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[Intervention Protocol]

Valproate add-on therapy for drug-resistant focal epilepsy

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ABSTRACT

Objectives

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

To assess the efficacy and tolerability of valproate when used as add-on therapy for people with drug-resistant focal epilepsy.

BACKGROUND

Description of the condition

Epilepsy is the most common neurological disease, which translates to around 50 million people worldwide (WHO 2019). It is a neurological condition characterised by abnormal electrical discharges that can initially affect either part of the brain (focal seizures) or the entire brain (generalised seizures) (Scheffer 2017).

Antiepileptic drugs (AEDs) are commonly used to treat epilepsy. Around 70% of the people with epilepsy receiving a single AED will be free from seizures for a prolonged period (Cockerell 1997). However, 30% of the people treated with a single AED (monotherapy) will experience drug-resistant epilepsy (Sander 1993). People with drug-resistant epilepsy are more likely to have a lower quality of life (QoL) and experience loss of function (WHO 2019). In addition, the financial costs to society can be considerable (Chen 2013; Hamer 2006). Add-on therapy is commonly used for drug-resistant epilepsy. Valproate is an antiepileptic drug that can be used as an add-on treatment for people with drug-resistant epilepsy.

Description of the intervention

Valproate and its other forms (sodium valproate, semi sodium valproate, and valproic acid) is primarily used to treat epilepsy and is a different name for 2-n-propylpentanoic acid (also called n-dipropylacetic acid). It is commonly used as monotherapy or add-on therapy for focal impaired-awareness seizures, generalised, and focal aware seizures.

Valproate is rapidly absorbed by the gastrointestinal tract and the bioavailability is 80% after oral administration. It is extensively absorbed by the liver, predominantly by β-oxidation, and 3% to 7% is excreted unchanged by the urine. Valproate's anticonvulsant therapeutic range is at 50 mL to 100 mL.

Valproate can also be used to treat bipolar disorder and migraines, although the mechanism underlying valproate's actions in these conditions is unknown.

How the intervention might work

Valproate's anticonvulsant activity is similar to that of phenytoin. Both drugs prolong the recovery of voltage-gated sodium channels from inactivation. The mechanism of action for valproate is unclear. Its efficacy has been mostly focused on the effects on γ-amminobutyric acid (GABA) (Turner 1980). More specifically, it has been shown that sodium valproate can raise cerebral GABA levels in animals and, as a result, it is assumed that this effect is related to the protection from seizures.

Why it is important to do this review

To our knowledge, this is the first systematic review that focuses on the efficacy and tolerability of valproate as an add-on therapy for epilepsy. This review will summarise all the available evidence from randomised controlled trials (RCTs). Findings from this review will contribute to an overview of reviews and an Individual Participant Data Network Meta-Analysis of antiepileptics used as add-on treatment for people with drug-resistant focal epilepsy.

OBJECTIVES

To assess the efficacy and tolerability of valproate when used as add-on therapy for people with drug-resistant focal epilepsy.

METHODS

Criteria for considering studies for this review

Types of studies

Trials will be required to meet the following criteria.

1. Randomised controlled trials (RCTs) or quasi-RCTs using an adequate method of concealment of randomisation (e.g. allocation of sequentially-numbered, sealed packages of medication, sealed, opaque envelopes, telephone randomisation).
2. Double-blind, single-blind, or unblinded.
3. Parallel or cross-over design.
4. Treatment period of at least eight weeks.

Types of participants

People of any age, gender, and ethnicity with drug-resistant focal epilepsy (focal aware and focal impaired awareness seizure with or without secondary generalised seizures), will be included in the review.

Types of interventions

1. The active treatment group will receive valproate in addition to an existing antiepileptic drug (AED) regimen at the time of randomisation.
2. The control group will receive matched placebo or another AED in addition to an existing AED regimen at the time of randomisation.

Types of outcome measures

Primary outcomes

1. Proportion of participants experiencing 50% or greater reduction in seizure frequency in comparison to pre-randomisation or baseline period.

Secondary outcomes

1. Seizure freedom, defined as the proportion of participants with a complete cessation of seizures compared to pre-randomisation or baseline period.
2. Treatment withdrawal, defined as proportion of participants withdrawing from the treatment during the trial for any reason.
3. Treatment withdrawal, defined as the proportion of participants withdrawing from the treatment during trial due to adverse events.
4. Proportion of participants experiencing any of the following adverse effects: ataxia, dizziness, fatigue, nausea, skin rash, sedation, weight gain, sleep disturbance, and any adverse events of special interest (AESI) such as carnitine depletion etc.
5. Quality of life (using validated scales).

Search methods for identification of studies

Electronic searches

We will search the following databases.

