Effectiveness of hands-off therapy in the management of primary headache : a systematic review and meta-analysis

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Abstract

A number of hands-off therapies have been widely reported and are used in the management of headache. This systematic review and meta-analysis aimed to assess evidence supporting these therapies on selected headache outcomes. A systematic literature search for randomized clinical trials reporting on the effects of hands-off therapies for headache was performed in two electronic databases; PubMed and Web of Science (PROSPERO: CRD42018093559). Risk of bias was assessed using the Cochrane risk of bias tool. Meta-analysis was performed using Review Manager v5.4. Thirty-five studies, including 3403 patients with migraine, tension-type or chronic headaches were included in the review. Methodological quality of the studies ranged from poor to good. Result-synthesis revealed moderate evidence for aerobic exercises, relaxation training and pain education for reducing pain intensity and disability. Other hands-off interventions were either weak or limited in evidence. Meta-analysis of 22 studies indicated that the effect of hands-off therapies significantly differed from one another for pain intensity, disability and quality of life ($p<0.05$). Relaxation training, aerobic and active/stretching exercises had significant effect on pain intensity and disability ($p<0.05$). To conclude, few hands-off therapies were effective on selected headache outcomes. Evidence to support other hands-off therapies is limited by paucity of studies.

Keywords: Effectiveness, hands-off, therapy, headache, trials

Background

Headache is a major public health problem (Molarius & Tegelberg, 2006; Saylor & Steiner, 2018; Stovner, Zwart, Hagen, Terwindt, & Pascual, 2006), with impact on both patients and society (Rasmussen, 1999; Seddik et al., 2020). Throughout the world, people who are affected by headache and professionals working in the field of headache know that these disorders often continue lifelong (Saylor & Steiner, 2018; Steiner, 2005). Headache is classified as either primary headache, which refers to persistent head pain without any underlying cause, this includes migraine, tension type headache, cluster headache and chronic headache (Dodick, 2003; Stovner et al., 2006), or secondary headache, which results from trauma or another underlying systemic disorder or medical cause (Benoliel et al., 2019; Dodick, 2003). The global prevalence of three common types of headaches; migraine, tension type headache and chronic daily headache, is estimated at 10%, 38% and 3%, respectively (Jensen & Stovner, 2008).

To achieve high quality care and reduction of cost burden, correct treatment is important in the management of headache. However, effective long-term management can be challenging, because these disorders are complex and often present with heterogeneous triggers, expression and impact (Rathier & Roth, 2015). The treatment approaches of headache mainly include pharmacological/drug-therapy (Evers et al., 2009) and non-pharmacological treatments. Additionally, most of the non-pharmacological therapies used for headache can appropriately fit into either a hands-on or hands-off therapy. Hands-on therapy involves the use of manual contact by the therapist (Jull & Moore, 2012; Pierce-Williams, Saccone, & Berghella, 2019), whereas hands-off therapy involves giving instructions, guidance, self-administered treatment, all lacking a direct patient-therapist physical contact (Jull & Moore, 2012). Hands-off therapies include psychological treatment, biofeedback therapy, behavioral and cognitive therapy, patient education

(Andersson, Lundström, & Ström, 2003) and physical training (Ylinen, Nikander, Nykänen, Kautiainen, & Häkkinen, 2010), etc., while hands-on therapies include acupuncture, manipulation and massage etc. (Castien, Van Der Windt, Dekker, Mutsaers, & Grooten, 2009; Torelli, Jensen, & Olesen, 2004). The improvement of biopsychosocial model and modern neuroscience approach in the management of chronic pain lead to increased use of hands-off treatments (Gaul et al., 2009). Although patients may wish to have a physical treatment contact with therapists (Bishop, Bialosky, & Cleland, 2011; Lurie et al., 2008; Verbeek, Sengers, Riemens, & Haafkens, 2004), evidence on the effectiveness, the increase in self-efficacy and the affordability of interventions may be more important in decision making. Furthermore, considering the enormous burden of headache on patients, their jobs, social and family life, as well as on the health care system and insurance companies, it is important to investigate the effectiveness of alternative therapies that require less hospital visits, less dependency and improve productivity. Previous reviews have investigated the effectiveness of non-pharmacological therapies (self-management) for headache (without physical therapy, exercises and biofeedback) (Probyn et al., 2017) and the effects of interventions that are a mix of hands on and hands-off therapies (Baillie, Gabriele, & Penzien, 2014; Biondi, 2005; Luedtke, Allers, Schulte, & May, 2016). However, to our knowledge, no systematic review has investigated the effect of hands-off therapies in the management of headache. Therefore, the aim of the present systematic review (SR) is to summarize the evidence for the effectiveness of hands-off therapy on pain intensity and disability, quality of life, and sleep quality in the management of headache based on the results of existing randomized clinical trials (RCTs).

Methods

The present SR is reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guideline (Moher, Liberati, Tetzlaff, & Altman, 2009). In addition, the review protocol was pre-registered in PROSPERO (CRD42018093559) prior to starting the literature search. The research question of the SR was determined using the PICOS approach: what is the effectiveness of hands-off therapy (I=intervention) on pain intensity, disability, quality of life and sleep quality (O=outcome) in patients suffering from primary headache (migraine, tension type headache and chronic headache) (P=patient) when compared to controls (C=comparison) in RCT's (S=study design). The focus of this review was on studies in which patients with headache were managed with interventions that were either self-administered by the patients or do not require physical contact between the therapist and the patients.

Information sources and search strategy

To identify relevant articles, the online databases of PubMed (1966 to 2020) and Web of Science (1955 to 2020) were searched for published articles using a search strategy that was created based on the PICOS approach (Table 1). PubMed being an optimal tool in biomedical electronic research was used for the data search (Falagas, Pitsouni, Malietzis, & Pappas, 2008). Web of Science was also searched for its multidisciplinary nature and strong coverage (Aghaei Chadegani et al., 2013). We consider the coverage of the two databases sufficient as they mostly cover fields of other specialized databases.

The database search was carried in July 2018, and later updated on the 27th January 2020. In both instances, the reference list of the potentially relevant studies was screened to make the review as complete as possible.

Eligibility criteria

To be included in this review, studies had to meet these criteria: 1) adults (≥ 18 years) with any of headache, migraine, cephalgia or head pain, 2) studies that included assessment of effectiveness of 'hands-off therapy' (including pain education, neuroscience education, exercise therapy, stretching, relaxation, ergonomics, graded activity, graded exposure, cognitive behavioral therapy, exercise, aerobics, yoga, motor control, movement control, body movement therapy, sauna, mindfulness and meditation), 3) evaluation of pain intensity, disability, QoL and sleep quality, and 4) available full-text RCTs in English. The focus of the review is on effectiveness of interventions, therefore only RCTs were included in the review.

Study selection

The screening consisted of two phases. Firstly, the articles were screened based on titles and abstracts (eligibility criteria derived from the PICOS question). In the second screening, the full-text reports of articles that were considered potentially eligible and relevant were retrieved. The assessors independently performed both the eligibility assessment and the evaluations. Conflicts were later discussed via a physical meeting to obtain consensus for all the studies included. The screening procedure was performed by two researchers; a PhD student (NBM) and post-doctoral researcher (JM) who are experienced in systematic reviews and conservative management of chronic pain on the Rayyan software (https://rayyan.qcri.org).

Assessment of risk of bias and evidence synthesis

The risk of bias (Tikhonova et al.) in the included studies was evaluated by two assessors (authors; NBM and JM) who were initially blinded from each other's evaluation. The Cochrane collaboration's tool for assessing ROB in randomized trials (Higgins et al., 2011) was used for assessing the quality of the included studies, and each study could be graded as having good, fair or poor quality. The two assessors (NBM, JM) and a third author (MM) agreed a priori that, if a study has only one item rated unclear, while the remaining items were rated low ROB across the other domains, a second step analysis was performed. Depending on the appraisal whether the unclear item rated was likely to have biased the outcome or not, such a study was considered as fair or good quality, respectively.

On a general note, the overall methodological quality of the included RCTs was classified as either good, fair or poor after taking into account all the domain scores as presented below:

i. Nine out of the 35 studies were graded as having good methodological quality following assessment (Aguirrezabal et al., 2019; Alvarez-Melcon, Valero-Alcaide, Atin-Arratibel, Melcon-Alvarez, & Beneit-Montesinos, 2018; John, Sharma, Sharma, & Kankane, 2007; Kanji, Weatherall, Peter, Purdie, & Page, 2015; Lin & Wang, 2015; Madsen, Søgaard, Andersen, Tornøe, & Jensen, 2018; Seng et al., 2019; Söderberg, Carlsson, Stener-Victorin, & Dahlöf, 2011; Varkey, Cider, Carlsson, & Linde, 2011);
ii. Thirteen studies were found to have fair quality (Bhombal, Usman, & Ghufran, 2014; Bromberg et al., 2012; Calhoun & Ford, 2007; D'Souza, Lumley, Kraft, & Dooley, 2008; Kleiboer, Sorbi, van Silfhout, Kooistra, & Passchier, 2014; Lee & Lee, 2019; Martin et al., 2014; Merelle, Sorbi, van Doornen, & Passchier, 2008; Rothrock et al., 2006; Sertel, Bakar, & Simsek, 2017; Slavin-Spenny, Lumley, Thakur, Nevedal, & Hijazi, 2013; Soderberg, Carlsson, & Stener-Victorin, 2006; Sorbi, Kleiboer, van Silfhout, Vink, & Passchier, 2015); and
iii. Thirteen studies were found to be of poor methodological quality (Abbott, Hui, Hays, Li, & Pan, 2007; Abdoli, Rahzani, Safaie, & Sattari, 2012; Bakhshani, Amirani, Amirifard, & Shahrakipoor, 2015; Devineni & Blanchard, 2005; Dittrich et al., 2008; Holroyd et al., 2001; Khazraee, Omidi, Kakhki, Zanjani, & Sehat, 2018; Lockett & Campbell, 1992; McGrady, Wauquier, McNeil, & Gerard, 1994; Narin, Pinar, Erbas,

Ozturk, & Idiman, 2003; Peres, Mercante, & de Oliveira, 2019; Rashid-Tavalai, Bakhshani, Amirifard, & Lashkaripour, 2015; Tavallaei, Rezapour-Mirsaleh, Rezaiemaram, & Saadat, 2018).

Most of the poor quality studies did not have sufficient information (unclear risk) concerning random sequence generation, allocation concealment and blinding (participants/outcomes assessment) (Figure 2)

Data extraction

From all the included studies, the two assessors (NBM and JM) independently extracted and harmonized information on population, study country, age range/mean, study groups, nature of intervention/control, outcomes/measures and results.

Narrative synthesis

We performed the qualitative synthesis of the available information by adopting and modifying the scale used by Bakker et al (Bakker, Verhagen, van Trijffel, Lucas, & Koes, 2009). The number of studies evaluating an intervention, the methodological quality of the studies and the consistency of the available evidence was used to generate a 5-level of evidence using the modified scale as presented in Table 2 while the evidence of the included studies is contained in Table 3.

