Systematic review of cognitive behavioural therapy for the management of headaches and migraines in adults

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ABSTRACT

Aim: This paper is a systematic review of trials investigating the clinical effectiveness of cognitive behavioural therapy (CBT) in adults with chronic non-malignant headache or migraines.

Methods: Standard, rigorous and transparent methods for evidence synthesis were employed. Evidence was systematically sought, appraised and synthesised by an independent academic team with extensive experience in the methods of systematic reviews, and clinical experts were consulted. The included trials were based on a systematic search of 8 databases (AHMED, Cinahl, Embase, Ovid Medline, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Psychinfo, the Cochrane library, and Web of Science) and carried out by an experience information scientist. Essential components of CBT were included in all the studies that met the inclusion criteria.

Results: Heterogeneity of the studies precluded quantitative meta-analysis for any of the outcomes in any of the comparisons. Physical improvements in headaches or migraines were noted for CBT when it was compared with a waiting list control group. and in CBT plus relaxation with relaxation alone or with antidepressants, although not for all outcomes. CBT plus placebo compared with CBT plus antidepressants, clinic-based CBT compared with self-managed CBT, and CBT compared with biofeedback were not statistically superior to the active treatment comparator in improving the physical symptoms of headache or migraine. There was no statistical comparison between CBT plus biofeedback with biofeedback alone.

Conclusions: These findings provide some evidence in support of the suggestion that people experiencing headaches or migraines can benefit from CBT and that CBT can reduce the physical symptoms of headache and migraines. However, all the results must be interpreted with caution due to the methodological limitations of the studies.

Keywords: chronic non-malignant headache, migraine, cognitive behavioural therapy, systematic review, randomised controlled trial.

Around 95% of the general population have experienced headache at some point in their life.(1) Precise estimates of incidence or prevalence are difficult to obtain due to the intermittent and episodic nature of headaches and migraines,(2) however the global adult prevalence of headaches is around 46% and 11% for migraines.(1) Headaches have been estimated to be problematic in around 40% of people in the UK at some time in their lives.(3)

The prevalence of headaches and migraines make treatment a widespread problem in clinical practice(4) and one of the most common neurological problems presented to general practitioners and neurologists in the UK(5). A primary care-based study set in 18 general practices in the south Thames region of England (urban and rural areas), based on 141,100 patients (aged 18 to 75 years) registered with general practitioners (GPs), involved interviews with people reporting problematic experience of headache in order to establish health care use and the cost ~~as~~ associated with the provision of services to people with headaches. Figures extrapolated to the whole of the UK put the total annual cost of migraines and headaches in 2011 at around £4.8 billion including lost employment, with around £956 million due to healthcare use(6). Authors suggest that one of the limitations of the study is that these figures are most likely underestimations,(6) as most headaches are self-managed with over-the-counter medication.(7)

According to the British Association for the Study of Headache (BASH) guidelines, evidence suggests that headache disorders are under-diagnosed and under-treated in the UK, as well as Europe and the USA.(3) Data from the World Health Organisation (WHO) proposes that in the UK and USA, only half of those identified with migraine had seen a doctor for headache-related reasons in the previous 12 months.(8) In addition, a WHO factsheet on headaches states that around one-third of cases receive an incorrect diagnosis.(8) In the UK, GPs appear to find the specific diagnosis of headache difficult.(9) This may be because the aetiology of primary headaches is not well understood, or because of limited understanding of the classification system used to diagnose headaches and migraines.(10) To aid in the diagnosis and management of the most common primary headache disorders, the UKs National Institute of Health and Care Excellence (NICE) published standards for the treatment of headaches in young people and adults in 2012, which cover the diagnosis and management of the most common primary headache disorders.(10) The NICE guidelines limit the treatment for chronic headache and migraine to medication, with an emphasis on the prevention of medication overuse. Mild headaches are usually self-managed through the use of simple analgesics, but their efficacy tends to decrease with frequent use.(11) Regular intake of simple analgesics on ≥15 days a month or of codeine-containing analgesics on ≥10 days a month is sufficient to induce medication overuse, another cause of headaches. Apart from medication overuse, important limitations of pharmacological therapies include the high cost associated of on-going medication, contraindications, medication intolerance and their limited effectiveness.(12)

While medication contributes to the management of conditions such as chronic headaches or migraines, psychological comorbidity is common in these individuals, (13) with a variety of functions such as sleep (fatigue-related problems), as well as activities such as exercise and emotions (stress-related problems) affected. (11) Furthermore, it has been found that the anticipation of a headache can cause significant anxiety between episodes(5) and that depression is three times more common in individuals experiencing severe headaches or migraines than in headache-free individuals.(8) However, the measurement of depression in pain patients is said to suffer from criterion contamination by somatic items (i.e. pain, fatigue), as most of the questionnaires were not developed in pain populations.(14) Experience of both excess anxiety and low mood can restrict an individual's ability to work or maintain a relationship, and results from a meta-analysis of 25 trials suggest that depression increases non-compliance with medical treatment recommendations, further compounding the problem.(15) While it is suggested that an effective psychological intervention based on cognitive behavioural principles could substantially improve quality of life for sufferers, there are few data supporting the use of these interventions to manage chronic headache disorders.(10) Interventions such as cognitive behavioural therapy (CBT) include a variety of techniques such as stress management, biofeedback and relaxation, aiming to bring about changes in emotions, cognitions (thoughts) and behaviours (actions). Management of headache or migraine triggers through the devolvement of coping mechanisms and life style changes (e.g. diet, sleep) may reduce the frequency of episodes, therefore altering the pain experience.

Existing reviews of chronic pain and CBT have found that CBT delivered by experienced staff was helpful in the management of chronic pain.(16) Uncertainty remains about the type of components that work best for different types of individuals.(16) Earlier reviews assessing CBT and behaviour therapy(17) or psychological therapies for the management of chronic pain(18) specifically excluded headache and UK national guidelines do not recommend this type of therapy as a treatment alternative in place of pharmacological solutions due to the lack of evidence.(10) This systematic review aims to establish if CBT can reduce the physical symptoms of chronic headache and migraines, which would provide a long-term treatment solution which could reduce or eliminate some of the side-effects and costs of medication, as well as other associated health service and personal costs.

Methods

Evidence for the clinical-effectiveness of CBT on the physical symptoms of chronic headaches and migraines in adults was systematically sought, appraised and synthesised.

