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Reprint of: Efficacy, tolerability, and safety of non-pharmacological therapies for chronic pain: An umbrella review on various CAM approaches☆

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ABSTRACT

Background: Complementary and alternative medicine (CAM) therapies may be used as a non-pharmacological approach to chronic pain management. While hundreds of trials about individual CAM modality have been conducted, a comprehensive overview of their results is currently lacking for pain clinicians and researchers.
Aim: This umbrella review synthesized the quality of meta-analytic evidence supporting the efficacy, tolerability and safety of CAM therapies for the management of chronic pain.
Materials & methods: MEDLINE, EMBASE, CINAHL, and CENTRAL were searched from October 1991 to November 2016. Reviews of clinical trials (randomized and non-randomized) with meta-analysis investigating the utility of any CAM modality for chronic pain were eligible. Pain relief post-intervention was the main outcome and secondary outcomes included patients' adherence and incidence of adverse effects during CAM protocol.
Results: Twenty-six reviews (207 clinical trials, > 12,000 participants) about 18 CAM modalities, falling under natural products, mind and body practices or other complementary health approaches were included. Inhaled cannabis, graded motor imagery, and Compound Kushen injection (a form of Chinese medicine) were found the most efficient (with moderate-to-high effect sizes and low heterogeneity) and tolerable (≥ 80% of adherence to study protocols) for chronic pain relief. When reported, adverse effects related to these CAM were minor.
Conclusion: Although several CAM were found effective for chronic pain relief, it remains unclear when these modalities are a reasonable choice against or in conjunction with mainstream treatments. In that sense, future research with a clear emphasis on concurrent evaluation of CAM overall efficacy and patient adherence/tolerance is needed.

1. Introduction

Chronic pain is recognized as pain that persists for > 3 months, even in the absence of any past injury (Bonica, 1953), and may present in the form of headaches, musculoskeletal pain, visceral pain or neuropathic pain (e.g. pain resulting from damage to the peripheral nerves or to the central nervous system) (Treede et al., 2015). Chronic pain afflicts > 1.5 billion people around the world, with incidence rate increasing with age (Global Industry Analysts Inc, 2015). Despite accounting for nearly one-fifth of physician visits (Mäntyselkä et al., 2001), < 2% of chronic pain patients are treated by a pain specialist and an alarming 40% report inadequate pain relief (Breivik et al., 2006). Acute and episodic pains are most often self-treated with over the counter analgesics, mainly anti-inflammatory (Gallup survey conducted by the Gallup Organization from May 21 to June 9, 1999, n.d.; Whelton, 2000). Clinical guidelines addressed to general practitioners recommend non-opioids analgesics as first-line treatments of chronic non-cancer pain, and warn against potential harms and risks of opioids (Busse et al., 2017). Indeed, long-term administration of non-steroidal anti-inflammatory drugs have been linked to numerous complications, such as stomach ulcers, liver failure, and cardiovascular toxicity (Ong et al., 2007). Similarly, opioids have been associated with many adverse effects, like nausea, constipation, and present a serious risk of dependency for patients with a history of substance abuse (Kouyanou

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et al., 1997; Moore and McQuay, 2005; Porter and Jick, 1980). Although treatment of psychiatric co-morbidity such as anxiety and depression is common to improve management of chronic pain, benzodiazepines and tricyclic antidepressants have been linked to greater pain severity and lower feelings of self-efficacy (Nielsen et al., 2015; Raja et al., 2002). Even if well tolerated, efficacy of opioids is rarely maintained over prolonged treatments despite escalating doses (Ballantyne and Shin, 2008). As a result, about two-third of chronic pain patients will eventually turn to non-pharmacological treatments for additional relief (Breivik et al., 2006).

Complementary and Alternative Medicine (CAM) is a non-pharmacological option frequently contemplated by chronic pain patients (Penney et al., 2017). Whereas complementary medicine generally refers to therapies that are used in conjunction to traditional western medicine, alternative medicine refers to therapeutic approaches taken in place of standard treatments (Eisenberg et al., 2001). Despite the fact that several CAM therapies have been used as remedies for thousands of years, their incorporation to more mainstream healthcare practices has been seriously hampered by a lack of research funding (Ernst, 1996; Tabish, 2008). Thus, CAM is principally defined by the World Health Organization (WHO) as 'a broad set of healthcare practices that are not integrated into the dominant healthcare system' (Organization WH, n.d.). In the early 90's, the National Institutes of Health (NIH) launched the National Center for Complementary and Integrative Health (NCCIH – initially known as NCCAM). The mission of the NCCIH is "to define, through rigorous scientific investigation, the usefulness and safety of CAM interventions and their roles in improving health and health care" (NCCIH, n.d.-b). Overall, CAM therapies can be categorized into one of these three subgroups: a) natural products; b) mind and body practices; c) other complementary health approaches (NCCIH, n.d.-a). In 2011, the Cochrane review working group (Wieland et al., 2011) provided an official list of modalities to be considered within the CAM field's scope. Aside from generally agreed upon CAM modalities such as massage and homeopathy, the Cochrane review group also included therapies that are not uniformly integrated into the health care system despite stronger empirical evidence, depending on training of professionals and regional legislation. Therapeutic marijuana, as well as many forms of energy therapies such as transcranial direct-current stimulation (tDCS) and repetitive transcranial magnetic stimulation (rTMS) fall in this latter category.

Since the NCCIH launch, several academic and governmental groups have identified CAM as legitimate chronic pain management strategies. The latest American Pain Society's guidelines recommend yoga, acupuncture, massage therapy, progressive relaxation, and spinal manipulation to improve management of chronic low back pain (Chou et al., 2007). In 2014, the College of Family Physicians of Canada published its first recommendations for physicians prescribing smoked cannabis for chronic non-cancer pain (Kahan et al., 2014). Although most CAM modalities seem inoffensive, they may still cause serious adverse effects especially when taken at higher doses and over a long period. In fact, something in appearance as harmless as high-dose vitamins supplementation, has been associated to headaches, gastrointestinal discomfort, and increased mortality (Bhardwaj et al., 2009; Bjelakovic et al., 2004). Thus, any physician who cares for patients with chronic pain should be informed about the benefits and potential risks of these therapies, to guide patients in making evidence-based, well informed decisions about their use.

1.1. Why is it important to do this review?

Owning to the significant burden chronic pain has on quality of life and the limitations of conventional therapies, patients are increasingly turning to CAM for additional pain relief. Even in the general population, the main reason for using CAM therapies are improvements in acute pain and functional limitations (Carlson and Krahn, 2006; Okoro et al., 2012). Over the last three decades, several reviews and meta-analyses have pointed to the efficacy and safety of individual CAM therapies for the management of chronic pain. We are the first research team to propose a comprehensive synthesis of these reviews, targeting only the best level of evidence (e.g. meta-analytic results), and focusing on three important patient-centered outcomes, namely efficacy, tolerability, and safety.

2. Materials & methods

2.1. Study design and protocol registration

This study was conducted using an umbrella review approach. Unlike systematic reviews focusing on one intervention, an umbrella review combines the findings of several individual reviews about a specific body of research (Aromataris et al., 2015). It also compiles and compares the pooled benefits and harms of study intervention(s) into a single document, bringing a whole new level of evidence (Ioannidis, 2009). Such overviews are critical for research planning, translation, and clinical decision support.