1. Cochrane Register of Studies (CRS Web), using the search strategy shown in Appendix 1. 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.
2. MEDLINE (Ovid) 1946 onwards using the search strategy shown in Appendix 2.

No language restrictions will be made.

Searching other resources

We will search the reference lists of all the included trials for any relevant studies. We will also contact the manufacturers of valproate for any information about unpublished or ongoing trials.

Data collection and analysis

Selection of studies

We will merge the search results using reference management software. At least two review authors (MG, RB, and RH) will independently screen all the titles, abstracts, and text of the trials identified by the searches to assess their eligibility. Trials that do not meet the inclusion criteria will be excluded. We will resolve disagreements by discussion. If a disagreement persists, a fourth review author (AGM) will arbitrate.

Data extraction and management

Two review authors will independently extract the following information from all the included studies. Disagreements will be resolved through discussion.

Methods

1. Study design
2. Method of randomisation
3. Allocation concealment
4. Blinding
5. Study duration

Participants

1. Age
2. Gender
3. Ethnicity
4. Type of seizure
5. Seizure frequency
6. Epilepsy duration
7. Inclusion criteria
8. Exclusion criteria
9. Total number of participants recruited
10. Total number of participants randomised
11. Number of concomitant antiepileptic drugs

Interventions

1. Dosage
2. Administration method
3. Treatment duration

Outcomes

1. 50% or greater seizure reduction
2. Seizure freedom
3. Treatment withdrawal due to any reason
4. Treatment withdrawal due to adverse events
5. Adverse events
6. Quality of life

Follow-up data

1. Duration of follow-up period
2. Total number of participants followed up
3. Number of losses to follow-up
4. Reasons for treatment withdrawal
5. Reasons for losses to follow-up

Assessment of risk of bias in included studies

The methodological quality of the included studies will be assessed using the Cochrane 'Risk of bias' tool as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). There are seven parameters examined that the Cochrane 'Risk of bias' tool examines: (1) random sequence allocation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessors, (5) incomplete outcome data, (6) selective outcome reporting, and (7) other biases. Bias for each of the parameters above will be assessed ('low', 'high', or 'unclear') according to *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Measures of treatment effect

Risk ratios with 95% confidence intervals will be used for dichotomous outcomes (50% or greater reduction in seizure frequency, seizure freedom, treatment withdrawal due to any reason, treatment withdrawal due to adverse events and adverse effects). There is no consensus as to which instruments should be used to assess quality of life (Cochrane 1998). As a result, we will provide a narrative summary of the effects of valproate on quality of life and we will not synthesise the results in a meta-analysis.

Unit of analysis issues

Cross-over studies introduce unit of analysis issues. Should we identify any cross-over studies for inclusion, if the study is well-conducted and methodologically sound, then the data from the paired analysis will be used. For any problematic cross-over studies (i.e. carryover effect – when the treatment given in the first period is carried over to the second period), we will only use data from the first treatment period.

Dealing with missing data

We will contact the authors and manufacturers of the original trials to identify any missing trials, or data. In the case that we do not receive the missing outcome data, we will use intention-to-treat analysis. This means that participants with inadequate seizure data

or those who did not complete the follow-up will be considered as non-responders.

Assessment of heterogeneity

We will assess clinical heterogeneity by comparing the distribution of important patient factors (age, gender, seizure type, seizure frequency, duration of epilepsy, number of concomitant antiepileptic drugs taken at time of randomisation), interventions (dosage, administration method and duration, co-treatments), and study design (randomisation, allocation concealment, blinding methods) between studies.

We will evaluate statistical heterogeneity among trials by using Chi^2 test with significance set at 0.10, along with I^2 statistic. If the P value of the Chi^2 test is greater than 0.10 (P > 0.10), then we will assume that there is no statistically significant heterogeneity (Deeks 2019). If the P value of the Chi^2 test if less or equal to 0.10, then we will interpret statistical heterogeneity according to the percentage ranges of the I^2 statistic:

1. 0% to 40%: might not be important;*
2. 30% to 60%: may represent moderate heterogeneity;*
3. 50% to 90%: may represent significant heterogeneity;*
4. 75% to 100%: represents considerable heterogeneity.*

*The importance of the observed value of the I^2 statistic depends on (1) the magnitude and direction of effect, and (2) the strength of evidence for heterogeneity (e.g. P value from the Chi^2 test or confidence interval for the I^2 statistic.

Assessment of reporting biases

If more than ten studies are included in the review, we will assess funnel plot asymmetry. Possible reasons for asymmetry are: 1. publication bias, 2. outcome reporting bias, 3. language bias, 4. citation bias, 5. poor methodological design, and 6. heterogeneity. All these reasons will be assessed for each trial.

