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Review article



## Hypnosis to manage musculoskeletal and neuropathic chronic pain: A systematic review and meta-analysis

Pascaline Langlois<sup>a</sup>, Anaick Perrochon<sup>b</sup>, Romain David<sup>a,c</sup>, Pierre Rainville<sup>d,e</sup>, Chantal Wood<sup>a</sup>, Audrey Vanhauzenhuyse<sup>f</sup>, Benjamin Pageaux<sup>e,g</sup>, Amine Ounajim<sup>a,h</sup>, Martin Lavallière<sup>i</sup>, Ursula Debarnot<sup>j,k</sup>, Carlos Luque-Moreno<sup>l</sup>, Manuel Roulaud<sup>a</sup>, Martin Simoneau<sup>m,n</sup>, Lisa Goudman<sup>o,p</sup>, Maarten Moens<sup>o,p</sup>, Philippe Rigoard<sup>a,q,r</sup>, Maxime Billot<sup>a,\*</sup>

<sup>a</sup> PRISMATICS Lab (Predictive Research in Spine/Neuromodulation Management and Thoracic Innovation/Cardiac Surgery), Poitiers University Hospital, Poitiers, France

<sup>b</sup> Laboratoire HAVAE, EA6310, Université de Limoges, Limoges, France

<sup>c</sup> Department of Physical Medicine and Rehabilitation, Poitiers University Hospital, Poitiers, France

<sup>d</sup> Département de stomatologie, Université de Montréal, Montréal, Canada

<sup>e</sup> Centre de recherche de l'Institut universitaire de gériatrie de Montréal (CRIUGM), Montréal, Canada

<sup>f</sup> Sensation & Perception research Group, University of Liège, Belgium and Interdisciplinary Algology Center, CHU of Liège, Belgium

<sup>g</sup> École de kinésiologie et des sciences de l'activité physique (EKSAP), Faculté de médecine, Université de Montréal, Montréal, Canada

<sup>h</sup> Laboratoire de Mathématiques Appliquées (LMA), Faculty of Sciences, Poitiers University, 86000 Poitiers, France

<sup>i</sup> Module de kinésiologie, Département des sciences de la santé, CISD, & Lab BioNR, Université du Québec à Chicoutimi, Chicoutimi, QC, Canada

<sup>j</sup> Univ. Lyon, UCBL-Lyon 1, Laboratoire Interuniversitaire de Biologie de la Motricité, EA 7424, Université Claude Bernard Lyon1, Villeurbanne, France

<sup>k</sup> Institut Universitaire de France, Paris, France

<sup>l</sup> Department of Physiotherapy, University of Seville, Seville, Spain

<sup>m</sup> Centre Interdisciplinaire de Recherche en Réadaptation et en Intégration Sociale (CIRRSIS), Laval University, Quebec City, QC, Canada

<sup>n</sup> Department of Kinesiology, Laval University, Quebec City, QC, Canada

<sup>o</sup> Department of Neurosurgery, Universitair Ziekenhuis Brussel, Laarbeeklaan 101, 1090 Brussels, Belgium

<sup>p</sup> STIMULUS consortium (reSearch and Teaching neuroModULATION Uz bruSsel), Vrije Universiteit Brussel, Laarbeeklaan 103, 1090 Brussels, Belgium

<sup>q</sup> Department of Spine Neurosurgery & Neuromodulation, Poitiers University Hospital, Poitiers, France

<sup>r</sup> Institut Pprime UPR 3346, CNRS, ISAE-ENSMA, University of Poitiers, Poitiers, France

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## ABSTRACT

This systematic review and meta-analysis aims to identify and quantify the current available evidence of hypnosis efficacy to manage pain in patients with chronic musculoskeletal and neuropathic pain. Randomized Control Trials (RCTs) with hypnosis and/or self-hypnosis treatment used to manage musculoskeletal and/or neuropathic chronic pain in adults and assessing pain intensity were included. Reviews, meta-analyses, non-randomized clinical trials, case reports and meeting abstracts were excluded. Five databases, up until May 13th 2021, were used to search for RCTs using hypnosis to manage chronic musculoskeletal and/or neuropathic pain. The protocol is registered on PROSPERO register (CRD42020180298) and no specific funding was received for this review. The risk of bias assessment was conducted according to the revised Cochrane risk of bias tool for randomized control trials (RoB 2.0). Nine eligible RCTs including a total of 530 participants were considered. The main analyses showed a moderate decrease in pain intensity (Hedge's  $g$ :  $-0.42$ ;  $p = 0.025$  after intervention, Hedge's  $g$ :  $-0.37$ ;  $p = 0.027$  after short-term follow-up) and pain interference (Hedge's  $g$ :  $-0.39$ ;  $p = 0.029$ ) following hypnosis compared to control interventions. A significant moderate to large effect size of hypnosis compared to controls was found for at 8 sessions or more (Hedge's  $g$ :  $-0.555$ ;  $p = 0.034$ ), compared to a small and not statistically significant effect for fewer than 8 sessions (Hedge's  $g$ :  $-0.299$ ;  $p = 0.19$ ). These findings suggest that a hypnosis treatment lasting a minimum of 8 sessions could offer an effective complementary approach to manage chronic musculoskeletal and neuropathic pain. Future research is needed to delineate the relevance of hypnosis in practice and its most efficient prescription.

\* Correspondence to: PRISMATICS Lab (Predictive Research in Spine/Neuromodulation Management and Thoracic Innovation/Cardiac Surgery), Poitiers University Hospital, 2 Rue de la Milétrie, 86 021 Poitiers, France.

E-mail address: [maxime.billot@chu-poitiers.fr](mailto:maxime.billot@chu-poitiers.fr) (M. Billot).

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## 1. Introduction

According to the International Association for the Study of Pain (IASP), chronic pain is defined as pain that persists or recurs longer than 3 months (Barke et al., 2021; Merskey and International Association for the Study of Pain, 1994; Treede et al., 2019). Chronic pain represents a common and growing worldwide problem affecting more than 2 billion people that leads to a societal and financial burden of several billion dollars (Gaskin and Richard, 2012; Mills et al., 2019). Musculoskeletal and neuropathic pains represent the most prevalent sets of chronic pain conditions (Breivik et al., 2006; Perrot et al., 2019; Rice et al., 2016; Scholz et al., 2019; van Hecke et al., 2014). Chronic musculoskeletal is defined as a pain “experienced in muscles, bones, joints, or tendons”, while chronic neuropathic pain is characterized by “lesions or diseases involving the somatosensory nervous system” leading to a loss of function and increased pain sensitivity (International Classification of Disease-11) (Perrot et al., 2019; Scholz et al., 2019). Musculoskeletal and neuropathic pain often co-occur but the neuropathic component often goes undetected and may be particularly difficult to treat, e.g. in low back pain (Baron et al., 2016). In addition, a musculoskeletal component may complicate the clinical presentation of central neuropathic pain in patients suffering from disease or lesion of the central nervous system (e.g. multiple sclerosis, Parkinson’s disease, etc.) (Perrot et al., 2019; Blanchet and Brefel-Courbon, 2018).

Both chronic musculoskeletal and neuropathic pain can substantially alter general health, daily life, social and professional activities, psychological well-being and, finally, quality of life (Attal et al., 2011; Blyth and Noguchi, 2017; Boutron et al., 2008; Colloca et al., 2017; Jensen et al., 2007; Naiditch et al., 2021b, 2021a; Ounajim et al., 2021; Rigoard et al., 2021; Schmader, 2002; Smith and Torrance, 2012; Wittkopf et al., 2017). To date, pharmacological treatment remains the primary indication to manage chronic musculoskeletal and neuropathic pain (World Health Organization, 2008). While beneficial in some cases, medication can be ineffective or may produce negative side effects such as dependence, cardiovascular disease, nausea, cognitive impairment, misuse and addiction (Cohen et al., 2021; Hylands-White et al., 2017; Scholz et al., 2019; The Lancet, 2021). Given this context, non-pharmacological approaches, such as hypnosis, are nowadays considered as unavoidable therapeutic strategies to improve quality of life in the chronic pain population (Hylands-White et al., 2017; Jensen et al., 2006; Jensen and Patterson, 2014).

The Society of Psychological Hypnosis defines hypnosis as a procedure where “one person (the subject) is guided by another (the hypnotist) to respond to suggestions for changes in subjective experience, alterations in perception, sensation, emotion, thought or behavior” (Green et al., 2005). Previous systematic reviews and meta-analyses focusing on pain during labor and childbirth (Madden et al., 2016), fibromyalgia (Bernardy et al., 2011; Zech et al., 2017), temporo-mandibular disorders (Zhang et al., 2015), multiple chronic pain such as headache, irritable bowel syndrome, spinal cord injury, cancer, experimental pain, etc. (Adachi et al., 2014; Montgomery et al., 2000; Vanhaudenhuyse et al., 2018), minimally invasive procedures (Noergaard et al., 2019) and experimental pain (Thompson et al., 2019; Vanhaudenhuyse et al., 2009a) have reported significant efficacy of hypnosis to relieve pain. However, to the best of our knowledge, there is no systematic evidence of a hypnosis-related effect on chronic musculoskeletal and neuropathic pain established by a systematic review and meta-analysis (Amatya et al., 2018; Boldt et al., 2014). To date, claims on the efficacy of hypnosis in the overall chronic pain population (e.g., headache, cancer-related pain, etc.) and associated recommendations on the number of sessions to perform “very brief or brief hypnosis treatment” ( $\leq 7$  sessions) or “hypnosis treatment” ( $\geq 8$  sessions) (Jensen and Patterson, 2006) have been only provided via narrative reviews (Jensen and Patterson, 2006; Jensen et al., 2006; Patterson and Jensen, 2003). Therefore, there is an urgent need for a systematic review to validate the use of hypnosis and to provide guidelines on the minimum number of

sessions needed to observe a positive effect on pain management.

The aim of this systematic review and meta-analysis was to provide a synthesis of the current literature on hypnosis in order to determine its efficacy to reduce pain intensity in patients presenting with chronic musculoskeletal and/or neuropathic pain. Secondary objectives were to determine (i) the minimum number of hypnosis sessions required to observe a positive effect on pain, (ii) the effects of hypnosis intervention on pain interference, and (iii) the effects of hypnosis intervention on pain intensity and interference after a follow-up period.

## 2. Material and methods

The current systematic review and meta-analysis was performed in line with the conventional methodology outlined in the Centre for Reviews and Dissemination (CRD) guidance for conducting reviews in health care (Centre for Reviews and Dissemination, 2009). This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009; Page et al., 2021). The protocol for this review is registered on PROSPERO (CRD42020180298).