We registered our study to PROSPERO, an international prospective register of systematic review protocols (Houzé et al., 2016). Minor changes in formulation of the research questions and inclusion criteria were made since the first review protocol submission. We initially targeted only reviews of randomized controlled trials (RCTs) comparing CAM interventions with a sham or placebo procedure. We extended it to any type of clinical trials with a control condition.

2.2. Literature search strategy

A search of the literature was performed with the assistance of an experienced librarian to identify any relevant meta-analysis quantifying the utility of CAM for the management of chronic pain. MEDLINE, EMBASE, the Cumulative Index of Nursing and Allied Health (CINAHL), and the Cochrane Central Register of Controlled Trials (CENTRAL) databases were searched from October 1991 (period corresponding to the NCCIH inauguration) to November 2016. To find as many studies as possible, we used a loose research strategy combining keywords and Medical Subject Heading (MeSH) in combination with Boolean operators. The keywords 'chronic pain' and 'meta-analysis' were both searched as free terms and as connected MeSH terms. Both terms were connected to an extensive list of CAM modalities identified through the Cochrane CAM taxonomy (Wieland et al., 2011) and fitting one of the NCCIH CAM categories (Table 1 – see Appendix 1 for details about our search strategy). In the instance where a CAM modality could not be found in the descriptor tree of a database, we added it as an additional search terms and combined it to the current search using the Boolean operator 'OR'. The search was limited to reviews of human trials published in English or French. The reference list of identified reviews was searched manually for additional reviews. The abstract of potentially eligible reviews was retrieved independently by two reviewers (BH and CA). The following PICO formulation was used to facilitate the identification of potentially eligible articles by the research team:

P (Problem): Chronic pain.
I (Intervention): Any intervention not generally considered to be a part of conventional medicine in most Western countries and falling under one of the NCCIH CAM category.
C (Comparison): No treatment, placebo, sham, wait list, and/or standard care.
(Outcome): Pain relief post-intervention.

2.3. Study selection and data extraction

Study selection was made independently by two reviewers (BH and CA) and disagreements in the selection process were resolved during a consensus meeting with a third reviewer (HEK). The following

Table 1
The NCCIH classification of complementary and alternative medicines.
Adapted from (NCCIH, n.d.-a).

Current CAM category	Former CAM category	Definition	Examples of modality
Natural products	Natural products	Use substances found in nature to promote health	Nutrition (e.g. vitamins) and herbal therapies (e.g. cannabinoids), hydrotherapy
Mind & body practices	Mind-body interventions	Uses a variety of techniques to enhance the mind's capacity to affect bodily function and symptoms.	Biofeedback, hypnosis, meditation, relaxation techniques, sensory art therapies, Tai Chi, Yoga
Other complementary health approaches	Alternative medical system	Complete systems of theory and practice outside the conventional allopathic model	Ayurvedic, Chinese, Japanese, Tibetan traditional medicines, homeopathy, naturopathy
	Energy therapies	Involves the use of energy fields, either the unconventional use of electromagetic fields, or the manipulation of energy fields that purportedly surround and penetrate the human body.	Acupuncture therapies, breathing exercises (e.g. Qi Gong), electromagnetic therapies (e.g. tDCS, TMS, therapeutic touch, reiki)
	Manipulative and body-based methods	Based on manipulation and/or movement of parts of the body	Chiropractic methods, massage (e.g. ostheopathy), reflexology

NCCIH: National Center for Complementary and Integrative Health, tDCS = transcranial Direct-Current Stimulation; TMS = Transcranial Magnetic Stimulation.

eligibility criteria were used:

(1) Types of studies: Systematic reviews of clinical trials (randomized or non-randomized) testing the utility of one specific CAM modality for managing chronic pain and of sufficient quality to be submitted, at least in some proportion, to a meta-analysis were included. Reviews investigating the usefulness of a pain management protocol combining multiple CAM modalities and/or for acute pain relief were excluded.
(2) Types of participants: Adults (18 years and older) with a chronic pain condition fitting the criteria of an endorsed pain organization (ex: the American College of Rheumatology). Although no strict definition of chronic pain was used, it had to be clear that the trials included in the review were performed in patients experiencing constant and/or recurrent pain for at least 3 months.
(3) Types of interventions: Reviews investigating a CAM modality and using one or more of the following control condition: no treatment, placebo, sham treatment, wait list, or standard care. As blinding is not always possible or practical in the administration of CAM, it was not a criterion for inclusion.
(4) Types of outcome measures: Decreased pain intensity at post-intervention was the principal outcome of interest. Consideration of other pain-related outcomes such as global improvement in functional disability, mood, and/or quality of life was optional. When available, information about participants' adherence to the CAM research protocol was retrieved, but was not a criterion for inclusion. Likewise, data about CAM safety served as secondary outcome measures.

2.4. Quality assessment and risk of bias

The methodological quality of each review was appraised independently by two reviewers (BH and CA) using the NIH Quality Assessment tool for Systematic reviews and Meta-Analyses (NIH, n.d.). One point was assigned in favor of the quality of review: if it was based on a focused and adequately formulated question (+1); if the inclusion and exclusion criteria were predefined and specified (+1); if the literature plan was systematic (+1); if titles, abstracts, full-text articles were dually and independently reviewed for inclusion (+1); if the quality of each included trial was scored independently by two reviewers following a standard method (+1); if a resume of each included trials characteristics was showed (+1); if publication bias was assessed (+1); if the heterogeneity of trials was assessed (+1). Inter-rater agreement between the two raters regarding individual items and the total score was assessed using Cohen's kappa (Cohen, 1960). Kappa coefficients were interpreted as slight (0.00–0.20), fair (0.21–0.40), moderate (0.41–0.60), substantial (0.61 to 0.80), and almost perfect-to-perfect agreement (0.81–1.00) (Landis and Koch, 1977). Disagreement between the reviewers on individual items or on total scores was resolved by a third reviewer (HEK). Risk of bias was evaluated based upon two key domains of the Cochrane Risk of Bias Tool: random sequence generation and allocation concealment (Higgins et al., 2011b), as there is empirical evidence of the influence of these types of bias on trials outcomes (Higgins et al., 2011a).

2.5. Data extraction and analysis

For all included reviews, key characteristics (e.g. CAM modality under study, first author, chronic pain diagnosis, number of trials included, frequency of administration and length of exposure to the CAM intervention, and comparison) were independently extracted by two reviewers (BH and CA). In the instance where the two entries did not match, a third person (HEK) was involved for verification. Each time multiple reviews about one specific CAM modality were identified, the number of trials overlapping between these reviews was assessed.

