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General Information

Key Personnel (in addition to PI):
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Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.

Project Funding Source: The Liverpool Reviews and Implementation Group, a University-based non-commercial academic centre, as part of its capacity development funding from the UK National Institute for Health Research.

How did you learn about the YODA Project?: Colleague

Conflict of Interest

https://yoda.yale.edu/system/files/myrsini_gianatsi_coi_form.pdf
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_catrin_tudur_smith.docx
https://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestors_2019_7_0.docx

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

1. YP - A double-blind, randomized trial of topiramate as adjunctive therapy for partial-onset seizures in children
2. NCT00236847 - Y2 - Double-Blind, Parallel Comparison of Topiramate 300 mg Twice Daily to Placebo in Patients With Refractory Partial Epilepsy
3. NCT00236730 - YD - Double-Blind Parallel Comparison of Three Doses of Topiramate and Placebo in Refractory Partial Epilepsy
4. NCT00236873 - Y1 (CC2604-C-101) - Double-Blind Parallel Comparison of Topiramate 200 mg Twice Daily to Placebo in Patients With Refractory Partial Epilepsy
5. NCT00236860 - Y3 (CC2604-C-103) - Double-Blind Parallel Comparison of Topiramate 400 mg Twice Daily to Placebo in Patients With Refractory Partial Epilepsy

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Add-on treatment for refractory focal-onset epilepsy: Individual Participant Data Network Meta-Analysis

Narrative Summary:

Epilepsy is the most common neurological disorder which is treated with anti-epileptic drugs (AEDs). However, about 30% of the patients will fail to respond to treatment, having to face significant psychological and quality of life outcomes and will require therapy with a combination of different AEDs.

In this review we will examine the efficacy & safety of 14 common AEDs. We will search for all relevant clinical trials that have compared the effectiveness of any of the included drugs as add-on treatment for refractory focal-onset epilepsy. In our analysis, we will use data from trials that have directly compared pairs of drugs under investigation or compared against placebo.
Scientific Abstract:

Background
Epilepsy is the most common neurological disorder which is treated with AEDs. The majority of people with epilepsy are successfully treated with AED monotherapy. However, about 30% of the patients will fail to respond to treatment, having to face significant psychological and quality of life outcomes, due to continued and unpredictable seizures, side effects of drugs, and reduced educational and employment prospects. As a result, these patients will require treatment with a combination of different anti-epileptic drugs.

Objective
Compare the efficacy & tolerability of AEDs taken as add-on treatment for refractory focal-onset epilepsy and to generate a clinically useful ranking of available AEDs.

Study Design
Randomised clinical trials (placebo- or active-controlled) that compare the effectiveness of the included add-on AEDs.

Participants
Adults and children with drug-resistant focal epilepsy.

Main Outcome measure
Efficacy: 50% or greater reduction in seizure frequency, & seizure freedom
Safety: Treatment withdrawal & adverse effects

Statistical Analysis
Systematic review and IPD Network Meta-Analysis (two-stage IPD NMA approach) will be conducted to assess the effectiveness and safety of add-on AEDs.

Brief Project Background and Statement of Project Significance:

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. 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). However, these 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).

Specific Aims of the Project:
The aim of this proposed research is to compare the efficacy and tolerability of anti-epileptic drugs (AEDs) taken as add-on treatment for refractory focal-onset epilepsy and to generate a clinically useful ranking of available AEDs.

What is the purpose of the analysis being proposed? Please select all that apply.
New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations
New research question to examine treatment safety
Summary-level data meta-analysis
Summary-level data meta-analysis pooling data from YODA Project with other additional data sources
Participant-level data meta-analysis
Participant-level data meta-analysis pooling data from YODA Project with other additional data sources
Other

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

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.

Main Outcome Measure and how it will be categorized/defined for your study:

Primary outcomes:
• 50% or greater reduction in seizure frequency in the treatment period compared to the pre-randomisation baseline period
• 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:
• The monthly seizure rate during the treatment period
• The percentage change in monthly seizure rate during the treatment period compared to the pre-randomisation baseline period
• Complete cessation of seizures during the treatment period compared to the pre-randomisation baseline period
• As different AEDs have different adverse effect profiles, we will only include descriptive summaries.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

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.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

N/A

Statistical Analysis Plan:

Data synthesis
Individual Participant Data 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 or RStudio; 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 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. 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

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).

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-squared test for heterogeneity, and I-squared statistic to assess the evidence of heterogeneity within each pair-wise meta-analysis based on direct evidence.

Software Used:
I am not analyzing participant-level data / plan to use another secure data sharing platform

Project Timeline:
Suggested project timeline
Project start date: September 2021
Analysis completion date: September 2022
Date manuscript drafted: September 2022
Date reported back to the YODA Project: September 2022

Dissemination Plan:
The findings of this study will be published as a Cochrane review, as well as a part of a PhD thesis at the University of Liverpool.

Bibliography:


Supplementary Material:

https://yoda.yale.edu/sites/default/files/artie_ipd_protocol_0.pdf
https://yoda.yale.edu/sites/default/files/clinical_trials_ncts_ids_sponsors.docx
https://yoda.yale.edu/sites/default/files/myrsini_gianatsi_coi_form.pdf
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