Appendix 2: Systematic review protocol

Benefits and harms of pregabalin in the management of neuropathic pain: a rapid systematic review and meta-analysis of randomized clinical trials

Igho J Onakpoya
University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, Oxford, United Kingdom

Elizabeth T Thomas
Faculty of Health Sciences and Medicine, Bond University, Australia

Joseph Lee
University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, Oxford, United Kingdom

Ben Goldacre
University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, Oxford, United Kingdom

Carl J Heneghan
University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, Oxford, United Kingdom

Corresponding author: Igho Onakpoya, University of Oxford, Centre for Evidence-Based Medicine, Nuffield Department of Primary Care Health Sciences, Radcliffe Primary Care Building, Radcliffe Observatory Quarter, Oxford United Kingdom OX2 6GG. Email: igho.onakpoya@phc.ox.ac.uk.

BACKGROUND

Pregabalin is a gabapentinoid licensed for treatment of neurologic disorders. It is one of the earlier drugs approved by the FDA (2004) for the treatment of painful diabetic neuropathy (PDN) and post-herpetic neuralgia (PHN) [1]. Pregabalin is thought to exert its analgesic action through antagonistic activity at the voltage gated Ca2+ channels where it binds to the alpha-2-delta subunit [1,2].

Prescriptions of pregabalin (and gabapentin) have markedly increased over the last few years. In the US, prescriptions for pregabalin rose from 39 million in 2012 to 64 million in 2016 *versus* (spend increased from approximately $2 billion to $4.4 billion over the same period [3]. In the UK, pregabalin use increased 350% over a five year period between 2008 and 2013 [4]. In England alone, there were over 6.2 million prescriptions of pregabalin across GP practices in 2017 costing about $440 million [5].

There is, however, some evidence of increased mortality attributed pregabalin in the UK [6], and this has led some authors to caution clinicians about the risk of harms when prescribing [7]. The risks are thought to be particularly acute for patients who use heroin and those who misuse gabapentinoids. Indeed, the UK government is soon to classify the drug as a class C controlled substance because of its abuse potential and increased reports of deaths attributed to its use [8]. Practicing clinicians have also recently called for the evidence for the effectiveness of pregabalin to be re-examined in the light of its potential to cause harms [3,4].

OBJECTIVES

To rapidly evaluate the evidence for benefits and harms of pregabalin in the treatment of neuropathic pain in adults, using evidence from published randomized clinical trials (RCTs).

METHODS

Search strategy

We will conduct electronic searches in the following databases:

- Medline;
- Embase; and
- The Cochrane Central Register of Clinical Trials

Each database will be searched from inception till January 2018. No language restrictions will be imposed. We will also hand search the bibliography of eligible studies. Two review authors will independently assess the eligibility of studies for inclusion. Any disagreements will be resolved through discussion.

Types of studies

We will include phase III double-blinded placebo-controlled RCTs assessing the effects of pregabalin on neuropathic pain aged 18 years and above. We will include studies on neuropathic pain based on the definition of the International Association for the Study of Pain (IASP) definition [9]. These include trials on diabetic neuropathy, HIV-related neuropathy, lumbar radiculopathy, post-herpetic neuralgia, and chronic postsurgical pain. We will include RCTs irrespective of study size and duration. If we include RCTs with a cross-over design, we will use data from only the first phase of the study. We will exclude phase IV trials because they are typically unblinded. We will also exclude studies that combine pregabalin with other types of intervention; however, co-interventions will be allowed. Trials that randomized participants based on response to pregabalin therapy in the run-in phase will also be excluded.

Outcomes

Primary outcomes

- Pain (as measured using validated scales)

- Adverse events

Secondary outcomes

- Sleep disturbance;
- Quality of life (QOL);
- Patient global impression of change (PGIC);
- Clinician global impression (CGI);
- Overall discontinuations; and
- Discontinuations because of adverse events.

Risk of bias assessment

We will assess the risk of bias for each included study using Cochrane criteria [10] which examines the following domains:

- Method of randomisation;
- Concealment of allocation;
- Blinding of participants and personnel;
- Blinding of outcome assessment;
- Incomplete outcome data;
- Selective reporting;
- Other bias (e.g. industry funding, conflicts of interest, etc).

Two review authors will independently assess the risk of bias. Any disagreements will be resolved through discussion.

Data extraction:

We will use a customized excel spreadsheet to extract relevant data from included studies. Data to be extracted will include:

- Study ID (first author, publication year, journal, country)

- Participants (numbers, medical condition, demographics, etc.)
- Intervention (type of intervention and duration)
- Results (primary and secondary outcome measures, effect size, adverse events)
- Sources of funding

Five review authors will independently extracted the data. Any disagreements will be resolved through discussion.

