggregate data available in trial publications for each trial, to allow subsequent sensitivity analyses to explore the impact of missing IPD.

Assessment of risk of bias in included studies

Two review authors (MG, RH) will independently assess the risk of bias using the Cochrane 'Risk of bias' tool as described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We will classify risk as low, high, or unclear, according to the 'Risk of bias' criteria. We will resolve disagreements by consensus.

Measures of treatment effect

We will use risk ratio (RR) to measure dichotomous data (50% or greater reduction in seizure frequency, treatment withdrawal, seizure freedom, adverse effects, and cognitive effects), difference in means for continuous data (quality of life), risk ratio for count data, along with their respective credible intervals (seizure rate, percentage change in seizure rate).

Unit of analysis issues

We will deal with any unit of analysis issues using the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2020).

Dealing with missing data

We recognise that IPD may not be available for every trial, and there is a potential for data availability bias. We will supplement IPD with relevant aggregate data from trials without IPD, wherever needed (Sutton 2008). We will undertake sensitivity analyses to explore the impact of missing IPD on results and conclusions of the NMA.

Assessment of heterogeneity

We will assess the homogeneity assumption by comparing the Deviance Information Criterion (DIC) of fixed-effect and random-

effects models, and observing the between-trial variance. We will prefer the model with the smaller DIC value to the one with larger DIC (Dias 2014). We will examine the forest plots, Chi^2 test for heterogeneity, and I^2 statistic to assess the evidence of heterogeneity within each pair-wise meta-analysis based on direct evidence. The Chi^2 test is included in the forest plots, and it examines whether different results of the studies are attributed to chance alone. Heterogeneity is evident with a low P value (P < 0.10) of this test. As heterogeneity may be inevitable, the I^2 statistic can be used as a percentage indicator of it. More specifically, high percentages of the I^2 statistic depict high heterogeneity: 0% to 40% heterogeneity might not be important, 30% to 60% = moderate, 50% to 90% = substantial, and 75% to 100% = substantial heterogeneity (Higgins 2020). The interpretation of I^2 will also depend on the evidence of heterogeneity from the rest of the sources (Chi^2 test, and comparison of DIC between fixed-effect and random-effects models) and on the direction and magnitude of treatment effects.

Assessment of reporting biases

Validity of an NMA depends on the assumption that there is no effect modification of the pair-wise intervention effects, or that the prevalence of effect modifiers is similar in the different studies. We will compare the plausibility of this key assumption (often referred to as transitivity, similarity, and consistency) by comparing the inclusion and exclusion criteria of trials to make a judgement about whether participants, trial protocols, doses, administration, etc. are similar in ways that might modify treatment effect. In particular, the 14 AEDs of interest have been licensed over a period of 41 years, and inevitable changes in clinical practice would have occurred over this period (e.g. number and type of people on AED will have increased over time, and people recruited into more recent trials may be more refractory than those recruited to earlier trials; more recent trials are more likely to be larger, international studies) that may impact upon the assumption of transitivity. We will use model fit and selection statistics to informally assess whether inconsistency is evident, along with a formal analysis using a 'node-splitting' approach (Dias 2010).

Data synthesis

Information flow in the network.

We will use network plots to present the available evidence for each outcome. In this graph, each node will represent a different drug, and the size of the nodes will be proportional to the number of participants randomised for that specific drug. We will use the edges between nodes to reflect direct comparisons among the available drugs. The width of the edges will depend on the number of trials comparing two drugs.

Network meta-analysis

We will use a Bayesian hierarchical meta-analysis model to synthesise the available IPD, supplemented with aggregate data, if necessary, to estimate the relative treatment effect (risk ratio for categorical data, difference in means for continuous data, risk ratio for count data), and credibility interval for each pair-wise comparison, based on direct evidence.

We will conduct a NMA for each outcome using WinBUGs 1.4.3; we will assess the 'goodness of fit' by calculating the posterior mean residual deviance, using DIC as a basis for model comparison.