### 2.1. Search strategy

Electronic databases MEDLINE, Scopus, PEDro, CINAHL and The Cochrane Library were searched until May 13th 2021. The search strategies, based on text words, their synonyms and index terms (e.g. MeSH), were initially developed for MEDLINE and subsequently adapted for use in the other databases (Appendix A) without any filter. To avoid missing relevant articles, we also searched the grey literature (Google Scholar).

### 2.2. Study selection

After removing duplicates, using Zotero® software, two review authors (PL, MB) independently screened title and abstract to identify the potentially relevant studies to be considered. The same reviewers assessed the full texts of all trials using the eligibility criteria for inclusion. Disagreements were resolved through discussion or, if necessary, in consultation with a third reviewer (AP).

### 2.3. Eligibility criteria

The inclusion criteria were (i) patient aged more than 18 years presenting with musculoskeletal and/or neuropathic pain that persists or recurs longer than 3 months, (ii) quantitative assessment of pain intensity, (iii) hypnosis treatment including suggestions that a patient experiences changes in sensations, perceptions, thoughts, or behavior either delivered by a therapist trained in clinical hypnosis and/or administered as a self-hypnosis treatment with or without audio-tape recording, without any combination with another practice (e.g., massage, relaxation, etc.), (iv) Randomized Control Trials (RCTs) design, and (vi) full scientific papers written in English.

The exclusion criteria were (i) reviews, meta-analyses, non-randomized clinical trials, case reports, case series, protocols communication or meeting abstracts, (ii) hypnosis combined with other(s) intervention(s), (iii) no pain outcome or pain intensity reported as a secondary outcomes, (iv) no hypnosis treatment.

### 2.4. Data extraction

A data extraction form was designed in a table with the following items: authors and year, overall population groups (i.e sample size, women/men, age), pain characteristics (musculoskeletal and/or neuropathic, onset), hypnosis treatment modalities (i.e., number, duration and frequency of sessions, and modalities of self-hypnosis), control intervention modalities (i.e., type, number, duration and

frequency of sessions, and modalities of self-intervention), outcomes (i. e., type and rating scale of pain intensity, pain interference, depression, anxiety, quality of life, sleep quality) and results after intervention and after a follow-up period. Pain was assessed with the Visual Analog Scale (VAS) where the patient is asked to indicate his/her perceived pain intensity on a 100 mm horizontal line (Boonstra et al., 2008), the Numerical Rating Scale (NRS) where the patient is asked to rate his/her pain intensity between 0 (no pain) and 10 (the worst pain imaginable), or the Brief Pain Inventory (BPI) (0 = no pain and 10 = the worst pain imaginable) (Cleeland and Ryan, 1994; Erdemoglu and Koc, 2013; Ferreira-Valente et al., 2011). The pain interference section of the BPI, expressed as mean score over 10, consists in 7 Likert scales where the patient is asked to report the number of ways in which, over the previous week, pain had interfered with their (i) general activity, (ii) walking capacity, (iii) normal work (household), (iv) mood, (v) enjoying life, (vi) relationships with people, and (vii) sleep. Depression was assessed with the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983), the 8-item Patient Health Questionnaire (PHQ-8; Kroenke et al., 2009), or the 20-item Center for Epidemiologic Studies-Depression Scale (CES-D; Radloff, 1977). Anxiety was assessed with the Hospital Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1983). Quality of life was assessed with EuroQol 5-Dimension 5-level (EQ-5D-5 L; Herdman et al., 2011), the Short Form-36v2 Health Survey (Ware et al., 2000), or A36 Hemofilia-QoL (Remor et al., 2005). Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989).

The extraction and coding of study data were independently performed by two reviewers (PL, MB). Disagreements were resolved through discussion or, if necessary, by a third reviewer (AP).

## 2.5. Risk of bias and quality of evidence assessment

The risk of bias assessment of included studies was conducted according to the revised Cochrane risk of bias tool for randomized control trials (RoB 2.0) using five domains: (i) randomization process; (ii) deviations from intended interventions; (iii) missing outcome data; (iv) measurement of the outcome; and (v) selection of the reported results (Sterne et al., 2019). Each RCT was rated as “low risk of bias”, “some concern” or “high risk of bias”, for each domain and overall judgement. The risk of bias assessment was undertaken by two reviewers (PL, AO) helped by using the RoB 2.0 tool provided by Cochrane. Any disagreements was resolved by a third reviewer (MB).

Quality of evidence was assessed using the Grades of Recommendations, Assessment, Development and Evaluation system (GRADEpro GDT, <https://gradepr.org>). GRADE transparent approach which provides guidance on rating the overall quality of research indicating four levels of evidence (high, moderate, low, and very low) based on five factors: risk of bias, inconsistency, indirectness, imprecision and publication bias (Guyatt et al., 2011). The GRADE assessment for each meta-analysis was undertaken independently by two reviewers (PL, AO) using the <http://www.gradepr.org> software. Any disagreements were resolved by a third reviewer (MB).

## 2.6. Data synthesis

In the quantitative analysis, mean pain relief following hypnosis compared to control was estimated. Both hypnosis and control arms data were used in the analyses.

When available, the mean change between baseline and follow-up and its standard deviation were extracted for hypnosis and control groups. When the standard deviation of the pain intensity score change was not reported, it was calculated using pre- and post- standard deviations according to the formula for imputing standard deviations for changes from baseline (Higgins et al., 2011):

$$SD_{change} = \sqrt{SD_{baseline}^2 + SD_{follow-up}^2 - 2 \times Corr \times SD_{baseline} \times SD_{follow-up}},$$

The correlation for the within-subject design was calculated using the method described in the Cochrane handbook for systematic reviews of interventions (section 16.1.3.2, Higgins et al., 2011). The correlation calculations were based on studies where the reported standard deviation of change, standard deviation at baseline and standard deviation at follow-up were reported. Correlation was imputed for studies where one of these standard deviations was not available using the correlation coefficient from a study with similar results and outcome measures. When no similar study was available, we considered 0.7 as a correlation coefficient to calculate the SD change. This value of 0.7 represents the expected correlations in within-subject test-retest measurement (Plichta et al., 2012).

In cases where several control treatments were used in the same study, we pooled data from these controls by combining the groups to create a single control group as recommended in the Cochrane handbook for systematic reviews of interventions (section 7.7.3.8, Higgins and Green, 2011). Heterogeneity between studies was tested quantitatively using the Cochran's Q test and the  $I^2$  statistic. Heterogeneity was also evaluated graphically using a forest plot. Since heterogeneity between the included studies was observed, the DerSimonian and Laird random-effects model was used to estimate an overall treatment effect, combining the results from included studies in our outcome (DerSimonian and Laird, 1986).

Results were pooled across studies using the inverse variance method. Hedges' g was used to estimate the effect sizes of our included studies (Hedges, 1983). Hedges' g is an adjusted standardized mean difference summary statistic used when trials assess the same outcome, and it can be measured using different scales (e.i., NRS, VAS, BPI).

Based on the recommendations provided by Jensen and Patterson (2006) about the number of hypnosis session to be delivered, a subgroup analysis was also conducted in order to estimate the effects of hypnosis treatment duration using studies where patients had 8 or more sessions of hypnosis, while another analysis used studies where patients had fewer than 8 sessions of hypnosis.

The statistical significance threshold was set at 0.05. Statistical analysis was conducted using the R software version 3.6.1 (R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). The two R packages *METAFOR* and *META* were used for the meta-analysis.

## 2.7. Sensitivity analysis

We conducted a leave-1-out (Jackknife) sensitivity analysis to test the robustness of the results for the pooled meta-analysis of the primary outcome. In the leave-1-out method, we iteratively repeated the analysis while excluding 1 study at each iteration. The results are considered robust if the pooled effect sizes and heterogeneity measures remain similar in all or most combinations of studies (Wang et al., 2014).

## 2.8. Analysis of heterogeneity and publication bias

Publication bias was assessed using the funnel plot asymmetry rank correlation test (Begg and Mazumdar, 1994), the Egger's regression test (Sterne and Egger, 2005) and Tang test conducted by using a regression of the intervention effect estimate on the variable  $1/\sqrt{N_{tot}}$  ( $N_{tot}$  being the study sample size), with weights  $N_{tot}$  (Tang and Liu, 2000). Since we only conducted the meta-analysis on 9 studies, they not provide enough power to detect asymmetry. To address this issue, we considered the test to be significant if its p-value was lower than 0.1. However, the results of this analysis needs to be considered cautiously due to the small number of trials included in this meta-analysis (9 RCTs). We also intended to assess publication bias for the secondary analyses using funnel plot techniques, Begg's rank test and Egger's regression test, but the secondary analyses included a very low number of studies (4–6 RCTs), rendering these methods inappropriate.

### 3. Results

#### 3.1. Study selection

The PRISMA flow chart detailing the screening process for the review is presented in Fig. 1. The initial database research indicated 1281 potentially relevant articles. After removing 232 duplicates, 1049 papers were screened. After the title and abstract screening, 23 studies were analyzed as full-text publications, and 14 more studies were excluded. The characteristics of excluded studies are detailed in Appendix B. Nine studies were included in the final review (Ardigo et al., 2016; Gay et al., 2002; Hosseinzadegan et al., 2017; Jensen et al., 2020, 2009a, 2009b; Paredes et al., 2019; Razak et al., 2019; Tan et al., 2015).

