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► To cite this version:

Pascaline Langlois, Anaick Perrochon, Romain David, Pierre Rainville, Chantal Wood, et al.. Hypnosis to manage musculoskeletal and neuropathic chronic pain: A systematic review and meta-analysis. *Neuroscience and Biobehavioral Reviews*, 2022, 135, pp.104591. 10.1016/j.neubiorev.2022.104591 . hal-03710932

HAL Id: hal-03710932

<https://hal.science/hal-03710932>

Submitted on 22 Jul 2024

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1 **Hypnosis to manage musculoskeletal and neuropathic chronic pain: a**
2 **systematic review and meta-analysis**

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72 Number text pages: 43

73 Number of figures: 7

74 Number of tables: 1

- 1 **Hypnosis to manage musculoskeletal and neuropathic chronic pain: a**
- 2 **systematic review and meta-analysis**

3 **Abstract**

4 This systematic review and meta-analysis aims to identify and quantify the current available
5 evidence of hypnosis efficacy to manage pain in patients with chronic musculoskeletal and
6 neuropathic pain. Randomized Control Trials (RCTs) with hypnosis and/or self-hypnosis
7 treatment used to manage musculoskeletal and/or neuropathic chronic pain in adults and
8 assessing pain intensity were included. Reviews, meta-analyses, non-randomized clinical
9 trials, case reports and meeting abstracts were excluded. Five databases, up until May 13th
10 2021, were used to search for RCTs using hypnosis to manage chronic musculoskeletal and/or
11 neuropathic pain. The protocol is registered on PROSPERO register (CRD42020180298) and
12 no specific funding was received for this review. The risk of bias assessment was conducted
13 according to the revised Cochrane risk of bias tool for randomized control trials (RoB 2.0).
14 Nine eligible RCTs including a total of 530 participants were considered. The main analyses
15 showed a moderate decrease in pain intensity (Hedge's g : -0.42; $p=0.025$ after intervention,
16 Hedge's g : -0.37; $p=0.027$ after short-term follow-up) and pain interference (Hedge's g : -
17 0.39; $p=0.029$) following hypnosis compared to control interventions. A significant moderate
18 to large effect size of hypnosis compared to controls was found for at 8 sessions or more
19 (Hedge's g : -0.555; $p=0.034$), compared to a small and not statistically significant effect for
20 fewer than 8 sessions (Hedge's g : -0.299; $p=0.19$). These findings suggest that a hypnosis
21 treatment lasting a minimum of 8 sessions could offer an effective complementary approach
22 to manage chronic musculoskeletal and neuropathic pain. Future research is needed to
23 delineate the relevance of hypnosis in practice and its most efficient prescription.

24

25 **Keywords:** Complementary therapy; Analgesia; Pain perception; Pain management; Pain
26 treatment; Non-pharmacologic treatment; Neuralgia.

27 **Introduction**

28 According to the International Association for the Study of Pain (IASP), chronic pain
29 is defined as pain that persists or recurs longer than 3 months (Barke et al., 2021; Merskey
30 and International Association for the Study of Pain, 1994; Treede et al., 2019). Chronic pain
31 represents a common and growing worldwide problem affecting more than 2 billion people
32 that leads to a societal and financial burden of several billion dollars (Gaskin and Richard,
33 2012; Mills et al., 2019). Musculoskeletal and neuropathic pains represent the most prevalent
34 sets of chronic pain conditions (Breivik et al., 2006; Perrot et al., 2019; Rice et al., 2016;
35 Scholz et al., 2019; van Hecke et al., 2014). Chronic musculoskeletal is defined as a pain
36 “experienced in muscles, bones, joints, or tendons”, while chronic neuropathic pain is
37 characterized by “lesions or diseases involving the somatosensory nervous system” leading to
38 a loss of function and increased pain sensitivity (International Classification of Disease-11)
39 (Perrot et al., 2019; Scholz et al., 2019). Musculoskeletal and neuropathic pain often co-occur
40 but the neuropathic component often goes undetected and may be particularly difficult to
41 treat, e.g. in low back pain (Baron et al., 2016). In addition, a musculoskeletal component
42 may complicate the clinical presentation of central neuropathic pain in patients suffering from
43 disease or lesion of the central nervous system (e.g. multiple sclerosis, Parkinson’s disease,
44 etc.) (Perrot et al., 2019; Blanchet and Brefel-Courbon, 2018).