A literature search was conducted by an experienced information scientist using eight electronic (AHMED, Cinahl, Embase, Ovid Medline, Ovid MEDLINE(R) In-Process & Other Non-Indexed

Citations, Psychinfo, the Cochrane library, and Web of Science). Databases were searched from 1980 (cognitive and behavioural techniques did not emerge until the 1980s(19)) until January 2013. Searches were restricted to English language. Hand searches of the biographies of included publications were conducted. For further details of the search strategy see Appendix 1.

Inclusion criteria:
Studies had to include all of the following:

- Randomised controlled trials (RCTs)
- CBT as an intervention in an adult population suffering from headaches or migraines not associated with an underlying pathology or due to medication overuse
- CBT to include cognitive and behavioural elements in order to be included as CBT
- A comparator (any)
- Headache inclusion criterion or classification
- Frequency and duration of the condition or condition described as a chronic
- Clinician verified headache/migraine diagnosis
- Headache-specific outcomes (such as headache days, headache frequency or intensity, functional status, resource use or headache-specific quality of life)

Psychological outcomes were excluded from this review, as they are often varied in this type of research, with little apparent consensus in the outcome measure employed. Author-designed participant-reported outcomes were not included in the review since the validity and clinical interpretation of some these measures are unreliable. Abstract or conference presentations were only included if they presented sufficient details to allow an appraisal of the methodology and assessment of the results.

Title and abstract screening was conducted by two reviewers independently using the above criteria. Inclusion criteria to full papers were applied, data extracted and study quality (risk of bias) assessed by one reviewer and checked by a second. Other aspects of study quality relating to statistical procedures, outcome measurement and generalisability were also assessed and recorded in the data extraction forms (available from the corresponding author upon request). Methodological quality and the risk of bias were assessed using standard criteria.(20) Disagreements were resolved through discussion between the reviewers.

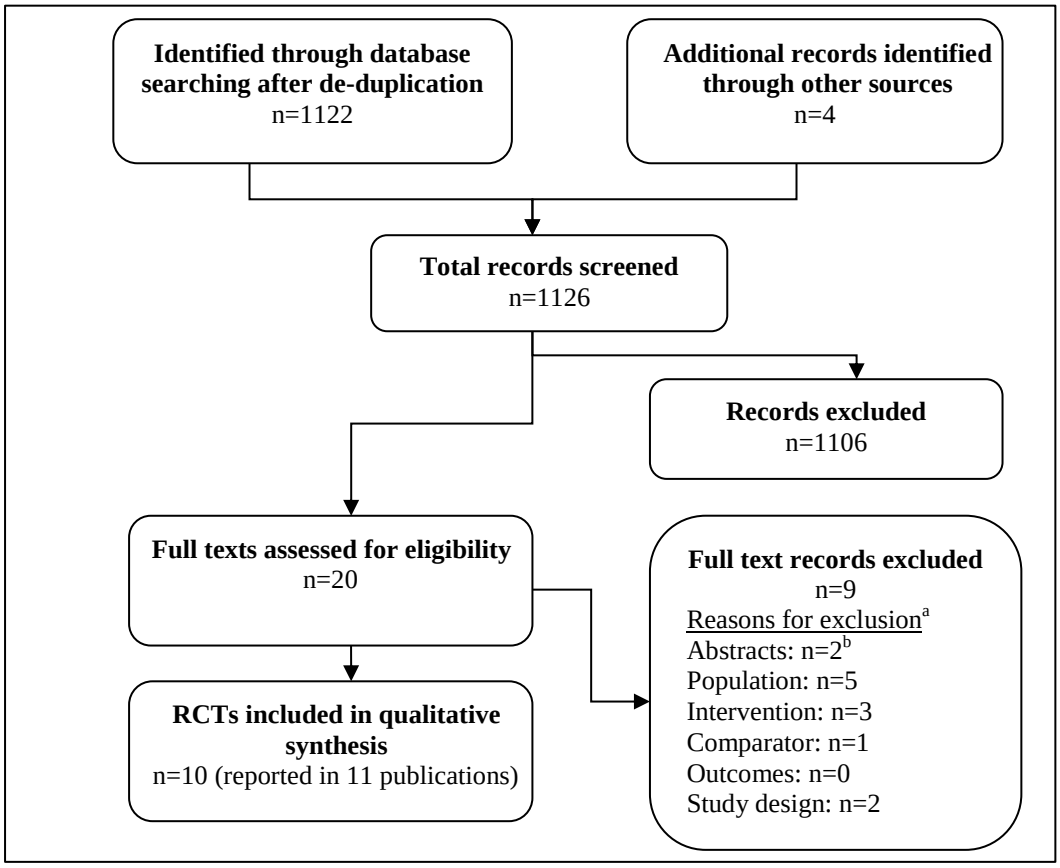
Methods of data synthesis

Studies were synthesised narratively with tabulation of results of all included studies. The RCTs differed in the ways the outcomes were measured and/or reported, which precluded the pooling of any outcomes across the RCTs in a meta-analysis.

Results

A total of 1122 titles and abstracts were screened and 1102 references excluded. We retrieved 19 full papers, excluded 10 papers for various reasons (see Figure 1) and included 10 studies based on 11 publications in the review.

Figure 1. Flow chart for the identification of studies



[a] Papers could be excluded for more than one reason. [b] Excluded due to insufficient information.

Study characteristics

Of the 10 included trials, four trials had two comparators, (21-24) three trials had three comparators(25-27) and three had four comparators.(28-30) Six studies were conducted in the USA, two in Australia and one each in Canada and Germany. Studies were published between1988 to 2007

and sample size varied from 27(24) to 203.(30) However, the number of participants per treatment arm varied from as little as nine(26) to 50.(21)

For ease of comparison, all interventions are abbreviated CBT and the two types of biofeedback (temporal pulse amplitude biofeedback training and thermal biofeedback) as BF. For details of the interventions and comparators see Table 1.