#### 3.2. Study design and sample characteristics

The main characteristics of the included studies published between 2002 and 2020 are summarized in Table 1. Studies included chronic musculoskeletal and/or neuropathic pain such as chronic back pain (Ardigo et al., 2016; Jensen et al., 2020, 2009b; Tan et al., 2015), osteoarthritis (Ardigo et al., 2016; Gay et al., 2002), multiple sclerosis (Hosseinzadegan et al., 2017; Jensen et al., 2020, 2009a), brachial neuralgia (Razak et al., 2019), spinal cord injury pain (Jensen et al., 2020, 2009b) and hemarthrosis/heamatomas (irreversible muscle or

joint damage) (Paredes et al., 2019). Five studies included several types of chronic musculoskeletal and/or neuropathic pain (Ardigo et al., 2016; Jensen et al., 2020, 2009a, 2009b; Paredes et al., 2019), and 4 studies focused on only one pathology (Gay et al., 2002; Hosseinzadegan et al., 2017; Razak et al., 2019; Tan et al., 2015). Taken together, the studies included 530 participants aged from 34 to 81 years. Duration of hypnosis treatment ranged from 3 (Ardigo et al., 2016) to 12 weeks (Jensen et al., 2020, 2009a, 2009b). The follow-up period was reported in 7 studies with a time frame of 10 (Hosseinzadegan et al., 2017) to 24 weeks (Gay et al., 2002; Tan et al., 2015). The number of hypnosis sessions ranged from 3 (Ardigo et al., 2016) to 10 (Jensen et al., 2009a, 2009b) sessions, and the frequency of the sessions was once a week for 5 studies (Ardigo et al., 2016; Gay et al., 2002; Hosseinzadegan et al., 2017; Paredes et al., 2019; Razak et al., 2019), while it was not reported in the remaining 4 studies (Jensen et al., 2020, 2009a, 2009b; Tan et al., 2015). The interventions lasted from 30 to 90 min in 7 studies (Ardigo et al., 2016; Gay et al., 2002; Hosseinzadegan et al., 2017; Jensen et al., 2020, 2009b; Paredes et al., 2019; Razak et al., 2019), whereas 2 others did not report any length (Jensen et al., 2009a; Tan et al., 2015). Hypnosis suggestions were directly targeted to pain in 7 studies (Ardigo et al., 2016; Hosseinzadegan et al., 2017; Jensen et al., 2020, 2009a, 2009b; Paredes et al., 2019; Razak et al., 2019), while 2 studies did not specify the focus of suggestion (Gay et al., 2002; Tan et al., 2015). After the hypnotic intervention with a practitioner, 4 studies used audiotape

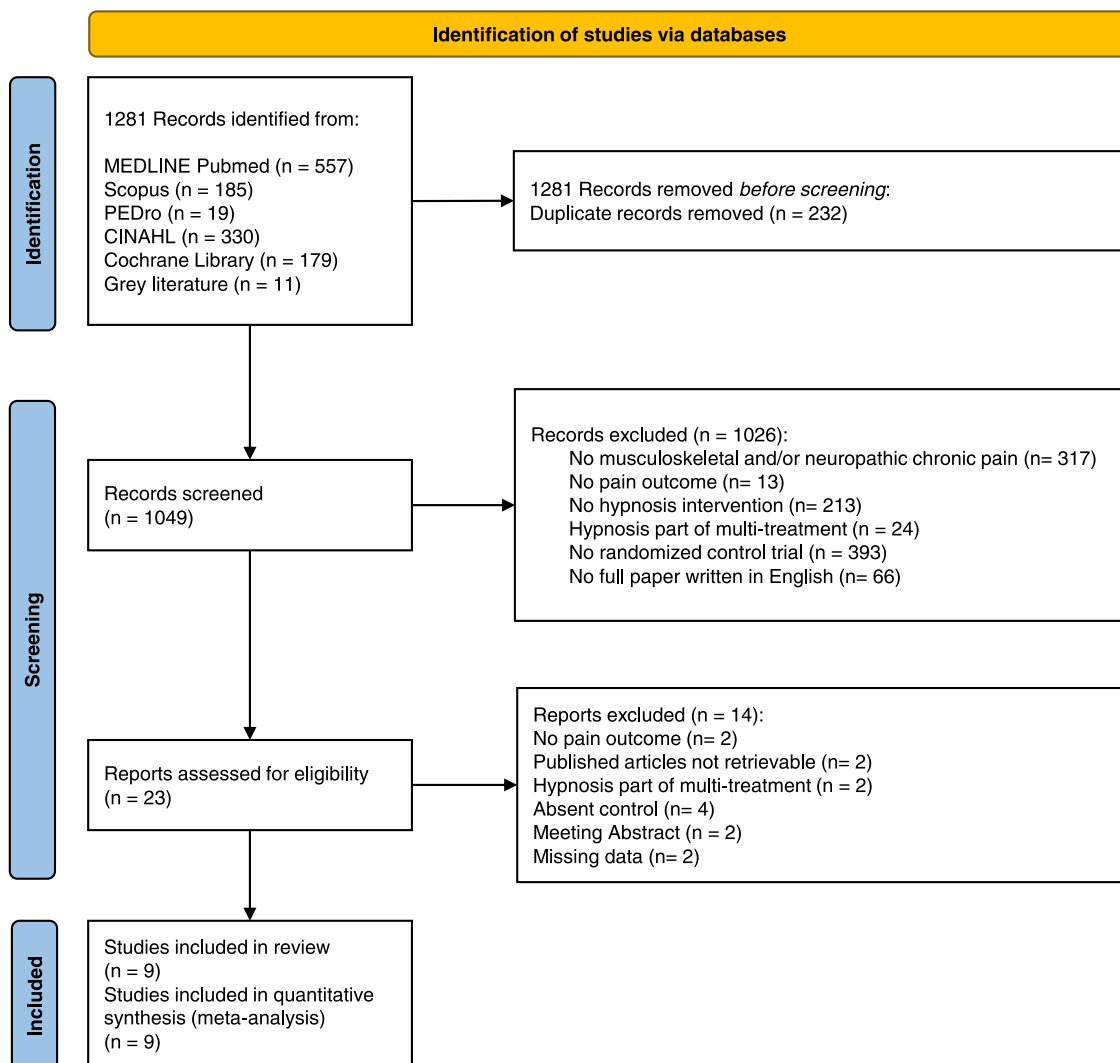


Fig. 1. Study selection flowchart.

**Table 1**  
Main characteristics of the 9 included randomized control trials.

Author (Year)	Overall Population Groups Sample size (Women/Men), Age	Type of Pain Outset of pain	Hypnosis treatment Duration of the intervention Number, durations and frequency of session Self-hypnosis or not Follow-up	Control intervention Control modalities Duration of the intervention Number, duration and frequency of session Self-intervention or not Follow up	Outcomes Pain intensity Pain interference	Results After intervention After follow-up
Ardigo et al. (2016)	53 (39/14), 80.6 ± 8.2 y HG: 26 (21/5) CG: 27 (18/9)	MCP and NCP: 26 chronic back pain, 11 arthritis, 8 neuropathic pain, 5 fibromyalgia, 3 others 6.3 ± 4.2 years	3 wks 3 sessions, 30 min, 1/wk Self-hypnosis: taught and encouraged to practice 12 wks	Massage 3 wks, 3 sessions, 30 min, 1 /wk No self-intervention 12 wks	Pain intensity: BPI NRS Pain interference: BPI Depression: HADS <sup>D</sup> Anxiety: HADS <sup>A</sup>	After intervention: ↓ BPI NRS, HG > CG ↓ BPI, HG = CG = HADS <sup>D</sup> = HADS <sup>A</sup> After 12 wks: = BPI NRS = BPI = HADS <sup>D</sup> = HADS <sup>A</sup>
Gay et al. (2002)	36 (33/3), 64.7 ± 5.5 y HG: 13 (13/0) CG1: 13 (11/2) CG2: 10 (9/1)	MCP: Arthritis 5.0 ± 2.4 years	8 wks 8 sessions, 30 min, 1/wk No self-hypnosis 12 and 26 wks	CG1 Relaxation 8 wks, 8 sessions, 30 min, 1/wk No self-intervention 12 and 26 wks CG2 No intervention 12 and 26 wks	Pain intensity: VAS	After intervention: ↓ VAS, HG = CG1 ↓ VAS, HG > CG2 After 12 wks: ↓ VAS, HG = CG1 ↓ VAS, HG > CG2 After 26 wks: = VAS
Hosseinzadegan et al. (2017)	60 (60/0), 33.7 ± 8.0 y HG: 30 (30/0) CG: 30 (30/0)	MCP and NCP: Multiple sclerosis 4.3 ± 3.5 years	6 wks 6 sessions, 30 min, 1 /wk Self-hypnosis: 10 times/day at least 10 wks	Standard care 6 wks 10 wks	Pain intensity: NRS	After intervention: ↓ NRS, HG > CG After 10 wks: ↓ NRS, HG > CG
Jensen et al. (2009a)	22 (16/6), 51.7 y (range = 27–75 y) HG: 15 (NR) CG: 7 (NR)	MCP and NCP: Multiple sclerosis, Others > 6 months	NR, 10 sessions, NR, NR Self-hypnosis: listening audiotapes/ CDs or without records, minimum 1 session/day 12 wks	Muscle Relaxation NR, 10 sessions, NR, NR Self-intervention: audiotapes/CDs or without records, ≥ 1 session/day 12 wks	Pain intensity: NRS Pain interference: BPI	After intervention: ↓ NRS, HG > CG ↓ BPI, HG > CG After 12 wks: ↓ NRS, HG > CG ↓ BPI, HG > CG
Jensen et al. (2009b)	28 (6/22), 49.5 y (range = 19–70 y) HG: 18 (NR) CG: 10 (NR)	MCP: 9 low back pain, 7 overuse pain, 4 visceral pain NCP: 12 spinal cord injury, 4 joint pain, 1 Radicular Pain > 6 months	NR, 10 sessions, 40 min, NR Self-hypnosis: listening audiotapes/CDs or without recording, minimum 1 session/day 12 wks	Biofeedback NR 10 sessions, ~40 min, NR Self-Intervention: listening audiotapes/CDs or without recording, minimum 1 session/day 12 wks	Pain intensity: NRS Pain interference: BPI Depression: CES-D	After intervention: ↓ NRS, HG = CG = BPI = CES-D, HG ↑ CES-D, CG After 12 wks: ↓ NRS, HG > CG = BPI = CES-D
Jensen et al. (2020)	173 (102/71), 55.1 ± 12.7 y HG: 43 (25/18) CG1: 42 (25/17) CG2: 44 (25/19) CG3: 44 (27/17)	MCP: Low back pain, pain due to multiple sclerosis, spinal cord injury, amputation, muscular dystrophy > 6 months	NR 4 sessions, 60 min, NR Self-hypnosis: workbooks, home practice material and audio recordings, minimum 1 session/day 12 wks 26 wks 52 wks	Pain Education Therapy Group (CG1) Cognitive Therapy Group (CG2) Hypnotic Cognitive Therapy Group (CG3) NR 4 sessions, 60 min, NR Self-intervention: read educational handouts, audio recordings 12 wks 26 wks 52 wks	Pain intensity: NRS Pain interference: BPI Depression: PHQ-8	After intervention: ↓ NRS, HG = all CG ↓ BPI, HG = all CG ↓ PHQ-8, HG = all CG 12 wks: ↓ NRS, HG = all CG ↓ BPI, HG = all CG ↓ PHQ-8, HG = all CG