45 Both chronic musculoskeletal and neuropathic pain can substantially alter general
46 health, daily life, social and professional activities, psychological well-being and, finally,
47 quality of life (Attal et al., 2011; Blyth and Noguchi, 2017; Boutron et al., 2008; Colloca et
48 al., 2017; Jensen et al., 2007; Naiditch et al., 2021b, 2021a; Ounajim et al., 2021; Rigoard et
49 al., 2021; Schmader, 2002; Smith and Torrance, 2012; Wittkopf et al., 2017). To date,
50 pharmacological treatment remains the primary indication to manage chronic musculoskeletal
51 and neuropathic pain (World Health Organization, 2008). While beneficial in some cases,

52 medication can be ineffective or may produce negative side effects such as dependence,
53 cardiovascular disease, nausea, cognitive impairment, misuse and addiction (Cohen et al.,
54 2021; Hylands-White et al., 2017; Scholz et al., 2019; The Lancet, 2021). Given this context,
55 non-pharmacological approaches, such as hypnosis, are nowadays considered as unavoidable
56 therapeutic strategies to improve quality of life in the chronic pain population (Hylands-White
57 et al., 2017; Jensen et al., 2006; Jensen and Patterson, 2014).

58 The Society of Psychological Hypnosis defines hypnosis as a procedure where “one
59 person (the subject) is guided by another (the hypnotist) to respond to suggestions for changes
60 in subjective experience, alterations in perception, sensation, emotion, thought or behavior”
61 (Green et al., 2005). Previous systematic reviews and meta-analyses focusing on pain during
62 labor and childbirth (Madden et al., 2016), fibromyalgia (Bernardy et al., 2011; Zech et al.,
63 2017), temporo-mandibular disorders (Zhang et al., 2015), multiple chronic pain such as
64 headache, irritable bowel syndrome, spinal cord injury, cancer, experimental pain, etc.
65 (Adachi et al., 2014; Montgomery et al., 2000; Vanhaudenhuyse et al., 2018), minimally
66 invasive procedures (Noergaard et al., 2019) and experimental pain (Thompson et al., 2019;
67 Vanhaudenhuyse et al., 2009a) have reported significant efficacy of hypnosis to relieve pain.
68 However, to the best of our knowledge, there is no systematic evidence of a hypnosis-related
69 effect on chronic musculoskeletal and neuropathic pain established by a systematic review
70 and meta-analysis (Amatya et al., 2018; Boldt et al., 2014). To date, claims on the efficacy of
71 hypnosis in the overall chronic pain population (e.g., headache, cancer-related pain, etc.) and
72 associated recommendations on the number of sessions to perform “very brief or brief
73 hypnosis treatment” (≤ 7 sessions) or “hypnosis treatment” (≥ 8 sessions) (Jensen and
74 Patterson, 2006) have been only provided via narrative reviews (Jensen and Patterson, 2006;
75 Jensen et al., 2006; Patterson and Jensen, 2003). Therefore, there is an urgent need for a

76 systematic review to validate the use of hypnosis and to provide guidelines on the minimum
77 number of sessions needed to observe a positive effect on pain management.

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

85

86 **Material and methods**

87 The current systematic review and meta-analysis was performed in line with the
88 conventional methodology outlined in the Centre for Reviews and Dissemination (CRD)
89 guidance for conducting reviews in health care (Centre for Reviews and Dissemination,
90 2009). This systematic review is reported in accordance with the Preferred Reporting Items
91 for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009; Page et al.,
92 2021). The protocol for this review is registered on PROSPERO (CRD42020180298).

93

94 1. *Search strategy*

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

100

101 2. *Study selection*

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

107

108 3. *Eligibility criteria*

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

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

121

122 4. *Data extraction*

123 A data extraction form was designed in a table with the following items: authors and year,
124 overall population groups (i.e sample size, women/men, age), pain characteristics
125 (musculoskeletal and/or neuropathic, onset), hypnosis treatment modalities (i.e., number,

