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[Intervention Protocol]

Psychological therapies for the prevention of migraine in adults

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess beneficial and adverse effects of psychological treatment versus active alternative treatment or no treatment in adults with migraine, using methods that allow comparison with reviews of psychological interventions for other painful conditions.

BACKGROUND

Description of the condition

Migraine is a commonly experienced condition and prevalence is estimated to be between 14% and 16% (Stovner 2007). The Global Burden of Disease study indicated that migraine was the third most prevalent of all medical conditions (Vos 2012), and ranked the burden associated with migraine as the highest of any neurological disorder (Leonardi 2013). The cost of migraine is estimated to be EUR 1222 per person per year, which amounts to an estimated EUR 50 to 111 billion annually across Europe (Linde 2012). Similar estimates from the USA suggest that chronic migraine is associated with costs of USD 1036 per person per year and in Canada of CAN 471 per person per year (Stokes 2011).
The International Headache Society (IHS) defines four types of primary headache: migraine, tension-type headache, trigeminal autonomic cephalgias and other primary headache disorders (IHS 2013). This Cochrane Review will focus on migraine in adults. The two major subtypes of migraine are migraine with and without aura. An aura refers to neurological symptoms that are noticed shortly before the migraine begins. Migraine may also be classified as either chronic or episodic: chronic migraine is distinguished from episodic migraine by headache occurrence on 15 or more days per month for at least three months, with migrainous features on at least eight days per month (IHS 2013).

Migraines without aura

Migraine without aura is an episodic, recurrent condition characterized by a specific set of symptoms and features that distinguish it from other forms of headache (e.g. cluster headache or tension-type headache). IHS criteria are as follows.

- At least five attacks that fulfil the following conditions (B to D).
- The attacks last four to 72 hours (untreated or unsuccessfully treated).
- Headaches have two of the following four characteristics:
  - unilateral location;
  - pulsating quality;
  - moderate or severe pain intensity;
  - aggravation by or causing avoidance of routine physical activity.
- During headache one of the two following:
  - nausea or vomiting, or both;
  - photophobia and phonophobia.
- Not better accounted for by another International Classification of Headache Disorders - 3 (ICHD-3) diagnosis (IHS 2013).

Migraines with aura

In addition to migraines without aura, some people experience migraine with aura, which is characterized by neurological symptoms that typically precede and predict the headache, although for some patients these symptoms can continue with the headache. IHS criteria are as follows.

- At least two attacks that fulfil conditions B and C.
- One or more of the following fully reversible aura symptoms:
  - visual symptoms;
  - sensory symptoms;
  - speech and language;
  - motor;
  - brainstem;
  - retinal.
- Headaches have at least two of the following four characteristics:
  - at least one aura symptom spreads gradually over ≥ five minutes, or two or more symptoms that occur in succession, or both;
  - each individual aura symptom lasts for between five and 60 minutes;
  - at least one aura symptom is unilateral;
  - the aura is accompanied or followed within 60 minutes by headache.
- Not better accounted for by another ICHD-3 diagnosis, and transient ischaemic attack has been excluded.

In this review, we are interested in people who experience migraine with typical aura, rather than migraine with brainstem aura, hemiplegic migraine or retinal migraine.

Description of the intervention

Our review aims to add to the currently available Cochrane Review that investigates the efficacy of psychological interventions for chronic pain excluding headache (Eccleston 2009; Williams 2012), and the Cochrane Review currently underway into psychological interventions for tension-type headache (McGuire 2014). Most psychological treatments focus on the provision of skills that individuals can use to better cope with their symptoms of migraine. Typically, these skills include a range of cognitive and behavioural strategies aimed at reducing stress, changing interpretations about the migraine experience or dealing with the symptoms of migraine once they occur. Hence we will employ the same definition of eligible interventions as in those reviews: any credible psychological treatment. To be defined as credible, the intervention will need to do the following.

- include psychotherapeutic content that is clearly definable.
- be conducted by a healthcare professional appropriately qualified to administer the intervention.

Therefore, we will exclude purely physical treatments (e.g. yoga). We will ask trial authors for details about the training of therapists in the trial, and ensure that we reach a consensus regarding the inclusion of trials. We will include all modalities of intervention including face-to-face individual or group treatment; telephone-administered intervention or online treatment.