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Table 1 (continued)

Author (Year)	Overall Population Groups Sample size (Women/Men), Age	Type of Pain Outset of pain	Hypnosis treatment Duration of the intervention Number, durations and frequency of session Self-hypnosis or not Follow-up	Control intervention Control modalities Duration of the intervention Number, duration and frequency of session Self-intervention or not Follow up	Outcomes Pain intensity Pain interference	Results After intervention After follow-up
						26 wks: ↓ NRS, HG = all CG ↓ BPI, HG = all CG ↓ PHQ-8, HG = all CG 52 wks: ↓ NRS, HG = all CG ↓ BPI, HG = all CG ↓ PHQ-8, HG = all CG
Parades et al. (2019)	18 (0/18), 45 ± 9.48 y HG: 8 (NR) CG: 10 (NR)	MCP: Heamarthrosis, heamatomas (irreversible muscles and joints damages) > 6 months	4 wks 4 sessions, 60 min, 1/wk Self-hypnosis: taught and encouraged to practice	Medical treatment and standard care 4 wks	Pain intensity: NRS Pain interference: BPI Depression: HADS <sup>D</sup> Anxiety: HADS <sup>A</sup> Quality of life: EQ-5D-5 L / A36 Hemofilia QoL	After intervention: = NRS ↓ BPI, HG > CG = HADS <sup>D</sup> = HADS <sup>A</sup> ↑ EQ-5D-5 L, HG > CG ↑ A36 Hemofilia QoL, HG > CG
Razak et al. (2019)	40 (0/40), 35.8 ± 12.5 y HG: 20 (0/20) CG: 20 (0/20)	NCP: Brachial neuralgia ~ 3 years	4 wks 4 sessions, 90 min, 1/wk Self-hypnosis: taught and encouraged to practice 16 wks	Acupressure 4 wks 2 sessions application of acupressure patches to specific meridians points 1 session/2 wks No self-intervention 16 wks	Pain intensity: NRS Pain interference: BPI Quality of life: SF-36v2	After intervention: ↓ NRS, HG = CG ↓ BPI, HG = CG ↑ SF-36v2 After 16 wks: ↓ NRS, HG > CG ↓ BPI, HG = CG ↑ SF-36v2
Tan et al. (2015)	100 (21/79), ~55 y (range = 25–83 y) HG1: 25 (NR) HG2: 25 (NR) HG3: 25 (NR) CG: 25 (NR)	MCP: Chronic Low Back Pain > 6 months	Hypnosis-8 (HG1) NR 8 sessions, NR, NR Self-hypnosis: with or without audio recording, ≥ 1 session/day Hypnosis-Practice-8 (HG2) NR 8 sessions, NR, NR Self-hypnosis: with or without audio recording, ≥ 1 session/day Hypnosis-Practice-2 (HG3) NR 2 sessions, NR, NR Self-hypnosis: with or without audio recording, ≥ 1 session/day 26 wks	Biofeedback NR 8 sessions, NR, NR No self-intervention 26 wks	Pain intensity: BPI NRS Pain interference: BPI Sleep quality: PSQI	After intervention: ↓ BPI NRS, HG > CG ↓ BPI, HG > CG ↓ PSQI After 26 wks: = BPI NRS ↓ BPI, HG = CG ↓ PSQI

**Notes:** BPI, Brief Pain Inventory; CG, Control Group; CES-D, 20-item Center for Epidemiologic Studies-Depression Scale; EQ-5D-L, EuroQol 5-Dimension 5-Level; HADS<sup>D/A</sup>, Hospital Anxiety and Depression Scale Depression/Anxiety; HG, Hypnosis group; MCP, Musculoskeletal Chronic Pain; nb, number; NCP, Neuropathic Chronic Pain; NR, Not Reported; NRS, Numerical Rating Scale; PHQ-8, 8-item Patient Health Questionnaire; PSQI-Pittsburgh Sleep Quality Index; SF-36v2, 36-item Short-Form Health Survey; VAS, Visual Analogue Scale; wk(s), week(s).

recording to perform self-hypnosis (Jensen et al., 2020, 2009a, 2009b; Tan et al., 2015). In addition, self-hypnosis was encouraged in 4 studies without any audiotape recordings (Ardigo et al., 2016; Hosseinzadegan et al., 2017; Paredes et al., 2019; Razak et al., 2019). The remaining study did not involve self-hypnosis (Gay et al., 2002).

No intervention (Gay et al., 2002), standard care (Hosseinzadegan et al., 2017; Paredes et al., 2019), relaxation (Gay et al., 2002), progressive muscular relaxation (Jensen et al., 2009a), massage (Ardigo

et al., 2016), acupressure (Razak et al., 2019), biofeedback (Jensen et al., 2009b; Tan et al., 2015), pain education (Jensen et al., 2020), or cognitive therapy (Jensen et al., 2020) were performed in the control groups. The number, the frequency and the duration of the control sessions were similar to the hypnotic intervention in 6 studies (Ardigo et al., 2016; Gay et al., 2002; Jensen et al., 2020, 2009a, 2009b; Tan et al., 2015). Regarding the remaining studies, one provided 2 acupressure versus 4 hypnosis sessions (Razak et al., 2019), and 2 did

not indicate the control intervention duration (Hosseinzadegan et al., 2017; Paredes et al., 2019).

### 3.3. Efficacy of hypnosis on pain intensity after intervention

The results of the narrative synthesis are reported in the Table 1. While 4 studies out of 9 reported a significant greater decrease in pain intensity in the hypnosis group compared to the control group (Ardigo et al., 2016; Hosseinzadegan et al., 2017; Jensen et al., 2009a, 2009b), 4 others reported a significant decrease in both the hypnosis group and the control group groups without any differences between groups (Gay et al., 2002; Jensen et al., 2020; Razak et al., 2019; Tan et al., 2015). The remaining study reported no significant pain relief in either group (Paredes et al., 2019). The reduction of pain intensity after hypnosis treatment ranged from 2% (Paredes et al., 2019) to 56% (Gay et al., 2002) (Fig. 2).

The 9 studies were included in the primary pain intensity outcome meta-analysis. Pain intensity was assessed using VAS, NRS, or BPI. All 9 studies reported the mean pain intensity at baseline and post-intervention (ranging from 3 to 12 weeks) for the hypnosis group and control groups. Statistical analysis showed a moderate decrease in pain intensity following hypnosis compared to control intervention (random effects, 9 RCTs, 13 comparisons, n = 475, Hedge's g: -0.42; CI95%: [-0.7763; -0.0696]; p-value: 0.025). Different random effect sizes and the overall effect are presented in Fig. 2. Heterogeneity was graphically and statistically observed. The I<sup>2</sup> of 59.8% [16.4%; 80.7%] and the Cochrane Q test (p = 0.011) indicated moderate heterogeneity. The funnel plots (Fig. 3) showed that the overall estimated Hedges' g was equal to -0.42 while the study by Jensen et al. (2020) had a different Hedges' g: 0.19 and SE: 0.19. This study had a large sample size (n = 120, excluding the hypnotic cognitive therapy group, which did not meet the inclusion criteria). Furthermore, the control group (education and cognitive therapy) had a larger effect size than the hypnosis group in this study (Jensen et al., 2020).

A sensitivity analysis was conducted on the 9 studies included in this meta-analysis using the leave-1-out method to evaluate the robustness of the results when we remove one study at a time from the meta-analysis. Following the sensitivity analysis, the effect sizes of the 9 datasets of 8 studies ranged from -0.53 CI95%: [-0.786; -0.265] to -0.33 CI95%: [-0.634; -0.020] and all effects were statistically significant. However, we observed a large decrease in heterogeneity when the study with the largest sample size by Jensen et al. (2020) was removed (I<sup>2</sup>=23%, tau<sup>2</sup>=0.031).

The funnel plot of the 9 studies included in this analysis was considered symmetrical given the fact that neither the Rank Correlation test nor Egger's and inverse of the sample size Regression Tests were statistically significant (p > 0.4) (Fig. 3). This result suggests that there is no need for publication bias correction.

### 3.4. Efficacy of hypnosis on pain intensity after follow-up period

Eight studies out of 9 assessed pain intensity after a follow-up period (Ardigo et al., 2016; Gay et al., 2002; Hosseinzadegan et al., 2017; Jensen et al., 2020, 2009a, 2009b; Razak et al., 2019; Tan et al., 2015). Pain relief remained greater for the hypnosis group compared to the control group after a follow-up period of 10 weeks (Hosseinzadegan et al., 2017), 12 weeks (Jensen et al., 2009a, 2009b), and 16 weeks (Razak et al., 2019). One study reported a significant pain intensity decrease without difference between groups at 12-week follow-up period (Gay et al., 2002). Two studies reported that pain intensity decrease was not maintained after a follow-up period of 12 weeks (Ardigo et al., 2016) and 24 weeks (Tan et al., 2015). One study reported that the lack of effect of hypnosis was maintained at 12, 26, and 52 weeks (Jensen et al., 2020).

The meta-analysis specifically including the 7 studies with a short-term follow-up of 10–16 weeks yielded a statistically significant moderate effect size (random effects, 7 RCTs, 9 comparisons, n = 331, Hedge's g: -0.37; CI95%: [-0.79; 0.05]; p-value=0.027) (Ardigo et al., 2016; Gay et al., 2002; Hosseinzadegan et al., 2017; Jensen et al., 2020, 2009a, 2009b; Razak et al., 2019). Heterogeneity between these 7 studies was statistically significant (I<sup>2</sup>=55%; CI95%: [0.0%; 80.7%], Cochrane Q p-value: 0.038) (Fig. 4).

For the long-term follow-up, 2 studies reported no significant effect of hypnosis treatment after a 24-week follow-up period (Hedge's g: -0.669, CI95% = [-1.544; 0.205] (Gay et al., 2002); and Hedges's g: -0.202, CI95% = [-0.729; 0.323] (Tan et al., 2015)). One study reported a significant pain decrease at 12-month follow-up without any significant difference between hypnosis and control groups (Hedge's g: 0.182, CI95% = [-0.212; 0.576]) (Jensen et al., 2020).