Data synthesis

We will use Review Manager Web to analyse all the available data (RevMan Web 2020). Depending on the observed heterogeneity, fixed-effect or random-effects models will be employed. More specifically, the fixed-effect model will be used, if the available data are clinically appropriate and there is no evidence of statistically significant heterogeneity (P > 0.10 for Chi^2 test and $I^2 \leq 50\%$). If substantial heterogeneity is observed (P ≤ 0.10 for Chi^2 test and I^2 >50%), then we will explore the factors that contribute towards this heterogeneity and the random-effects model will be used to perform the meta-analysis.

Subgroup analysis and investigation of heterogeneity

If possible, we will perform subgroup analysis according to:

1. age of the participants (children younger than 18 years old versus adults);
2. dose of valproate;
3. subtype of epilepsy.

Sensitivity analysis

We plan to examine the robustness of the meta-analysis by conducting the following sensitivity analysis.

1. Repeating the analysis excluding unpublished studies.
2. Repeating the analysis excluding the studies published only as abstracts.

As clinical trials of valproate may be quite old, we may find some quasi-RCTs. We will conduct sensitivity analysis excluding those studies.

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) to rate the certainty of the available evidence and interpret findings. GRADE has four levels of evidence – very low, low, moderate, and high. Factors that can reduce the certainty of evidence are risk of bias, inconsistency of results, indirectness of evidence, imprecision, and publication bias.

We will also use GRADE profiler (GRADEpro) GDT software (GRADEpro GDT) to create 'Summary of findings' tables for the primary outcome (50% or greater reduction in seizure frequency), and secondary outcomes (seizure freedom, treatment withdrawal, and adverse effects).

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APPENDICES

Appendix 1. CRS Web search strategy

1. MESH DESCRIPTOR Valproic Acid EXPLODE ALL AND CENTRAL:TARGET

2. (Avugane OR Baceca OR Convulex OR Delepsine OR Depacon OR Depakene OR Depakine OR Depakote OR Deproic OR DPA OR Encorate OR Epiject OR Epilex OR Epilim OR Episenta OR Epival OR Ergenyl OR Mylproin OR Orfiril OR Orlept OR Selenica OR Stavzor OR Valcote OR Valparin OR Valpro* OR VPA):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

3. #1 OR #2

4. MESH DESCRIPTOR Epilepsy EXPLODE ALL AND CENTRAL:TARGET

5. MESH DESCRIPTOR Seizures EXPLODE ALL AND CENTRAL:TARGET

6. (epilep* OR seizure* OR convuls*):AB,KW,KY,MC,MH,TI AND CENTRAL:TARGET

7. #4 OR #5 OR #6 AND CENTRAL:TARGET

8. eclampsia:TI AND CENTRAL:TARGET

9. #7 NOT #8 AND CENTRAL:TARGET

10. #3 AND #9

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

12. #10 NOT #11

Appendix 2. MEDLINE search strategy

This strategy includes the Cochrane Highly Sensitive Search Strategy for identifying randomized trials (Lefebvre 2019).

1. exp Valproic Acid/

2. (Avugane or Baceca or Convulex or Delepsine or Depacon or Depakene or Depakine or Depakote or Deproic or DPA or Encorate or Epiject or Epilex or Epilim or Episenta or Epival or Ergenyl or Mylproin or Orfiril or Orlept or Selenica or Stavzor or Valcote or Valparin or Valpro $ or VPA).tw.

3. 1 or 2

4. exp Epilepsy/

5. exp Seizures/

6. (epilep$ or seizure$ or convuls$).tw.

7. 4 or 5 or 6

8. exp *Pre-Eclampsia/ or exp *Eclampsia/

9. 7 not 8

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

11. clinical trials as topic.sh.

12. trial.ti.

13. 10 or 11 or 12

14. exp animals/ not humans.sh.

15. 13 not 14

16. 3 and 9 and 15

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

18. 16 not 17

19. remove duplicates from 18

CONTRIBUTIONS OF AUTHORS

MG and RB wrote the protocol. RH, SN, CTS and AGM critically revised the text and provided methodological and clinical advice on the protocol.

DECLARATIONS OF INTEREST

MG: none known.
RB: none known.
RH: Ruaraidh Hill declares a financial, non-personal, non-specific interest. RH has delivered educational workshops on health economics, medicines management and HTA for cancer specialists - unrestricted sponsorship by the pharmaceutical industry and an industry association (March 2019). Not specific to the topic of this review.
SN: none known.
AGM: a consortium of pharmaceutical companies (GSK, EISAI, UCB Pharma) funded the National Audit of Seizure Management in Hospitals (NASH) through grants paid to the University of Liverpool. Professor Tony Marson is part funded by the National Institute for Health Research Applied Research Collaboration North West Coast (NIHR ARC NWC).
CTS: none known.

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- National Institute for Health Research (NIHR), UK

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