The mean age of participants ranged from 28(24) to 44(25) years in nine of the studies. Participants in the remaining study were older with a mean age of 68 years (range 60 to 78 years).(26) Nine out of the ten studies had a higher proportion of female participants, ranging from 62%(28) to 85%.(27) Only one study had a higher proportion of male participants (69%).(23)

Mean years of reported headache ranged between 8(24) and 37 years,(26) with differences in the inclusion criteria for types of headaches between studies. One study did not report the duration, describing the patients as chronic only.(21) Five studies required a diagnosis of tension headache,(22;24;26;28;30) two of either migraine or tension headache,(21;25) and one each of chronic headache (migraine, headache or mixed),(23) migraine(27) or vascular headache (describes as migraine or mixed migraine and tension headache).(29) Frequency varied from at least one per week(23) to at least three per week.(24)

Two of the studies evaluated clinic-based CBT with self-managed CBT.{300}{304} Six of the studies employed mixed interventions (see Table 1), of which three studies combined some form of CBT with relaxation,{1168}{1298,}{1371} and one study offered additional physical treatments such as such as pain medication, nerve blocks, acupuncture, massage and physical therapy.{1710} One study employed CBT combined with thermal biofeedback or with relaxation,{873} while another used CBT (stress-management) combined with placebo or with antidepressant medication (amitriptyline or nortriptyline).{197} In addition, one trial also used a mixed comparator by providing additional physical treatments such as pain medication, nerve blocks, acupuncture, massage and physical therapy to the waiting list control group.{1710} Some studies included more than one comparator group, including relaxation in three studies,{1168}{1298}{1371} placebo in two,{1168}{873} antidepressant medication in two{282}{197} or biofeedback in one.{95} Relaxation and biofeedback could therefore be part of the intervention or a comparator, making comparison between studies difficult. Non-treatment comparators included a waiting list control group in five studies{1168}{873}{95}{1298}{304} and a placebo group in three studies.{1168}{873}{197}

Table 1. Study Characteristics of included studies

Author, country, (sample size); F-up	Intervention/s (sample size); duration	Comparator/s (sample size)
Basler et al. (1996),(21) Germany (n=126); F-up: 6 mths. Mean age: 40.0 years (SD 11.4). Headache diagnosis: 26% migraine, 36% tension headache, 37% both. Mean years of pain: 14.2 (SD 11.0).	CBT (+ physical treatments) (n=50); Treatment duration: 12 weeks (12 sessions)	1. Waiting list control (+ physical treatments) (n=38)
Blanchard et al. (1990),(28) USA (n=77); F-up: 12 weeks. Mean age: 38.6 years (range 21-67). Headache diagnosis: tension headache. Mean years of pain: 14.1 (SD 10.6-14.1).	CBT (cognitive therapy) + relaxation (progressive muscle relaxation) (n=17); Treatment duration: 8 weeks (11 sessions)	1. Relaxation (progressive muscle relaxation) (n=19) 2. Placebo (pseudo-medication) (n=16) 3. Waiting list control (headache monitoring) (n=15)
Blanchard et al. (1990),(29) USA (n=148); F-up: 12 weeks. Mean age: 38.6 years (range 21-61). Headache diagnosis: 64% migraine or mixed migraine; 36% tension headache. Mean years of pain: 15.6 (SD 8.6-12.4).	CBT (cognitive therapy) + biofeedback (thermal biofeedback) (n=30); Treatment duration: 8 weeks (16 sessions)	1. Relaxation training + biofeedback (thermal biofeedback) (n=32) 2. Placebo (pseudo-medication) (n=24) 3. Waiting list control (headache monitoring) (n=30)
Holroyd et al. (1991),(22) USA (n=41); F-up: 12 weeks. Mean age: 32.3 years (range 19-55). Headache diagnosis: recurrent tension headache. Mean years of pain: 10.7 (range 1-28).	CBT+ relaxation (n=19); Treatment duration: 8 weeks (3 sessions)	1. Antidepressant medication (amitriptyline) (n=17)
Holroyd et al. (2001 & 2009),(30;31) USA (n=203); F-up:6mths. Mean age: 37 years (SD 0.85). Headache diagnosis: chronic tension-type headache. Mean years of pain: 12.6 (SD 0.79).	CBT (stress management therapy) + placebo (n=38); Treatment duration: 8 weeks (3 sessions)	1. CBT (stress management therapy) + antidepressant medication[a] (n=45) 2. Antidepressant medication[a] (n=48) 3. Placebo (n=38)
Martin et al. (1989),(23) Australia (n=64); F-up: 4 + 12mths . Mean age: 38.4 (SD: CBT 9.81, SM-CBT 8.41).	Clinic-based CBT (n=31); Treatment duration: 12 weeks (12 sessions)	1. Self-managed CBT (n=31)

Headache diagnosis: migraine CBT 50.0%/SM-CBT 37.9%; tension headache CBT 26.9%/ SM-CBT 41.4%; mixed CBT 23.1%/ SM-CBT 20.7%. Mean years of pain: 16.5 (SD: CBT 8.88, SM-CBT 11.71)		
Martin et al. (2007),(25) Australia (n=64); F-up: 12mths. Mean age: 44.0 (SD 9.6). Headache diagnosis: 59% migraine, 41% tension-type headache. Mean years of pain: 24.7 (SD 11.7).	CBT (n=20); Treatment duration: 8 weeks (8 sessions)	1. Biofeedback (temporal pulse amplitude biofeedback trg. (n=19) 2. Waiting list control (n=12)
Mosley et al.(1995),(26) USA (n=37); F-up: 12 weeks + 4mths. Mean age: 68 years (range 60-78). Headache diagnosis: recurrent tension headache. Mean years of pain: 37 (range 9-55).	CBT + relaxation (n=11); Treatment duration: 12 weeks (12 sessions)	1. Relaxation (n=10) 2. Waiting list control (n=9)
Richardson &McGrath (1989),(27) Canada (n=51); F-up:6mths. Mean age: 35.6 (range 23-48). Headache diagnosis: common migraine (not classic migraine). Mean years of pain: 16.7 (range 2-40).	Clinic-based CBT (n=15); Treatment duration: 8 weeks (8 sessions)	1. Self-managed CBT (n=15) 2. Waiting list control (n=17)
Tobin et al. (1988),(24) USA (n=27); F-up: 3mths. Mean age: 28 (SD 6.6). Headache diagnosis: recurrent tension headache. Mean years of pain: 8 (SD 5.7).	CBT + relaxation (n=12); Treatment duration: 8 weeks (3 sessions)	1. Relaxation (n=12)

CB: Cognitive behavioural. CBT: Cognitive behavioural therapy. F-up: Follow-up. [a]: Amitriptyline or nortriptyline. Mths: months.

Note: Some studies had more than one follow-up point. The results for the follow-up point with the most compete data are reported. For detailed data extraction forms please contact the corresponding author.

Five studies had a follow-up of 3 months,(22;24;25;28;29) one of 4 months,(26) three of 6 months(21;27;30) and one study of 12 months.(23) Results for the waiting list control groups were reported at the end of the treatment periods only. Studies reported a variety of outcomes, but none of the studies reported headache-specific or generic quality of life. There was generally little consensus in the use of psychological outcome measures amongst the studies.