Quantitative synthesis

Meta-analysis was conducted using *Review Manager (version 5.4).* Data for meta-analysis was extracted from studies that the data allow for meta-analyses using Microsoft Excel by the first author (NBM) and verified by another author (JM). Only studies with control group (placebo or wait-list or treatment as usual) were considered for the pairwise meta-analysis. For studies with two or more intervention groups, each intervention group was compared to the same control group by first calculating the standard error (SE) and subjecting it to approximate adjustment as recently described (Rücker, Cates, & Schwarzer, 2017). This was necessary in order to conform with pairwise analysis, and also avoid unit of analysis error. Where appropriate, the standard error of the outcomes were calculated using the statistical calculator available on the *Review Manager*. The pairwise comparison for each outcome was based on the Generic inverse variance (IV) method based on a random effects (RE) as analysis in view of the variation in the outcome measures in the studies. Only subtotal analyses were performed in order to quantify the effect of each hands-off therapy. The results were presented as standardized mean differences (SMD), SE with their correspondent 95% confidence interval (CI). Statistical significance was achieved at 0.05 alpha probability level.

Results

Study selection

As shown in Figure 1, a total of 2190 records were retrieved from the online databases search. After the duplicates were removed, 1909 unique items remained. Of these, 1847 articles were excluded for not fulfilling the eligibility criteria (title and abstract screening). Thereafter, the full-text reports of the remaining 62 articles were retrieved and evaluated based on the inclusion and exclusion criteria. 35 articles met the inclusion criteria for the review and were included for the qualitative evidence synthesis. During the full-text screening, the assessors had 84% agreement. The conflict on the remaining 16% difference (7 articles) was resolved after meeting.

Twenty two studies contributed to the meta-analysis. Of these, 5 studies compared more than one treatment group with the same control group (Abdoli et al., 2012; D'Souza et al., 2008; Sertel et al., 2017; Slavin-Spenny et al., 2013). The remaining thirteen studies not included in the meta-analyses were only excluded because the available data was not appropriate for meta-analysis

(Abbott et al., 2007; Abdoli et al., 2012; Aguirrezabal et al., 2019; Calhoun & Ford, 2007; Dittrich et al., 2008; Seng et al., 2019), or there was a lack of appropriate control group (Lee & Lee, 2019; Peres et al., 2019; Rothrock et al., 2006; Soderberg et al., 2006; Söderberg et al., 2011), and/or the data was of poor quality (Lockett & Campbell, 1992). Of the four outcomes reported in the systematic review, only studies reporting on pain intensity, disability and quality of life outcomes were included in the meta-analysis. Sleep quality was only reported in the systematic review.

Risk of bias within studies

Initially, the assessors had 83% agreement (203 out of 245 items). After an additional discussion, a consensus lead to 99% agreement. The remaining differences were solved by the consultation of the third assessor (MM). As for the overall assessment/grading of the included studies (good, fair or poor quality), there was only disagreement for 3 studies, and this was resolved after discussing with the third assessor (MM).

Study characteristics

A total of 3403 (2797 females) patients with different types of headaches participated across the included studies. Majority of the participants were females (82%) mainly having migraine, TTH and chronic headache. Twenty-three out of the 35 studies reported on migraine (Aguirrezabal et al., 2019; Bakhshani et al., 2015; Bhombal et al., 2014; Bromberg et al., 2012; Calhoun & Ford, 2007; D'Souza et al., 2008; Devineni & Blanchard, 2005; Dittrich et al., 2008; John et al., 2007; Khazraee et al., 2018; Kleiboer et al., 2014; Lockett & Campbell, 1992; Martin et al., 2014; McGrady et al., 1994; Merelle et al., 2008; Narin et al., 2003; Peres et al., 2019; Rashid-Tavalai et al., 2015; Rothrock et al., 2006; Seng et al., 2019; Sorbi et al., 2015; Tavallaei et al., 2018; Varkey et al., 2011), 15 reported on tension type headache (Abbott et al., 2007; Abdoli et al., 2012; Alvarez-Melcon et al., 2018; Bakhshani et al., 2015; D'Souza et al., 2008; Devineni & Blanchard, 2005; Holroyd et al., 2001; Kanji et al., 2015; Lee & Lee, 2019; Madsen et al., 2018; Peres et al., 2019; Sertel et al., 2017; Soderberg et al., 2006; Söderberg et al., 2011; Tavallaei et al., 2018), while four studies investigated patients with primary chronic headaches (Khazraee et al., 2018; Lin & Wang, 2015; Peres et al., 2019; Slavin-Spenny et al., 2013). The sample size of included studies varied from 20 to 368.

The hands-off interventions reported are; aerobic exercises (Dittrich et al., 2008; Lockett & Campbell, 1992; Narin et al., 2003; Peres et al., 2019; Sertel et al., 2017; Soderberg et al., 2006; Söderberg et al., 2011; Varkey et al., 2011), avoidance training (Martin et al., 2014), behavioral/cognitive therapy (Bhombal et al., 2014; Bromberg et al., 2012; Calhoun & Ford, 2007; Devineni & Blanchard, 2005; Kleiboer et al., 2014; Martin et al., 2014; Merelle et al., 2008; Seng et al., 2019; Sorbi et al., 2015; Tavallaei et al., 2018), biofeedback exercises (Lee & Lee, 2019), guided imagery (Abdoli et al., 2012), pain education (Aguirrezabal et al., 2019; Rothrock et al., 2006), learning to cope with triggers (Martin et al., 2014; Rashid-Tavalai et al., 2015), psychotherapy (acceptance and commitment therapy) (Khazraee et al., 2018), relaxation training (D'Souza et al., 2008; McGrady et al., 1994; Peres et al., 2019; Slavin-Spenny et al., 2013; Soderberg et al., 2006; Söderberg et al., 2011; Varkey et al., 2011), stress management therapy (Holroyd et al., 2001), Tai-Chi (Abbott et al., 2007), sauna (Kanji et al., 2015) and yoga (John et al., 2007). Other hands-off interventions tested in the studies are self-administered; strength training (Madsen et al., 2018) and stretching exercises (Lee & Lee, 2019; Lin & Wang, 2015). For the outcomes: pain intensity in the studies was majorly assessed by Visual Analogue Scale (VAS) (Abdoli et al., 2012; Alvarez-Melcon et al., 2018; Narin et al., 2003; Sertel et al., 2017; Varkey et al., 2011) and Numeric Rating Scale (NRS) (Bakhshani et al., 2015; John et al., 2007; Kanji et al., 2015; Lin & Wang, 2015; Madsen et al., 2018; Martin et al., 2014; Sorbi et al., 2015); quality of life (QoL) was assessed by migraine specific quality of life (MSQOL) (Kleiboer et al., 2014; Merelle et al., 2008; Sorbi et al., 2015; Varkey et al., 2011), world health organization quality of life (WHOQOL) (Rashid-Tavalai et al., 2015) and SF-36 questionnaires (Abbott et al., 2007; Bakhshani et al., 2015; Sertel et al., 2017); disability was assessed using migraine disability assessment scale (MIDAS) (Aguirrezabal et al., 2019; Bromberg et al., 2012; D'Souza et al., 2008; Merelle et al., 2008; Rothrock et al., 2006; Seng et al., 2019; Slavin-Spenny et al., 2013; Sorbi et al., 2015; Tavallaei et al., 2018), pain disability index (PDI) (Narin et al., 2003; Sertel et al., 2017) and headache disability index/inventory (HDI) (Devineni & Blanchard, 2005; Holroyd et al., 2001; Khazraee et al., 2018; Lee & Lee, 2019; Seng et al., 2019); and sleep quality was assessed by Minor Symptom Evaluation Profile questionnaire (MSEP) (Söderberg et al., 2011) and sleep characteristics inventory (Calhoun & Ford, 2007). In this review, twenty-six (Abdoli et al., 2012; Aguirrezabal et al., 2019; Alvarez-Melcon et al., 2018; Bakhshani et al., 2015; Bhombal et al., 2014; Dittrich et al., 2008; John et al., 2007; Kanji et al., 2015; Khazraee et al., 2018; Kleiboer et al., 2014; Lin & Wang, 2015; Lockett & Campbell, 1992; Madsen et al., 2018; Martin et al., 2014; McGrady et al., 1994; Merelle et al., 2008; Narin et al., 2003; Peres et al., 2019; Rashid-Tavalai et al., 2015; Seng et al., 2019; Sertel et al., 2017; Slavin-Spenny et al., 2013; Soderberg et al., 2006; Sorbi et al., 2015; Tavallaei et al., 2018; Varkey et al., 2011), ten (Bakhshani et al., 2015; Bhombal et al., 2014; Dittrich et al., 2008; Kleiboer et al., 2014; Merelle et al., 2008; Narin et al., 2003; Rashid-Tavalai et al., 2015; Sertel et al., 2017; Sorbi et al., 2015; Varkey et al., 2011), eighteen (Aguirrezabal et al., 2019; Bromberg et al., 2012; D'Souza et al., 2008; Devineni & Blanchard, 2005; Holroyd et al., 2001; Kanji et al., 2015; Khazraee et al., 2018; Kleiboer et al., 2014; Lee & Lee, 2019; Merelle et al., 2008; Narin et al., 2003; Peres et al., 2019; Rothrock et al., 2006; Seng et al., 2019; Sertel et al., 2017; Slavin-Spenny et al., 2013; Sorbi et al., 2015; Tavallaei et al., 2018) and three (Calhoun & Ford, 2007; Kanji et al., 2015; Söderberg et al., 2011) RCTs reported on pain intensity, QoL, disability and sleep quality, respectively.

Narrative synthesis of the review results

Exercise training

Twelve studies (Alvarez-Melcon et al., 2018; Dittrich et al., 2008; Lee & Lee, 2019; Lin & Wang, 2015; Lockett & Campbell, 1992; Madsen et al., 2018; Narin et al., 2003; Peres et al., 2019; Sertel et al., 2017; Soderberg et al., 2006; Söderberg et al., 2011; Varkey et al., 2011) reported treatment effects of different types of exercise interventions in headache management. Aerobic exercises/physical training for headache was reported in 8 studies (Dittrich et al., 2008; Lockett & Campbell, 1992; Narin et al., 2003; Peres et al., 2019; Sertel et al., 2017; Soderberg et al., 2006; Söderberg et al., 2011; Varkey et al., 2011), of which seven (Dittrich et al., 2008; Lockett & Campbell, 1992; Narin et al., 2003; Sertel et al., 2017; Soderberg et al., 2006; Varkey et al., 2011) assessed pain intensity as the study outcome. The results indicated that pain intensity was only significantly reduced in patients with headaches compared to control subjects in 4 studies (Dittrich et al., 2008; Narin et al., 2003; Peres et al., 2019; Sertel et al., 2017). Three other studies (Lockett & Campbell, 1992; Soderberg et al., 2006; Varkey et al., 2011), reported no significant reduction in pain intensity compared to control.

Quality of life was reported across three studies (Narin et al., 2003; Sertel et al., 2017; Varkey et al., 2011), of which two recorded significant improvements (Narin et al., 2003) (Sertel et al., 2017). Furthermore, two studies reported significant reduction in disability level following exercise training (Narin et al., 2003; Sertel et al., 2017). One study investigated sleep quality and no significant difference existed when compared with the control (Söderberg et al., 2011). One study (Alvarez-Melcon et al., 2018) reported that active exercises of head, neck and shoulder decreases pain intensity, while two studies reported different results for the efficacy of stretching exercises of the neck and chest regions in decreasing pain intensity among patients with headache (Lee & Lee, 2019; Lin & Wang, 2015). Lastly, Madsen et al. investigated the effects of progressive strength training for headache patients and they found that there was no significant difference in pain intensity compared to the control after intervention (Madsen et al., 2018).