126 duration and frequency of sessions, and modalities of self-hypnosis), control intervention
127 modalities (i.e., type, number, duration and frequency of sessions, and modalities of self-
128 intervention), outcomes (i.e., type and rating scale of pain intensity, pain interference,
129 depression, anxiety, quality of life, sleep quality) and results after intervention and after a
130 follow-up period. Pain was assessed with the Visual Analog Scale (VAS) where the patient is
131 asked to indicate his/her perceived pain intensity on a 100 mm horizontal line (Boonstra et al.,
132 2008), the Numerical Rating Scale (NRS) where the patient is asked to rate his/her pain
133 intensity between 0 (no pain) and 10 (the worst pain imaginable), or the Brief Pain Inventory
134 (BPI) (0 = no pain and 10 = the worst pain imaginable) (Cleeland and Ryan, 1994; Erdemoglu
135 and Koc, 2013; Ferreira-Valente et al., 2011). The pain interference section of the BPI,
136 expressed as mean score over 10, consists in 7 Likert scales where the patient is asked to
137 report the number of ways in which, over the previous week, pain had interfered with their (i)
138 general activity, (ii) walking capacity, (iii) normal work (household), (iv) mood, (v) enjoying
139 life, (vi) relationships with people, and (vii) sleep. Depression was assessed with the Hospital
140 Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1988), the 8-item Patient Health
141 Questionnaire (PHQ-8; Kroenke et al., 2009), or the 20-item Center for Epidemiologic
142 Studies-Depression Scale (CES-D; Radloff, 1977). Anxiety was assessed with the Hospital
143 Anxiety and Depression Scale (HADS; Zigmond and Snaith, 1988). Quality of life was
144 assessed with EuroQol 5-Dimension 5-level (EQ-5D-5L; Herdman et al., 2011), the Short
145 Form-36v2 Health Survey (Ware et al., 2000), or A36 Hemofilia-QoL (Remor et al., 2005).
146 Sleep quality was assessed with the Pittsburgh Sleep Quality Index (PSQI; Buysse et al.,
147 1989).

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

151

152 *5. Risk of bias and quality of evidence assessment*

153 The risk of bias assessment of included studies was conducted according to the revised
154 Cochrane risk of bias tool for randomized control trials (RoB 2.0) using five domains : (i)
155 randomization process; (ii) deviations from intended interventions; (iii) missing outcome data;
156 (iv) measurement of the outcome; and (v) selection of the reported results (Sterne et al.,
157 2019). Each RCT was rated as “low risk of bias”, “some concern” or “high risk of bias”, for
158 each domain and overall judgement. The risk of bias assessment was undertaken by two
159 reviewers (PL, AO) helped by using the RoB 2.0 tool provided by Cochrane. Any
160 disagreements was resolved by a third reviewer (MB).

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

169

170 *6. Data synthesis*

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

173 When available, the mean change between baseline and follow-up and its standard
174 deviation were extracted for hypnosis and control groups. When the standard deviation of the
175 pain intensity score change was not reported, it was calculated using pre- and post- standard

176 deviations according to the formula for imputing standard deviations for changes from
177 baseline (Higgins et al., 2011):

$$178 \quad SD_{change} = \sqrt{SD_{baseline}^2 + SD_{follow-up}^2 - 2 \times Corr \times SD_{baseline} \times SD_{follow-up}},$$

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

188 In cases where several control treatments were used in the same study, we pooled data
189 from these controls by combining the groups to create a single control group as recommended
190 in the Cochrane handbook for systematic reviews of interventions (section 7.7.3.8, Higgins
191 and Green, 2011). Heterogeneity between studies was tested quantitatively using the
192 Cochran's Q test and the I² statistic. Heterogeneity was also evaluated graphically using a
193 forest plot. Since heterogeneity between the included studies was observed, the DerSimonian
194 and Laird random-effects model was used to estimate an overall treatment effect, combining
195 the results from included studies in our outcome (DerSimonian and Laird, 1986).

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

200 Based on the recommendations provided by Jensen and Patterson (2006) about the
201 number of hypnosis session to be delivered, a subgroup analysis was also conducted in order
202 to estimate the effects of hypnosis treatment duration using studies where patients had 8 or
203 more sessions of hypnosis, while another analysis used studies where patients had fewer than
204 8 sessions of hypnosis.

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

209 7. *Sensitivity analysis*

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

215

216 8. *Analysis of heterogeneity and publication bias*

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

225 publication bias for the secondary analyses using funnel plot techniques, Begg's rank test and
226 Egger's regression test, but the secondary analyses included a very low number of studies (4
227 to 6 RCTs), rendering these methods inappropriate.

228

229 **Results**

230 *1. Study selection*

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

238

239 *2. Study design and sample characteristics*

240 The main characteristics of the included studies published between 2002 and 2020 are
241 summarized in Table 1. Studies included chronic musculoskeletal and/or neuropathic pain
242 such as chronic back pain (Ardigo et al., 2016; Jensen et al., 2020, 2009b; Tan et al., 2015),
243 osteoarthritis (Ardigo et al., 2016; Gay et al., 2002), multiple sclerosis (Hosseinzadegan et al.,
244 2017; Jensen et al., 2020, 2009a), brachial neuralgia (Razak et al., 2019), spinal cord injury
245 pain (Jensen et al., 2020, 2009b) and hemarthrosis/heamatomas (irreversible muscle or joint
246 damage) (Paredes et al., 2019). Five studies included several types of chronic musculoskeletal
247 and/or neuropathic pain (Ardigo et al., 2016; Jensen et al., 2020, 2009a, 2009b; Paredes et al.,
248 2019), and 4 studies focused on only one pathology (Gay et al., 2002; Hosseinzadegan et al.,
249 2017; Razak et al., 2019; Tan et al., 2015). Taken together, the studies included 530