To answer our first research question about the efficacy and tolerability of CAM for the management of chronic pain, the number of trials included in the meta-analysis, as well as the pain scores modulation measure [generally in the form of standard mean difference (SMD) or Cohen's d, but occasionally as risk ratio (RR) and odd ratio (OR)] observed between the intervention and the control group was extracted. The effect size of CAM modalities for pain relief was interpreted as either small (≤ 0.49), moderate (0.50–0.79) or large (≥ 0.80) when estimated from Cohen's d or the absolute value of SMD (Cohen, 1988), and as small ($= 1.50$), moderate ($= 2.50$) or large ($= 4.50$) when estimated from OR (Chen et al., 2010). For each review, inconsistency in trials' outcome was quantified using the Chi square test (χ^2). The Higgins test (I^2) was used to assess whether differences in results were compatible with chance alone. $I^2 > 50\%$ was regarded to indicate considerable trials inconsistency, and a p value < 0.10 was regarded to indicate significant heterogeneity (Higgins and Thompson, 2002). For each review, the pooled number of chronic pain patients who started the CAM protocol and the pooled number of patients who completed the protocol were retrieved as an estimate for patients' tolerance to the CAM intervention. Although there is no consensus on the acceptable minimum adherence level in clinical trials, $\geq 80\%$ pooled adherence was considered satisfactory and indicative of good patient tolerability (Robiner, 2005). To answer our second question of whether CAM is safe for the management of chronic pain, information about the type and frequency of adverse effects was extracted whenever possible.

3. Results

3.1. Search results

The initial search yielded 210 articles. The title and abstract of each one was reviewed and 115 articles were excluded as they were either not relevant to the topic, were duplicates, or did not fit our eligibility

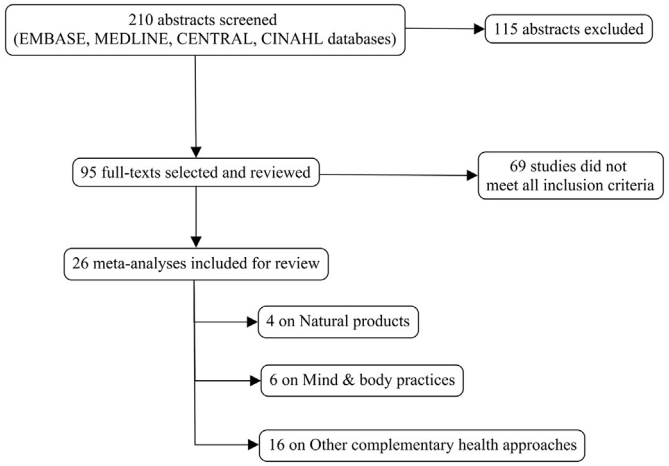

Fig. 1. Study-flow diagram of selected meta-analyses. The diagram shows how many reviews were kept and excluded from the umbrella review at each step of the literature search process and illustrates the total of meta-analyses fallen in each NCCIH category.

criteria. The full-text of the remaining 95 articles was retrieved, but most were excluded as 31 investigated several interventions, 15 were not about chronic pain, 16 did not perform any meta-analysis, and 7 included children. In total, 26 reviews were extracted for further analysis, including 4 about natural products, 6 on mind and body practices and 16 on other complementary health approaches (see Fig. 1 for a flow diagram of selected studies). All of them were published in English.

3.2. Characteristics of included reviews

Of all 26 reviews (Adachi et al., 2014; Ahmed Ali et al., 2014; Andreae et al., 2015; Bai et al., 2015; Bowering et al., 2013; Brosseau et al., 2002; Chen et al., 2015; Christensen et al., 2008; Cramer et al., 2013; Ebadi et al., 2014; Holtzman and Beggs, 2013; Huang et al., 2015; Jin et al., 2015; Kessler et al., 2015; Khadilkar et al., 2013; Martín-Sánchez et al., 2009; Mehta et al., 2015; O'Connell et al., 2014; Rutjes et al., 2009; Vickers et al., 2012; Ward et al., 2013; Wong Lit Wan et al., 2015; Xu et al., 2013; Yan et al., 2013; Yanju et al., 2014; Zhao et al., 2015), 88% were published from 2013 onwards and most were from China (n = 7) (Chen et al., 2015; Huang et al., 2015; Jin et al., 2015; Xu et al., 2013; Yan et al., 2013; Yanju et al., 2014; Zhao et al., 2015), Australia (n = 4) (Bowering et al., 2013; O'Connell et al., 2014; Ward et al., 2013; Wong Lit Wan et al., 2015) or Canada (n = 4) (Brosseau et al., 2002; Khadilkar et al., 2013; Mehta et al., 2015; Rutjes et al., 2009). Efficacy of CAM was frequently investigated for managing chronic pain of non-specific etiology (n = 7) or low back pain (n = 7). The most commonly reviewed CAM modalities were acupuncture/auriculotherapy (n = 4), yoga (n = 3) and transcutaneous electrical nerve stimulation (TENS, n = 3). Altogether, the reviews enrolled 353 clinical trials (n = 38 for natural products, n = 60 for mind and body practices and n = 255 for other complementary health approaches), of which, 47 were duplicates. Of them, n = 207 (59%) were used for meta-analysis. The average review included a median of 11 trials (range: 3–44) and combined a median of 197 participants (range: 83–2417). Frequency of administration and duration of the intervention protocol varied greatly between reviewed trials. Standard care was the most common control condition (n = 11), followed by placebo (n = 9), exercise (n = 7), and wait list (n = 6). Detailed characteristics of included reviews are presented in Table 2 and number of trials overlapping among meta-analyses investigating the same CAM in Table 3. See Appendix 2 for a list of pain diagnoses covered in reviews about non-specific chronic pain.

3.3. Review quality and risk of bias

The quality assessment of the 26 reviews is presented in Table 4. Scores on the NIH Quality Assessment tool ranged from 5 to 8 with n = 22 (85%) reviews meeting high-quality standards in terms of reporting quality (e.g. with a score ≥ 7). Kappa analysis of inter-rater agreement on the use of the NIH Quality Assessment tool indicated there was substantial agreement among raters regarding the overall quality of the included reviews (Kappa = 0.639 for the total scores, see Table 4). The itemized analysis showed there was perfect agreement (Kappa = 1.00) for 5 out of 8 questions. Substantial agreement (Kappa = 0.766) was obtained on the question about whether publication bias was assessed, moderate agreement (Kappa = 0.454) was obtained on the question about whether trials were dually reviewed for inclusion, and only slight agreement (Kappa = 0.152) was obtained on the question whether trials were dually assessed for quality. Publication bias was evaluated by means of funnels plots in only n = 11 (42%) reviews and no clear evidence of such bias was observed. Risk of bias in general was investigated in n = 17 (65%) reviews. High risk of bias regarding random sequence generation and allocation concealment was present in 34% and 54% of reviewed trials respectively.

3.4. Efficacy and tolerability of CAM interventions for chronic pain

Results about efficacy and tolerability of CAM interventions for chronic pain are presented in Table 5. For most studies (n = 18) (Ahmed Ali et al., 2014; Bai et al., 2015; Brosseau et al., 2002; Chen et al., 2015; Cramer et al., 2013; Ebadi et al., 2014; Huang et al., 2015; Jin et al., 2015; Kessler et al., 2015; Khadilkar et al., 2013; Martín-Sánchez et al., 2009; O'Connell et al., 2014; Rutjes et al., 2009; Ward et al., 2013; Wong Lit Wan et al., 2015; Xu et al., 2013; Yan et al., 2013; Zhao et al., 2015), negative SMD values were reported reflecting the difference in mean pain decrease between CAM intervention and control condition. On the other hand, some studies reported positive values for SMD or CD (n = 6) (Adachi et al., 2014; Bowering et al., 2013; Christensen et al., 2008; Holtzman and Beggs, 2013; Mehta et al., 2015; Vickers et al., 2012), as well as for RR and OR (n = 2) (Andreae et al., 2015; Yanju et al., 2014), reflecting the gain in pain reduction of CAM interventions over control conditions. Either way, negative or positive effect size results always expressed superiority of CAM intervention for pain relief compared to control conditions.