It was concluded that **aerobic exercises** are effective in reducing **pain intensity** among patients with headache (*moderate evidence*). The evidence to support reduction in **disability and** improvement in **sleep quality** among patients with headache following aerobic exercises is *weak*. Meanwhile, *conflicting evidence* was found on the effects of aerobic exercises in enhancing **QoL.**

Furthermore, there is *weak evidence* to support the use of **active and stretching exercises** of the head, neck and shoulder in reducing **pain intensity** among patient with headache. Lastly, *weak evidence* suggests that **progressive resistance training** is not effective in reducing **pain intensity** for these patients.

Behavioral and/or Cognitive therapies

The effects of behavioral and/or cognitive therapy in the management of headache was investigated across ten studies (Bhombal et al., 2014; Bromberg et al., 2012; Calhoun & Ford, 2007; Devineni & Blanchard, 2005; Kleiboer et al., 2014; Martin et al., 2014; Merelle et al., 2008; Seng et al., 2019; Sorbi et al., 2015; Tavallaei et al., 2018). Pain intensity was assessed in 7 studies (Bhombal et al., 2014; Kleiboer et al., 2014; Martin et al., 2014; Merelle et al., 2008; Seng et al., 2019; Sorbi et al., 2015; Tavallaei et al., 2018), however, a significant reduction in pain intensity among patients with headaches compared to control group was only found in 3 studies (Bhombal et al., 2014; Sorbi et al., 2015; Tavallaei et al., 2018), the remaining studies reported comparable results (Kleiboer et al., 2014; Martin et al., 2014; Merelle et al., 2008; Seng et al., 2019). Of the seven studies that assessed the effects of behavioral and/or cognitive therapy on disability level (Bromberg et al., 2012; Devineni & Blanchard, 2005; Kleiboer et al., 2014; Merelle et al., 2008; Seng et al., 2019; Sorbi et al., 2015; Tavallaei et al., 2018), only four studies recorded significant reductions in disability scores (Devineni & Blanchard, 2005; Kleiboer et al., 2014; Seng et al., 2019; Tavallaei et al., 2018). Quality of life was assessed by 4 studies (Bhombal et al., 2014; Kleiboer et al., 2014; Merelle et al., 2008; Sorbi et al., 2015), and significant improvement in QoL scores was reported in only two of these studies (Bhombal et al., 2014; Kleiboer et al., 2014). Lastly, one study investigated and found sleep quality to be significantly improved following behavioral therapy (Calhoun & Ford, 2007).

It was concluded that there is *conflicting evidence* to support the effectiveness of **behavioral and/or cognitive therapies** in improving **pain intensity, QoL and disability** levels, while the evidence to support their efficacy on **sleep quality** of patients with headache is *limited*.

Relaxation training

The use of relaxation training for managing patients with headache was reported across 7 studies (D'Souza et al., 2008; McGrady et al., 1994; Peres et al., 2019; Slavin-Spenny et al., 2013; Soderberg et al., 2006; Söderberg et al., 2011; Varkey et al., 2011). Out of four studies that reported the effects of relaxation training on pain intensity (McGrady et al., 1994; Peres et al., 2019; Soderberg et al., 2006; Varkey et al., 2011), two studies reported significant pain reduction among patients with headaches compared to control (McGrady et al., 1994; Peres et al., 2019). D’Souza et al (D'Souza et al., 2008) and Slavin-Spenny et al (Slavin-Spenny et al., 2013) investigated and found that relaxation training significantly reduced the disability scores of patients with headaches compared to the control groups. In contrast, two studies investigated the impact of relaxation training on the QoL, but did not find any significant difference between the experimental and other groups comprising of stand-alone interventions (acupuncture, exercise training and topiramate drug) (Söderberg et al., 2011; Varkey et al., 2011). Lastly, one study assessed the impact of relaxation training on sleep quality and the results indicated that the intervention had no significant effect on sleep quality (Söderberg et al., 2011)**.**

There is *moderate level evidence* to support the effect of **relaxation training** in reducing **disability** and **pain intensity**. The evidence to support the use of relaxation training on **sleep quality** is *weak.* The use of relaxation training does not improve **QoL** of patients with headache *(strong evidence).*

Avoidance, coping and stress management techniques

Avoidance, coping and/or stress management techniques were reported in four studies (Bakhshani et al., 2015; Holroyd et al., 2001; Martin et al., 2014; Rashid-Tavalai et al., 2015). Bakhshani et al (Bakhshani et al., 2015) and Holroyd et al (Holroyd et al., 2001) found significant improvement in pain intensity, disability and QoL of patients with headache following stress management. Secondly, while Martin et al (Martin et al., 2014) found coping techniques to significantly reduce pain intensity, Rashid-Tavalai et al (Rashid-Tavalai et al., 2015) did not find any significant impact. Finally, Martin et al (Martin et al., 2014) reported the effect of avoidance of triggers and it was not effective in reducing pain intensity.

There is *weak evidence* to support the use of **stress management therapy** for improving **pain intensity, disability and QoL** of patients with headache. There is *conflicting evidence* to support the effect of **coping techniques** on **pain intensity**, the evidence to support the use of **avoidance of triggers** in managing **pain intensity** among patients with headache is *limited*.

Education

Two studies by Rothrock et al (Rothrock et al., 2006) and Aguirrezabal et al (Aguirrezabal et al., 2019) reported on the effect of pain education in the management of headache. In comparison with control group, education was found to significantly reduce disability levels in both studies, while pain intensity was significantly reduced in one study (Aguirrezabal et al., 2019) among patients with headaches.

There is *moderate* and *weak* level evidence to support using **pain education** for reducing **disability** and **pain intensity** among headache patients, respectively.

Other interventions

The effects of psychotherapy in form of *acceptance and commitment therapy (ACT)* in patients with headache was reported by Khazraee et al (Khazraee et al., 2018), and their results indicated significant reduction in pain intensity and disability. One study by Lee and Lee reported that *biofeedback* exercises led to significant reduction in headache related disability (Lee & Lee, 2019). Abdoli et al (Abdoli et al., 2012) assessed the effects of *guided imagery* in the management of patients with headache, and they found a significant reduction in headache pain intensity. Abbott et al (Abbott et al., 2007) reported on the effects of *Tai-Chi* in the treatment of headache patients, and reported a significant improvement in QoL among the patients compared to the control group. Kanji et al reported on the effects of *Sauna* in managing pain intensity, disability and sleep quality among patients with headache patients (Kanji et al., 2015). Their results indicated significant reduction in pain intensity and disability, but not sleep quality among patients with headache compared to the control group. John et al (John et al., 2007) assessed the effect of *Yoga* in the management of headache, and they reported a significant reduction in pain intensity among the experimental group in comparison to the control group.

For improvement in **pain intensity**, the evidence to support the use of **sauna bathing** and **yoga** in patients with headache is *weak* while **ACT** and **guided imagery** are supported by *limited evidence*. Additionally, there is *weak* evidence supporting the effectiveness of **biofeedback exercises,** and **sauna bathing** in improving **disability** in patients with headache whereas **ACT** is supported by *weak evidence*. Lastly, there is *limited* evidence supporting the effectiveness of **Tai-Chi** in improving **QoL** of patients with headache.

Quantitative synthesis of the review results

The results of the pairwise meta-analyses indicated the effect of 14, 8 and 5 hands-off therapy on pain intensity, disability and quality of life respectively (Figure 3a, 3b & 3c). The sub-group analyses showed that the effect of hands-off therapies significantly differed for all the three outcomes analyzed as follows; pain intensity (X^2=161.80; I^2=92%; p=0.00001), disability (X^2=20.01; I^2=64%; p=0.006) and quality of life (X^2=18.55; I^2=78.4%; p=0.0010). Behavioral/Cognitive therapy was the mostly reported hands-off therapy. However, the results indicated that it had only a small effect on pain intensity (Effect size = -0.17; CI= -0.30 to -0.04; I^2=; 0%; p=0.010), moderate effect on disability (Effect size = -0.5; CI= -0.88 to -0.13; I^2=; 88%; p=0.009) and no significant effect on quality of life (Effect size = -0.09; CI; -0.24 to 0.05; I^2=; 9%; p=0.22). Aerobic exercise training also showed a large effect on pain intensity (Effect size = -2.23; CI= -2.81 to -1.66; I^2=; 0%; p<0.00001), but not for disability level (Effect size = -1.96; CI= -5.04 to 1.11; I^2=; 96%; p=0.21). Relaxation training showed moderate effect on both pain intensity (Effect size = -0.40; CI= -0.76 to -0.03; I^2=; 0%; p=0.03), and disability level (Effect size = -0.42;

CI= -0.76 to -0.07; I^2=; 0%; p=0.02). Finally, active and stretching exercises also had a moderate effect on pain intensity of patients with headache (Effect size = -0.41; CI= -0.68 to -0.14; I^2=; 0%; p=0.003).

The remaining studies included in the sub-group pairwise meta-analyses per outcome were single studies. Nevertheless, the results indicated that some of the hands-off interventions had either significant effect on either pain intensity or disability. The interventions include body awareness therapy and anger awareness therapy, stress management, yoga, and body awareness therapy. Interventions such as sauna, progressive resisted exercise, avoidance therapy, acceptance and commitment, coping, and written and emotional disclosure did not have any significant effect. On the overall, beside stress management, none of the other hands-off therapies was effective in improving the quality of life of patients with headache.

Discussion

The present SR and meta-analysis evaluated the existing evidence for the effectiveness of hands-off therapy in the management of patients suffering from primary headache. To our knowledge, this is the first study to categorize hands-off therapies as an intervention group and review its effectiveness. Although some of the therapies may be administered as adjuvant therapies, a lot of other therapies are prescribed as standalone treatment thereby necessitating evidence for their effectiveness. The results of this SR, as supported by moderate evidence, found aerobic exercises, relaxation training and pain education as the effective hands-off therapies for primary headache management. In a somewhat similar fashion, the meta-analysis result found hands-off therapies such as aerobic exercise and relaxation training to be effective in decreasing pain intensity and disability, but rarely for improving quality of life for primary headache patients.

Exercise training

Although several hands-off therapy methods were reported in the included studies of this SR, there are varying effects of the interventions used. Self-administered exercises were the most common hands-off therapy used in managing headache patients. Aerobic exercises were the most frequent type of exercises used in reducing pain and disability among these patients in the SR (moderate evidence). This is not surprising because aerobic exercises were considered as a new approach for migraine prevention and treatment (Nicholson, Buse, Andrasik, & Lipton, 2011). Moreover, exercises have been reported to induce analgesia by activation of central inhibitory pathways (Lima, Abner, & Sluka, 2017). On the other hand, weak evidence (SR) was mostly found to support improvement in sleep quality and a conflicting evidence on QoL. The meta-analysis results only included a few of the studies reporting on aerobic exercise studies. Only two aerobic exercise studies were entered for meta-analysis (Narin et al., 2003;

Sertel et al., 2017) as the remaining were excluded because of lack of appropriate control group. Despite this a conclusive evidence was found. The range of the exercise duration per session as reported by the included studies was 40-45mins, the frequency was 2-5 times weekly and all exercises lasted for 6 weeks to 3 months. Although we found many studies reporting aerobic exercises and there is consistency in their findings, the design and conduct of the studies had tendencies for ROB, and this accounted for the moderate evidence reached for the intervention in our results. Improvement in disability was supported by a weak evidence, which is insufficient for judgment, likewise sleep quality which has weak evidence indicating lack of improvement. Sleep quality is seldom reported in the headache studies, as only 3 out of the 35 included studies measured sleep quality.