250 participants aged from 34 to 81 years. Duration of hypnosis treatment ranged from 3 (Ardigo
251 et al., 2016) to 12 weeks (Jensen et al., 2020, 2009a, 2009b). The follow-up period was
252 reported in 7 studies with a time frame of 10 (Hosseinzadegan et al., 2017) to 24 weeks (Gay
253 et al., 2002; Tan et al., 2015). The number of hypnosis sessions ranged from 3 (Ardigo et al.,
254 2016) to 10 (Jensen et al., 2009a, 2009b) sessions, and the frequency of the sessions was once
255 a week for 5 studies (Ardigo et al., 2016; Gay et al., 2002; Hosseinzadegan et al., 2017;
256 Paredes et al., 2019; Razak et al., 2019), while it was not reported in the remaining 4 studies
257 (Jensen et al., 2020, 2009a, 2009b, Tan et al., 2015). The interventions lasted from 30 to 90
258 minutes in 7 studies (Ardigo et al., 2016; Gay et al., 2002; Hosseinzadegan et al., 2017;
259 Jensen et al., 2020, 2009b; Paredes et al., 2019; Razak et al., 2019), whereas 2 others did not
260 report any length (Jensen et al., 2009a; Tan et al., 2015). Hypnosis suggestions were directly
261 targeted to pain in 7 studies (Ardigo et al., 2016; Hosseinzadegan et al., 2017; Jensen et al.,
262 2020, 2009a, 2009b; Paredes et al., 2019; Razak et al., 2019), while 2 studies did not specify
263 the focus of suggestion (Gay et al., 2002; Tan et al., 2015). After the hypnotic intervention
264 with a practitioner, 4 studies used audiotape recording to perform self-hypnosis (Jensen et al.,
265 2020, 2009a, 2009b; Tan et al., 2015). In addition, self-hypnosis was encouraged in 4 studies
266 without any audiotape recordings (Ardigo et al., 2016; Hosseinzadegan et al., 2017; Paredes
267 et al., 2019; Razak et al., 2019). The remaining study did not involve self-hypnosis (Gay et
268 al., 2002).

269 No intervention (Gay et al., 2002), standard care (Hosseinzadegan et al., 2017; Paredes et
270 al., 2019), relaxation (Gay et al., 2002), progressive muscular relaxation (Jensen et al.,
271 2009a), massage (Ardigo et al., 2016), acupuncture (Razak et al., 2019), biofeedback (Jensen
272 et al., 2009b; Tan et al., 2015), pain education (Jensen et al., 2020), or cognitive therapy
273 (Jensen et al., 2020) were performed in the control groups. The number, the frequency and the
274 duration of the control sessions were similar to the hypnotic intervention in 6 studies (Ardigo

275 et al., 2016; Gay et al., 2002; Jensen et al., 2020, 2009a, 2009b; Tan et al., 2015). Regarding
276 the remaining studies, one provided 2 acupressure versus 4 hypnosis sessions (Razak et al.,
277 2019), and 2 did not indicate the control intervention duration (Hosseinzadegan et al., 2017;
278 Paredes et al., 2019).

279

280 3. *Efficacy of hypnosis on pain intensity after intervention*

281 The results of the narrative synthesis are reported in the Table 1. While 4 studies out of 9
282 reported a significant greater decrease in pain intensity in the hypnosis group compared to the
283 control group (Ardigo et al., 2016; Hosseinzadegan et al., 2017; Jensen et al., 2009a, 2009b),
284 4 others reported a significant decrease in both the hypnosis group and the control group
285 groups without any differences between groups (Gay et al., 2002; Jensen et al., 2020; Razak
286 et al., 2019; Tan et al., 2015). The remaining study reported no significant pain relief in either
287 group (Paredes et al., 2019). The reduction of pain intensity after hypnosis treatment ranged
288 from 2% (Paredes et al., 2019) to 56% (Gay et al., 2002) (Figure 2).