### 3.5. Effect of number of hypnosis sessions on pain intensity

When considering data from the 6 studies with fewer than 8 sessions of hypnosis delivered (Ardigo et al., 2016; Hosseinzadegan et al., 2017; Jensen et al., 2020; Paredes et al., 2019; Razak et al., 2019; Tan et al., 2015), the effect size was small and not statistically significant (random effects, 6 RCTs, 8 comparisons, n = 341, Hedge's g: -0.299; CI95%: [-0.795; 0.197]; p-value: 0.19) (Fig. 5a). Moderate heterogeneity was observed between these 6 studies (I<sup>2</sup>=67.6%; CI95%: [23.2%; 86.4%], Cochrane Q p-value: 0.0086).

Four studies reported outcomes in patients who underwent at least 8 sessions of hypnosis (Gay et al., 2002; Jensen et al., 2009b, 2009a; Tan et al., 2015). When pooling the results of these studies, we found a significant moderate to large effect size of hypnosis compared to controls (random effects, 4 RCTs, 5 comparisons, n = 159, Hedge's g: -0.555; CI95%: [-1.033; -0.077]; p-value=0.034) (Fig. 5b). Heterogeneity was not observed between these 4 studies (I<sup>2</sup>=0.01%; CI95%: [0.0%; 80.3%], Cochrane Q p-value: 0.51).

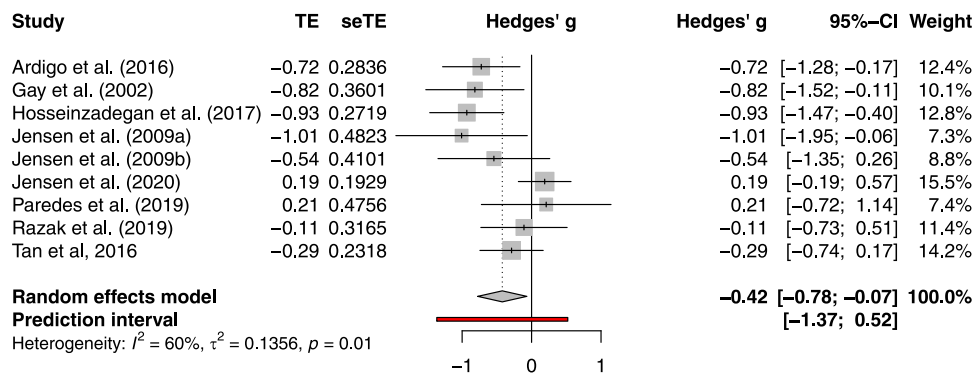


Fig. 2. Forest plot of standardized mean differences (with 95% confidence intervals) and study weights for 9 pain intensity studies. The overall effect is plotted as a diamond. TE: Treatment Effect; se: Standard Error.

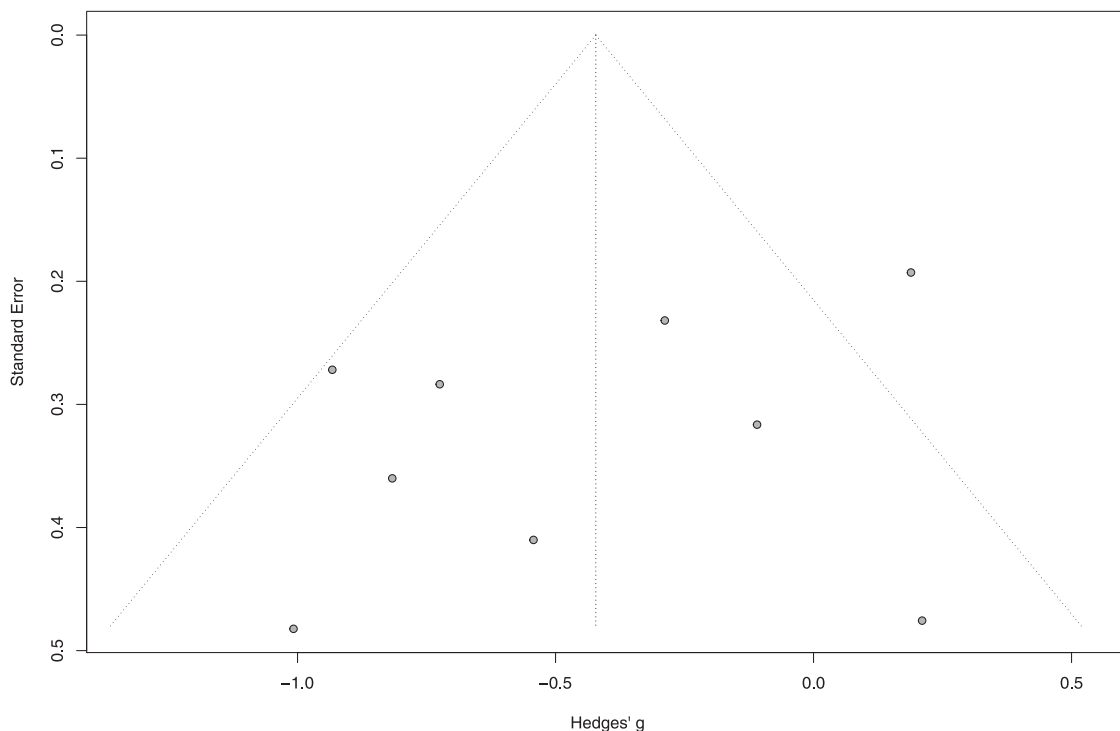


Fig. 3. Funnel plot of the effect sizes (Hedges' g) of the 9 studies included in the meta-analysis.

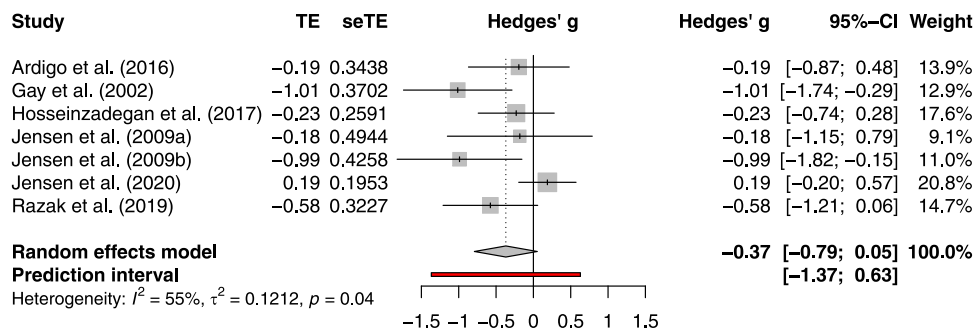


Fig. 4. Forest plot of standardized mean differences (with 95% confidence intervals) and study weights for 5 studies assessing the pain intensity outcome with a short-term follow-up. The overall effect is plotted as a diamond. TE: Treatment Effect; se: Standard Error.

### 3.6. Efficacy of hypnosis on pain interference after intervention

Seven studies assessed pain interference with daily activities (Ardigo et al., 2016; Jensen et al., 2020, 2009a, 2009b; Paredes et al., 2019; Razak et al., 2019; Tan et al., 2015). One study (Jensen et al., 2009a) reported significantly greater decrease in pain interference in hypnosis group compared to control group, 4 studies reported no significant difference between hypnosis group and control group (Ardigo et al., 2016; Jensen et al., 2020; Razak et al., 2019; Tan et al., 2015), and 2 studies did not show any effect, regardless of interventions between hypnosis and control groups (Jensen et al., 2009b; Paredes et al., 2019).

Six studies were included for meta-analysis of the pain interference outcome (Ardigo et al., 2016; Jensen et al., 2020, 2009a, 2009b; Paredes et al., 2019; Tan et al., 2015). Statistical analysis showed moderate improvement of pain interference following hypnosis relative to a control intervention (random effects, 6 RCTs, n = 339, Hedge's g: -0.39; CI95%: [-0.7253; -0.0595]; p-value: 0.029). Different random effect sizes and the overall effect can be found in Fig. 6. Heterogeneity was not observed either graphically or statistically. We found an  $I^2$  of 18.6% [0%; 63.4%] indicating negligible heterogeneity, and the Cochran Q test had a p-value of 0.292, indicating no statistically significant

heterogeneity.

### 3.7. Efficacy of hypnosis on pain interference after follow-up period

Six studies out of 9 assessed pain interference after a follow-up period (Ardigo et al., 2016; Jensen et al., 2009a, 2009b, 2020; Razak et al., 2019; Tan et al., 2015). After a 12-week follow-up period, one study showed that pain interference decrease was greater in the hypnosis than in the control group with significance level set at 0.1 (Hedge's g: -0.402, CI95% = [-1.308; 0.504]) (Jensen et al., 2009a). Three studies showed a decrease in pain interference in both groups without any difference between groups at 12-week (Razak et al., 2019; Jensen et al., 2020), 26-week (Tan et al., 2015; Jensen et al., 2020) and 52-week follow-up (Jensen et al., 2020) (Hedge's g: -0.379, CI95% = [-0.835; 0.077] for Tan et al., 2015, effects not reported for Razak et al., 2019 and Hedge's g: 0.279, CI95% = [-0.623; 1.180] for Jensen et al., 2020). Two studies reported no significant effect regardless of the groups at 12-week follow-up (Hedge's g: -0.084, CI95% = [-0.623; 0.454] for Ardigo et al., 2016 and Hedge's g: -0.435, CI95% = [-1.235; 0.364] for Jensen et al., 2009b).



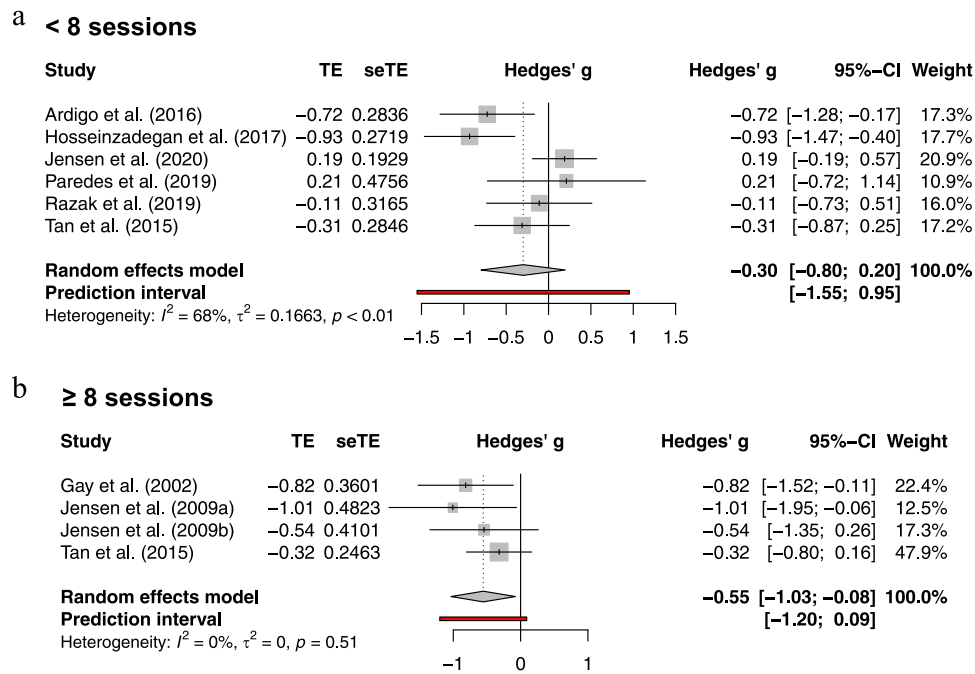


Fig. 5. Forest plot of Standardised Mean Differences (with 95% confidence intervals) and study weights for pain intensity studies with fewer than 8 sessions of hypnosis (upper panel), and with 8 sessions or more (lower panel). The overall effect is plotted as a diamond. TE: Treatment Effect; se: Standard Error.