We found conflicting evidence concerning the QoL outcome among the aerobic exercise studies. Four studies (Dittrich et al., 2008; Narin et al., 2003; Soderberg et al., 2006; Varkey et al., 2011) reported QoL and each of the studies used a different tool to assess the QoL, and these differences may have been a source of the results variation (Middel & Van Sonderen, 2002). For the exercise protocols, we did not notice a lot of variations among the studies and the population was slightly heterogeneous. For example, whereas three studies recruited migraine patients, one study recruited TTH, which might have also contributed in the QoL variations.

Active and stretching exercises of the head, neck and shoulder mostly resulted in weak evidence. However, this was mainly because there were no adequate studies on these types of exercises that permit strong judgement, nevertheless, the few studies under this category were well designed and with minimal risk of biases (2 good quality and 1 fair quality studies). Moreover, meta-analysis found these exercises to effectively reduce pain intensity.

Behavioral/cognitive therapy (BT)

In this SR behavioral therapy comprising ten studies resulted in conflicting/limited evidence concerning the effectiveness of BT in improving pain, QoL, disability and sleep quality among headache patients. On the other hand, meta-analysis found BT to be marginally effective in reducing pain intensity and disability, but not quality of life. The conflict in the SR results of the BT studies is not likely to be associated with the studies' population because, all the ten studies recruited migraine patients, except in three studies that included migraine or TTH or both. The variation in the results may be related to the type of BT. Moreover, there was a high level of heterogeneity found among the studies reporting on behavioral/cognitive therapy in the meta-analysis. The method of BT was found to differ across the studies. Some of the studies used web-based method (Bromberg et al., 2012; Devineni & Blanchard, 2005; Kleiboer et al., 2014; Sorbi et al., 2015), while some used a face to face method and other studies used a self-home training method and a previous meta-analysis has reported differences in outcomes between web-based and non-web-based interventions in favor of web-based intervention for behavioral outcomes (Wantland, Portillo, Holzemer, Slaughter, & McGhee, 2004). This pattern might have contributed to the conflict in our SR results, as web-based and non-web-based BT were not appraised separately. Additionally, corroborating our finding is another previous review on CBT for headache, which reported mixed findings in their review (Harris, Loveman, Clegg, Easton, & Berry, 2015). Interestingly, in our meta-analysis, BT was only marginally effective for both pain intensity and disability. In the case of disability, the results were highly heterogenous, which is contrary to the mixed-findings reported by Harris et al (2015). Another potential source of variations in the SR result may be related to the duration of the intervention. Most of the studies did not report the duration, frequency and the time frame for the intervention. The few that reported, have a wide range of training duration with 20mins being the minimum training duration reported, while 2 hours was the maximum. Additionally, intervention duration last for between 2 weeks to 3 months, which may also be a source of conflicts in the outcomes reported in this review. Behavioral/cognitive therapy have for long been considered the first-line preventive options and has been suggested the most effective non-pharmacological intervention for migraine and tension headache based on RCTs findings (Nicholson et al., 2011), our meta-analysis has shown that the efficacy may not be clinically substantial.

Relaxation training

Another frequently used hand-off intervention is relaxation training, which was reported in 7 of the included studies. A strong evidence (SR) found that QoL was not improved after relaxation for headache patients, but it reduces disability and pain intensity (moderate evidence). The reduction in pain intensity and disability following relaxation training was also found following the meta-analysis. It is important to note that the studies focusing on quality of life were not suitable for meta-analysis. Hence, the strong evidence that was achieved meant that relaxation training did not improve QoL of headache patients despite being reported by two good quality studies (Söderberg et al., 2011; Varkey et al., 2011). No difference between relaxation groups and the comparing groups were found probably because exercise training, acupuncture and topiramate (drug), that could be potentially effective, were used as the control group instead of a wait-list/usual care/placebo control group. This limitation did not also permit us to include the studies in the meta-analysis despite their good quality. Although not all the studies have reported the details of the relaxation training but some have used standard and cited methods as reported by Larson and Daleflod (Jacobsen, 1929; Schultz & Luthe, 1959), and Larson and Andrasik (Larsson & Andrasik, 2002). A weak evidence was reported for the effect of relaxation on sleep quality because only one study was available which was not suitable for meta-analysis. Moreover, only few of the included studies of this review assessed sleep quality (Calhoun & Ford, 2007; Kanji et al., 2015; Söderberg et al., 2011).

Avoidance, coping and stress management

Four of the reviewed studies reported the effects of avoidance, coping and stress management in the treatment of headache, however, these studies were not enough to permit conclusive judgments in both narrative and quantitative synthesis. In general, most of the hands-off therapies were only scantily reported. For example, avoidance and stress management were represented by one study each, while coping was reported by two studies that resulted in two conflicting results which may be related to the difference in coping interventions given in the studies.

Pain education

Pain education has a moderate evidence supporting its effectiveness in reducing disability and a limited evidence that it reduces pain intensity among headache patients. Although there is consistency in their findings, only 2 studies reported this intervention and both were not suitable for meta-analysis. Therefore, additional studies are still warranted.

Other interventions

Sauna and yoga were found to have weak evidence, because they were represented by single, although well designed (good quality), studies respectively. Lastly, a number of other interventions such as acceptance and commitment therapy, biofeedback exercises, guided imagery and Tai-Chi were graded as limited evidence mainly because they were represented by just one and poorly designed studies. All the studies in this category entered meta-analysis as a single study per intervention, which makes them unfit for conclusive judgements.

Implications

From the results of our SR and meta-analysis, several hands-off therapy methods are being used in the management of headache, which is an indication of the efforts put in by researchers in finding effective alternative methods for treating headache. Reports have shown that health-care is changing towards a greater involvement of the patients in their own care so that clinicians' contribution is reduced to increase the self-efficacy of the patient (Peters, Abu-Saad, Vydelingum, Dowson, & Murphy, 2004) and the current evidence of our review has shown that active and autonomous therapies in the form of aerobic exercises and relaxation training; and a passive therapy in form of pain education are likely to be successful for managing headaches. This is highly important in chronic and more frequent medical conditions like headache (Tyreman, 2005).

From the current evidence of our review, hands-off therapies like aerobic exercises and relaxation training showed the better promise for improving headache outcomes. Further studies focusing on other hands-off therapies with sound methodological quality are still needed to conclude on the topic area.

Limitations

The quality of the studies included varied and only nine of the included studies are of good methodological quality. Although the tool (Higgins et al., 2011) used to assess the methodological quality of the studies is very critical, care has to be taken in interpreting these results. Also, many studies did not report data that will be suitable for meta-analysis. This also calls for the need for more high quality and well-designed trials in the subject area going forward.

Some studies were excluded from the review because they reported pain index (headache index), which comprises of pain severity, frequency and intensity rather than pain intensity. Moreover, a recent review (Haywood et al., 2018) has recommended headache frequency as a standard outcome for headache, but the findings were not available at the start of our review. To this extent, it may therefore be possible that, some studies reporting the effects of some hands-off therapy might have been missed, if they reported only pain index or frequency (did not report pain intensity or disability or QoL or quality of sleep as predefined in our PICOS). Sertel et al (Sertel et al., 2017), one of the included studies, did not report the gender distribution of the study participants. However, when one of the authors was contacted this was provided. This means we utilized information outside what was published in the paper, but this has no effect on the results and conclusions of this review.

There is no clear definition and lists by experts on which treatments are exclusively considered hands-off therapy. All the treatments included in this review were considered hands-off with the guidance of the two senior researchers in the study (MM and BC) who are experienced physiotherapists and have trained and mentored several other physiotherapists. Hence, our interpretation of hands-off therapy might have led to exclusion of other relevant studies and or search databases. Lastly, we categorized some interventions because of their similarity, which simplifies the result presentation, but variations in the interventions may exist within the same category which makes the interventions not exactly the same.

Conclusion

Based on our findings, current evidence seems to support the use of hands-off therapy in the form of aerobic exercises and relaxation training for reducing pain intensity and disability levels in patients with primary headache. However, no evidence seems to support the use of hand-off therapy for improving quality of life of these patients. The evidence to support other hands-off therapy interventions is limited by paucity of studies (weak or limited evidence) or marginal efficacy. Nevertheless, additional studies with better methodological qualities are still needed for conclusive evidence for most of these interventions.

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Table 1: Search strategy used in the PubMed and Web of Science databases

PubMed	
1	"headache"[MeSH Terms] OR headache[TIAB] OR “head pain”[TIAB] OR “cephalgia”[TIAB] OR “migraine disorders"[MeSH Terms] OR “migraine”[TIAB]
2	“hands off therapy”[TIAB] OR “hands off treatment”[TIAB] OR “pain education”[TIAB] OR “neuroscience education”[TIAB] OR “pain neuroscience education”[TIAB] OR “exercise therapy”[TIAB] OR “stretching”[TIAB] OR “relaxation”[TIAB] OR “ergonomics”[TIAB] OR “graded activity”[TIAB] OR “graded exposure”[TIAB] OR "Cognitive Therapy"[Mesh] OR cognitive psychotherap*[TIAB] OR cognitive therap*[TIAB] OR cognition therap*[TIAB] OR cognitive behavior therap*[TIAB] OR “motor control”[TIAB] OR “movement control”[TIAB] OR “body movement therap*”[TIAB] OR “meditation”[TIAB] OR “mindfulness”[TIAB]
3	"pain"[MeSH Terms] OR pain[TIAB] OR “disability”[TIAB] OR "Quality of Life"[Mesh] OR life qualit*[TIAB] OR "quality of life"[TIAB] OR life qualit*[TIAB] OR living qualit*[TIAB] OR "quality of living"[TIAB] OR "Activities of Daily Living"[Mesh] OR "activities of daily living"[TIAB] OR "activity of daily living"[TIAB] OR "activities of daily life"[TIAB] OR "activity of daily life"[TIAB] OR daily living activit*[TIAB] OR daily life activit*[TIAB] OR "adl"[TIAB] OR "chronic limitation of activity"[TIAB] OR self care*[TIAB] OR "Health Status"[Mesh] OR "health status"[TIAB] OR "level of health"[TIAB] OR health level*[TIAB] OR "qol"[TIAB] OR "hrql"[TIAB] OR "hrqol"[TIAB] OR "sleep"[MeSH Terms] OR “sleep”[TIAB] AND “quality”[TIAB]
4	1 AND 2 AND 3
Web of Science	
1	TS=("headache" OR “head pain” OR “cephalgia” OR “migraine”)
2	TS=(“hands off therapy” OR “hands off treatment” OR “pain education” OR “neuroscience education” OR “pain neuroscience education” OR “exercise therapy” OR “stretching” OR “relaxation” OR “ergonomics” OR “graded activity” OR “graded exposure” OR “cognitive behavioural therapy” OR “cognitive behavioral therapy” OR “motor control” OR “movement control” OR “body movement therapy” OR “meditation” OR “mindfulness”)
3	TS=("pain" OR “disability” OR "quality of life" OR “sleep quality”)
4	1 AND 2 AND 3

Table 2: Modified Bakker scale

Level of evidence	**Criteria (Based on good, fair and poor quality studies)**
Strong evidence	Consistent findings in 2 or more good quality studies, or 1 good quality and at least 2 fair quality studies
Moderate evidence	Consistent findings in 1 good quality study plus 1 fair quality study, or 2 fair quality studies
Limited evidence	Only one fair or poor quality study is available
Conflicting evidence	Inconsistent findings in the available studies
Weak evidence	Consistent findings in 1 fair quality study plus 1 or more poor, or two or more poor, or just one study is available but of good quality