Risk of bias

The potential risk for bias, based on that published for systematic reviews by the Centre for Reviews and Dissemination (CRD),(20) varied between the studies. In eight out of the ten categories of potential bias, one or more of the studies provided insufficient information to allow for a conclusion about the potential risk to be reached and only four categories included studies that seemed to have methods that would minimise potential bias adequately (see Table 2).

Four studies(22;24;26;28) were deemed at risk of selection bias due to inadequate methods for random sequence generation in the randomisation procedure, while the risk was unclear in the six remaining studies due to a lack of reported information.(21;23;25;27;29;30) The risk of selection bias due to allocation concealment was unclear in all ten studies again due to a lack of reported information.(21-30)

The risk of performance bias due to not blinding care providers to participant's treatment allocation and risk of performance bias due to not blinding participants to their treatment allocation was partially addressed in just one study,(30) as blinding was to the medical /placebo component only. The remaining studies provided insufficient information for a judgement to be made. The risk of performance bias due to not blinding outcome assessors to participant's treatment allocation was unclear in all ten studies due to insufficient reported information.

There seemed to be little risk of attrition bias (differences between groups in withdrawals from the study) in five studies.(21;22;24;25;28) However, this was not adequately addressed in the remaining five studies, with differences in drop-out rates between the treatment groups in four of these studies(23;26;29;30) and a poor retention rate in the fifth study.(29)

There appeared to be a risk of bias due to selective reporting (differences between reported and unreported findings) in two studies,(23;29) but the risk was unclear in the remainder of the studies. One of the studies analysed several of the process measures to clarify 'disappointing results',(29) while in the second study diaries were re-analysed to separate headache activity (no data per treatment group reported) and an 'improved' criterion of a reduction in headache activity was applied.(23)

Two studies(22;30) reported the use of an intention-to-treat (ITT) approach for all analyses performed. However, only one study(30) included all randomised participants in this approach, while the second study(22) reported data excluding drop-outs. In the remaining eight studies,(21-23;25-29) there was a potential risk of bias in the trial results due to the majority of studies excluding drop-outs from the results. Therefore missing data appeared to have been adequately dealt with in one study,(30) partially in another,(22) inadequately in six studies,(23;25-29) but considered unclear in two studies, which failed to report details.(21;24)

Overall, the assessment of study quality suggests that results of the included RCTs should be interpreted with caution as there is a risk of bias.

Table 2. Risk of bias

Author / Bias	Basler(21)	Blanchard(28)	Blanchard(29)	Holroyd(22)	Holroyd(30)	Martin(23)	Martin(25)	Mosley(26)	Richardson(27)	Tobin(24)
Random sequence generation?	U	I	U	I	U	U	U	I	U	I
Allocation concealment?	U	U	U	U	U	U	U	U	U	U
Groups similar at the outset?	A	I	A	A	A	A	A	A	A	A
Performance bias: blinding of car providers?	U	U	U	U	P	U	U	U	U	U
Performance bias: blinding of participants?	U	U	U	U	P	U	U	U	U	U
Detection bias: blinding of outcome assessors?	U	U	U	U	U	U	U	U	U	U
Unexpected imbalances in drop-outs between groups?	A	A	I	A	I	I	A	I	I	A
Free of selective reporting?	U	U	I	U	U	I	U	U	U	U
ITT analysis?	I	I	I	I	A	I	I	I	I	U
Did the analysis account for missing data?	U	I	I	P	A	I	I	I	I	U

A: adequate; I: inadequate; P: partial; U: unknown/unclear.

Outcomes

The outcome data of the studies are grouped by their main comparator. Some studies had more than one follow-up point and the results for the follow-up point reporting the most comprehensive data are reported. Reporting of adverse events was limited to tricyclic antidepressants as treatment comparator and reported in two studies (not data extracted).(22;30)

Cognitive behaviour therapy vs. waiting list control

This comparison was reported by three studies.(21;25;27) At follow-up in the study by Basler et al.,(21) the waiting list control group had also received CBT and data were amalgamated, hence only post-treatment data (4 weeks) are reported. Martin et al.(25) reported results for more than one follow-up point and the latest follow-up point of 12 months is reported here (see Appendix 2). The study by Richardson and McGrath(27) only reported results for subgroups of 'more severe' and 'less severe' resulting in very small participant numbers at 8 weeks post-treatment, and it is unclear if the study was powered for this type of comparison. Heterogeneity of the studies precluded quantitative meta-analysis for any of the outcomes in this comparison. Other comparator treatments included in two of the studies (biofeedback(25) and self-management CBT (27)) are discussed below.

CBT was statistically significantly superior to a waiting list in reducing headache intensity in one out of two studies, in reducing headache frequency and headache-free days, each reported by one study, and for responder rate in one out of two studies (see Table 3). CBT was not statistically significantly superior to a waiting list in the reduction of headache activity reported by one study, or pain medication - although only one of three studies reported a statistical comparison for pain medication. However, results must be treated caution as there were issues around the risk of bias in all three trials, drop-outs were excluded from the results in all three trials, there was a failure to report p values in a number of instances and two studies had very low participants numbers (7 to 10).(25;27)

Table 3. Cognitive behaviour therapy vs. waiting list control – results overview

Outcome	**CBT statistically significant, study**	**CBT statistically non-significant, study**
Headache intensity		Richardson and McGrath(27) (no p value) Basler et al.(21) (no p value)
Headache activity	Martin et al.(25)(p=0.057)[a]	
Headache frequency	Richardson & McGrath(27) (no p value)	
Headache-free days	Basler et al.(21) (p<0.05)	
Responder rate		Martin et al.(25) (no p value) Richardson and McGrath(27) (no p value)
Medication use		Basler et al.(21) (no p value)[b]

[a] Covariate adjusted post-treatment). [b] Neither Martin *et al.*(25) nor Richardson and McGrath(27) reported a statistical comparison. Due to an administrative error, data for only half of the participants were available in the study by Richardson and McGrath.(27)

Cognitive behaviour therapy plus relaxation vs. relaxation

Three RCTs compared CBT plus relaxation with relaxation only (Table 4).(24;26;28) Apart from relaxation, Mosley *et al.*(26) included a waiting list group as a second comparator, while Blanchard *et al.*(28) included a waiting list control and placebo group as comparators (see Appendix 2). Both Blanchard *et al*(28) and Mosley *et al.*(26) reported post-treatment data only. All three studies excluded drop-outs. Heterogeneity of the studies precluded quantitative meta-analysis in any of the outcomes for this comparison.