Cannabis (inhaled or in preparations) was the only CAM intervention from the natural products group that showed significant medium effect on chronic pain relief (Andreae et al., 2015; Martín-Sánchez et al., 2009). In contrast, antioxidants and *Rosa canina* were found to only have small effect on pain (Ahmed Ali et al., 2014; Christensen et al., 2008). Moreover, the heterogeneity of the pooled studies for cannabis was low ($I^2 \leq 50\%$) and high tolerability was observed with adherence > 90%. In the review about inhaled cannabis however, only 3 out of the 5 trials reported on participants' history of prior cannabis consumption (Andreae et al., 2015). It is also unclear whether participants were instructed not to smoke more cannabis than what was prescribed in the study protocol and how this aspect was controlled for in the trials.

Regarding mind and body practices, graded motor imagery, hypnosis, and yoga, were found to provide moderate-to-high relief for chronic pain (Adachi et al., 2014; Bowering et al., 2013; Holtzman and Beggs, 2013; Ward et al., 2013). However, heterogeneity was significantly high ($I^2 > 50\%$) for the pooled studies about hypnosis (Adachi et al., 2014). Even though yoga was found an efficacious adjunctive treatment for musculoskeletal pain in two reviews, this finding is limited by contrasting results about heterogeneity, a lack of appropriate control condition in most trials (i.e. an active group following a traditional exercise program) (Holtzman and Beggs, 2013; Ward et al., 2013) and a high rate of attrition in one review (55%) (Holtzman and Beggs, 2013). More convincingly, graded motor imagery (a 3-step

Table 2
Characteristics of reviews included in umbrella review.

	CAM	Reference	Chronic pain diagnosis	No. trials in review	Intervention		Comparison
					Frequency	Length of exposure	
Natural products	Antioxidants	Ahmed Ali et al., 2014	Chronic pancreatitis	12	1–4 times/d	45 h–6 m	C, SC, P
	Cannabis (inhaled)	Andreae et al., 2015	Neuropathic pain	5	1–3 + times/d	1 h–5d	P
	Cannabis	Martín-Sánchez et al., 2009	Miscellaneous[a]	18	NR	1d–5 w	P
	Rosa canina	Christensen et al., 2008	Osteoarthritis (knee, hip, neck, shoulders, hand)	3	NR	12–16 w	P
Mind & body practices	Graded motor imagery	Bowering et al., 2013	Miscellaneous[a]	6	5–7 times/w	4–6 w	SC, sham
	Hypnosis	Adachi et al., 2014	Miscellaneous[a]	12	1–7 times/w	3–12 sessions	C, SC, WL
	Yoga	Cramer et al., 2013	Low back pain	10	1–7 times/w	1–24 w	EDU, EX, C, SC, WL
	Yoga	Holtzman and Beggs, 2013	Low back pain	8	1–7 times/w	1–24 w	EDU, EX, SC, WL
	Yoga	Ward et al., 2013	Musculoskeletal pain	17	1–7 times/w	1–24 w	C, EDU, EX, SC, WL
	Tai-Chi	Yan et al., 2013	Osteoarthritis (knee, hip)	7	1–3 times/w	8–24 w	C, EDU, EX, SC, WL
Other complementary health approaches	Acupuncture	Vickers et al., 2012	Miscellaneous[a]	29	NR	NR	Sham
	Acupuncture (local and distant)	Wong Lit Wan et al., 2015	Musculoskeletal pain	19	1–3 times/w	1–15 sessions	NT, SC, sham
	Acupuncture	Xu et al., 2013	Low back pain	13	NR	NR	SC, sham
	Auriculotherapy (different type)	Zhao et al., 2015	Miscellaneous[a]	15	1–7 times/w	1–12 w	Acupuncture, CM, sham
	Ayurveda	Kessler et al., 2015	Osteoarthritis (knee, ankles, hip)	33	1–3 times/d	1–36 w	EX, P, Pain Rx
	Compound Kushen injection	Yanju et al., 2014	Bone cancer pain	7	1 time/d	2–8 w	SC
	LLLT	Chen et al., 2015	Temporomandibular disorders	14	NR	NR	P
	LLLT	Huang et al., 2015	Low back pain	7	2–5 times/w	2–6 w	EX, P
	rTMS	Jin et al., 2015	Neuropathic pain	25	–	2–10 sessions	Sham
	rTMS, tDCS	O'Connell et al., 2014	Miscellaneous[a]	44	1–10 times/d	1 d–10 w	Sham
	TENS	Brosseau et al., 2002	Low back pain	5	2–21 times/w	1–4 w	EDU, heat, NT, Pain Rx
	TENS	Khadilkar et al., 2013	Low back pain	4	5–21 times/w	2–4 w	P
	TENS	Rutjes et al., 2009	Knee osteoarthritis	18	3 times/w	1 d–12 w	NT, sham
	tDCS	Mehta et al., 2015	Neuropathic pain	5	–	1–20 sessions	Sham
	Qigong (internal and external)	Bai et al., 2015	Miscellaneous[a]	10	1–7 times/w	2–24 w	P, SC, WL
	Ultrasounds	Ebadi et al., 2014	Low back pain	7	1–5 times/w	2–6 w	EX, sham

LLLT = low level laser therapy; rTMS = repetitive Transcranial Magnetic Stimulation, tDCS = transcranial Direct-Current Stimulation; h = hour; d = day; w = week; m = month; C = Counselling; CM = Chinese medicine; EDU = Education; EX = Exercise; NR = not reported; NT = No treatment; SC = Standard care; P = Placebo WL = Wait list.

[a] See Appendix 2 for an exhaustive list of chronic pain diagnoses for these reviews.

Table 3
Number of trials overlapping among meta-analyses investigating the same CAM.

CAM modality	Acupuncture			rTMS		tDCS		TENS			Yoga		
Reference	Vickers et al., 2012	Wong Lit Wan et al., 2015	Xu et al., 2013	Jin et al., 2015	O'Connell et al., 2014	Mehta et al., 2015	O'Connell et al., 2014	Brosseau et al., 2002	Khadilkar et al., 2013	Rutjes et al., 2009	Cramer et al., 2013	Holtzman and Beggs, 2013	Ward et al., 2013
	n = 29	n = 19	n = 13	n = 25	n = 11	n = 5	n = 8	n = 5	n = 4	n = 18	n = 10	n = 8	n = 17
Vickers et al., 2012		3	9										
Wong Lit Wan et al., 2015	3		0										
Xu et al., 2013	9	0											
Jin et al., 2015					4								
O'Connell et al., 2014				4									
Mehta et al., 2015							2						
O'Connell et al., 2014						2							
Brosseau et al., 2002									1	0			
Khadilkar et al., 2013								1		0			
Rutjes et al., 2009								0	0				
Cramer et al., 2013												8	12
Holtzman and Beggs, 2013											8		8
Ward et al., 2013											12	8	

rTMS = repetitive Transcranial Magnetic Stimulation, tDCS = transcranial Direct-Current Stimulation.