We will appropriately account for correlation between treatment effects from multi-arm trials (e.g. a trial may have compared active AED dose level 1 versus active AED dose level 2 versus placebo). In random-effects NMA models, it is conventional to assume the between-trial variance is the same for each comparison. We will check this assumption by fitting pair-wise models, based on direct evidence, and assessing whether the variance is similar for each comparison. If the assumption appears unrealistic, we will explore other variance structures for the NMA model.

Treatment ranking

For each outcome, we will calculate and summarise the probability that a treatment is best, and the probability that a particular treatment would be most likely to be effective for a specific participant profile.

Data on potential effect modifiers

For each trial, we will request, or extract data on the following study, intervention, and population characteristics, which may act as effect modifiers:

- Level of blinding
- Study design (parallel versus cross-over)
- Definition of refractory
- Age at randomisation
- Dose (this may be recorded at the trial level, participant level, or both)
- Co-interventions at randomisation (number and type of AED in addition to the trial treatments)
- Previous AEDs (number and type of AED trialled prior to randomisation)
- Year of publication
- Time since diagnosis

We will explore the effect of characteristics that may modify treatment effects using hierarchical models, with treatment by covariate interaction effects, based on direct evidence initially, and then subsequently, in a NMA of the IPD, and aggregate data when IPD is unavailable. We will separate the effect of covariates within and between trials. We will also explore the underlying consistency assumption of these models.

Subgroup analysis and investigation of heterogeneity

We will conduct subgroup analysis according to participant covariates specified in Data extraction and management as potential effect modifiers.

Sensitivity analysis

We will undertake sensitivity analyses to explore the impact of missing IPD on results and conclusions of the NMA. We will conduct further sensitivity analyses to assess the robustness of results to different priors in the Bayesian analyses.

Summary of findings and assessment of the certainty of the evidence

We will use the GRADE approach, as outlined in the GRADE Handbook (Schünemann 2013) and CINeMA (Nikolakopoulou 2020), to rate the certainty of the available evidence and interpret findings.

We will create 'Summary of findings' tables for the primary outcome (50% or greater reduction in seizure frequency) and the secondary outcomes (seizure rate, percentage change in seizure rate, seizure freedom, treatment withdrawal, adverse events).

ACKNOWLEDGEMENTS

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APPENDICES

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

1. (Brivaracetam*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

2. #1 AND >09/10/2018:CRSCREATED AND CENTRAL:TARGET

3. (Aedon OR Anxirloc OR Castilium OR Chlorepin OR Clarmyl OR Clobam OR Clobamax OR Clobator OR Clobazam* OR Clofritis OR Clopax OR Clorepin OR Frisium OR Grifoclobam OR Karidium OR Lucium OR Mystan OR Noiafren OR Onfi OR Sederlona OR Sentil OR Urbadan OR Urbanil OR Urbanol OR Urbanyl):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

4. #3 AND >09/10/2018:CRSCREATED AND CENTRAL:TARGET

5. (Eslicarbazepin* OR Exalief OR Stedesa OR Zebinix):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

6. #5 AND >06/12/2016:CRSCREATED AND CENTRAL:TARGET

7. (Gabapentin* OR Aclonium OR Fanatrex OR Gabapetin OR Gabarone OR GBP OR Gralise OR Neogab OR Neurontin OR "Novo-Gabapentin" OR Nupentin):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

8. #7 AND >20/03/2018:CRSCREATED AND CENTRAL:TARGET

9. (Erlosamide OR Harkoseride OR Lacosamid* OR Vimpat):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

10. #9 AND >22/08/2019:CRSCREATED AND CENTRAL:TARGET

11. (Lamotrigin* OR Elmendos OR Epilepax OR "GW 273293" OR Lamictal OR Lamictin OR Lamitor OR Lamitrin OR Lamogine OR Lamotrine OR LTG):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

12. #11 AND >13/12/2018:CRSCREATED AND CENTRAL:TARGET

13. (Levetiracetam* OR Keppra OR LEV OR Levitiracetam):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