289 The 9 studies were included in the primary pain intensity outcome meta-analysis. Pain
290 intensity was assessed using VAS, NRS, or BPI. All 9 studies reported the mean pain
291 intensity at baseline and post-intervention (ranging from 3 to 12 weeks) for the hypnosis
292 group and control groups. Statistical analysis showed a moderate decrease in pain intensity
293 following hypnosis compared to control intervention (random effects, 9 RCTs, 13
294 comparisons, n=475, Hedge's g: -0.42; CI95%: [-0.7763; -0.0696]; p-value: 0.025). Different
295 random effect sizes and the overall effect are presented in Figure 2. Heterogeneity was
296 graphically and statistically observed. The I² of 59.8% [16.4%; 80.7%] and the Cochran Q
297 test (p = 0.011) indicated moderate heterogeneity. The funnel plots (Figure 3) showed that the
298 overall estimated Hedges' g was equal to -0.42 while the study by Jensen et al. (2020) had a
299 different Hedges' g: 0.19 and SE: 0.19. This study had a large sample size (n=120, excluding

300 the hypnotic cognitive therapy group, which did not meet the inclusion criteria). Furthermore,
301 the control group (education and cognitive therapy) had a larger effect size than the hypnosis
302 group in this study (Jensen et al., 2020).

303 A sensitivity analysis was conducted on the 9 studies included in this meta-analysis using
304 the leave-1-out method to evaluate the robustness of the results when we remove one study at
305 a time from the meta-analysis. Following the sensitivity analysis, the effect sizes of the 9
306 datasets of 8 studies ranged from -0.53 CI95%: [-0.786; -0.265] to -0.33 CI95%: [-0.634; -
307 0.020] and all effects were statistically significant. However, we observed a large decrease in
308 heterogeneity when the study with the largest sample size by Jensen et al. (2020) was
309 removed ($I^2=23%$, $\tau^2=0.031$).

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

314

315 *4. Efficacy of hypnosis on pain intensity after follow-up period*

316 Eight studies out of 9 assessed pain intensity after a follow-up period (Ardigo et al. 2016;
317 Gay et al., 2002; Hosseinzadegan et al., 2017; Jensen et al., 2020, 2009a, 2009b; Razak et al.,
318 2019; Tan et al., 2015). Pain relief remained greater for the hypnosis group compared to the
319 control group after a follow-up period of 10 weeks (Hosseinzadegan et al., 2017), 12 weeks
320 (Jensen et al., 2009a, 2009b), and 16 weeks (Razak et al., 2019). One study reported a
321 significant pain intensity decrease without difference between groups at 12-week follow-up
322 period (Gay et al., 2002). Two studies reported that pain intensity decrease was not
323 maintained after a follow-up period of 12 weeks (Ardigo et al., 2016) and 24 weeks (Tan et

324 al., 2015). One study reported that the lack of effect of hypnosis was maintained at 12, 26, and
325 52 weeks (Jensen et al., 2020).

326 The meta-analysis specifically including the 7 studies with a short-term follow-up of 10-
327 16 weeks yielded a statistically significant moderate effect size (random effects, 7 RCTs, 9
328 comparisons, n=331, Hedge's g: -0.37; CI95%: [-0.79; 0.05]; p-value=0.027) (Ardigo et al.
329 2006; Gay et al., 2002; Hosseinzadegan et al., 2017; Jensen et al., 2020, 2009a, 2009b; Razak
330 et al., 2019). Heterogeneity between these 7 studies was statistically significant ($I^2=55%$;
331 CI95%: [0.0%; 80.7%], Cochran Q p-value: 0.038) (Figure 4).

332 For the long-term follow-up, 2 studies reported no significant effect of hypnosis treatment
333 after a 24-week follow-up period (Hedge's g: -0.669, CI95% = [-1.544; 0.205] (Gay et al.,
334 2002); and Hedges's g: -0.202, CI95% = [-0.729; 0.323] (Tan et al., 2015)). One study
335 reported a significant pain decrease at 12-month follow-up without any significant difference
336 between hypnosis and control groups (Hedge's g: 0.182, CI95% = [-0.212; 0.576]) (Jensen et
337 al., 2020).

338

339 5. *Effect of number of hypnosis sessions on pain intensity*

340 When considering data from the 6 studies with fewer than 8 sessions of hypnosis
341 delivered (Ardigo et al., 2016; Hosseinzadegan et al., 2017; Jensen et al., 2020; Paredes et al.,
342 2019; Razak et al., 2019; Tan et al., 2015), the effect size was small and not statistically
343 significant (random effects, 6 RCTs, 8 comparisons, n=341, Hedge's g: -0.299; CI95%: [-
344 0.795; 0.197]; p-value: 0.19) (Figure 5a). Moderate heterogeneity was observed between
345 these 6 studies ($I^2=67.6%$; CI95%: [23.2%; 86.4%], Cochran Q p-value: 0.0086).