Combined CBT plus relaxation was statistically significantly superior to relaxation in two out of two studies in reducing headache intensity and headache activity, in one out of one study in reducing headache frequency, and in one out of three studies in reducing medication use, but was not statistically significantly superior in the two studies reporting a responder rate. It should be noted that in the study by Tobin et al.(24) only four participants reported regularly taking prescribed medication and the variable was excluded from analysis, while the study by Blanchard et al.(28) did not report a statistical comparison between the active treatment groups. Results must be treated with caution as all three studies excluded drop-outs from the results and had low participant numbers per treatment group (9(26) to 16(28)).

Table 4. Cognitive behaviour therapy plus relaxation vs. relaxation – results overview

Outcome	**CBT statistically significant, study**	**CBT statistically non-significant, study**
Headache intensity	Mosley et al.(26) ($p<0.05$) Tobin et al.(24) ($p<0.05$)	
Headache activity	Blanchard et al.(28) ($p=0.001$) Tobin et al.(24) ($p<0.05$)	
Headache-free days	Tobin et al.(24) ($p<0.05$)	
Responder rate		Blanchard et al.(28) (no p value) Mosley et al.(26) (no p values)
Medication use	Mosley et al.(26) ($p<0.01$)	

Cognitive behaviour therapy plus relaxation vs. antidepressants (amitriptyline)

One study reported a comparison of CBT plus relaxation with antidepressant medication.(22) Holroyd et al.(22) assessed headache-related outcomes at 12 weeks post-treatment (see Appendix 2). All statistical analyses were based on an intention to treat principle, however the reported data excluded drop-outs.

CBT plus relaxation was statistically significantly superior to treatment with amitriptyline in reducing the mean level of headache pain, increasing headache-free days and in responder rate (statistically

significantly more likely to be categorised as moderately or substantially improved), but not in the reduction of medication use or headache peak in the one study assessing this comparison (see Table 5). Caution in the interpretation of the results is required, as the study had a small sample size (CBT plus relaxation n=19, Medication n=17), there were imbalances in headache medication use at baseline (amitriptyline group nearly double to that in the CBT plus relaxation group) and the study had a high drop-out rate (12%). This was nearly four times higher in amitriptyline group and may have been related to possible side-effects of the antidepressant medication.

Table 5. Cognitive behaviour therapy plus relaxation vs. antidepressants (amitriptyline) – results overview

Outcome	**CBT statistically significant, study**	**CBT statistically non-significant, study**
Headache intensity		Holroyd et al.(22) (no p value)
Headache index	Holroyd et al.(22) ($p<0.001$)	
Headache-free days	Holroyd et al.(22) ($p<0.05$)	
Responder rate	Holroyd et al.(22) ($p<0.05$)	
Medication use		Holroyd et al.(22) (no p value)

Cognitive behaviour therapy plus placebo vs. CBT plus antidepressants (amitriptyline or nortriptyline)
The study by Holroyd et al.(30) compared CBT plus placebo with CBT plus antidepressants, antidepressants alone or placebo. While p values were reported, data were presented in graph format and means were estimated from the graphs by reviewers (see Appendix 2). Authors note that the trial did not have enough power to detect small treatment effects.

While authors reported statistically significant differences for the CBT plus placebo group compared with placebo alone in headache activity, headache-free days and pain medication, no statistical comparison with CBT plus antidepressants was reported for these outcomes. For the responder rate, CBT plus antidepressants was statistically superior to antidepressants alone ($p=0.006$). Caution in the interpretation of the results is required, as the study had an overall drop-out rate of 29% at 6 months follow-up, which was highest in the placebo group (46%) followed by the CBT plus placebo (31%) and differences were statistically significant ($p=0.01$).

Cognitive behaviour therapy vs. CBT self-management
Two studies compared clinic-based CBT with a self-managed form of CBT.(23;27) The study by Martin et al.,(23) reported data at several time points, with 12 months follow-up data reported here (see

Appendix 2). Richardson and McGrath(27) had an additional waiting list control arm (reported above). As previously mentioned, the authors grouped the majority of their results into subgroups of 'more severe' and 'less severe', leading to very small samples sizes per subgroup. Heterogeneity of the studies precluded quantitative meta-analysis in any of the outcomes for this comparison.

There with no statistically significant differences between groups for any of the outcomes (see Table 6). It is unclear if the study by Richardson and McGrath(27) had enough power to detect differences in the very small reported subgroups. Authors attributed the lack of statistical difference in the responder rate to the small sample size and therefore low power. Authors also stated that medication use was only recorded for half of the participants (8 to 9 per treatment group) due to 'an administrative error' and warned that results must be treated with caution. Both studies excluded drop-outs from their reported results.

Table 6. Cognitive behaviour therapy vs. CBT self-management – results overview

Outcome, no. of studies reporting outcome	**CBT statistically significant, study**	**CBT statistically non-significant, study**
Headache intensity – 1 study		Richardson and McGrath(27) (no p value)
Headache activity – 1 study		Martin et al.(23) (no p value)
Headache-frequency – 1 study		Richardson and McGrath(27) (no p value)
Responder rate – 1 study		Richardson and McGrath(27) (no p value)
Medication use – 1 study		Richardson and McGrath(27) (no p value)

Cognitive behaviour therapy vs. biofeedback

One study by Martin et al.(25) reported a comparison between CBT and temporal pulse amplitude biofeedback, with the addition of a waiting list control group (reported above). The study had a small sample size (CBT n=18, BF n=19). Reported results excluded data for drop-outs, resulting in an even smaller sample size (CBT n=10, BF n=11) at 12 weeks follow-up (see Appendix 2). As previously stated, the authors reported results for more than one follow-up point and the latest follow-up point of 12 months is reported here.

There were no statistically significant differences between the treatment groups for headache activity. No statistical comparison for pain medication use or responder rate (headache ratings and pain medication)

was reported. Authors state that there was no significant association between treatment condition and the presence of clinically significant change *(*p value not reported). Results should be interpreted with caution, as data for drop-outs were excluded and results were based on a small sample size.

Table 7. Cognitive behaviour therapy vs. biofeedback – results overview

Outcome	**CBT statistically significant, study**	**CBT statistically non-significant, study**
Headache activity		Martin et al.(25) (p=0.057[a])
Responder rate Headache ratings Medication use	?	**?**
Medication use	?	**?**

[a] Covariate adjusted post-treatment.