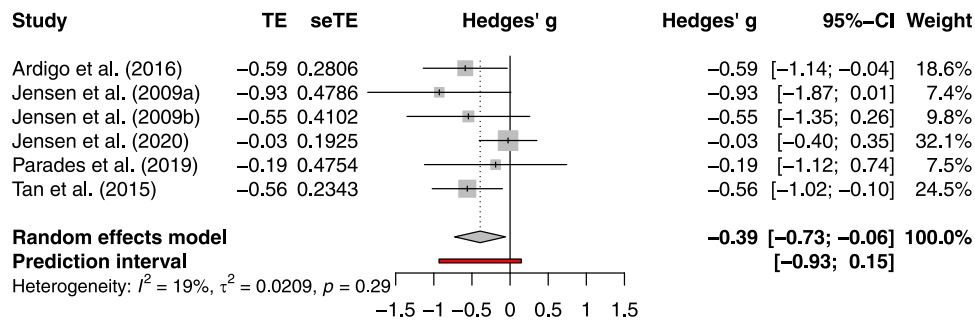


Fig. 6. Forest plot of Standardised Mean Differences (with 95% confidence intervals) and study weights for 6 pain interference studies. The overall effect is plotted as a diamond. TE: Treatment Effect; se: Standard Error.

3.8. Efficacy of hypnosis on depression, anxiety, quality of life and sleep quality

Four studies have assessed depression (Ardigo et al., 2016; Jensen et al., 2020, 2009b; Paredes et al., 2019). One study reported a significant decrease of depression score without any difference between groups (Jensen et al., 2020). One study reported no significant difference of depression score in hypnosis, whereas depression score increased in the control group (Jensen et al., 2009b). The remaining two studies showed no hypnosis treatment effect on depression score in hypnosis and control groups (Ardigo et al., 2016; Paredes et al., 2019). No significant effect was reported in any follow-up assessments (Ardigo et al., 2016; Jensen et al., 2009b).

Two studies assessed anxiety and reported no effect after intervention in hypnosis and control groups (Ardigo et al., 2016; Paredes et al., 2019).

The quality of life was assessed in 2 studies (Paredes et al., 2019; Razak et al., 2019), which reported a significant improvement in quality of life for both groups, with a slightly greater improvement in hypnosis compared to control group in 1 study (Paredes et al., 2019), and maintenance of the effect after a 12-week follow-up period in the remaining study (Razak et al., 2019).

Sleep quality was assessed in 1 study (Tan et al., 2015), which reported a significant improvement of sleep quality in hypnosis and control groups after treatment, without any difference between groups. The improvement was maintained at follow-up assessment.

3.9. Methodological quality

The Cochrane RoB 2.0 was used to assess the risk of bias of the nine included studies. We wanted to assess the effect of "assignment to intervention", and therefore the "intention to treat" effect was selected in the RoB 2.0 tool. The summary of risk of bias judgements for each study is presented in Fig. 7 and the summary of risk of bias judgements presented as percentages across all included studies in Fig. 8.

The randomization process, including random sequence generation, concealment and baseline comparability, was rated as "low risk of bias" for 6 out of 9 studies (Hosseinzadegan et al., 2017; Jensen et al., 2020, 2009b; Paredes et al., 2019; Razak et al., 2019; Tan et al., 2015). Two out of 9 studies (Ardigo et al., 2016; Gay et al., 2002) were rated as "some concerns" because there was a significant difference between groups at baseline in terms of pain condition and there was no detailed information on randomization and concealment. One study (Jensen et al., 2009a) was rated as "high risk of bias" because 8 participants in a

pilote study were included in the hypnosis group after randomization. All the nine included studies were rated as “low risk of bias” for deviations from intended interventions. Even if it was not possible to blind participants or clinicians, no clues were found for serious deviations from intended interventions. The domain missing outcome data was rated as “low risk of bias” except for one study (Tan et al., 2015) because there were a lot of dropouts and it was rated as “some concerns”. All of the included studies were rated as “low risk of bias” for the measurement of the outcome. Even though the blinding of outcome assessors was not generally detailed, the methods of measuring were appropriate and the same for both groups. For selection reporting, 6 out of 9 studies were rated as “low risk of bias” because we retrieved their registry information or trial protocol. One study (Gay et al., 2002) was rated as “some concerns” because there was no information about registry trial protocol and two studies (Jensen et al., 2009a, 2009b) were rated as “high risk of bias” because there was no information about registry trial and there were multiple eligible analyses of the data (e.g. the pain intensity outcome was analysed using absolute change and percentage of decrease).

The overall bias was rated automatically by the Cochrane algorithm. Four out of nine studies were rated as “low risk of bias” (Jensen et al., 2020, 2009a, 2009b; Paredes et al., 2019), 3 out of 9 studies as “some concerns” (Ardigo et al., 2016; Gay et al., 2002; Tan et al., 2015) and 2 out of 9 studies as “high risk of bias” (Jensen et al., 2009a, 2009b).

### 3.10. GRADE assessment

Overall evidence of the 5 meta-analyses conducted in this review was qualified using GRADE. Moderate quality of evidence (i.e., the true effect is probably close to the estimated effect) indicates that chronic musculoskeletal and neuropathic pain might have a moderate decrease in pain intensity following hypnosis compared to control intervention. Low quality of evidence (i.e., the true effect might be different from the estimated effect) shows that the decrease of pain intensity may have moderate short-term benefit and that 8 sessions or more may produce moderate to large effect size of hypnosis compared to controls in the decrease of pain intensity. Low quality of evidence shows that chronic musculoskeletal and neuropathic pain may have moderate improvement of pain interference following hypnosis compared to control intervention. The level of evidence for RCTs was downgraded in inconsistency due to the moderate heterogeneity and various treatments in control groups and in imprecision due to a very small number of included studies in each meta-analysis. The GRADE data are shown in Table 2.

## 4. Discussion

This systematic review and meta-analysis included 9 RCTs with a total of 530 chronic musculoskeletal and neuropathic pain patients. The

results reveal that a hypnosis treatment relieves pain immediately after the intervention period with limited protracted effects after a short follow-up period. All in all, (i) hypnosis treatment yielded a moderate effect on pain intensity and pain interference, (ii) fewer than 8 hypnosis sessions did not reach significant effect size, (iii) 8 hypnosis sessions or more provided statistically significant moderate to large effect size.

### 4.1. Efficacy of hypnosis on chronic musculoskeletal and neuropathic pain intensity

The current systematic review and meta-analysis study showed that hypnosis led to a significant reduction in pain intensity ranging from 2% (Paredes et al., 2019) to 56% (Gay et al., 2002), when compared to control interventions. Control interventions were highly heterogeneous, including acupuncture (Razak et al., 2019), biofeedback (Jensen et al., 2009b; Tan et al., 2015), progressive muscular relaxation (Jensen et al., 2009a), massage (Ardigo et al., 2016), cognitive therapy (Jensen et al., 2020) relaxation (Gay et al., 2002) pain education (Jensen et al., 2020), standard care (Hosseinzadegan et al., 2017; Paredes et al., 2019), and no intervention (Gay et al., 2002). To address this issue, we recommend intervention with “minimal-effect” in control conditions such as group education to standardize intervention and to limit the fading of treatment effect (Jensen and Patterson, 2005). While moderate hypnosis effect was observed in comparison to control group with active interventions, our results highlighted the fact that 6 studies (out of 9) showed pain relief up to 30% (Ardigo et al., 2016; Gay et al., 2002; Hosseinzadegan et al., 2017; Jensen et al., 2009a; Razak et al., 2019; Tan et al., 2015), including 2 higher than 50% (Ardigo et al., 2016; Gay et al., 2002), corresponding to “much improved” and “very much improved” related to the established guidelines for major changes (Dworkin et al., 2008; Farrar et al., 2001; Salaffi et al., 2004). In a narrative review, Jensen and Patterson (2006) similarly reported hypnosis efficacy (from 2% to 57%) in managing pain in patients with several chronic pain diseases such as headache, cancer-related pain, fibromyalgia, mixed chronic problems, low back pain, sickle cell disease or temporomandibular pain. In addition, the recent systematic and meta-analysis by Thompson et al. (2019), including 64 studies and 3039 healthy participants, showed that hypnosis effectively relieves experimental pain in medium (42%) and high (29%) hypnotic suggestibility participants. Therefore, it is safe to assume that hypnosis treatment focusing on pain management is an effective technique to treat patients with chronic musculoskeletal and neuropathic pain on a short-term basis, whereas limited long-term efficacy has also been reported. In a home-based hypnosis treatment in elderly women suffering from chronic pain, Dumain et al. (2021) reported that a continuum of hypnosis exposure through booster sessions in addition to self-hypnosis could be effective to maintain pain relief for at least 12 months. In this study, 7 hypnosis sessions were delivered during 12 months divided into 3 sessions the

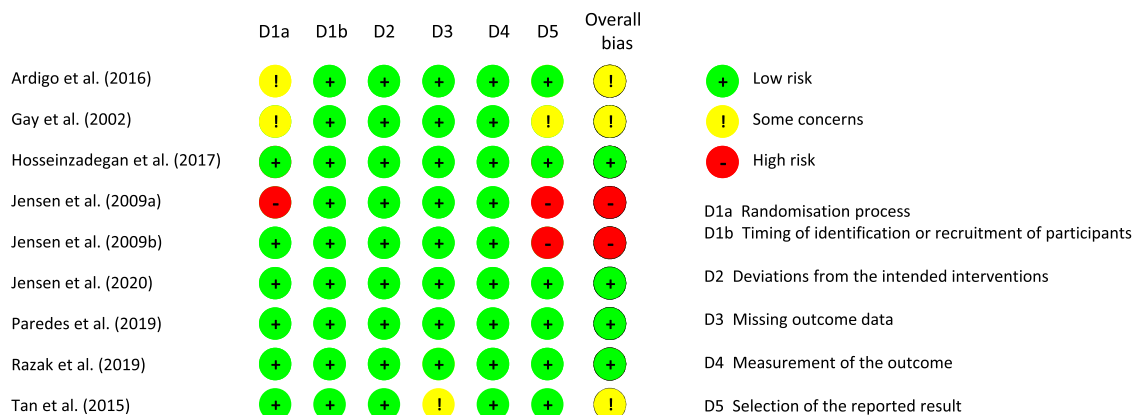


Fig. 7. The summary of risk of bias judgements for each study.