Data analyses:

We will compute standardized mean differences (SMDs) and 95% confidence intervals (CIs) for continuous outcomes and risk ratios with 95% CI for binary outcomes. We will use the random effects model (Mantel-Haenszel) of the standard meta-analysis software (RevMan 5.3) [11] for meta-analysis. For continuous outcomes, pre- to post-intervention changes will be used to compute the data. When two or more pregabalin arms are present, the arms will be combined to create single pair-wise comparisons [12]. If we are unable to statistically combine the data, the results will be presented in a narrative format. If $\geq$ 10 studies are available for statistical pooling, we will use a funnel plot to test for publication bias. Two review authors will independently enter the data onto RevMan, and will also independently cross-check each other's entry.

Subgroup analysis and investigation of heterogeneity

We will assess heterogeneity using the I-squared statistic: values of 25%, 50% and 75% will represent mild, moderate and substantial heterogeneity respectively. We will conduct subgroup analyses based on the predominant pathway for neuropathic pain - central or peripheral neuropathic pain. We will conduct sensitivity based on study quality (studies that adequately report randomization and blinding procedures) and intervention duration (shorter or longer duration of therapy). We will visually inspect funnel plots to determine publication bias.

Rating the quality of the evidence

We will use the GRADEpro software (version 3.6) [13] to rate the overall quality of the body of evidence for each outcome based on the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) [14] criteria which examines the following domains:

- Study design;
- Risk of bias;
- Inconsistency;
- Indirectness; and
- Imprecision.

The overall quality of the body of the evidence will rated from high to very low as follows:

- High - Further research is very unlikely to change our confidence in the estimate of effect
- Moderate - Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate
- Low - Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate
- Very low - We are very uncertain about the estimate

We will use Summary of findings (SOF) tables to present these results.

Patient public involvement

Because this is a rapid review, we will not enlist the services of patient representatives.

Sources of funding

None

Conflicts of interest

None

REFERENCES

1 Verma V, Singh N, Singh Jaggi A. Pregabalin in neuropathic pain: evidences and possible mechanisms. Curr Neuropharmacol. 2014 Jan;12(1):44-56.

2 Taylor CP, Angelotti T, Fauman E. Pharmacology and mechanism of action of pregabalin: the calcium channel alpha2-delta (alpha2-delta) subunit as a target for antiepileptic drug discovery. Epilepsy Res. 2007 Feb;73(2):137-50

3 Goodman CW, Brett AS. Gabapentin and Pregabalin for Pain - Is Increased Prescribing a Cause for Concern? N Engl J Med. 2017 Aug 3;377(5):411-414.

4 Spence D. Bad medicine: gabapentin and pregabalin. BMJ. 2013 Nov 8;347:f6747. doi: 10.1136/bmj.f6747.

5 OpenPrescribing.net. High-level prescribing trends for Pregabalin (BNF code 0408010AE) across all GP practices in NHS England, since August 2010. Available at: https://openprescribing.net/chemical/0408010AE/ [Last accessed 8th March, 2018]

6 Lyndon A, Audrey S, Wells C, Burnell ES, Ingle S, Hill R, Hickman M, Henderson G. Risk to heroin users of polydrug use of pregabalin or gabapentin. Addiction. 2017 Sep;112(9):1580-1589

7 Morrison EE, Sandilands EA, Webb DJ. Gabapentin and pregabalin: do the benefits outweigh the harms? J R Coll Physicians Edinb 2017; 47: 310–3

8 Iacobucci G. UK government to reclassify pregabalin and gabapentin after rise in deaths. BMJ. 2017 Sep 25;358:j4441. doi: 10.1136/bmj.j4441.

9 International Association for the Study of Pain. What is neuropathic pain? https://s3.amazonaws.com/rdcms-iasp/files/production/public/AM/Images/GYAP/What%20is%20Neuropathic%20Pain.pdf [Accessed 19th January, 2018]

10 Higgins JP, Altman DG, Gøtzsche PC, . The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Br Med J 2011; 343: d5928–d5928

11 Review Manager (RevMan) (Computer program). Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2011

12 Cochrane Handbook of Systematic Reviews. How to include multiple groups from one study. Chapter 16 (Section 5.4). http://handbook.cochrane.org/chapter_16/16_5_4_how_to_include_multiple_groups_from_one_study.htm [Accessed 20 June 2016]

13 GRADEpro. Computer program on www.gradepro.org. Version 3.6. McMaster University, 2014.

14 GRADE Working Group. Grading quality of evidence and strength of recommendations. BMJ 2004; 328(7454): 1490.