Cognitive behaviour therapy plus biofeedback vs. relaxation plus biofeedback

One study assessed the comparison, with the additional of a placebo and a waiting list control group as comparators (see Appendix 2). Blanchard et al.(29) reported statistical comparisons between the treatment groups through an ANOVA. While authors reported data for more than one time point (no data reported for 12 months follow-up), the most complete results were for 12 weeks post-treatment (reported here).

Statistical comparisons were only between the active treatment and the non-active treatment groups. Visual inspection of the data would appear to show lower average daily headache activity, a greater responder rate and a lower pain medication index for the CBT plus biofeedback group at 12 weeks follow-up, but it is unclear if this is statistically significant. For medication use, authors state that both biofeedback groups as well as the placebo group showed significant reductions in medication use at 12 weeks post-treatment, but adding CBT yielded no advantage (ns, p value not reported). Drop-outs were excluded from the reported data.

Discussion

Headaches and migraines present an important health problem and, while they are generally not life threatening, they are a cause of personal and social burden, with substantial economic impact.(32) CBT could offer an effective treatment countering the burden and impact.

Statement of principal findings

CBT vs. waiting list control: of the three studies in this comparison, some had statistically significantly better results for those treated with CBT compared with a waiting list group in reduction of headache intensity (reported by 1 out of 2 studies), headache frequency (1/1), headache-free days (1/1) and responder rate (1/2). Differences in headache activity (1/1) and pain medication (1/3) between the groups were not statistically significant. These findings provide some support for common therapeutic factors in the provision of therapeutic support for people with headaches, giving no clear support for any additional specific benefits of CBT. A comparison of CBT with other active psychotherapies would allow exploration of the relative contributions made by therapeutic contact and CBT based techniques.

CBT plus relaxation vs. relaxation: of the three studies in this comparison, CBT plus relaxation was statistically significantly superior compared with relaxation alone in the reduction of headache intensity (2/2), headache activity (2/2), headache frequency (1/1) and pain medication use (1/3), but not for responder rate (2/2). These findings provide some support for CBT above and beyond common therapeutic factors.

CBT plus relaxation vs. antidepressants: in the one study assessing this comparison, CBT plus relaxation was statistically superior to antidepressants in reducing headache pain, increasing headache-free days and responder rate, but not in the reduction of medication use or in mean headache peak. These findings provide some support for CBT and/or common therapeutic factors. Negative side effects of antidepressant medication may have confounded outcomes, reflecting the possibility that adverse side effects for some individuals counter any possible benefits in others.

CBT plus placebo vs. CBT plus antidepressants: in the one study assessing this comparison, CBT plus antidepressants was not statistically superior to CBT plus placebo in any of the outcomes. These findings provide no support for the addition of antidepressants to CBT.

Clinic-based CBT vs. self-managed CBT: in the two studies assessing this comparison, there were no statistically significant differences between treatment groups in headache intensity (1/1), headache activity (1/1), headache frequency (1/1), use of pain medication (1/1) or responder rate (1/1). These findings suggest that individuals can benefit from structured psycho-therapeutic interventions even without the benefit of common therapeutic factors associated with therapist contact.

CBT vs. biofeedback: in the one study assessing this comparison, there were no statistically significant differences between treatment groups in headache activity. No statistical comparisons for pain medication use or responder rate were reported. These findings suggest that individuals can benefit from structured therapeutic interventions without CBT specific ingredients.

CBT plus biofeedback vs. relaxation plus biofeedback: in the one study assessing this comparison, no statistical comparisons between CBT plus biofeedback and relaxation plus biofeedback were reported.

This systematic review used standard rigorous methods for evidence synthesis, and evidence for clinical-effectiveness was systematically sought, appraised and synthesised. Experts in CBT have been consulted for input into the review. Quantitative pooling of outcomes across clinical effectiveness studies in a meta-analysis was not possible as the included studies differed in the way they presented outcomes. Results of the RCTs should be interpreted with caution as no good quality contemporary evidence was identified for cognitive behavioural therapy. Known methodological problems in this type of research include difficulties in blinding trials; the absence of standardisation and detailed description of patient groups, interventions, delivery of interventions and outcome measures; the inclusion of self-selected patients;(33) and the use of waiting list control groups.

Strengths and limitations of the assessment

The strengths of this review are that standard, rigorous and transparent methods for evidence synthesis were employed, that evidence was systematically sought, appraised and synthesised by an independent academic team with extensive experience in the methods of systematic reviews, and that clinical experts were consulted.

Limitations of this review are the inclusion of some relatively old studies, the small number of participants in some studies, the sub-optimal reporting of some studies and the potential uncertain or high risk of bias related to the included studies. Results had to be synthesised narratively, as heterogeneity of studies precluded quantitative meta-analysis.

Other relevant factors

Some studies were selective in the reporting of their results, omitting statistical comparisons between the active comparators for some of the outcomes. Comparison between the studies was further compounded by the use of non-standardised outcomes. Studies generally had short follow-up times, which were often even shorter for the waiting list control groups.

Conclusions

Overall, these findings provide evidence in support of the suggestion that people experiencing headaches or migraines can benefit from structured psycho-therapeutic interventions even without the benefit of common therapeutic factors associated with contact with therapist. There is little support for the use of antidepressants with individuals from these studies. There is little support for suggestion that CBT offers any benefit over structured therapeutic intervention with or without client-therapist contact. However, all the results must be interpreted with caution due to the methodological limitations of the studies.

Suggested research priorities

It has been suggested that a trial of a CBT for headache/migraine in primary care might be beneficial.(6) The trial should be against an active comparator and based on step-wise treatment to enable the identification of the specific component/s of CBT responsible for reducing the physical symptoms of headaches/migraines.

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Appendices

Appendix 1 – Search strategy

Ovid MEDLINE(R) 1946 to December Week 4 2012 - Searched 9th January 2013. Search strategy was used and adjusted for all other database searches.