How the intervention might work

In addition to what is described above in Description of the intervention, in the migraine literature, earlier programmes also provided education to avoid triggers of migraine with a view to reducing the frequency, but this approach has been criticized because such avoidance can lead to further sensitization to those triggers and significantly restrict everyday activities. More recent approaches have included an element of exposure to triggers with a view that people will habituate during the exposure and thereby become less sensitive to their migraine triggers (Martin 2009; Martin 2010).

Why it is important to do this review

The NICE guidelines for headache highlight the fact that psychological therapies have been found to be effective for chronic pain problems in general, and therefore have the potential to be an important adjunct to medical management of headache and related conditions, such as migraine (NICE 2012). Psychological treatments that have the potential to reduce both the personal and economic burden associated with migraine are needed.

Although there have been previous meta-analytic reviews of behavioural treatments, most have included all types of study designs (e.g. before and after studies, randomized controlled trials (RCTs)) which has led to a possible overestimation of the treatment effect (Rains 2005). The only meta-analysis that included only RCTs was prepared on behalf of the Agency for Health Care Policy in 1999 (Goslin 1999) , and therefore it is important to have an up-to-date synthesis of evidence. This review aims to fill that gap in the literature.

OBJECTIVES

To assess beneficial and adverse effects of psychological treatment versus active alternative treatment or no treatment in adults with migraine, using methods that allow comparison with reviews of psychological interventions for other painful conditions.

METHODS

Criteria for considering studies for this review

Types of studies

We will include the following studies in the review.

- Randomized controlled trials (RCTs) and cluster RCTs.
- Studies should have at least 15 participants in any treatment or control arm included in our analysis at the post-treatment assessment.

Types of participants

Inclusion criteria

Adults (18 years or older) that report episodic or chronic migraine with or without aura; if a trial includes other headache participants, we will use data for migraine patients only if the trial authors report the data separately. If data are unavailable separately for the group with migraine, we will exclude. For the purposes of this meta-analysis, we will not require International Classification of Headache Disorders (ICHD) verified diagnoses, although we will extract this data in order to examine diagnostic confirmation as a potential mediator of response.

Exclusion criteria

We will exclude trials where the following occurs.

- Migraine is secondary to an acute or progressive neurological condition (e.g. giant cell arteritis, raised intracranial pressure, multiple sclerosis, infection).
- The primary pain complaint of the participant is not migraine.
- Participants have a headache other than migraine (e.g. tension-type headache, cluster headache, medication overuse headache).

Types of interventions

We will include RCTs designed to test the efficacy of psychological treatment as an active treatment of primary interest if at least one arm of the trial provides a psychological intervention and there is a comparison arm. We will define credible psychological treatment as a treatment with definable psychotherapeutic content that an appropriately qualified healthcare professional delivered or supervised. The comparison arm can include another active treatment (psychological or medical), an attention-placebo (e.g. supportive counselling) or other placebo group, routine care or waiting list control. We will include all RCTs regardless of treatment dose, migraine intensity and frequency, mode of delivery (e.g. individual, group) or medium of treatment delivery (e.g. face-to-face, Internet).

Types of outcome measures

We will include outcomes as either categorical or continuous data. The following outcomes draw on the recommendations proposed by the International Headache Society Clinical Trials Subcommittee (Tfelt-Hansen 2000) and the guidelines for behavioural treatments of recurrent headache (Penzien 2005).

Primary outcomes

- Reduction in migraine frequency (we define migraine frequency as the number of days with migraine in a four week period based on participant report using a headache diary).

Secondary outcomes

- Responder rate: percentage of participants for whom there was a reduction of 50% or greater in attack frequency in the four weeks after treatment. As smaller symptom reductions can also be meaningful for participants, and in order to be comparable to the review McGuire 2014 proposed, we will also calculate responder rate for those participants that experience a 30% or greater reduction in symptoms.

We will investigate the secondary outcomes below to compare measures before and after psychological therapy compared to control. Hence, the outcome refers to the reduction in each measure.

- Migraine intensity (average intensity of migraine headache based on a simple numerical rating scale measuring pain intensity from mild, moderate to severe).
- Migraine duration (number of hours of migraine per day from a headache diary).
- Number of days with migraine per four weeks.
- Mood (self-reported scales measuring depressive symptoms, anxiety-related symptoms or distress, such as the Hospital Anxiety and Depression Scales, Centre for Epidemiological Study Depression Scale).
- Migraine medication usage (defined as (i) the number of migraines that are treated with acute symptomatic treatment; and (ii) the number of doses consumed).
- Self-reported questionnaire measures that assess the impact of migraine on quality of life.
- Migraine-related disability.
- Adverse events (the proportion of participants that report an adverse event during the study).