Note: Consistent finding is when at least 75% of the available studies reported the same conclusion

Table 3: Evidence table of included studies

Reference Country	Sample	Experimental group (EG)	Control group (CG)	Outcome(s) Follow-up moments	Results	Evidence
	Aerobic exercises					
•(Dittrich et al., 2008) Austria	Migraine: 30♀ EG: 15♀(33.7±12.5 years) CG: 15♀(32.1±12.1 years)	*Aerobic exercise group (6w)* 45' 2x/w + standard medical care	*Standard-care control*: Study information + standard medical care	Pain: SES QoL: PLCK	Pain ↓ (P=0.024) QoL →	***Moderate evidence:*** **Pain intensity ↓** ***Weak evidence:*** **Disability ↓ and sleep quality →** ***Conflicting evidence:*** **QoL**
• (Lockett & Campbell, 1992) Canada	Migraine: 20♀ EG: 11 (32.5 years) CG: 09 (32.2 years)	*Low impact aerobics (6w)* 45mins (dancing and calisthenics), 3x/w	*Waitlist control*: Asked to wait for 12w due to lack of space	Pain: WHMPI	Pain →	
• (Narin et al., 2003) Turkey	Migraine: 40♀ (20-50 years) EG: 20 (35.20±10.23 years) CG: 20 (40.0±8.3 years)	*Aerobics group (8w)* 60' 3x/w + medication	*Control group*: Only medication	Pain : VAS Disability: PDI QoL: ?	Pain ↓ Disability↓(P<0.05) QoL ↑	
• (Peres et al., 2019) Brazil	Migraine/TTH/Chronic headache: 74 EG: 5♂, 19♀ (38.0±13.1 years) CG (RLX): 4♂, 21♀ (41.1±16.4 years) CG (RLX+PA): 5♂, 20♀(41.8±19.7 years)	*Aerobics group*: *(6m)* 20-30' 3x/w (6 months)	*Relaxation group*: 6m 3x/d, 3x/w *Relaxation + aerobics*: aerobics and relaxation together	Pain: ?	Pain ↓ (P<0.01)	
	TTH: 60♀ (39.26±9.23 years) EG:20 (36.20±7.86 years) CG (BAT):20 (42.60±9.5 years) CG:20 (39.0±9.53 years)					

• (Sertel et al., 2017) Turkey • (Soderberg et al., 2006) Sweden • (Söderberg et al., 2011) Sweden • (Varkey et al., 2011) Sweden	TTH: 90 (18-59 years) EG:7♂, 23♀ (18-56 years) CG (ACU): 7♂, 23♀ (18-59 years) CG (RLX): 9♂, 27♀ (22-59 years) TTH: 90 (18-59 years) EG:7♂, 23♀ (18-56 years) CG (ACU): 7♂, 23♀ (18-59 years) CG (RLX): 9♂, 27♀ (22-59 years) Migraine: 91 (9♂, 82♀) EG:30; 5♂, 25♀ (47.0±10.8 years) CG (RLX):30; 2♂,28♀ (41.50±11.4 years) CG (Drug):31; 2♂, 29♀ (44.4±9.2 years)	*Aerobics group (6w)* 60' 3x/w *Physical training group (10w)* 45' 2x/w (5w)+ home training 3x/w (5w) or 1 training at the clinic + 1 or 2 home training/w (10w) *Physical training group (10w)* 45' 2x/w (5w)+ home training 3x/w (5w) or 1 training at the clinic + 1 or 2 home training/w (10w) *Exercise (aerobics) group (12w)* 40' 3x/w	*Body awareness therapy group (6w)* 60' 1x/w *Control group*: No treatment *Acupuncture group (10-12w)* 10-12 sessions *Relaxation group (10-12w)* 1x/w *Acupuncture group (10-12w)* 10-12 sessions, 1x/w *Relaxation group (10-12w)* 1x/w *Relaxation group (12w)* 20-30' 3x/w *Topiramate drug group:*	Pain: VAS Disability: PDI QoL: SF-36 3m, 6m, 12m Pain: [?] 3m, 6m Sleep-quality: MSEP 6m	Pain ↓ Disability ↓ QoL ↓ (P<0.05) Pain → (P>0.05) Sleep quality →	

			Individualized prescription	Pain : VAS QoL: MSQOL 6m	Pain → QoL →	
	Active and stretching exercises					
• (Alvarez-Melcon et al., 2018) Spain • (Lee & Lee, 2019) Korea • (Lin & Wang, 2015) Taiwan	TTH: 152 (68♂, 84♀) EG:76; 26♂, 50♀ (20.23±2.50 years) CG:76; 42♂, 34♀ (20.62±2.21 years) TTH: 62 (26♂, 36♀; 19-29 years) EG: 21; 6♂, 15♀ (22.10±2.31years) CG (Biofeedback): 21; 7♂, 14♀ (22.91±2.84 years) CG (Manual therapy): 20; 6♂, 14♀ (21.40±2.47 years) Chronic headache: 60♀ EG: 30 (31.7±6.1 years) CG: 30 (31.2±5.2 years)	*Head, neck & shoulder exercise group (4w)* Exercises + ergonomics and hygiene + relaxation + autogenic training 7x/w *Stretching exercise group (4w)* 25' 3x/w (Ylinen et al) *Stretching exercises group (30')* 25' neck stretching	*Control group (4w)* Ergonomics and hygiene + relaxation + autogenic training 7x/w *Biofeedback group (4w)* 13' 3x/w *Manual therapy group (4w)* 20' 3x/w	Pain: VAS 3m Disability: HDI 2w	Pain ↓ (P=0.015 & P=0.006 at follow up) Disability →	***Weak evidence:*** **Pain intensity ↓**

			Control group Management as usual	Pain: NRS	Pain ↓ (P=0.01)	
	Progressive resistance training					
• (Madsen et al., 2018) Denmark	TTH: 60 (19♂, 41♀) EG:30; 8♂, 22♀ (32(28-37) years) CG:30; 11♂, 19♀ (35(31-39) years)	*Strength training group (10w)* 3x/w (70%-80% of maximal intensity)	*Control group* Ergonomics and posture correction	Pain: NRS 19-22w	Pain → (P=0.375)	***Weak evidence:*** **Pain intensity** →
	Behavioural/Cognitive therapies					
• (Bhombal et al., 2014) Pakistan • (Bromberg et al., 2012) USA	Migraine: 90 (18♂, 72♀) EG:45; 6♂, 39♀ (36.7±1.5 years) CG:45; 12♂, 33♀ (34.6±1.8 years) Migraine: 185 (20♂, 165♀) EG:93; 10♂, 83♀ (43.32±11.49 years) CG:92; 10♂, 82♀ (41.91±11.53 years)	*BT group (2w)* Daily + standard pharmacological treatment *BT group (4w)* Web-based BT, 20' 2x/w + 20'sessions 5x follow up (1m) *BT group (6w)*	*Control group;*: Standard pharmacological treatment *Control:* No treatment *Control;*	Pain: ? QoL: ? 4w Disability: MIDAS m, 6m	Pain ↓ (P=0.001) QoL ↑ (P=0.001) Disability →	

• (Calhoun & Ford, 2007) USA • (Devineni & Blanchard, 2005) USA • (Kleiboer, Sorbi, Merelle, Passchier, & van Doornen, 2009) Netherlands • (Martin et al., 2014) Australia	Migraine: 43♀ EG: 23 (33.5 years) CG: 20 (35.0 years) Migraine, TTH or Mixed: 139 (29♂, 110♀) EG: 39; 05♂, 34♀ (43.6±12 years) CG: 47; 10♂, 37♀ (41.0±11.8 years) Dropout: 53; 14♂, 39♀ (39.2±14.7 years) Migraine: 368 (54♂, 314♀) EG: 26♂, 169♀ (43±12 years) CG: 28♂, 145♀ (44.3±11 years) Migraine: 127 (43♂, 84♀) EG: 15♂, 19♀ (48.94±13.65) CG(Avoidance): 11♂, 18♀ (48.28±12.57) CG (Coping): 12♂, 20♀ (44.53±13.85) CG: 05♂, 27♀ (46.91±15.15) Migraine: 127 (13♂, 87♀) EG: 60; 09♂, 51♀ (25-59) CG: 67; 07♂, 60♀ (18-65)	Behavioral sleep modification (BSM) instructions + usual care *BT group (4w)* internet-delivered BT, 1x/w *BT group (3m)* Online BT for 8 sessions (60' per session) + home works *CBT + Avoidance group (8w)* Avoidance of triggers + CBT 1x/w	Sham instructions + usual care *Control group* symptom monitoring waitlist control *Control group;:* Wait list *Avoidance group (8w)* 1x/w Avoidance of triggers *Coping group (8w)* learning to cope with triggers 1x/w *Control group:* WLC *Control group:* Wait list (care as usual)	Sleep quality: SCI Disability: HDI Pain: ? QoL: MSQOL Disability: MIDAS Pain → [NRS] 4m, 12m	Sleep quality ↑ (P=0.01) Disability ↓ (P<0.05) Pain → (P>0.05) QoL ↑ Disability ↓ Pain →	***Conflicting evidence:*** **Pain intensity, QoL, disability** ***Limited evidence:*** **Sleep quality ↑**

• (Merelle et al., 2008) Netherlands • (Seng et al., 2019) USA • (Sorbi et al., 2015) Netherlands • (Tavallaei et al., 2018) Iran	Migraine: 60 (5♂, 55♀) EG: 02♂, 29♀ (36.2±10.6) CG: 03♂, 26♀ (44.2±11.5) Migraine: 368 (54♂, 314♀) EG: 26♂, 169♀ (43.0±12.0) CG: 28♂, 145♀ (44.3±11.0) Migraine, TTH: 30♀ EG: 15 (32.47 ± 9.11) CG: 15 (34.87 ± 9.12)	*BT group (10w)* 7, 120' sessions of home based BT *BT group (8-10w)* 8 individual 75' sessions of mindfulness-based cognitive therapy *BT group (3.6months)* 8 lessons of online BT for 60' + 60'-120'of homework *BT group (8w)* Mindfulness based stress reduction (MBSR) weekly + MTAU	*Control:* Waitlist/treatment as usual *Control:* WLC/no treatment *Control:* Medical treatment as usual (MTAU)	Pain: ? Disability: MIDAS QoL: MSQOL Pain: HD Disability: HDI Pain: NRS Disability: MIDAS QoL: MSQOL 6m Pain: MPQ Disability: MIDAS	Pain → Disability → QoL → Pain → Disability ↓ Pain ↓ (P<0.032) Disability → (P>0.05) QoL → (P=0.051)	