346 Four studies reported outcomes in patients who underwent at least 8 sessions of hypnosis
347 (Gay et al., 2002; Jensen et al., 2009b, 2009a; Tan et al., 2015). When pooling the results of
348 these studies, we found a significant moderate to large effect size of hypnosis compared to

349 controls (random effects, 4 RCTs, 5 comparisons, n=159, Hedge's g: -0.555; CI95%: [-1.033;
350 -0.077]; p-value=0.034) (Figure 5b). Heterogeneity was not observed between these 4 studies
351 ($I^2=0.01\%$; CI95%: [0.0%; 80.3%], Cochrane Q p-value: 0.51).

352

353 *6. Efficacy of hypnosis on pain interference after intervention*

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

361 Six studies were included for meta-analysis of the pain interference outcome (Ardigo
362 et al., 2016; Jensen et al., 2020, 2009a, 2009b; Paredes et al., 2019; Tan et al., 2015).

363 Statistical analysis showed moderate improvement of pain interference following hypnosis
364 relative to a control intervention (random effects, 6 RCTs, n=339, Hedge's g: -0.39; CI95%:
365 [-0.7253; -0.0595]; p-value: 0.029). Different random effect sizes and the overall effect can be
366 found in Figure 6. Heterogeneity was not observed either graphically or statistically. We
367 found an I^2 of 18.6% [0%; 63.4%] indicating negligible heterogeneity, and the Cochrane Q
368 test had a p-value of 0.292, indicating no statistically significant heterogeneity.

369

370 *7. Efficacy of hypnosis on pain interference after follow-up period*

371 Six studies out of 9 assessed pain interference after a follow-up period (Ardigo et al.,
372 2016; Jensen et al., 2009a, 2009b, 2020; Razak et al., 2019; Tan et al., 2015). After a 12-week
373 follow-up period, one study showed that pain interference decrease was greater in the

374 hypnosis than in the control group with significance level set at 0.1 (Hedge's g : -0.402,
375 $CI_{95\%} =]-1.308; 0.504[$) (Jensen et al., 2009a). Three studies showed a decrease in pain
376 interference in both groups without any difference between groups at 12-week (Razak et al.,
377 2019; Jensen et al., 2020), 26-week (Tan et al., 2015; Jensen et al., 2020) and 52-week
378 follow-up (Jensen et al., 2020) (Hedge's g : -0.379, $CI_{95\%} =]-0.835; 0.077[$ for Tan et al.,
379 2015, effects not reported for Razak et al., 2019 and Hedge's g : 0.279, $CI_{95\%} =]-0.623;$
380 $1.180[$ for Jensen et al., 2020). Two studies reported no significant effect regardless of the
381 groups at 12-week follow-up (Hedge's g : -0.084, $CI_{95\%} =]-0.623; 0.454 [$ for Ardigo et al.,
382 2016 and Hedge's g : -0.435, $CI_{95\%} =]-1.235; 0.364[$ for Jensen et al., 2009b).

383

384 *8. Efficacy of hypnosis on depression, anxiety, quality of life and sleep quality*

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

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

395 The quality of life was assessed in 2 studies (Paredes et al. 2019; Razak et al. 2019),
396 which reported a significant improvement in quality of life for both groups, with a slightly
397 greater improvement in hypnosis compared to control group in 1 study (Paredes et al. 2019),

398 and maintenance of the effect after a 12-week follow-up period in the remaining study (Razak
399 et al. 2019).

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

403

404 9. Methodological quality

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

410 The randomization process, including random sequence generation, concealment and
411 baseline comparability, was rated as "low risk of bias" for 6 out of 9 studies (Hossein-zadegan
412 et al., 2017; Jensen et al., 2020, 2009b; Paredes et al., 2019; Razak et al., 2019; Tan et al.,
413 2015). Two out of 9 studies (Ardigo et al., 2016; Gay et al., 2002) were rated as "some
414 concerns" because there was a significant difference between groups at baseline in terms of
415 pain condition and there was no detailed information on randomization and concealment. One
416 study (Jensen et al., 2009a) was rated as "high risk of bias" because 8 participants in a pilote
417 study were included in the hypnosis group after randomization. All the nine included studies
418 were rated as "low risk of bias" for deviations from intended interventions. Even if it was not
419 possible to blind participants or clinicians, no clues were found for serious deviations from
420 intended interventions. The domain missing outcome data was rated as "low risk of bias"
421 except for one study (Tan et al., 2015) because there were a lot of dropouts and it was rated as
422 "some concerns". All of the included studies were rated as "low risk of bias" for the

423 measurement of the outcome. Even though the blinding of outcome assessors was not
424 generally detailed, the methods of measuring were appropriate and the same for both groups.
425 For selection reporting, 6 out of 9 studies were rated as “low risk of bias” because we
426 retrieved their registry information or trial protocol. One study (Gay et al., 2002) was rated as
427 “some concerns” because there was no information about registry trial protocol and two studies
428 (Jensen et al., 2009a, 2009b) were rated as “high risk of bias” because there was no
429 information about registry trial and there were multiple eligible analyses of the data (e.g. the
430 pain intensity outcome was analysed using absolute change and percentage of decrease).