1 exp Psychotherapy/ (140730)
2 exp Cognitive Therapy/ or exp Behavior Therapy/ (47326)
3 CBT.ti,ab. (3658)
4 (cognit* adj2 (therap* or treatment* or training or educat* or strateg* or technique* or psychotherap* or program* or intervention* or analys* or method* or approach* or modif* or adapt*)).mp. (23562)
5 (behav* adj2 (therap* or treatment* or training or educat* or strateg* or technique* or psychotherap* or program* or intervention* or analys* or method* or approach* or modif* or adapt*)).mp. (59882)
6 (relax* adj2 (therap* or treatment* or training or educat* or strateg* or technique* or psychotherap* or program* or intervention* or analys* or method* or approach* or modif*)).mp. (10217)
7 (psychological* adj therap*).ti,ab. (728)
8 psychological treatment*.ti,ab. (1856)
9 (behav* adj5 rehabilitat*).ti,ab. (627)
10 (cognit* adj5 rehabilitat*).ti,ab. (1105)
11 (behav* adj5 remed*).ti,ab. (168)
12 (group* adj therap*).ti,ab. (3442)
13 (psychological adj therap*).ti,ab. (726)

14 (psychological adj intervention*).ti,ab. (1835)
15 or/1-14 (184410)
16 headache/ or exp headache disorders/ (43230)
17 (chronic adj headache*).ti,ab. (1168)
18 migraine.ti,ab. (20796)
19 Migraine Disorders/ (18955)
20 or/16-19 (46720)
21 Randomized Controlled Trials as Topic/ or Clinical Trials as Topic/ (240537)
22 Controlled Clinical Trial/ (84845)
23 controlled clinical trial.pt. (84845)
24 randomized controlled trial.pt. (336117)
25 Random Allocation/ (75747)
26 double blind method/ or single blind method/ (132975)
27 ((singl* or doubl* or trebl* or tripl*) adj (blind* or mask*)).ti,ab. (114477)
28 research design/ (71861)
29 ((random* or control*) adj5 (trial* or stud*)).ti,ab. (446902)
30 (randomised or randomized or randomly).ti,ab. (447654)
31 Comparative Study/ (1596353)
32 Evaluation Studies as Topic/ (118993)
33 (control* adj (trial* or stud* or evaluation*)).mp. (629074)
34 (comparison group* or control* group*).mp. (252016)
35 Meta-Analysis/ (36248)
36 meta analy*.ti,ab. (42103)
37 "Outcome Assessment (Health Care)"/ (43499)
38 Intervention Studies/ (5584)
39 Prospective Studies/ (327783)
40 follow up studies/ (454863)
41 (systematic* adj (review* or methodolog* or research* or search*)).ti,ab. (39736)
42 ((hand or manual or computer or electronic or database) and search*).ti,ab. (39236)
43 (hand adj search*).ti,ab. (3012)
44 (medline or embase or cinahl or psychlit or psychinfo or scisearch or cochrane or "web of science").ab. (51033)
45 (electronic* adj search*).ab. (2017)
46 (synthes* adj5 (literature* or research* or studies or data)).ab. (19124)
47 (synthes* adj5 (literature* or research* or studies or data)).ti. (4825)
48 or/21-47 (3281915)
49 15 and 20 and 48 (495)
50 limit 49 to (english language and humans) (456)
51 (comment or editorial or letter).pt. (1148493)
52 50 not 51 (444)

Appendix 2 - Results of included studies grouped by intervention and comparator

CBT vs. Waiting list control		
Patient reported headache intensity, mean (SD)	**CBT**	**Comparator**
Basler et al. (1996)(21) (4 weeks post-treatment)	**(n=38)**	**WL (n=38)**
Intensity (4 times daily, 11-point scale 0-10/best-worst)	3.52 (1.56)	3.66 (1.35)
Richardson & McGrath (1989)(27)(8 weeks post)	**(n=7,7)**	**WL (n=9,8)**
Peak intensity (4 times daily, 6-point scale 0-5/best-worst),		
More severe	3.03 (0.38)	4.09 (0.61)
Less severe	3.13 (0.96)	3.16 (0.37)
Patient reported headache activity, mean (SD)	**CBT**	**Comparator**
Martin et al. (2007)(25)(12 months F-up)	**(n=10)**	**WL (n=8)**
Headache ratings (combined intensity, duration and frequency; 6-point scale) covariate adjusted post-treatment, p	0.207 (0.225)	0.434 (0.737)

=0.057)		
Patient reported headache frequency, mean (SD)	**CBT**	**Comparator**
Richardson & McGrath, 1989(27) (8 weeks post)	**(n=7,7)**	**WL (n=9,8)**
Frequency, mean (SD)		
More severe	11.86 (2.67)	18.67 (8.65)
Less severe	5.86 (1.77)	11.13 (8.46)
Patient reported headache-free days, mean (SD)	**CBT**	**Comparator**
Basler et al. (1996)(21) (4 weeks post)	**(n=38)**	**WL (n=38)**
Days without headache per week	3.00 (2.32)	3.07 (2.23)
Responder rate, n (%)	**CBT**	**Comparator**
Martin et al. (2007)(25) (8 weeks post)	**(n=20)**	**WL (n=12)**
>50% reduction in headache rating	14 (77.8)	3 (23.1)
>50% reduction medication use	11 (61.1)	4 (36.4)
Richardson & McGrath (1989)(27) (8 weeks post)	**(n=15)**	**WL (n=17)**
≥50 % reduction in headache activity	7[a] (47)	3[a] (18)
Medication use, mean (SD)	**CBT**	**Comparator**
Basler et al. (1996(21) (4 weeks post)	**(n=38)**	**WL (n=38)**
Days with pain medication per week	1.06 (1.09)	1.77 (1.66)
Martin et al. (2007)(25)(12 months F-up)	**(n=10)**	**WL (n=8)**
Pill count	1.26 (1.87)	1.00 (1.46)
Richardson & McGrath, 1989(27)} (8 weeks post)	**(n=9)**	**WL (n=11)**
Pain medication index	51.11 (77.56)	53.2 (47.8)