Search methods for identification of studies

Electronic searches

We will search the following databases.

- Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library.
- MEDLINE (OVID).
- EMBASE (OVID).
- PsycINFO (OVID).
- CINAHL (EBSCO).

We will use Medical Subject Headings where applicable, and also text word searching. The MEDLINE search strategy is in Appendix 1. We will search for published and unpublished trials in all languages.

Searching other resources

In order to ensure that all available trials are represented, we will handsearch the reference lists of reviews and included trials, and perform citation searches of included trials and identified reviews. We will search the metaRegister of controlled trials (mRCT) (www.controlled-trials.com/mrct), clinicaltrials.gov (www.clinicaltrials.gov) and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (http://apps.who.int/trialsearch/) for ongoing trials. In addition, we will check reference lists of reviews and retrieved articles for additional studies and will perform citation searches on key articles. We will contact experts in the field for unpublished and ongoing trials. We will contact study authors where necessary for additional information.

Data collection and analysis

Selection of studies

Initially, we will merge the results of the individual searches and remove all duplicates from the database search. Two review authors will independently shortlist titles and abstracts of all identified articles. They will remove clearly irrelevant articles based on titles and abstracts, and will consult a third review author in the event of disagreement. Two review authors will independently assess the full-text reports of relevant articles to determine whether or not the design of the study meets the eligibility criteria. If there is ambiguity about whether a trial meets the inclusion criteria, we will contact the study authors for clarification. Finally, we will link multiple reports on the same study for the purposes of data extraction. Two review authors will list the full-text articles that are excluded in a Characteristics of excluded studies table, with the reason(s) for exclusion. To promote transparency of the search and systematic review process, we will produce a PRISMA flow diagram, as recommended in Chapter 6 of the Cochrane Handbook (Higgins 2011).

Data extraction and management

We will develop a data extraction form modified from those developed for similar Cochrane Reviews (e.g. McGuire 2014). We will extract data on important characteristics of the study design, characteristics of participants, diagnosis (migraine with or without aura), duration of migraine, type of intervention, treatment dosage, migraine intensity and frequency, mode of treatment delivery (e.g. individual treatment, face-to-face, group, Internet), control intervention, qualifications of the therapist and outcome measures. Two review authors will independently extract data from each of the included studies, and will enter these data into Characteristics of included studies tables in Review Manager (RevMan) (RevMan 2014). They will consult a third review author, if necessary, to resolve any disagreements.

Assessment of risk of bias in included studies

We will assess the risk of bias for each included study using the criteria developed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Two review authors will assess the following risks for biases and will resolve any discrepancies through consensus. The review authors will enter data into the Risk of bias tables and provide support for each judgement. We will also construct a Risk of bias figure(s).

Random sequence generation

We will determine the method the trial authors utilized to generate a random sequence. We will judge the trial to be at a low risk of bias

if the trial authors used a random method to assign participants to conditions (e.g. computerized generation of number sequence; toss of a coin, random number table etc). If the trial authors do not state the manner in which they determined randomization and are unable to provide this data, we will consider the study to have an unclear risk of bias. Where the trial does not determine randomization using a truly random procedure (e.g. counterbalanced, use of odd and even numbers etc), we will describe the study as having a high risk of bias.

Allocation concealment

We will assess the method the trial authors used to conceal allocation prior to assignment. We will rate those studies that adequately concealed allocation as having a low risk of bias. Where the concealment is unclear, we will deem the study to have an unclear risk of bias. Where the allocation sequence was available to investigators prior to randomization, we will determine the study to have a high risk of bias for this item.

Blinding of outcome assessment

Since psychological treatments cannot blind personnel involved in treatment delivery and can rarely blind participants, we will assess the risk of bias using the following.

- Equivalence of treatment expectations of participants across study arms
- Presentation of third party outcome assessments where the third party is blind to treatment allocation.

We will deem studies that blinded the assessors to the condition to which the participant was allocated or where treatment expectancy is shown to be equivalent as at low risk of bias. Where the trial authors do not state whether or not blinding was involved, we will rate the study as having an unclear risk of bias. Where outcome assessors were not blinded and the trial authors perform any assessment of treatment expectation, we will assign a high risk of bias.