431 The overall bias was rated automatically by the Cochrane algorithm. Four out of nine
432 studies were rated as “low risk of bias” (Jensen et al., 2020, 2009a, 2009b; Paredes et al.,
433 2019), 3 out of 9 studies as “some concerns” (Ardigo et al., 2016; Gay et al., 2002; Tan et al.,
434 2015) and 2 out of 9 studies as “high risk of bias” (Jensen et al., 2009a, 2009b).

435

436 *10. GRADE assessment*

437 Overall evidence of the 5 meta-analyses conducted in this review was qualified using
438 GRADE. Moderate quality of evidence (i.e., the true effect is probably close to the estimated
439 effect) indicates that chronic musculoskeletal and neuropathic pain might have a moderate
440 decrease in pain intensity following hypnosis compared to control intervention. Low quality
441 of evidence (i.e., the true effect might be different from the estimated effect) shows that the
442 decrease of pain intensity may have moderate short-term benefit and that 8 sessions or more
443 may produce moderate to large effect size of hypnosis compared to controls in the decrease of
444 pain intensity. Low quality of evidence shows that chronic musculoskeletal and neuropathic
445 pain may have moderate improvement of pain interference following hypnosis compared to
446 control intervention. The level of evidence for RCTs was downgraded in inconsistency due to
447 the moderate heterogeneity and various treatments in control groups and in imprecision due to

448 a very small number of included studies in each meta-analysis. The GRADE data are shown
449 in Table 2.

450

451 **Discussion**

452 This systematic review and meta-analysis included 9 RCTs with a total of 530 chronic
453 musculoskeletal and neuropathic pain patients. The results reveal that a hypnosis treatment
454 relieves pain immediately after the intervention period with limited protracted effects after a
455 short follow-up period. All in all, (i) hypnosis treatment yielded a moderate effect on pain
456 intensity and pain interference, (ii) fewer than 8 hypnosis sessions did not reach significant
457 effect size, (iii) 8 hypnosis sessions or more provided statistically significant moderate to
458 large effect size.

459

460 *Efficacy of hypnosis on chronic musculoskeletal and neuropathic pain intensity*

461 The current systematic review and meta-analysis study showed that hypnosis led to a
462 significant reduction in pain intensity ranging from 2% (Paredes et al., 2019) to 56% (Gay et
463 al., 2002), when compared to control interventions. Control interventions were highly
464 heterogeneous, including acupressure (Razak et al., 2019), biofeedback (Jensen et al., 2009b;
465 Tan et al., 2015), progressive muscular relaxation (Jensen et al., 2009a), massage (Ardigo et
466 al., 2016), cognitive therapy (Jensen et al., 2020) relaxation (Gay et al., 2002) pain education
467 (Jensen et al., 2020), standard care (Hosseinzadegan et al., 2017; Paredes et al., 2019), and no
468 intervention (Gay et al., 2002). To address this issue, we recommend intervention with
469 “minimal-effect” in control conditions such as group education to standardize intervention
470 and to limit the fading of treatment effect (Jensen and Patterson, 2005). While moderate
471 hypnosis effect was observed in comparison to control group with active interventions, our
472 results highlighted the fact that 6 studies (out of 9) showed pain relief up to 30% (Ardigo et

473 al., 2016; Gay et al., 2002; Hosseinzadegan et al., 2017; Jensen et al., 2009a; Razak et al.,
474 2019; Tan et al., 2015), including 2 higher than 50% (Ardigo et al., 2016; Gay et al., 2002),
475 corresponding to “much improved” and “very much improved” related to the established
476 guidelines for major changes (Dworkin et al., 2008; Farrar et al., 2001; Salaffi et al., 2004). In
477 a narrative review, Jensen and Patterson (2006) similarly reported hypnosis efficacy (from 2
478 to 57%) in managing pain in patients with several chronic pain diseases such as headache,
479 cancer-related pain, fibromyalgia, mixed chronic problems, low back pain, sickle cell disease
480 or temporomandibular pain. In addition, the recent systematic and meta-analysis by
481 Thompson et al. (2019), including 64 studies and 3039 healthy participants, showed that
482 hypnosis effectively relieves experimental pain in medium (42%) and high (29%) hypnotic
483 suggestibility participants. Therefore, it is safe to assume that hypnosis treatment focusing on
484 pain management is an effective technique to treat patients with chronic musculoskeletal and
485 neuropathic pain on a short-term basis, whereas limited long-term efficacy has also been
486 reported. In a home-based hypnosis treatment in elderly women suffering from chronic pain,
487 Dumain et al. (2021) reported that a continuum of hypnosis exposure through booster sessions
488 in addition to self-hypnosis could be effective to maintain pain relief for at least 12 months. In
489 this study, 7 hypnosis sessions were delivered during 12 months divided into 3 sessions the
490 first 3 months, 2 sessions the next 3 months, and sessions times the last 6 months. The need
491 for booster sessions and the long-term therapeutic success of hypnosis might be substantially
492 influenced by various elements, including the number of sessions.