					Pain ↓ (P<0.035) Disability ↓ (P<0.0001)	
	Relaxation training					
• (D'Souza et al., 2008) USA • (McGrady et al., 1994) USA • (Peres et al., 2019) Brazil • (Slavin-Spenny et al., 2013) USA	Migraine, TTH: 141 (19♂, 122♀) TTH: 51; 9♂,42♀ (20.3±2.30 years) Migraine: 90; 10♂,80♀ (21.4±5.47 years). Migraine: 23 (3♂, 20♀) EG: 12; 42 (29-59 years) CG: 11; 42 (29-53 years) Migraine/TTH/Chronic headache: 74 EG (RLX): 4♂, 21♀ (41.1±16.4 years) CG (RLX+PA): 5♂, 20♀(41.8±19.7 years) CG (PA): 5♂, 19♀ (38.0±13.1 years) Chronic headache: 147 (18♂,129♀) EG:** CG:**	*Relaxation group (2w)* 4, 20' sessions of self-administered relaxation *Relaxation group (8-12w)* 12 sessions + 2 daily home training) *Relaxation group*: 6m 3x/d, 3x/w *Relaxation group (4w)* Daily routines training	*Written emotional disclosure (2w)* 4, 20' sessions *Control;* Time management *Control (self relax) group* Self relax for 10-15mins twice weekly (8-12 weeks) *Relaxation + aerobics*: aerobics and relaxation together *Aerobics group*: *(6m)* 20-30' 3x/w (6 months) *Anger awareness therapy group (4w)* 3 sessions *Control (waitlist) group:* No treatment	Disability: MIDAS 1m, 3m Pain → [HPIS] 4-6w Pain: ?	Disability ↓ (P<0.05) Pain ↓ (P<0.01) Pain →	 ***Moderate evidence:***

• (Soderberg et al., 2006) Sweden	TTH: 90 (18-59 years) EG:7♂, 23♀ (18-56 years) CG (ACU): 7♂, 23♀ (18-59 years) CG (RLX): 9♂, 27♀ (22-59 years)	*Relaxation group (10-12w)* 1x/w	*Physical training group (10w)* 45' 2x/w (5w)+ home training 3x/w (5w) or 1 training at the clinic + 1 or 2 home training/w (10w) *Acupuncture group (10-12w)*	Disability: MIDAS	Disability ↓ (P=0.03)	**Pain intensity ↓, disability ↓** ***Weak evidence:*** **Sleep quality ↑, QoL →**
• (Söderberg et al., 2011) Sweden	TTH: 90 (18-59 years) EG:7♂, 23♀ (18-56 years) CG (ACU): 7♂, 23♀ (18-59 years) CG (RLX): 9♂, 27♀ (22-59 years)	*Relaxation group (10-12w)* 1x/w	*Physical training group (10w)* 45' 2x/w (5w)+ home training 3x/w (5w) or 1 training at the clinic + 1 or 2 home training/w (10w) *Acupuncture group (10-12w)*	Pain: ? 3m, 6m	Pain → (P>0.05)	
• (Varkey et al., 2011) Sweden	Migraine: 91 (9♂, 82♀) EG (RLX):30; 2♂,28♀ (41.50±11.4 years) CG (Aerobics):30; 5♂, 25♀ (47.0±10.8 years) CG (Drug):31; 2♂, 29♀ (44.4±9.2 years)		*Exercise (aerobics) group (12w)* 40' 3x/w *Topiramate drug group:* Individualized prescription	Sleep quality: MSEP 3m, 6m	Sleep quality ↑ (P<0.05)	

		Relaxation group (12w) 20-30' 3x/w		Pain: VAS QoL: MSQOL 3m, 6m	Pain → QoL →	
	Avoidance, coping and stress management					
• (Bakhshani et al., 2015) Iran • (Holroyd et al., 2001) USA • (Martin et al., 2014) Australia	Migraine, TTH: 40 (13♂, 27♀) EG: 20; 6♂,14♀ (30.6±9.08 years) CG: 20; 7♂,13♀ (31.5±9.57 years) TTH: 203 (48♂, 155♀) EG: 49; 10♂, 39♀ (37.4±1.7 years) CG (Drug + STM): 53; 10♂,43♀ (37.1±1.7 years) CG (Drug): 53; 18♂, 35♀ (35.6±1.5 years) CG: 48 Migraine: 127 (43♂, 84♀) EG(Avoidance): 11♂, 18♀ (48.28±12.57) EG (Coping): 12♂, 20♀ (44.53±13.85)	*Mindfulness based stress reduction group (8w)* MBSR therapy of 90'-120'/w + pharmacotherapy *Stress management therapy (STM) group (2m)* Counselor administered 3, 60' sessions	*Control group;*: pharmacotherapy *Anti-depressant +STM (2m)* Combination of the two *Control group:* Placebo *Anti-depressant group:* Medication only	Pain: NRS QoL: [SF-36] Disability: HDI 1m, 6m	Pain ↓ (P=0.001) QoL ↑ (P<0.05) Disability ↓ (P<0.01)	***Weak evidence:*** **Pain intensity ↓, QoL ↑, disability ↓ for stress management** ***Conflicting evidence:*** **Pain intensity**

• (Rashid-Tavalai et al., 2015) Iran	CG (CBT + Avoidance): 15♂, 19♀ (48.94±13.65) CG: 05♂, 27♀ (46.91±15.15)	*Avoidance group (8w)* 1x/w Avoidance of triggers *Coping group (8w)* learning to cope with triggers 1x/w	*CBT + Avoidance group (8w)* Avoidance of triggers + CBT 1x/w *Control group:* WLC	Pain: NRS	Pain ↓ (P=0.001) for coping group	**for coping techniques** ***Limited evidence:*** **Pain intensity ↓ for avoidance of triggers**
	Migraine: 35 (7♂, 28♀) EG: 03♂, 15♀ CG: 04♂, 13♀	*Coping skills group (7w)* 7, 120'/w sessions of coping skills + pharmacotherapy	*Control group:* *Pharmacotherapy*	Pain: HI QoL: WHOQOL	Pain → (P=0.26) QoL → (P=0.49)	
	Education					
• (Aguirrezabal et al., 2019) Spain	Migraine: 116 (21♂, 95♀) EG: 57; 13♂, 44♀ CG: 59; 08♂, 51♀	*Pain education group (2m)* Five, 105' sessions of pain neuroscience education + usual care	*Control group* Usual care (periodical primary care appointments)	Pain: ? Disability: MIDAS	Pain ↓ (P<0.005) Disability ↓ (P<0.001)	***Moderate evidence:*** **Disability ↓**
	Migraine: 100 (8♂, 92♀) EG: 50; 4♂, 46♀ (43.4 years) CG: 50; 4♂, 46♀ (41.6 years)	*Pain education group (1m)* 3 classes of 90' + usual care	*Control group:*			***Weak evidence:***

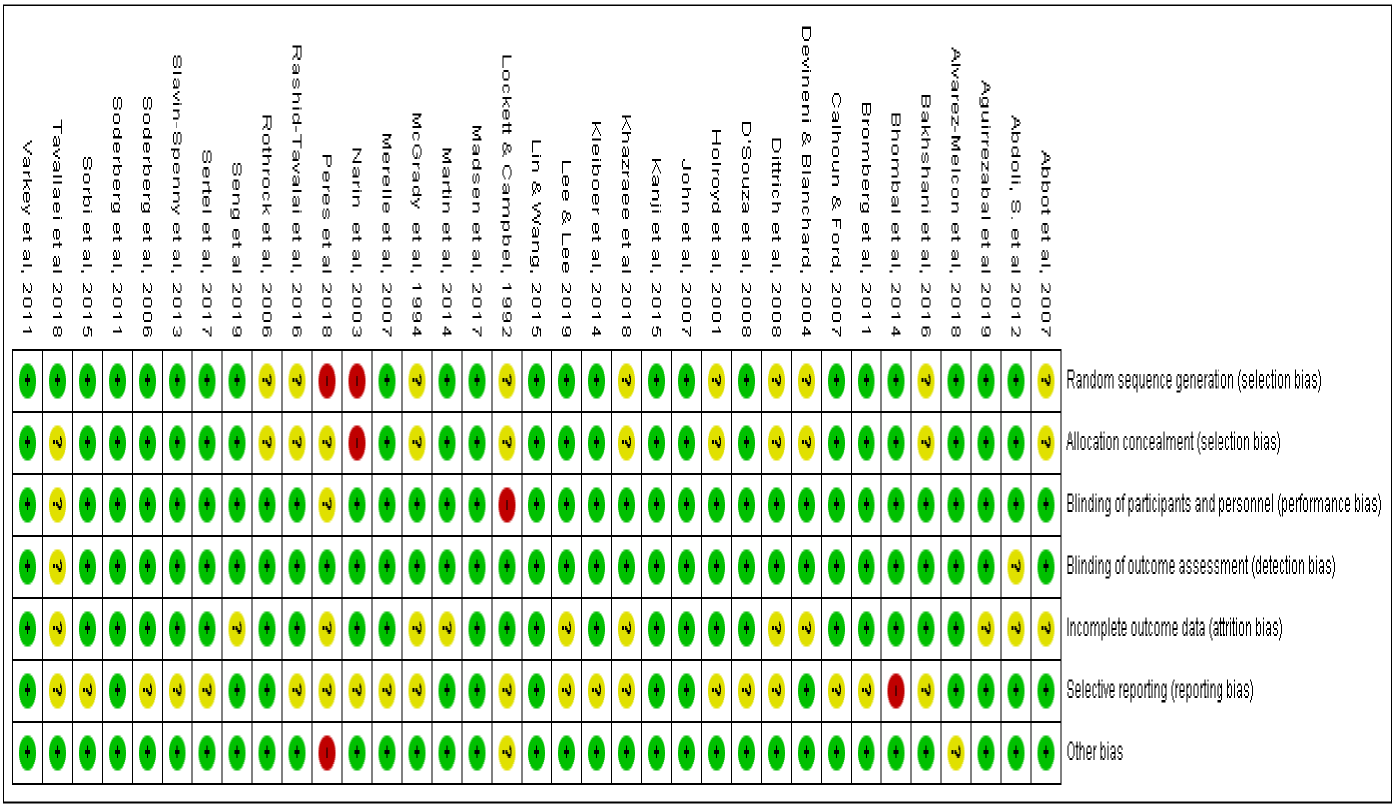
• (Rothrock et al., 2006) USA			Usual care	Disability: MIDAS 3m, 6m	Disability ↓ (P<0.05)	**Pain intensity ↓**
	Psychotherapy (Acceptance and commitment therapy)					
• (Khazraee et al., 2018) Iran	Migraine, Chronic headache: 40 (3♂, 30♀) EG: 02♂, 14♀ (33.76 years) CG: 01♂, 16♀ (33.24 years)	*Psychotherapy (acceptance and commitment therapy) (2m)* Eight 90'/w sessions + MTAU (2 months)	*Control group:* MTAU	Pain: HD Disability: HDI	Pain ↓ (P<0.05) Disability ↓ (P<0.05)	***Limited evidence:*** **Pain intensity ↓, disability ↓**
	Biofeedback exercises					
• (Lee & Lee, 2019) Korea	TTH: 62 (26♂, 36♀; 19-29 years) EG (Biofeedback): 21; 7♂, 14♀ (22.91±2.84 years) CG (Manual therapy): 20; 6♂, 14♀ (21.40±2.47 years) CG (Stretching): 21; 6♂, 15♀ (22.10±2.31years)	*Biofeedback group (4w)* 13' 3x/w	*Manual therapy group (4w)* 20' 3x/w *Stretching exercise group (4w)* 25' 3x/w (Ylinen et al)	Disability: HDI QoL: ? 2w	Disability ↓ (P<0.01) QoL ↑ (P<0.05)	***Weak evidence:*** **Disability ↓**
	Guided imagery					
• (Abdoli et al., 2012) Iran	TTH: 60 (18♂,42♀) EG (Imagery):20; 7♂, 13♀ (33.1(20-57)years) EG (Happy memory): 20; 5♂, 15♀ (32.7(19-53) years) CG: 20; 6♂, 14♀ (32.4(20-59) years)	*Guided imagery with tape (5w)* Imagery with tape, 3 times per week + individualized headache therapy *Guided imagery with perceived happy memory (5w)* Happiest personal memory, 3 times per	*Control group (5w)* Individualized headache therapy	Pain: VAS	Pain ↓ (P<0.0001)	***Limited evidence:*** **Pain intensity ↓**