Accounting for attrition

When participants are lost to follow-up, this introduces a source of potential bias to trials. Hence, we will include a measure of the completeness of the follow-up data and how study authors dealt with cases of missing data. We will judge studies to have a low risk of bias where there is a high proportion of participants who start the treatment that complete follow-up assessments ($\geq$ 90% data available) or where most (more than 70%) data are available and we will perform an intention-to-treat analysis (ITT) using a multiple imputation model. Where these criteria have not been met and high rates of attrition are present or ITT analyses rely on less stringent methods (e.g. last-observation-carried-forward), we will judge the trial as at a high risk of bias.

Selective reporting

We will identify entries in clinical registries for all clinical trials we include in the analyses to determine whether the trial authors analysed all primary and secondary end-points in the way in which they had originally planned. We will deem those studies that report all end-points using the analyses set out in the trial register to be of low risk of bias. Where a pre-registered trial is unavailable, the level of bias will remain unclear. Where pre-registered information demonstrates that the trial authors reported different primary outcomes or did not report all measures in the final trial report or performed a selective analysis, we will assign a judgement of high risk of bias for that study. If a protocol is unavailable, we will deem the study as at high risk of bias.

Treatment integrity

We will include two items to determine the integrity of the intervention administered. The first relates to the training of the therapist. We will deem trials that report on specific training of an appropriately qualified therapist for the purposes of the trial to be of low risk. The second item relates to treatment fidelity. We will judge trials that have a dedicated treatment manual and report an assessment of the degree to which therapists adhered to that manual to be of low risk. In order to be deemed at low risk of bias, protocols need to have both sufficient training and fidelity checks. We will only consider trials to be at low risk of bias if the therapists are well trained and there is evidence of treatment fidelity.

Other sources of bias

We will determine whether or not each included study was apparently free or not of other problems that could put it at a high risk of bias. For example, sources of funding that could be perceived as a conflict of interest, or small size of the trial could confirm an additional risk of bias. The Cochrane Pain, Palliative and Supportive Care (PaPaS) Review Group recommends the following for assessing the risk associated with the size of a study and hence we will use the conventions outlined below.

- Low risk of bias: more than 200 participants per treatment arm.
- High risk of bias: fewer than 50 participants per treatment arm.
- Unclear risk of bias: between 50 and 199 participants per treatment arm.

Measures of treatment effect

Where data are continuous, we will measure the standardized mean difference between the psychological treatment arm and the comparator arm (with 95% confidence intervals (CIs)). Where data are categorical (e.g. proportion of responders), we will determine the risk ratio (RR) and number needed to treat (NNT) for $\geq$ 50%

or ≥ 30% reduction in attack frequency over four weeks, for the intervention versus control group.

We will assess the standardized mean difference post-treatment and at follow-up. In the case of multiple time-points, we will define post-treatment as the assessment that is closest to the end of the intervention and within three months. In the case of follow-up, assessment must be made between three and 12 months after the end of the intervention. If more than one follow-up period meets this criterion, then we will use the longest available follow-up data.

Unit of analysis issues

We will analyse the trials arms separately but halve the N of the comparator arm where more than two active treatment arms meet criteria for a credible psychological treatment and are compared to one comparator arm. This is in order not to overly weight the results of that study where both arms are included in the same analysis.

Dealing with missing data

If data are missing from the original publication, we will contact the trial authors directly and request that they provide sufficient data to be able to calculate the effect size of interest. We will contact the trial authors and will give them one month to respond, and we will send a reminder email at the end of a month to give them a further week to provide the data. This includes studies where only a headache index is reported. In these instances we will contact the trial authors by email to provide the data on which they calculated the headache index was calculated. Where standard deviations are missing and unobtainable from the trial authors, we will calculate these where possible from F, t, or Pp values, or from standard error values. If this is not possible, we will treat the trial as though it has no useable data. We will consider the potential impact on the results of the missing data in the 'Discussion' section of the review.

Assessment of heterogeneity

We will assess heterogeneity by examining the CIs for each study and using the I^2 statistic and the Chi^2 statistic for each of the primary and secondary outcomes. If there is considerable heterogeneity, we would need to justify the combination of data from the studies. We will consider the implications of this decision in the 'Discussion' section of the review.