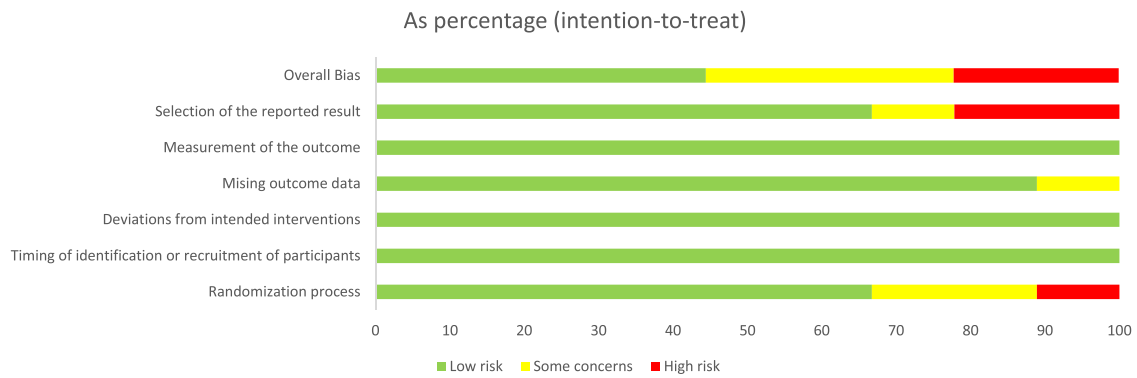


Fig. 8. The summary of risk of bias judgements presented as percentages across all included studies.

Table 2  
GRADE evidence profile.

Quality assessment							Number of patients		Effect		Quality
Number of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hypnosis	control	Relative (95% CI)	Absolute (95% CI)	
Effectiveness of hypnosis on pain intensity after intervention											
9	randomised trials	not serious	serious <sup>a</sup>	not serious	not serious	none	236	239	–	SMD 0.42 SD lower (0.78 lower to 0.07 lower)	⊕⊕⊕○ Moderate
Effect of number of hypnosis sessions on pain intensity (< 8 sessions)											
6	randomised trials	not serious	serious <sup>a</sup>	not serious	serious <sup>b</sup>	none	150	191	–	SMD 0.3 SD lower (0.8 lower to 0.2 higher)	⊕⊕○○ Low
Effect of number of hypnosis sessions on pain intensity (≥ 8 sessions)											
4	randomised trials	not serious	serious <sup>c</sup>	not serious	serious <sup>b</sup>	none	86	73	–	SMD 0.55 SD lower (1.03 lower to 0.08 lower)	⊕⊕○○ Low
Effectiveness of hypnosis on pain interference after intervention											
6	randomised trials	not serious	serious <sup>c</sup>	not serious	serious <sup>b</sup>	none	181	158	–	SMD 0.39 SD lower (0.73 lower to 0.06 lower)	⊕⊕○○ Low
Effectiveness of hypnosis on pain intensity after short follow-up period											
7	randomised trials	not serious	serious <sup>c</sup>	not serious	serious <sup>b</sup>	none	142	189	–	SMD 0.37 SD lower (0.79 lower to 0.05 lower)	⊕⊕○○ Low

CI: confidence interval; SMD: standardised mean difference

Explanations

- <sup>a</sup> Moderate heterogeneity and various treatments in control groups.
- <sup>b</sup> A very small number of included studies.
- <sup>c</sup> Various treatments in control groups.

first 3 months, 2 sessions the next 3 months, and sessions times the last 6 months. The need for booster sessions and the long-term therapeutic success of hypnosis might be substantially influenced by various elements, including the number of sessions.

As regards the attempts to standardize hypnosis practice, initiated by Jensen and Patterson (2006), we identified and categorized one study with “very brief hypnosis treatment” (3 sessions or less), 4 studies with “brief hypnosis treatment” (4–7 sessions), and 4 studies with “hypnosis treatment” (8 sessions or more). In light of the number of sessions associated with pain relief efficacy, our meta-analysis provides new insight. We determined that fewer than 8 sessions led to small or not significant effect, whereas 8 or more sessions should be considered as

more or less likely to achieve significant moderate to large effect to manage chronic musculoskeletal and neuropathic pain. As there is to date no strong evidence suggesting that more hypnosis sessions could provide further positive effects on pain outcomes, future studies are needed to test this possibility. On this subject, Dumain et al. (2021) reported that 4 hypnosis sessions spread out over 9 months at home in elderly women presenting with chronic pain were not able to improve the pain relief achieved after 3 sessions in 3 months (Billot et al., 2020b). Future studies are needed to determine the “dose-response” efficacy of hypnosis with potential distinctive underlying mechanisms, especially considering wide variety of diagnosis among chronic musculoskeletal and neuropathic pain patients.

#### 4.2. Efficacy of hypnosis on pain interference

It has been well-documented that pain interferes with the motor system (Bank et al., 2013; Billot et al., 2018; Corbeil et al., 2004; Hodges and Tucker, 2011; Rohel et al., 2021). Because physical activity has become a major area of interest to avoid loss of mobility (Billot et al., 2020a; Dent et al., 2019), pain management necessarily involves motor aspects. It has been reported that pain interference was associated with at least twice the risk of mobility difficulty in 634 community-dwelling older adults aged 65 and older (Eggermont et al., 2014). The authors concluded that multisite or widespread pain and pain interference could be considered as great predictors of mobility difficulty. In our meta-analysis, 6 studies underlined that hypnosis elicits moderate beneficial effects on pain interference with general activity (15–49%). These promising results must be carefully interpreted, especially when drawing up future studies designed to objectively assess motor components with tools such as connected soles or accelerometers. Hypnosis focused on pain might offer new opportunities to prevent gait impairment, falls and sedentary lifestyle in patients with chronic musculoskeletal and neuropathic pain.

By conducting a 2-year long-term follow-up study on 50 patients presenting with severe chronic (rheumatic, oncologic and neurologic) diseases and suffering from pain and anxiety, Brugnoli et al. (2018) reported that hypnosis treatment focused on the latter could relieve pain intensity and improve psychological outcomes. Similarly, in their systematic review and meta-analysis, including 6 RCTs, Provençal et al. (2018) reported hypnosis efficacy in burn wound pain and anxiety management. In addition, the systematic review and meta-analysis of Zech et al. (2017), including 7 RCTs and 387 patients with fibromyalgia, showed positive effects of guided imagery/hypnosis on psychological distress, fatigue and sleep. By combining self-hypnosis and self-care (i.e., aiming to retrain the patient to be an actor rather than an observer of his/her life condition based on cognitive-behavioral therapy) in a 9-month program, Vanhaudenhuyse et al., (2018, 2015) reported significant improvement in cancer patients' pain intensity, anxiety, depression, attitudes and belief regarding pain, and quality of life. Similar positive long-term outcomes on pain, emotional distress, sleep and quality of life were reported after a 7-month treatment and a 12-month follow-up in 52 chronic pain patients (Bicego et al., 2021). To sum up, it would seem advisable to combine hypnosis focusing on both pain and psychological distress with a self-care approach, the objective being to extend benefits on clinical outcomes.

#### 4.3. Mechanisms of hypnosis

Since the end of the 20th century, brain imaging has been considered as a means of determining the underlying mechanisms of hypnosis. Following the pioneering work of Rainville (1997), Rainville et al., (2002, 1999) and Faymonville et al., (2003, 2000), the recent meta-analysis of Del Casale et al. (2015) reported that hypnoanalgesic suggestions alter activity in cortical areas of the pain matrix, which include anterior cingulate cortex, insular and prefrontal areas. Neuroimaging studies of hypnotic analgesia using Positron Emission Tomography (PET) showed a significant increase in pain-evoked activity within the anterior cingulate cortex when hypnotic suggestions addressed increased pain (Rainville et al., 1999). The authors concluded that hypnosis can modulate the activation of emotions and behavior of individuals. More recently, Derbyshire et al. (2004) used Functional Magnetic Resonance Imaging (fMRI) to identify the brain areas directly involved in the generation of pain, using hypnotic suggestion to create an experience of pain in the absence of any noxious stimulus. They reported activation of thalamus and anterior cingulate, insula, prefrontal, and parietal cortices during pain induced by hypnotic suggestion. In line with this study, using a single-trial thulium-YAG laser fMRI paradigm to induce pain, Vanhaudenhuyse et al. (2009b) showed significantly less activation of the brainstem, right thalamus, left striatum, right striatum,

left insula, right insula, right primary somatosensory cortex, anterior cingulate cortex, right middle frontal gyrus, and right premotor cortex in hypnotic state compared to wakefulness condition (Vanhaudenhuyse et al., 2014). Additional research reported that structural properties and activation of the anterior cingulate and frontal regions differ across levels of suggestibility, i.e. tending to positively respond to hypnotic induction (Jensen et al., 2017; Jensen and Patterson, 2014), which may highlight the greater pain relief observed at a high rather than a low level of hypnotic suggestibility (Thompson et al., 2019). The cortical areas involved in the pain matrix are mirrored with those identified as playing a major role in pain modulation (Jensen and Patterson, 2014; Vanhaudenhuyse et al., 2014). Pain matrix potentially provides a neural basis for hypnotic analgesia.