Table 4
Inter-rater agreement on NIH – quality assessment criteria.

NIH criteria	1.	2.	3.	4.	5.	6.	7.	8.	Total score
Reference	Focused question	Predefined eligibility criteria	Comprehensive lit. search	Dually reviewed for inclusion	Quality assessed by 2 or + raters	Studies clearly listed	Assessment publication bias	Assessment heterogeneity	
Natural health products									
Ahmed Ali 2014	Y	Y	Y	Y	N	Y	Y	Y	7
Andrea 2015	Y	Y	Y	Y	Y	Y	Y	Y	8
Christensen 2008	Y	Y	Y	Y	Y	Y	N	Y	7
Martin-Sanchez 2009	Y	Y	Y	N	Y	Y	Y	Y	7
Mind & body practices									
Adachi 2014	Y	Y	Y	N	Y	Y	N	Y	6
Bowering 2013	Y	Y	Y	Y	Y	Y	N	Y	7
Cramer 2013	Y	Y	Y	Y	Y	Y	Y	Y	8
Holtzmann 2013	Y	Y	Y	N	N	Y	N	Y	5
Ward 2013	Y	Y	Y	Y	Y	Y	N	Y	7
Yan 2013	Y	Y	Y	Y	Y	Y	Y	Y	8
Other complementary health approaches									
Bai 2015	Y	Y	Y	Y	Y	Y	Y	Y	8
Brosseau 2002	Y	Y	Y	Y	Y	Y	N	Y	7
Chen 2015	Y	Y	Y	Y	Y	Y	N	Y	7
Ebadi 2014	Y	Y	Y	Y	Y	Y	N	Y	7
Huang 2015	Y	Y	Y	Y	N	Y	N	Y	6
Jin 2015	Y	Y	Y	Y	Y	Y	Y	Y	8
Khadilkar 2013	Y	Y	Y	Y	Y	Y	N	Y	7
Kessler 2015	Y	Y	Y	Y	N	Y	N	Y	6
Mehta 2015	Y	Y	Y	Y	Y	Y	N	Y	7
O'Connell 2014	Y	Y	Y	Y	Y	Y	Y	Y	8
Rutjes 2010	Y	Y	Y	Y	Y	Y	Y	Y	8
Vickers 2012	Y	Y	Y	Y	N	Y	Y	Y	7
Wong Lit Wan 2015	Y	Y	Y	Y	Y	Y	N	Y	7
Xu 2013	Y	Y	Y	Y	Y	Y	Y	Y	8
Yanju 2014	Y	Y	Y	Y	Y	Y	Y	Y	8
Zhao 2015	Y	Y	Y	Y	Y	Y	Y	Y	8
Kappa coefficient	1	1	1	0.454	0.152	1	0.766	1	0.639

Kappa inter-rater agreement interpretation
0.00–0.20 = slight
0.21–0.40 = fair
0.41–0.60 = moderate
0.61–0.80 = substantial
0.81–1.00 = almost perfect-to-perfect.

cognitive exercise program consisting of left/right judgements, motor imagery and mirror therapy) was found effective to provide chronic pain relief (Bowering et al., 2013). Mirror therapy alone [SMD: 1.85 (95% CI: 0.40–3.29)] could even be more effective than the complete graded motor imagery program [SMD: 1.06 (95% CI: 0.41–1.71)] to treat phantom limb pain (Chan et al., 2007). Participants' adherence to graded motor imagery treatments was also satisfactory (83% on average).

Several CAM modalities from the other complementary health approaches category were found to produce significant pain relief. Acupuncture and acupuncture-like therapies (including local acupuncture, auricular acupressure), Ayurveda, non-invasive stimulation therapies [including low-level laser therapy (LLLT), high-frequency repetitive transcranial magnetic stimulation (HF-rTMS), transcranial direct current stimulation (tDCS), TENS and ultrasounds], and internal Qigong were found to produce a significant medium-to-large effect on chronic pain (Bai et al., 2015; Huang et al., 2015; Jin et al., 2015; Kessler et al., 2015; Mehta et al., 2015; Rutjes et al., 2009; Vickers et al., 2012; Wong Lit Wan et al., 2015; Zhao et al., 2015). However, high, absent or conflicting results about trials heterogeneity were found for these interventions. While compound Kushen injection (CKI), a Chinese medicine, has shown a significant moderate effect on pain with a low heterogeneity, meta-analysis' authors cautioned against the efficacy of CKI as studies were generally of poor quality (Yanju et al., 2014). Although data about participants' adherence were missing from several reviews in this category, local acupuncture, Ayurveda, LLLT, HF-rTMS, tDCS, TENS, Qigong and ultrasounds were particularly well tolerated with an average adherence rate ≥ 93.8% across trials.

3.5. Adverse effects of CAM interventions

Adverse effects of CAM modalities were reported in only $n = 11$ (42%) reviews, and more frequently in the intervention group ($n = 661$) compared to the control groups ($n = 207$). Occurrence of adverse effects was particularly frequent with cannabis preparations among first-time cannabinoid users and included symptoms such as euphoria, dysphoria, alterations motor or cognitive function. While most adverse events were minor and rarely led to study withdrawal, rTMS led to three cases of seizure requiring medical assistance. For detailed information about adverse effects, see Table 6.

4. Discussion

While several reviews about CAM for chronic pain have been

Table 5
Synthesis of review findings on the efficacy and tolerability of CAM for chronic pain.