Assessment of reporting biases

We will assess the likelihood that publication bias affected the results of the meta-analysis by inspection of known protocols that were registered and not published. We will also use statistical methods to test for likely publication bias including the examination of funnel plots and the use of the trim and fill method.

Data synthesis

We will use Review Manager (RevMan) to analyse the data (RevMan 2014), and will use a random-effects model. We will include a 'Summary of findings' table of the main outcomes in the results section, which we will construct using GRADEpro Guideline Development Tool (GDT) (GRADEpro GDT 2015). We will rate the overall confidence in our findings using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Appendix 2). We will determine whether future research is likely to influence the findings, and therefore what level of confidence we can have in the results.

Subgroup analysis and investigation of heterogeneity

We intend to examine the relative effectiveness of treatments for different levels of frequency of migraine at pre-treatment (three or more attacks per four weeks versus less than three attacks every four weeks). We have chosen this frequency to be consistent with the reporting of outcomes for the tension headache protocol (McGuire 2014). In addition, we will investigate the relative efficacy of interventions for those with chronic versus episodic migraine; and participants with migraine with and without aura, if sufficient data are available. If sufficient data are available, we will also include whether participants in the study had ICHD-verified diagnoses of migraine.

In terms of treatment characteristics, we also intend to analyse separately those interventions with face-to-face treatment compared to those with only or predominantly phone or Internet contact, and group versus individual mode of delivery. We also plan to examine separately the effectiveness of cognitive behaviour therapy in the treatment of migraine. Should sufficient trials meet the inclusion criteria of this review, we will examine the relative efficacy of relaxation compared to biofeedback. Finally, if we include a sufficient number of trials, we will analyse those whose approach is to encourage avoidance of migraine triggers with those that advocate exposure to triggers.

Sensitivity analysis

We have planned no sensitivity analyses a priori, because we believe that the evidence base is likely to be too small for sensitivity analyses to be meaningful or reliable.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. MEDLINE search strategy (via OVID)

1 exp Psychotherapy/
2 psychotherap*.tw.
3 (psycho* adj3 therap*).tw.
4 Counseling/
5 counsel*.tw.
6 exp Behavior Therapy/
7 (relaxation or imagery or (behavio#r adj3 therap*)).tw.
8 biofeedback.tw.
9 (stress adj2 manag*).tw
10 or/1-9
11 exp Migraine Disorders/
12 (migrain* or (sick adj1 headache*)).tw.
13 11 or 12
14 10 and 13
15 randomized controlled trial.pt.
16 controlled clinical trial.pt.
17 randomized.ab.
18 placebo.ab.
19 drug therapy.fs.
20 randomly.ab.
21 trial.ab.
22 groups.ab.
23 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22
24 exp animals/ not humans.sh.
25 23 not 24
26 14 and 25

Appendix 2. GRADE: assessing the quality of the evidence

We have taken this section from the Cochrane Drugs and Alcohol Group recommended text. We will assess the overall quality of the evidence for each outcome using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (GRADEpro GDT 2015) and present the main findings of the review in a transparent and simple tabular format in the 'Summary of findings' tables. In particular, we will include key information concerning the quality of evidence, the magnitude of effect of the interventions examined, and the sum of available data on the main outcomes.

The GRADE system assesses the quality of the evidence as at one of the following four levels of quality.

- 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: any estimate of effect is very uncertain.

We will downgrade the quality of the evidence by the value we have given in brackets if there is:

- Serious (−1) or very serious (−2) limitation to study quality.
- An important inconsistency (−1).
- Some (−1) or major (−2) uncertainty about directness.
- Imprecise or sparse data (−1).
- A high probability of reporting bias (−1).

CONTRIBUTIONS OF AUTHORS

LS, IM and BM developed the concept for this review. LS wrote the first draft of the protocol, and all protocol authors commented on it. LS revised the protocol after all protocol authors commented. All protocol authors read and approved the final version of the protocol.

DECLARATIONS OF INTEREST

LS: none known. LS is a clinical psychologist and practices CBT with patients with a range of chronic health problems.

AW: none known.

PRM: none known. PRM is a clinical psychologist and practices CBT for patients with headache and migraine.

MN: none known.

MW: none known. MW is a clinical psychologist and practices CBT for patients with chronic pain.

IM: none known.

AB: none known; AB is a clinical psychologist and practices CBT for patients with a range of mental health problems.

JD: none known.

BM: none known. BM is a clinical psychologist and practices CBT for patients with headache and chronic pain.