#### 4.4. Quality of evidence

While the current systematic review and meta-analysis was based on studies with rigorous designs involving randomized control trials, the results must be interpreted with caution. First, the assessment of the overall risk of bias indicated 3 out of 9 studies with “some concerns (Ardigo et al., 2016; Gay et al., 2002; Tan et al., 2015) and 2 out of 9 studies as “high risk of bias” (Jensen et al., 2009a, 2009b). Potential biases were highlighted for the randomization process suggesting a possible imbalance between groups that may lead to a misinterpretation of the effect of the target intervention. Moreover, there was potential bias in the selection of the reported outcomes suggesting that some authors may have prioritized the report of positive findings to support vested interests or to be sufficiently noteworthy to merit publication.

GRADE was used to assess the quality of evidence and the strength of clinical recommendation. The quality assessment reflects the level of confidence that the estimates of an effect are correct to support a particular decision or recommendation. In our review, the level of confidence is moderate for the efficacy of hypnosis on pain intensity after intervention and low for the effect of number of hypnosis sessions on pain intensity, pain interference after intervention and pain intensity after a short follow-up.

#### 4.5. Limitations

The current systematic review and meta-analysis has several limitations. First, although, as previously shown in experimental pain (Thompson et al., 2019), hypnotic suggestibility could substantially impact hypnosis efficacy, the 9 RCTs included in this review did not discriminate, with regard to pain relief, between high and low hypnotic suggestibility patients. The moderate to large evidence of hypnosis efficacy reported in our meta-analysis could nonetheless be strengthened in high suggestibility patients and weakened in low hypnotic suggestibility patients presenting with chronic musculoskeletal and/or neuropathic pain. Hypnotic suggestibility has shown to be improved by training and practice (Patterson and Jensen, 2003), and should be included in future research to address this issue. Second, as medication intake was used primarily to treat pain in chronic pain patients, modification in its usage could influence clinical outcomes. Hypnosis treatment can be considered as an added value to manage pain when no modification of medication intake occurs (Ardigo et al., 2016; Jensen et al., 2020). Nevertheless, one study reported a potential double impact of hypnosis treatment by reporting clinical outcome improvement and medication intake reduction (Gay et al., 2002). Third, while hypnosis efficacy has been observed in young (Hossein-zadegan et al., 2017; Razak et al., 2019) and older adults (Ardigo et al., 2016; Billot et al., 2020b; Dumain et al., 2021; Gay et al., 2002), there is no evidence to determine the influence of age on hypnosis efficacy. Fourth, the very limited available data on depression, anxiety, quality of life, and sleep quality do not provide robust evidence about the effects of hypnosis on these outcomes. Fifth, we were unable to report evidence of hypnosis efficacy over a long-term period. Finally, the heterogeneity of the study should

be considered when interpreting our results, which need to be confirmed in future well-designed studies.

#### 4.6. Clinical implications, recommendations and future studies

This systematic review and meta-analysis has several clinical implications. Hypnosis may be considered as an effective complementary to medication for in management of chronic musculoskeletal and neuropathic pain. Hypnosis could be offered by a practitioner (e.g., psychologist, physiotherapist, nurse) during hospitalization (Ardigo et al., 2016; Gay et al., 2002; Paredes et al., 2019; Razak et al., 2019; Tan et al., 2015) or at home (Billot et al., 2020b; Dumain et al., 2021), and could also be provided as self-practice through audio-tape recording (Brugnoli et al., 2018; de la Vega et al., 2019; Eason and Parris, 2019). This systematic review and meta-analysis showed that a minimum of 8 sessions are needed in order to observe significant clinical effect. Furthermore, the benefits of hypnosis treatment on pain relief have got to be assessed in a long-term follow-up period, the objective being to determine the time frame effects (Dumain et al., 2021; Jensen et al., 2008, 2005). Hypnosis approach could also be combined with virtual reality to potentiate efficacy (Rousseaux et al., 2020a, 2020b; Thompson et al., 2010) particularly in low hypnotic suggestibility patients. In addition, hypnosis treatment focusing on a combination of pain, psychological distress and functional capacity could offer overall health-related benefits by reducing kinesiophobia (fear of movement), catastrophizing (imagining the worst possible outcome of an action or event), psychological distress and sleep disorders (Grégoire et al., 2018; Luque-Suarez et al., 2019; Vanhaudenhuyse et al., 2018).

In addition, and given the high cost of opioids delivery and a related worldwide crisis (Cohen et al., 2021; The Lancet, 2021), hypnosis seems to be a promising means of reducing the cost of pain management (Bernacki et al., 2012; Katz et al., 2016) and of providing a safe alternative with few or no side effects (Jensen et al., 2015; Wood et al., 2022). Hypnosis performed by medical or paramedical staff provides opportunities for managing pain in a preventive/curative way or as routine practice. Medico-economic analysis needs to be undertaken so as

to provide evidence of the cost-utility of hypnosis in daily practice.

## 5. Conclusion

The current meta-analysis showed, on the basis of 9 RCTs, evidence of effective hypnosis treatment in view of managing pain intensity and pain interference with daily activities in chronic musculoskeletal and neuropathic pain patients. This is the first time that an efficacy threshold has been identified based on the number of sessions, showing that 8 or more sessions should lead to moderate to large effects, and that fewer than 8 sessions should yield little or no effect. All in all, these findings suggest that hypnosis treatment may represent an effective and complementary approach to management of chronic pain. Further research is needed to delineate the long-term relevance of hypnosis in clinical practice and to determine the cost-utility of this approach.

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## Conflicts of interest statement

None.

## Data Availability

No data was used for the research described in the article.

## Appendix A. Search strategies for databases used in the review

### 1. MEDLINE (PubMed)

[Search date May 13th 2021].

The search string was: (chronic pain OR low back pain OR chronic widespread pain OR musculoskeletal pain OR persistent inflammation OR infection OR crystal deposition OR auto-immune disorder OR auto-inflammatory disorder OR osteoarthritis OR spondylosis OR musculoskeletal injury OR parkinson disease OR multiple sclerosis OR peripheral neurologic disease OR neuropathic pain OR trigeminal neuralgia OR peripheral nerve injury OR polyneuropathy OR postherpetic neuralgia OR radiculopathy OR spinal cord injury OR brain injury OR post-stroke pain) AND hypnosis.

**557 potential articles were retrieved.**

### 2. Scopus

[Search date May 13th 2021].

The search string was: (chronic pain OR low back pain OR chronic widespread pain OR musculoskeletal pain OR neuropathic pain) AND hypnosis.

**185 potential articles were retrieved.**

### 3. PEDro

[Search date May 13th 2021].

The search string was:

- *Substrat & title: hypnosis*
- *Therapy:  $\emptyset$*
- *Problem: pain*
- *Body Part:  $\emptyset$*
- *Subdiscipline:  $\emptyset$*

- Topic: chronic pain
- Method: clinical trial
- Match all search terms (AND)

19 potential articles were retrieved.

#### 4. CINAHL

[Search date May 13th 2021].

The search string was: (*hypnosis or hypnotherapy or hypnoses or hypnotism or hypnotherapies or hypnotic analgesia*) AND (*chronic pain OR low back pain OR musculoskeletal pain OR ( inflammation or inflammatory) OR auto immune disease OR inflammatory disease OR osteoarthritis OR spondylosis OR musculoskeletal injury OR parkinson's disease OR multiple sclerosis OR peripheral neuropathy OR neuropathic pain OR peripheral neuropathy OR trigeminal neuralgia OR peripheral nerve injury OR polyneuropathy OR ( postherpetic neuralgia or post-herpetic neuralgia) OR radiculopathy OR ( spinal cord injury or sci) OR multiple sclerosis OR post stroke pain*).

330 potential articles were retrieved.

#### 5. Cochrane Library

[Search date May 13th 2021].

The search string was: (*Hypnosis*) AND (*chronic pain OR low back pain OR chronic widespread pain OR Musculoskeletal Pain OR persistent inflammation OR infection OR crystal deposition OR auto-immune disorder OR auto-inflammatory disorder OR osteoarthritis OR spondylosis OR musculoskeletal injury OR Parkinson disease OR Multiple Sclerosis OR peripheral neurologic disease OR Neuropathic Pain OR trigeminal neuralgia OR peripheral nerve injury OR polyneuropathy OR postherpetic neuralgia OR radiculopathy OR spinal cord injury OR brain injury OR post-stroke pain*).

179 potential articles were retrieved.

### Appendix B

Author	Year	Title	Exclusionary ground
Ahmad et al.	2015	Hypnotherapy and acupuncture for brachial neuralgia.	Meeting abstract
Bolanos-Chamorro et al.	2017	Efficacy of hypnotic analgesia for the reduction of pain and negative emotional states in patients with rheumatoid arthritis of the hospital civil De guadalajara "fray antonio alcalde".	Meeting abstract
Buscher et al.	1995	Hypnosis and self-hypnosis, administered and taught by nurses, for the reduction of chronic pain: a controlled clinical trial.	Available article
Ciamarella et al.	2018	Person-centered management of chronic intractable pain: An observational study comparing conventional treatment with hypnosis and treatment of psychiatric comorbidity.	Missing data (pain intensity)
Delivet et al.	2018	Efficacy of Self-hypnosis on Quality of Life For Children with Chronic Pain Syndrome.	Hypnosis treatment combined with others interventions
Dorfman et al.	2013	Hypnosis for Treatment of HIV Neuropathic Pain: A Preliminary Report.	No control group
Edelson et al.	1989	A comparison of cognitive-behavioral and hypnotic treatments of chronic pain.	Missing data (pathology, pain intensity score and scale precision (0-5 scale but score > 5 without precisions)
Grondahl et al.	2008	Hypnosis as a treatment of chronic widespread pain in general practice: a randomized controlled pilot trial.	No pain intensity assessment
Jensen et al.	2010	Effects of self-hypnosis training and cognitive restructuring on daily pain intensity and catastrophizing in individuals with multiple sclerosis and chronic pain.	No control group
Jensen et al.	2008	Long-term outcome of hypnotic-analgesia treatment for chronic pain in persons with disabilities.	No control group
Malekzadeh et al.	2020	The Effectiveness of Group-based Cognitive Hypnotherapy on the Psychological Well-being of Patients with Multiple Sclerosis: A Randomized Clinical Trial.	No pain outcome
McCauley et al.	1983	Hypnosis compared to relaxation in the outpatient management of chronic low back pain.	Available article
Thornberry et al.	2007	An exploration of the utility of hypnosis in pain management among rural pain patients.	No control group
Vanhoudenhuysse et al.	2018	Psychological interventions influence patients' attitudes and beliefs about their chronic pain	Self-hypnosis treatment associated with self-learning care

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