	CAM	Reference	No. trials in meta-analysis	Effect size for pain relief post-intervention[a]				Heterogeneity			Tolerability	
				SMD or CD [95% CI]	OR/RR [95% CI]	Effect	p value	χ^2	I^2	p value	N beginning	N end (% adherence)
Natural products	Antioxidants	Ahmed Ali 2014	4	− 0.33 [− 0.64 to − 0.02]	–	S	*	0.54	≤ 50%	n.s.	151	123 (81%)
	Cannabis (inhaled)	Andreae 2015	5	–	OR: 3.22 [1.59 to 7.24]	M	NR	NR	≤ 50%	NR	189	178 (94%)
	Cannabis	Martin-Sanchez 2009	7	− 0.61 [− 0.84 to − 0.37]	–	M	NR[b]	5.31	≤ 50%	n.s.	183	172 (94%)
	Rosa Canina	Christensen 2008	3	0.37 [0.13 to 0.60]	–	S	**	0.18	≤ 50%	NR	306	287 (94%)
Mind & body practices	Graded motor imagery	Bowering 2013	2	1.06 [0.41 to 1.71]	–	L	**	1.18	≤ 50%	n.s.	63	63 (100%)
	Hypnosis	Adachi 2014	4	0.60 [0.03 to 1.17]	–	M	*	NR	> 50%	◊	NR	163 (–)
	Tai-Chi	Yan 2013	7	− 0.45 [− 0.70 to − 0.20]	–	S	***	7.57	≤ 50%	n.s.	NR	348 (–)
	Yoga	Cramer 2013	6	− 0.48 [− 0.65 to − 0.31]	–	S	**	3.21	≤ 50%	n.s.	741	584 (79%)
	Yoga	Holtzmann 2013	5	0.62 [0.38 to 0.87]		M	NR	5.16	≤ 50%	n.s.	851	381 (45%)
	Yoga	Ward 2013	4	− 0.61 [− 0.97 to − 0.26]	–	M	***	13.37	> 50%	◊	449	399 (87%)
Other complementary health approaches	Acupuncture (osteoarthritis)	Vickers 2012	5	0.26 [0.17 to 0.34]	–	S	***	NR	NR	◊	NR	1487 (–)
	Acupuncture (headache)	Vickers 2012	4	0.15 [0.07 to 0.24]	–	S	***	NR	NR	n.s.	NR	1414 (–)
	Acupuncture (musculoskeletal pain)	Vickers 2012	8	0.37 [0.27 to 0.46]	–	S	***	NR	NR	◊	NR	1417 (–)
	Acupuncture (shoulder pain)	Vickers 2012	3	0.62 [0.46 to 0.77]	–	M	***	NR	NR	n.s.	NR	564 (–)
	Acupuncture (local)	Wong Lit Wan 2015	10	− 0.91 [− 1.38 to − 0.45]	–	L	***	33.76	> 50%	◊	442	427 (97%)
	Acupuncture (distant)	Wong Lit Wan 2015	2	0.02 [− 0.59 to 0.62]	–	S	n.s.	0.52	≤ 50%	n.s.	52	42 (81%)
	Acupuncture	Xu 2013	7	≈ − 0.25 [− 0.65 to 0.05][c]	–	S	n.s.	NR	NR	NR	NR	2417 (–)
	Auricular acupressure	Zhao 2015	3	− 0.75 [− 1.26 to − 0.25]	–	M	**	NR	> 50%	NR	NR	180 (–)
	Auricular acupuncture	Zhao 2015	2	− 1.31 [− 4.33 to 1.72]	–	L	n.s.	NR	> 50%	NR	NR	174 (–)
	Auricular electro-stimulation	Zhao 2015	4	− 3.29 [− 5.87 to − 0.72]	–	L	**	NR	> 50%	NR	NR	131 (–)
	Ayurveda (Boswellia serrata)	Kessler 2015	4	− 3.20 [− 5.21 to − 1.18]	–	L	**	45.75	> 50%	◊	150	145 (97%)
	Ayurveda (Rumalaya)	Kessler 2015	2	− 3.73 [− 4.97 to − 2.5]		L	**	4.54	> 50%	◊	157	156 (99%)
	Chinese medicine (CKI)	Yanju 2014	7	–	RR: 1.25 [1.13 to 1.38]	M	***	4.77	≤ 50%	n.s.	521	521 (100%)
	LLLT	Chen 2015	10	− 19.39 [− 40.80 to 2.03]	–	L	n.s.	808.30	> 50%	◊	NR	368 (–)
	LLLT	Huang 2015	3	− 12 [− 2.02 to − 21.98]	–	L	*	NR	> 50%	NR	197	197 (100%)
	HF-rTMS	Jin 2015	22	− 0.86 [− 1.15 to − 0.56]	–	L	***	2.62	≤ 50%	n.s.	589	536 (91%)
	HF-rTMS	O'Connell 2014	20	− 0.27 [− 0.35 to − 0.20]	–	S	***	69.89	> 50%	◊	510	447 (88%)
	tDCS	Mehta 2015	5	0.51 [0.11 to 0.91]	–	M	*	NR	≤ 50%	n.s.	NR	83 (–)
	tDCS	O'Connell 2014	11	− 0.18 [− 0.46 to 0.09]	–	S	n.s.	21.07	> 50%	◊	224	183 (82%)

(*continued on next page*)

Table 5 (*continued*)

CAM	Reference	No. trials in meta-analysis	Effect size for pain relief post-intervention[a]				Heterogeneity			Tolerability	
			SMD or CD [95% CI]	OR/RR [95% CI]	Effect	p value	χ^2	I^2	p value	N beginning	N end (% adherence)
TENS	Brosseau 2002	3	− 4.32 [− 10.36 to 1.72]	–	L	n.s.	NR	NR	NR	214	213 (99%)
TENS	Khadilkar 2013	1	− 12.20 [− 26.83 to 2.43]	–	L	NR	NR	NR	NR	30	22 (73%)
TENS	Rutjes 2009	11	− 0.85 [− 1.36 to − 0.34]	–	M	***	64.9	> 50%	◊	493	465 (94%)
Qigong (internal)	Bai 2015	3	− 1.23 [− 2.23 to − 0.24]	–	L	*	13.90	> 50%	◊	175	172 (98%)
Qigong (external)	Bai 2015	7	− 0.13 [− 0.75 to 0.48]	–	S	n.s.	45.80	> 50%	◊	360	354 (98%)
Ultrasounds	Ebadi 2014	3	− 7.12 [− 17.99 to 3.75]	–	L	n.s.	8.73	> 50%	◊	123	121 (98%)

LLLT = low level laser therapy; HF-rTMS = high frequency repetitive Transcranial Magnetic Stimulation, tDCS = transcranial Direct-Current Stimulation; CD = Cohen's d; OR = odd ratios; RR = risk ratios; SMD = standard mean deviation; χ^2 = chi-square; I^2 = Higgins test; ◊ ≤ 0.1; * ≤ 0.05; ** ≤ 0.01; *** ≤ 0.001; n.s. = non-significant; NR = not reported.

[a] All effect size are in favor of CAM interventions.

[b] As upper limit did not cross the line of no effect (i.e. 0), the effect is significant, at least at $p \leq 0.05$.

[c] As authors did not report numerical values but graphic representation of the effect size, an approximation is provided.

conducted, this review is the first to provide systematic recommendations that could transcend individual CAM studies and be used in more integrative research examining the usefulness of non-pharmacological approaches for pain management. Using a comprehensive search strategy, findings from 26 reviews and meta-analyses conducted across 18 CAM modalities were synthetized. Even though most reviews have pointed to the potential benefices of CAM for chronic pain, very little translatable evidence could be extracted due to important limitations in the reviews and the reviewed trials. Still, inhaled cannabis, graded motor imagery, and Compound Kushen injection seemed the most promising CAM modalities for chronic pain as they were found: a) effective, as per significant moderate-to-high effect sizes for pain relief and consistent findings; b) tolerable, as per high rates of adherence to study protocols; and, c) safe of use, considering adverse effects associated to those CAM were mostly minors, infrequent, and rarely lead to study discontinuation.

About one third of meta-analyses (n = 8) reported a small significant effect of CAM intervention on pain relief (Ahmed Ali et al., 2014; Christensen et al., 2008; Cramer et al., 2013; O'Connell et al., 2014; Vickers et al., 2012; Yan et al., 2013) and an another third (n = 9) reported a moderate-to-large effect size, but with a heterogeneity > 50% (Adachi et al., 2014; Huang et al., 2015; Kessler et al., 2015; Rutjes et al., 2009; Ward et al., 2013; Wong Lit Wan et al., 2015; Zhao et al., 2015), failing to classify as effective therapy in this review. When compared with cannabis or graded motor imagery, these modalities were far less effective when administered individually. One would suggest that most CAM interventions may therefore qualify as *complementary* or *integrative* therapies rather than *alternative* therapies. Following the example of Yanju et al. (2014), one avenue would be to always study the utility of CAM in conjunction with conventional treatments or with other CAM modalities, as they may still have adjuvant properties. This exercise is absolutely crucial to clarify when these modalities are a reasonable choice against or in conjunction with more mainstream pain treatments.