		week + individualized headache therapy				
	Tai-chi					
• (Abbott et al., 2007) USA	TTH: 30 (8♂, 22♀) EG: 03♂, 10♀ (47 years) CG: 04♂, 12♀ (42 years)	*Tai-Chi group (15w)* Yang style short form of Tai Chi delivered bi-weekly	*Control (waitlist) group:* WLC	QoL: SF-36	QoL ↑ (P=0.016)	***Limited evidence:*** **QoL ↑**
	Sauna					
• (Kanji et al., 2015) New Zealand	TTH: 37 (8♂, 29♀) EG: 17; 05♂, 12♀(44.3±10.5 years) CG: 20; 03♂, 17♀(40.7±16.8 years)	*Sauna group (8w)* Self-directed soft tissue massage + 20' sauna 3x/w	*Control group:* Self-directed soft tissue massage	Pain: NRS Sleep quality: ?	Pain ↓ (P=0.002) Sleep quality → (P=0.77)	***Weak evidence:*** **Pain intensity ↓, disability ↓**
	Yoga					
• (John et al., 2007) India	Migraine: 65 (16♂, 49♀) EG: 10♂, 22♀ (34.38±8.74 years) CG: 06♂, 27♀ (34.21±9.66 years)	*Yoga group (12w)* 60' session, 5x/w	*Control group:* Self-care	Pain: NRS	Pain ↓ (P<0.001)	***Weak evidence:*** **Pain intensity ↓**

Legend abbreviations and signs: CBT= Cognitive behavioral therapy, **BT**= Behavioral therapy, **HD**= headache diary, **HDI**= headache disability index, **HI**= headache index, **HPIS** = headache pain intensity score, **MSEP**= Minor Symptom Evaluation Profile questionnaire, **PDI**= pain disability index, **MBSR**=mindfulness based stress reduction, **MIDAS**= migraine disability assessment score, **MPQ**= McGill pain questionnaire, **MSQOL**= migraine specific quality of life questionnaire, **MTAU**=medical treatment as usual, **NRS**= numeric rating scale, **PLCK**= profil der lebensqualität chronisch kranker, **QoL**= Quality of life, **SCI**= sleep characteristics inventory, **SES** = Schmerzempfindungsskala, **TTH**= Tension type headache, **SF-36**= short form 36, **VAS**= visual analogue scale, **WHMPI** = West Haven Yale multidimensional pain inventory, **WHOQOL**= world health organization quality of life, **WLC**=wait list control, ↑ = improvement through increase, ↓ = improvement through decrease, → = no difference in improvement , ? = name of outcome tool not specified by researcher(s), **= no group based data

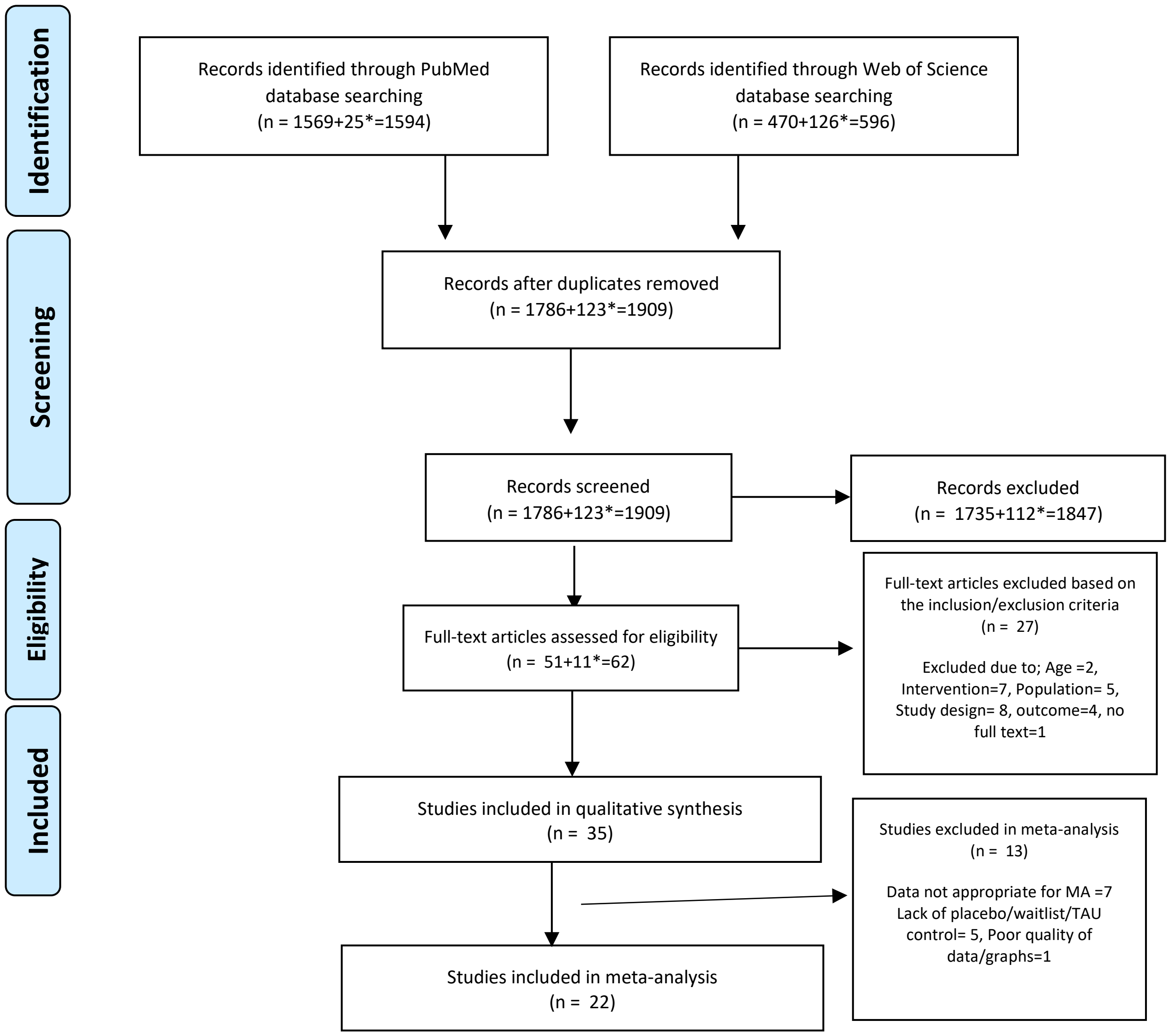
Note: Only studies that presented p-values were reflected in the table

Figure 1: Risk of bias/methodological quality assessment of the included studies



Key: + (low risk), - (high risk), ? (unclear risk)

Figure 1: PRISMA flow chart of the review process

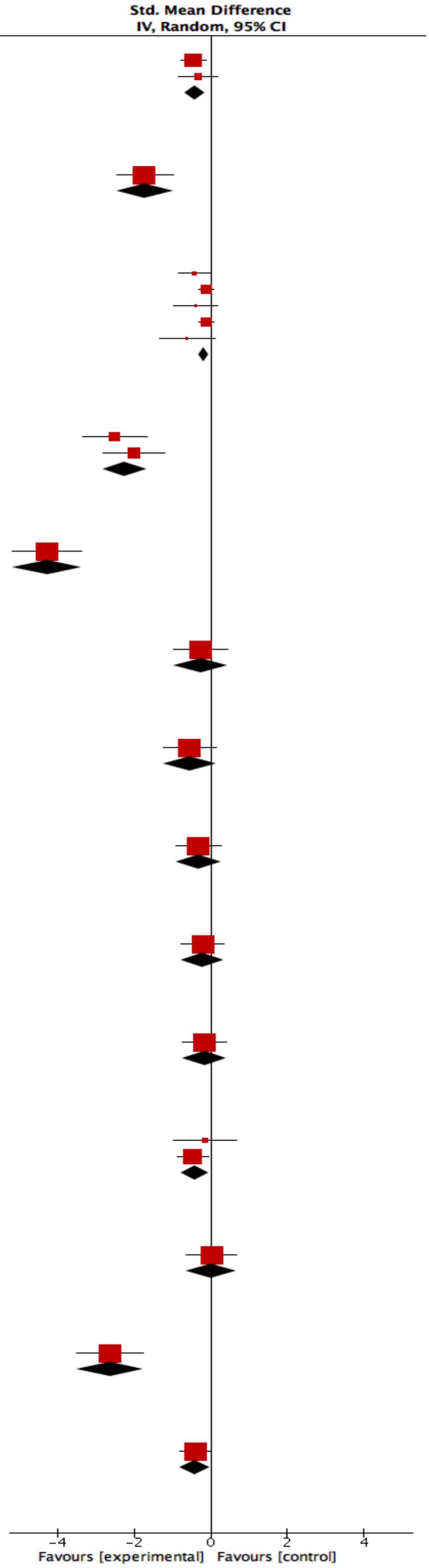


Note: *= Additional articles obtained due to update of the database search, MA=Meta-analysis, TAU=Treatment as usual

Figure 3:

A. Forest plot for pain intensity

Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
1.1.1 Active and stretching exercises				
Alvarez-Melcon et al, 2018	-0.4469	0.1643	71.5%	-0.45 [-0.77, -0.12]
Lin & Wang, 2015	-0.3228	0.26	28.5%	-0.32 [-0.83, 0.19]
Subtotal (95% CI)			**100.0%**	**-0.41 [-0.68, -0.14]**
Heterogeneity: Tau² = 0.00; Chi² = 0.16, df = 1 (P = 0.69); I² = 0%				
Test for overall effect: Z = 2.96 (P = 0.003)				
1.1.2 Stress management				
Bakhshani et al, 2016	-1.7183	0.3754	100.0%	-1.72 [-2.45, -0.98]
Subtotal (95% CI)			**100.0%**	**-1.72 [-2.45, -0.98]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 4.58 (P < 0.00001)				
1.1.3 Behavioral/Cognitive therapy				
Bhombal et al, 2014	-0.4103	0.2131	9.8%	-0.41 [-0.83, 0.01]
Kleiboer et al, 2014	-0.1138	0.1045	40.8%	-0.11 [-0.32, 0.09]
Martin et al, 2014	-0.3872	0.2887	5.3%	-0.39 [-0.95, 0.18]
Sorbi et al, 2015	-0.1117	0.1045	40.8%	-0.11 [-0.32, 0.09]
Tavallaei et al 2018	-0.6099	0.3748	3.2%	-0.61 [-1.34, 0.12]
Subtotal (95% CI)			**100.0%**	**-0.17 [-0.30, -0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 3.81, df = 4 (P = 0.43); I² = 0%				
Test for overall effect: Z = 2.58 (P = 0.010)				
1.1.4 Aerobic exercises				
Narin et al, 2003	-2.4985	0.4319	46.9%	-2.50 [-3.35, -1.65]
Sertel et al, 2017	-2.0021	0.4055	53.1%	-2.00 [-2.80, -1.21]
Subtotal (95% CI)			**100.0%**	**-2.23 [-2.81, -1.66]**
Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 1 (P = 0.40); I² = 0%				
Test for overall effect: Z = 7.56 (P < 0.00001)				
1.1.5 Yoga				
John et al, 2007	-4.2606	0.4585	100.0%	-4.26 [-5.16, -3.36]
Subtotal (95% CI)			**100.0%**	**-4.26 [-5.16, -3.36]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 9.29 (P < 0.00001)				
1.1.6 Sauna				
Kanji et al, 2015	-0.2563	0.3611	100.0%	-0.26 [-0.96, 0.45]
Subtotal (95% CI)			**100.0%**	**-0.26 [-0.96, 0.45]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.71 (P = 0.48)				
1.1.7 Aceptance and commitment therapy				
Khazraee et al 2018	-0.5421	0.3555	100.0%	-0.54 [-1.24, 0.15]
Subtotal (95% CI)			**100.0%**	**-0.54 [-1.24, 0.15]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.52 (P = 0.13)				
1.1.8 Progressive resistance training				
Madsen et al, 2017	-0.3223	0.304	100.0%	-0.32 [-0.92, 0.27]
Subtotal (95% CI)			**100.0%**	**-0.32 [-0.92, 0.27]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.06 (P = 0.29)				
1.1.9 Avoidance therapy + Behavioral/Cognitive therapy				
Martin et al, 2014	-0.2039	0.2866	100.0%	-0.20 [-0.77, 0.36]
Subtotal (95% CI)			**100.0%**	**-0.20 [-0.77, 0.36]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.71 (P = 0.48)				
1.1.10 Avoidance therapy				
Martin et al, 2014	-0.1638	0.2863	100.0%	-0.16 [-0.72, 0.40]
Subtotal (95% CI)			**100.0%**	**-0.16 [-0.72, 0.40]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.57 (P = 0.57)				
1.1.11 Relaxation training				
McGrady et al, 1994	-0.1473	0.4181	19.5%	-0.15 [-0.97, 0.67]
Slavin-Spenny et al, 2013	-0.4573	0.2058	80.5%	-0.46 [-0.86, -0.05]
Subtotal (95% CI)			**100.0%**	**-0.40 [-0.76, -0.03]**
Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 1 (P = 0.51); I² = 0%				
Test for overall effect: Z = 2.15 (P = 0.03)				
1.1.12 Coping				
Rashid-Tavalai et al, 2016	0.0267	0.3382	100.0%	0.03 [-0.64, 0.69]
Subtotal (95% CI)			**100.0%**	**0.03 [-0.64, 0.69]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.08 (P = 0.94)				
1.1.13 Body awarenesss therapy				
Sertel et al, 2017	-2.6245	0.4422	100.0%	-2.62 [-3.49, -1.76]
Subtotal (95% CI)			**100.0%**	**-2.62 [-3.49, -1.76]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 5.94 (P < 0.00001)				
1.1.14 Anger awareness therapy				
Slavin-Spenny et al, 2013	-0.3997	0.2031	100.0%	-0.40 [-0.80, -0.00]
Subtotal (95% CI)			**100.0%**	**-0.40 [-0.80, -0.00]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.97 (P = 0.05)				

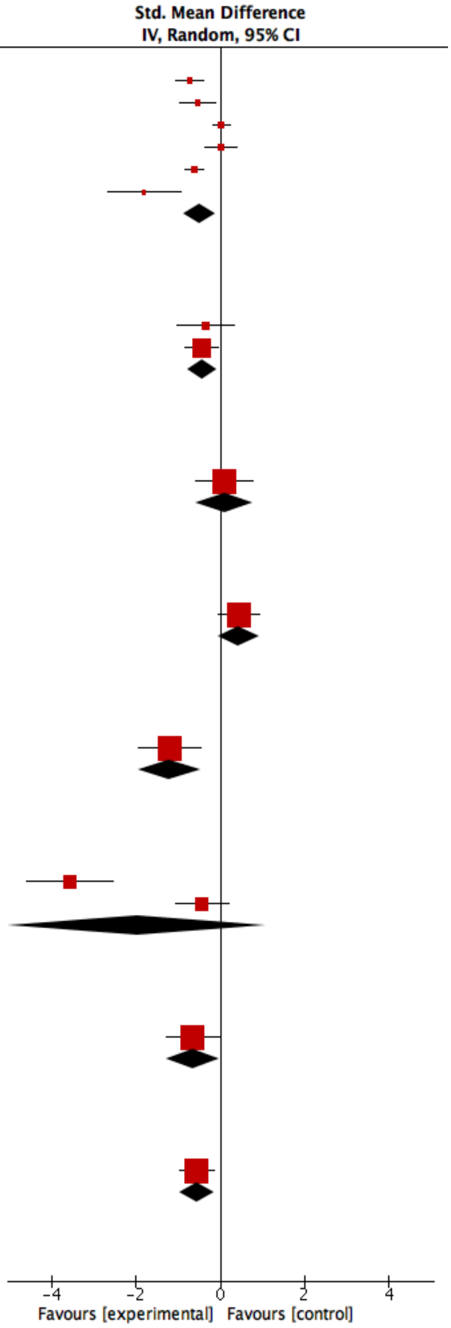


Test for subgroup differences: Chi² = 161.80, df = 13 (P < 0.00001), I² = 92.0%

B. Forest plot for disability

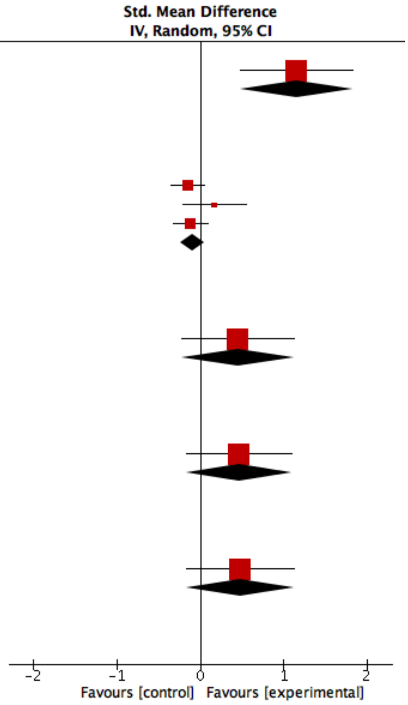
Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
1.2.1 Behavioral/Cognitive therapy				
Bromberg et al, 2011	-0.7194	0.1671	17.9%	-0.72 [-1.05, -0.39]
Devineni & Blanchard, 2004	-0.5336	0.2206	16.2%	-0.53 [-0.97, -0.10]
Kleiboer et al, 2014	0.0364	0.1045	19.5%	0.04 [-0.17, 0.24]
Merelle et al, 2007	0.026	0.1928	17.1%	0.03 [-0.35, 0.40]
Sorbi et al, 2015	-0.616	0.1069	19.4%	-0.62 [-0.83, -0.41]
Tavallaei et al 2018	-1.8091	0.4429	9.8%	-1.81 [-2.68, -0.94]
Subtotal (95% CI)			**100.0%**	**-0.50 [-0.88, -0.13]**
Heterogeneity: $Tau^2 = 0.18$; $Chi^2 = 40.08$, df = 5 ($P < 0.00001$); $I^2 = 88\%$				
Test for overall effect: Z = 2.62 (P = 0.009)				
1.2.2 Relaxation training				
D'Souza et al, 2008	-0.3387	0.3458	26.1%	-0.34 [-1.02, 0.34]
Slavin-Spenny et al, 2013	-0.4431	0.2057	73.9%	-0.44 [-0.85, -0.04]
Subtotal (95% CI)			**100.0%**	**-0.42 [-0.76, -0.07]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.07$, df = 1 (P = 0.80); $I^2 = 0\%$				
Test for overall effect: Z = 2.35 (P = 0.02)				
1.2.3 Written Emotional Disclosure				
D'Souza et al, 2008	0.1009	0.3432	100.0%	0.10 [-0.57, 0.77]
Subtotal (95% CI)			**100.0%**	**0.10 [-0.57, 0.77]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.29 (P = 0.77)				
1.2.4 Stress Management therapy				
Holroyd et al, 2001	0.4365	0.2512	100.0%	0.44 [-0.06, 0.93]
Subtotal (95% CI)			**100.0%**	**0.44 [-0.06, 0.93]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.74 (P = 0.08)				
1.2.5 Acceptance and commitment therapy				
Khazraee et al 2018	-1.2042	0.3825	100.0%	-1.20 [-1.95, -0.45]
Subtotal (95% CI)			**100.0%**	**-1.20 [-1.95, -0.45]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 3.15 (P = 0.002)				
1.2.6 Aerobic exercises				
Narin et al, 2003	-3.5589	0.525	49.1%	-3.56 [-4.59, -2.53]
Sertel et al, 2017	-0.4245	0.3289	50.9%	-0.42 [-1.07, 0.22]
Subtotal (95% CI)			**100.0%**	**-1.96 [-5.04, 1.11]**
Heterogeneity: $Tau^2 = 4.72$; $Chi^2 = 25.60$, df = 1 ($P < 0.00001$); $I^2 = 96\%$				
Test for overall effect: Z = 1.25 (P = 0.21)				
1.2.7 Body awareness therapy				
Sertel et al, 2017	-0.6489	0.3253	100.0%	-0.65 [-1.29, -0.01]
Subtotal (95% CI)			**100.0%**	**-0.65 [-1.29, -0.01]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.99 (P = 0.05)				
1.2.8 Anger awareness therapy				
Slavin-Spenny et al, 2013	-0.5504	0.2049	100.0%	-0.55 [-0.95, -0.15]
Subtotal (95% CI)			**100.0%**	**-0.55 [-0.95, -0.15]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 2.69 (P = 0.007)				

Test for subgroup differences: $Chi^2 = 20.01$, df = 7 (P = 0.006), $I^2 = 65.0\%$



C. Forest plot for quality of life

Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
1.3.1 Stress Management				
Bakhshani et al, 2016	1.1495	0.344	100.0%	1.15 [0.48, 1.82]
Subtotal (95% CI)			**100.0%**	**1.15 [0.48, 1.82]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 3.34 (P = 0.0008)				
1.3.2 Behavioral/Cognitive therapy				
Kleiboer et al, 2014	−0.1509	0.1046	43.0%	−0.15 [−0.36, 0.05]
Merelle et al, 2007	0.1699	0.1931	13.9%	0.17 [−0.21, 0.55]
Sorbi et al, 2015	−0.1154	0.1045	43.1%	−0.12 [−0.32, 0.09]
Subtotal (95% CI)			**100.0%**	**−0.09 [−0.24, 0.05]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.21$, df = 2 (P = 0.33); $I^2 = 9\%$				
Test for overall effect: Z = 1.24 (P = 0.22)				
1.3.3 Coping				
Rashid-Tavalai et al, 2016	0.4549	0.3431	100.0%	0.45 [−0.22, 1.13]
Subtotal (95% CI)			**100.0%**	**0.45 [−0.22, 1.13]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.33 (P = 0.18)				
1.3.4 Body awareness therapy				
Sertel et al, 2017	0.4684	0.321	100.0%	0.47 [−0.16, 1.10]
Subtotal (95% CI)			**100.0%**	**0.47 [−0.16, 1.10]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.46 (P = 0.14)				
1.3.5 Aerobic exercises				
Sertel et al, 2017	0.4795	0.33	100.0%	0.48 [−0.17, 1.13]
Subtotal (95% CI)			**100.0%**	**0.48 [−0.17, 1.13]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 1.45 (P = 0.15)				



Test for subgroup differences: $Chi^2 = 18.55$, df = 4 (P = 0.0010), $I^2 = 78.4\%$