CBT plus relaxation vs. relaxation, placebo or waiting list control

Patient reported headache intensity, mean (SD)	**CBT+RLX**	**Comparators**		
Mosley et al. (1995)(26) (12 weeks post)	**(n=11)**	**RLX (n=10)**	**WL (n=9)**	
Headache index (av. weekly intensity over 4wks rated 4 x daily; 11-point scale 0-10/best-worst)	3.73 (2.73)	5.29 (3.51)	7.13 (3.33)	
Tobin et al. (1988)(24) (3 months F-up)	**(n=12)**	**RLX (n=12)**		
Peak intensity (4 times daily, 11-point scale 0-10/best-worst)	2.91 (2.42)	4.60 (2.89)		
Patient reported headache activity, mean (SD)	**CBT+RLX**	**Comparators**		
Blanchard et al. (1990)(28) (4 weeks post)	**(n=16)**	**RLX (n=19)**	**PL (n=16)**	**WL (n=15)**
Average daily headache activity (combined intensity, frequency and duration rated 4 x daily; 6-point scale 0-5/best-worst)	3.20 (3.70)	3.82 (2.59)	4.63 (4.30)	4.45 (3.38)
Tobin et al. (1988)(24) (3 months F-up)	**(n=12)**	**RLX (n=12)**		
Headache index (the sum of 4 daily headache activity recordings av. over each week; 11-point scale with 5	0.68 (0.95)	3.10 (1.75)		

anchor points 0-10/best-worst)				
Patient reported headache-free days, mean (SD)	**CBT+RLX**	**Comparators**		
Tobin et al. (1988)(24) (3 months F-up)	**(n=12)**	**RLX (n=12)**		
Headache-free days per week	5.77 (2.07)	3.59 (3.17)		
Responder rate, n (%)	**CBT+RLX**	**Comparators**		
Blanchard et al (1990)(28) (4 weeks post)	**(n=16)**	**RLX (n=19)**	**PL (n=16)**	**WL (n=15)**
≥50% improvement	10 (62.5)	6 (31.6)	7 (43.8)	3 (20.0)
Mosley et al. (1995(26) (12 weeks post)	**(n=11)**	**RLX (n=10)**	**WL (n=9)**	
Index: >50% improvement	7[a] (63.6)	4[a] (40)	0	
Medication use, mean (SD)	**CBT+RLX**	**Comparators**		
Blanchard et al. (1990(28) (4 weeks post)	**(n=16)**	**RLX (n=19)**	**PL (n=16)**	**WL(n=15)**
Pain medication index (potency and daily dose per headache medication, mean 4wk score)	20.7 (33.9)	9.8 (10.4)	8.3 (13.6)	22.5 (25.1)
Mosley et al. (1995(26) (12 weeks post)	**(n=11)**	**RLX (n=10)**	**WL (n=9)**	
Pain medication (pill count, average weekly mean)	2.18 (1.72)	3.90 (4.43)	5.22 (2.49)	

CBT plus relaxation vs. Antidepressants (amitriptyline)

Holroyd et al. (1991)(22) (12 weeks F-up)	**Intervention**	**Comparator**
	CBT+RLX (n=19)	**AM (n=17)**
Patient reported headache peak (4 times daily; 11-point scale 0-10/best-worst), mean (SD)	4.33 (2.35)	4.55 (1.98)
Headache index (mean level of pain), mean (SD)	0.96 (0.65)	1.49 (1.11)
Patient reported headache-free days, days without headache (%), mean (SD)	54.7 (27.5)	42.3 (32.9)
Responder rate, moderately (33-66% reduction) or substantially improved (>66% reduction), n (%)	17 (90)	9 (53)
Pain medication, mean (SD)	0.26 (0.52)	0.82 (1.17)

CBT plus placebo vs. CBT plus medication, medication or placebo

Holroyd et al. (2001, 2009)(30) (6 months F-up)	**Intervention**	**Comparators**		
	CBT+PL (n=38)	**CBT+AM (n=45)**	**AM (n=48)**	**PL (n=38)**
Patient reported headache, overall activity index (rated 4 times daily; 11-point scale with 5 anchor points, 0-10/best-worst), mean	1.9[b]	1.65[b]	1.75[b]	2.6[b]
Patient reported days of least moderate pain (pain rating ≥5), mean	6.6[b]	6.6[b]	6.8[b]	11.8[b]
Responder rate, >50% reduction in headache index scores, n/N (%)	17/49 (35)	34/53 (64)	20/53 (38)	14/48 (29)
Pain medication index (potency and daily dose per headache medication), mean	29[b]	23[b]	22[b]	39[b]

Clinic-based CBT vs. self-management CBT		
Richardson & McGrath (1989)(27) (6 months F-up)	**Intervention**	**Comparator**
	CBT (n=7,7)	**CBT-SM (n=6,8)**
Patient reported peak headache intensity (4 times daily, 6-point scale 0-5/best-worst), mean (SD)		
More severe	3.03 (0.38)	3.47 (0.50)
Less severe	3.13 (0.96)	2.95 (1.17)
Patient reported headache frequency, mean (SD)		
More severe	11.86 (2.67)	14.33 (6.50)
Less severe	5.86 (1.77)	5.25 (1.83)
Responder rate, ≥50% reduction in headache activity	7[1] (47) (n=15)	5[1] (33) (n=15)
Medication use, pain medication index	51.11 (77.56) (n=9)	25.00 (35.53) (n=8**)**
Martin et al. (1989)(23) (12 months F-up)	**CBT (n=31)**	**CBT-SM (n=31)**
Patient reported daily headache activity index (frequency, intensity and duration; intensity rated hourly on 6-point scale - no details about the scale), mean	0.31[b]	0.37[b]
CBT vs. biofeedback		
Martin et al. (2007)(25)(12 months F-up), mean (SD)	**Intervention**	**Comparator**
	CBT (n=10)	**BF (n=11)**
Patient reported headache ratings (combined intensity, duration and frequency; 6-point scale)	0.207 (0.225)	0.364 (0.506)
Responder rate: >50% reduction in headache rating	14 (77.8)	12 (63.2)
>50% reduction medication use	11 (61.1)	11 (57.9)
Pain medication (pill count)	1.26 (1.87)	1.05 (1.95)

CBT plus biofeedback vs. biofeedback plus relaxation, placebo or waiting list				
Blanchard et al. (1990)(29) (12 weeks F-up), mean (SD)	**CBT+BF**	**Comparators**		
	(n=30)	**BF+RLX (n=32)**	**PL (n=24)**	**WL (n=30)**
Patient reported average daily headache activity (combined intensity, frequency and duration rated 4 times daily; 6-point scale 0-5/best-worst)	1.90 (2.16)	2.05 (2.22)	1.94 (1.65)	2.53 (2.53)
Responder rate, ≥ 50% improvement, n (%)	15 (50.0)	17 (53.1)	9 (37.5)	6 (20.0)
Pain medication index (potency and daily dose per headache medication, mean 4wk score)	8.4 (13.6)	11.2 (21.9)	11.9 (23.9)	20.7 (34.8)

[a] Data calculated by reviewers. [b] Data estimated from graph by reviewers. AM: Antidepressant medication. BF: Biofeedback. CBT: Cognitive Behaviour Therapy. CBT-SM: Cognitive Behaviour Therapy – Self-Managed. F-up: Follow-up. PL: Placebo. RLX: Relaxation. WL: Waiting List.