One of the most important limitations affecting this overview relates to the CAM modalities themselves and how they were administered. Indeed, great variations in the intervention protocols were noted across reviews. Taking natural products for instance, they were administered anywhere from 1 to 4 times/day and for a duration of 1 day to 6 months in reviewed trials (Ahmed Ali et al., 2014; Andreae et al., 2015; Christensen et al., 2008; Martín-Sánchez et al., 2009). In one particular review, results from cannabis preparation and those from cannabis spray were pooled together, even though the bio distribution of the medicinal compounds could be different (Martín-Sánchez et al., 2009). Similarly, in the mind-body methods category, great variability in the administration of CAM interventions was observed depending on the pain condition under study. Just for neuropathic pain, hypnosis and graded motor imagery were administered anywhere between 2 and 10 sessions of variant duration (15–90 min each) (Adachi et al., 2014; Bowering et al., 2013). Aside from limiting comparison across study, such variations in intervention protocols is a reminder that the underlying mechanisms of these CAM modalities remain poorly understood (Jensen et al., 2015; Moseley, 2006). Even in energy therapies, were the underlying mechanisms are known, TENS was administered 2–21 times/week and for up to 4 weeks in trials for chronic low back pain, whereas it was administered 3 times/week up to 12 weeks in the context of knee osteoarthritis (Brosseau et al., 2002; Khadilkar et al., 2013; Rutjes et al., 2009). Until a consensus about the therapeutic dose-effect is made, physicians and pain specialists will remain uncomfortable with recommending/prescribing CAM to optimize chronic pain management. Energy therapies including tDCS and rTMS appear more advanced than other CAM modalities in that sense, as therapeutic protocols for the management of neuro-psychiatric disorders already exist (Tortella et al., 2015). Accordingly, four reviews about non-invasive stimulation therapies (TENS, rTMS, tDCS) could identify a 'typical' dose-response for the management of chronic pain (Jin et al.,

Table 6
Reported adverse effects on CAM interventions for pain management.

	CAM	Reference	Adverse events	No. of reported cases (n) or percentage (%)		Led to withdrawal
				Study group	Control group	
Natural products	Antioxidants	Ahmed Ali 2014	Headache, nausea, constipation	16%	3%	Yes – all cases
	Cannabis (inhaled)	Andrea 2015	Major: psychosis, hypertension, hyperalgesia	2	1	Rarely – 3 cases
			Minor: anxiety, disorientation, difficulty concentrating, headache, dry eyes, burning sensation, dizziness, numbness, psychoactive effects	NR	NR	
	Cannabis	Martin-Sanchez 2009	Euphoria, dysphoria, alterations in perception/motor or cognitive function	381	56	Not specified
	Rosa Canina	Christensen 2008	Gastrointestinal discomfort	1	1	Rarely – 2 cases
Other complementary health approaches	Acupuncture	Wong Lit Wan 2015	Fainting, numbness, soreness, burning or coldness, increase pain	34	7	Not specified
	Auriculotherapy	Zhao 2015	Local pain, soreness, itching, hypotension, hematoma, redness, bleeding, sleep disturbance or pressure ulcer	46	–	Not specified
	Ayurveda (Boswellia serrata)	Kessler 2015	Gastrointestinal discomfort	47	50	Occasional – 9 cases
	Compound Kushen injection	Yanju 2014	Rash	1	0	No
	rTMS	Jin 2015	Major: Seizure	1	0	Rarely – 1 case
			Minor: Headache, dizziness	17	19	No
	rTMS	O'Connell 2014	Major: Seizure	2	0	Not specified
			Minor: headache, nausea, neck pain, worsening depression, tiredness, tinnitus, dizziness	84	48	
	tDCS	O'Connell 2014	Headache, neck pain, scalp pain, burning sensation over scalp, sleepiness, skin redness/tingling	25	4	Not specified
	TENS	Khadilkar 2013	Skin irritation	20	21	Rarely – 1 case

rTMS = repetitive Transcranial Magnetic Stimulation, tDCS = transcranial Direct-current Stimulation; NR = not reported.

2015; Khadilkar et al., 2013; Mehta et al., 2015; O'Connell et al., 2014). As with many other CAM, most energy therapies (TENS, LLLT, rTMS, tDCS) require extensive training and can only be administered by licenced professionals such as physiotherapists (Lindsay et al., 1995). These therapies also have strong empirical support to be used in conjunction with standard treatments, and as such, are increasingly incorporated into clinical guidelines and health government recommendations (Janicak et al., 2010).

Participant selection in CAM trials and comparison groups were also questionable. Although all trials included participants with a pain condition exceeding 3 months, only 38% considered pain duration and/or pain intensity in their inclusion criteria (Adachi et al., 2014; Bai et al., 2015; Bowering et al., 2013; Brosseau et al., 2002; Christensen et al., 2008; Jin et al., 2015; Khadilkar et al., 2013; Mehta et al., 2015; O'Connell et al., 2014; Xu et al., 2013). Over-representation of participants with complex and long lasting pain syndromes and/or with mild pain intensity may have led to significant ceiling or floor effects in the trials (Streiner et al., n.d.). This was discussed in one review about tDCS which noted that individuals with neuropathic pain duration of < 5 years were more likely to demonstrate a reduction in pain intensity after treatment compared with those with pain duration of 4–5 years (Mehta et al., 2015). The pooled analysis in this review also highlighted that individuals with high depressive symptoms were more likely to respond to tDCS treatment than those with no mood disruption. Unfortunately, psychological distress was not an explicit exclusion criterion and it was not accounted for in the analysis and discussion of the other reviews. Potentially interfering with conclusions about cannabis effectiveness, few trials (only 15 out of 23) reported on participants previous exposition to cannabis and discussed potential carryover effects (Andreae et al., 2015; Martín-Sánchez et al., 2009). Moreover, none of the reviewed trials about cannabis reported information regarding the potential addictive effect of this substance on the participants. Disappointingly, only one out of 26 reviews under study could meaningfully extract information about participants' analgesic consumption during CAM trials (Mehta et al., 2015). It is also important to highlight that most reviews supplied limited details on the dose of the intervention administered to pain participants. In addition, trials rarely reported details about exposition of the control group to the same experimental conditions than the experimental group. Future studies about CAM should undoubtedly discuss how the control group may have accounted for nonspecific aspects of the intervention such as the therapeutic environment, social support, schedule and duration of practice of the treatment and control activities, attention from study staff, and other factors.