14. #13 AND >26/11/2018:CRSCREATED AND CENTRAL:TARGET

15. (Oxcarbazepin* OR Actinium OR Barzepin OR Carbox OR Deprectal OR "GP 47680" OR Lonazet OR OCBZ OR Oxalepsy OR OXC OR Oxcarbamazepine OR Oxetol OR Oxpin OR Oxrate OR Oxtellar OR Oxypine OR Pharozepine OR Prolepsi OR Timox OR Trexapin OR Trileptal OR Trileptin):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

16. #15 AND >24/09/2018:CRSCREATED AND CENTRAL:TARGET

17. (E2007 OR Fycompa OR Perampanel*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

18. #17 AND >19/09/2019:CRSCREATED AND CENTRAL:TARGET

19. MESH DESCRIPTOR Pregabalin EXPLODE ALL AND CENTRAL:TARGET

20. (Lyrica OR Pregabalin*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

21. #19 OR #20 AND CENTRAL:TARGET

22. #21 AND >05/07/2018:CRSCREATED AND CENTRAL:TARGET

23. (Topiramat* OR Qudexy OR Tipiramate OR Topamax OR "Topiramic acid" OR TPM):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

24. #23 AND >02/07/2018:CRSCREATED AND CENTRAL:TARGET

25. MESH DESCRIPTOR Vigabatrin EXPLODE ALL AND CENTRAL:TARGET

26. (GVG OR Sabril OR Vigabatrin*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

27. #25 OR #26 AND CENTRAL:TARGET

28. #27 AND >04/02/2014:CRSCREATED AND CENTRAL:TARGET

29. (Zonisamid* OR Exceglan OR Excegram OR Excegran OR ZNS OR Zonegran):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

30. #29 AND >04/09/2017:CRSCREATED AND CENTRAL:TARGET

31. #2 OR #4 OR #6 OR #8 OR #10 OR #12 OR #14 OR #16 OR #18 OR #22 OR #24 OR #28 OR #30 AND CENTRAL:TARGET

32. MESH DESCRIPTOR Epilepsies, Partial EXPLODE ALL AND CENTRAL:TARGET

33. ((partial or focal) and (seizure* or epilep*)):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

34. #32 OR #33 AND CENTRAL:TARGET

35. #31 AND #34

36. (monotherap* NOT (adjunct* OR "add-on" OR "add on" OR adjuvant* OR combination* OR polytherap*)):TI AND CENTRAL:TARGET

37. #35 NOT #36

Appendix 2. MEDLINE Ovid (1946 -)

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

1. Brivaracetam*.tw.

2. limit 1 to ed=20181008-20191125

3. 1 not (1$ or 2$).ed.

4. 3 and (2018$ or 2019$).dt.

5. 2 or 4

6. exp Clobazam/

7. (Aedon or Anxirloc or Castilium or Chlorepin or Clarmyl or Clobam or Clobamax or Clobator or Clobazam* or Clofritis or Clopax or Clorepin or Frisium or Grifoclobam or Karidium or Lucium or Mystan or Noiafren or Onfi or Sederlona or Sentil or Urbadan or Urbanil or Urbanol or Urbanyl).tw.

8. 6 or 7

9. limit 8 to ed=20181008-20191125

10. 8 not (1$ or 2$).ed.

11. 10 and (2018$ or 2019$).dt.

12. 9 or 11

13. (Eslicarbazepin* or Exalief or Stedesa or Zebinix).tw.

14. limit 13 to ed=20161205-20191125

15. 13 not (1$ or 2$).ed.

16. 15 and (2016$ or 2017$ or 2018$ or 2019$).dt.

17. 14 or 16

18. exp Gabapentin/

19. (Gabapentin* or Aclonium or Fanatrex or Gabapetin or Gabarone or GBP or Gralise or Neogab or Neurontin or "Novo-Gabapentin" or Nupentin).tw.

20. 18 or 19

21. limit 20 to ed=20180319-20191125

22. 20 not (1$ or 2$).ed.

23. 22 and (2018$ or 2019$).dt.

24. 21 or 23

25. exp Lacosamide/

26. (Erlosamide or Harkoseride or Lacosamid* or Vimpat).tw.