Another important methodological issue observed in the included reviews relates to trials inclusion. Every clinical trial measuring a pain-related outcome was included in these reviews, whether or not pain relief was the primary outcome of interest. While this way of proceeding is consistent with Cochrane systematic review methodology (O'Connor et al., 2011), it may have impacted the meta-analytic analyses in several ways. Indeed, trials typically don't report extensive quantitative findings for secondary outcomes, and obtaining the missing data to conduct proper meta-analysis is not an easy task for the review team. In fact, 14 out of the 26 included reviews dealt with missing data while conducting their meta-analysis (Bowering et al., 2013; Brosseau et al., 2002; Chen et al., 2015; Ebadi et al., 2014; Kessler et al., 2015; Khadilkar et al., 2013; Martín-Sánchez et al., 2009; Vickers et al., 2012; Ward et al., 2013; Wong Lit Wan et al., 2015; Xu et al., 2013; Yan et al., 2013; Yanju et al., 2014; Zhao et al., 2015). Successful transmission of the missing data by the corresponding author of the trial was achieved in only 33% of cases. This suggests that not all reviews included in this overview were adequately powered to measure CAM efficacy for chronic pain. In addition, publication bias through funnel plot analysis was assessed in only $n = 11$ (42%) of the reviews included in this overview, due to the small number of trials (< 10) included in most meta-analyses (Ahmed Ali et al., 2014; Bai et al., 2015; Cramer et al., 2013; Jin et al., 2015; Martín-Sánchez et al., 2009; O'Connell et al., 2014; Rutjes et al., 2009; Vickers et al., 2012; Xu et al., 2013; Zhao et al., 2015). Risk of bias regarding random sequence generation and allocation concealment was reported and discussed in only $n = 16$ (62%) of reviews (Ahmed Ali et al., 2014; Andreae et al., 2015; Bai et al., 2015; Brosseau et al., 2002; Cramer et al., 2013; Ebadi et al., 2014; Holtzman and Beggs, 2013; Huang et al., 2015; Jin et al., 2015; Kessler et al., 2015; Khadilkar et al., 2013; Rutjes et al., 2009; Wong Lit Wan et al., 2015; Xu et al., 2013; Yanju et al., 2014; Zhao et al., 2015).

The large variability in meta-analyses methodologic quality reflects the need for standardization of reporting and conducting clinical trials about non-pharmacological approaches to chronic pain. In particular, when analyzing their results, future trials will have to make due allowance for participants' previous exposition and/or deviance to the CAM protocols. Trials about yoga, who commonly encourage participants to stay active outside of the research protocol, should also account for this aspect and provide adequate control condition (i.e. a physically active control group) to help identify the 'true' contribution of this CAM therapy to chronic pain management. We also recommend that procedures for random sequence generation and allocation concealment, as well as the results of power analyses to be reported in future CAM trials. Patient adherence/tolerance should also be addressed in all CAM RCTs. Regarding systematic reviews about CAM interventions, we cannot stress enough on the importance to register the protocol of the review in PROSPERO. The degree of overlap in the separate reviews about the same CAM is generally a function of the overlap in the review questions. Although the ability to replicate results strengthens our confidence in the results, the prospective registration of the review protocol in PROSPERO could have avoid the duplication of efforts and resources that were spent investigating the effectiveness of yoga for chronic low back pain in two very similar reviews (Cramer et al., 2013; Holtzman and Beggs, 2013).

5. Conclusion

Only one modality issued from natural products (inhaled cannabis), one from mind-body interventions (graded motor imagery), and one from other health approaches (Compound Kushen injection) classified as useful CAM modalities for chronic pain. Standardization of CAM protocols, better description of control group exposition to nonspecific aspects of the interventions, and a clear comparison of efficacy against mainstream treatments are needed to improve quality of CAM trials. Findings and recommendations from this umbrella review could encourage pain scientists and clinicians to include non-pharmacological approaches in research planning and pain management protocols.

Conflict of interests

The authors declare that they have no commercial association, financial involvement or relationship with any organization or entity relevant to this manuscript that might be perceived as a conflict of interest.

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Appendices

Appendix 1
Detailed literature research strategy by database.

EMBASE search strategy	
#1	Exp Complementary therapies/
#2	Exp Meta analysis/
#3	Exp Chronic pain/
#4	Exp natural products/
#5	Exp cannabis/
#6	Exp curcuma longa/or exp. plant extract/or exp. turmeric
#7	Exp curcumin/
#8	Exp ginger/
#9	Exp zingiber/
#10	Exp vitamin/
#11	Exp mineral/
#12	Exp yoga/or exp. meditation/or exp. tai chi/or exp. “quality of life”
#13	Exp acupuncture/
#14	Exp chiropractic/
#15	Exp massage/
#16	Exp physiotherapy/
#17	Exp osteopathic/or exp. manipulative medicine/
#18	Exp reiki/
#19	Exp Guided imagery/
#20	Exp Hypnosis/
#21	Exp qigong/or exp. breathing exercise/
#22	Exp feedback system/
#23	Exp low level laser therapy/
#24	Exp transcutaneous electrical nerve stimulation/
#25	Exp transcranial magnetic stimulation/
#26	Exp magneto therapy/
#27	Exp exercise/
#28	Exp diet/
#29	Exp homeopathy/
#30	Exp music therapy/
#31	Exp ayurveda/
#32	#1 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30
#33	#32 AND #2 AND #3 limited to adult
MEDLINE search	
#1	Exp Complementary therapies/
#2	Exp Meta analysis/
#3	Exp Chronic pain/
#4	Exp biological products/
#5	Exp plants/
#6	Exp vitamins/
#7	Exp minerals/
#8	Exp acupuncture/
#9	Exp chiropractic/
#10	Exp osteopathic medicine/
#11	Exp low-level light therapy/
#12	Exp electric stimulation therapy/
#13	Exp magnetic field therapy/
#14	Exp human activities/
#15	#1 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14
#16	#15 AND #2 AND #3
CINAHL & CENTRAL searches	
#1	Alternative therapies
#2	Meta-analysis
#3	Chronic Pain
#4	#1 AND #2 AND #3

Appendix 2
List of chronic pain diagnoses included in reviews about non-specific chronic pain.

	Reference	Chronic pain diagnosis
Natural products	Martin-Sanchez 2009	Brachial plexus avulsion
		Rheumatoid arthritis
		Cancer
		Multiple sclerosis
		Peripheral nerve lesion
		Muscoloskeletal pathology
		Fibromyalgia
		Chronic upper motor neuron syndrome
		Several pathologies
Mind & body practices	Adachi 2014	Temporomandibular disorders
		Persistent idiopathic orofacial pain
		Fibromyalgia
		Osteoarthritis (hip & knee)
		Post-spinal cord injury pain
		Multiple sclerosis
		Noncardiac chest pain
		Irritable bowel syndrome
		Headache
	Bowering 2013	Post-stroke pain
		Complex regional pain syndrome
		Phantom limb pain
Other complementary health approaches	Bai 2015	Chronic neck pain
		Low back pain
		Muscoloskeletal pain
		Neuralgia
	O'Connell 2014	Phantom limb pain
		Neuropathic pain
		Widespread pain
		Post-soinal cord injury pain
		Fibromyalgia
		Pelvic pain
		Pancreatitis pain
		Back and neck pain
		Deafferentation pain
		Osteoarthritis (hip & knee)
		Multiple sclerosis
		Diabetic neuropathy
		Complex regional pain syndrome type I
		Post-burn neuropathic pain
		Pain related to Parkinson's disease
		Neuromuscular pain
	Vickers 2012	Headache
		Back, neck pain
		Ostheoarthritis (knee)
		Shoulder pain
	Zhao 2015	Non-specific spinal pain
		Low back pain
		Headache
		Ostheoarthritis (knee)
		Pelvic pain
		Rhumatoid arthristis
		Neck pain
		Several pathologies

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