27. 25 or 26

28. limit 27 to ed=20190820-20191125

29. 27 not (1$ or 2$).ed.

30. 29 and 2019$.dt.

31. 28 or 30

32. exp Lamotrigine/

33. (Lamotrigin* or Elmendos or Epilepax or "GW 273293" or Lamictal or Lamictin or Lamitor or Lamitrin or Lamogine or Lamotrine or LTG).tw.

34. 32 or 33

35. limit 34 to ed=20181206-20191125

36. 34 not (1$ or 2$).ed.

37. 36 and (2018$ or 2019$).dt.

38. 35 or 37

39. exp Levetiracetam/

40. (Levetiracetam* or Keppra or LEV or Levitiracetam).tw.

41. 39 or 40

42. limit 41 to ed=20181121-20191125

43. 41 not (1$ or 2$).ed.

44. 43 and (2018$ or 2019$).dt.

45. 42 or 44

46. exp Oxcarbazepine/

47. (Oxcarbazepin* or Actinium or Barzepin or Carbox or Deprectal or "GP 47680" or Lonazet or OCBZ or Oxalepsy or OXC or Oxcarbamazepine or Oxetol or Oxpin or Oxrate or Oxtellar or Oxypine or Pharozepine or Prolepsi or Timox or Trexapin or Trileptal or Trileptin).tw.

48. 46 or 47

49. limit 48 to ed=20180921-20191125

50. 48 not (1$ or 2$).ed.

51. 50 and (2018$ or 2019$).dt.

52. 49 or 51

53. (E2007 or Fycompa or Perampanel*).tw.

54. limit 53 to ed=20190917-20191125

55. 53 not (1$ or 2$).ed.

56. 55 and 2019$.dt.

57. 54 or 56

58. exp Pregabalin/

59. (Lyrica or Pregabalin*).tw.

60. 58 or 59

61. limit 60 to ed=20180704-20191125

62. 60 not (1$ or 2$).ed.

63. 62 and (2018$ or 2019$).dt.

64. 61 or 63

65. exp Topiramate/

66. (Topiramat* or Qudexy or Tipiramate or Topamax or "Topiramic acid" or TPM).tw.

67. 65 or 66

68. limit 67 to ed=20180701-20191125

69. 67 not (1$ or 2$).ed.

70. 69 and (2018$ or 2019$).dt.

71. 68 or 70

72. exp Vigabatrin/

73. (GVG or Sabril or Vigabatrin*).tw.

74. 72 or 73

75. limit 74 to ed=20140203-20191125

76. 74 not (1$ or 2$).ed.

77. 76 and (2014$ or 2015$ or 2016$ or 2017$ or 2018$ or 2019$).dt.

78. 75 or 77

79. exp Zonisamide/

80. (Zonisamid* or Exceglan or Excegram or Excegran or ZNS or Zonegran).tw.

81. 79 or 80

82. limit 81 to ed=20170903-20191125

83. 81 not (1$ or 2$).ed.

84. 83 and (2017$ or 2018$ or 2019$).dt.

85. 82 or 84

86. 5 or 12 or 17 or 24 or 31 or 38 or 45 or 52 or 57 or 64 or 71 or 78 or 85

87. exp Epilepsies, Partial/

88. ((partial or focal) and (seizure$ or epilep$)).tw.

89. 87 or 88

90. 86 and 89

91. (monotherap$ not (adjunct$ or "add-on" or "add on" or adjuvant$ or combination$ or polytherap$)).ti.

92. 90 not 91

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

94. clinical trials as topic.sh.

95. trial.ti.

96. 93 or 94 or 95

97. exp animals/ not humans.sh.

98. 96 not 97

99. 92 and 98

100. remove duplicates from 99

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CTS and MG wrote the protocol. SJN, RH, AGM, and SD provided comments on drafts of the protocol.

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MG: none known
RH declares a financial - non-personal, non-specific interest, having delivered educational workshops on health economics, medicines management and HTA for cancer specialists supported by unrestricted sponsorship by the pharmaceutical industry and an industry association (March 2019). No fees received personally. Not specific to the topic of the review.
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