493 As regards the attempts to standardize hypnosis practice, initiated by Jensen and
494 Patterson (2006), we identified and categorized one study with “very brief hypnosis
495 treatment” (3 sessions or less), 4 studies with “brief hypnosis treatment” (4 to 7 sessions), and
496 4 studies with “hypnosis treatment” (8 sessions or more). In light of the number of sessions
497 associated with pain relief efficacy, our meta-analysis provides new insight. We determined

498 that fewer than 8 sessions led to small or not significant effect, whereas 8 or more sessions
499 should be considered as more or less likely to achieve significant moderate to large effect to
500 manage chronic musculoskeletal and neuropathic pain. As there is to date no strong evidence
501 suggesting that more hypnosis sessions could provide further positive effects on pain
502 outcomes, future studies are needed to test this possibility. On this subject, Dumain et al.
503 (2021) reported that 4 hypnosis sessions spread out over 9 months at home in elderly women
504 presenting with chronic pain were not able to improve the pain relief achieved after 3 sessions
505 in 3 months (Billot et al., 2020b). Future studies are needed to determine the “dose-response”
506 efficacy of hypnosis with potential distinctive underlying mechanisms, especially considering
507 wide variety of diagnosis among chronic musculoskeletal and neuropathic pain patients.

508

509 *Efficacy of hypnosis on pain interference*

510 It has been well-documented that pain interferes with the motor system (Bank et al.,
511 2013; Billot et al., 2018; Corbeil et al., 2004; Hodges and Tucker, 2011; Rohel et al., 2021).
512 Because physical activity has become a major area of interest to avoid loss of mobility (Billot
513 et al., 2020a; Dent et al., 2019), pain management necessarily involves motor aspects. It has
514 been reported that pain interference was associated with at least twice the risk of mobility
515 difficulty in 634 community-dwelling older adults aged 65 and older (Eggermont et al., 2014).
516 The authors concluded that multisite or widespread pain and pain interference could be
517 considered as great predictors of mobility difficulty. In our meta-analysis, 6 studies
518 underlined that hypnosis elicits moderate beneficial effects on pain interference with general
519 activity (15-49%). These promising results must be carefully interpreted, especially when
520 drawing up future studies designed to objectively assess motor components with tools such as
521 connected soles or accelerometers. Hypnosis focused on pain might offer new opportunities to

522 prevent gait impairment, falls and sedentary lifestyle in patients with chronic musculoskeletal
523 and neuropathic pain.

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

541

542 *Mechanisms of hypnosis*

543 Since the end of the 20th century, brain imaging has been considered as a means of
544 determining the underlying mechanisms of hypnosis. Following the pioneering work of
545 Rainville et al. (1997, 2002, 1999) and Faymonville et al. (2003, 2000), the recent meta-
546 analysis of Del Casale et al. (2015) reported that hypnoanalgesic suggestions alter activity in

547 cortical areas of the pain matrix, which include anterior cingulate cortex, insular and
548 prefrontal areas. Neuroimaging studies of hypnotic analgesia using Positron Emission
549 Tomography (PET) showed a significant increase in pain-evoked activity within the anterior
550 cingulate cortex when hypnotic suggestions addressed increased pain (Rainville et al., 1999).
551 The authors concluded that hypnosis can modulate the activation of emotions and behavior of
552 individuals. More recently, Derbyshire et al. (2004) used Functional Magnetic Resonance
553 Imaging (fMRI) to identify the brain areas directly involved in the generation of pain, using
554 hypnotic suggestion to create an experience of pain in the absence of any noxious stimulus.
555 They reported activation of thalamus and anterior cingulate, insula, prefrontal, and parietal
556 cortices during pain induced by hypnotic suggestion. In line with this study, using a single-
557 trial thulium-YAG laser fMRI paradigm to induce pain, Vanhaudenhuyse et al. (2009b)
558 showed significantly less activation of the brainstem, right thalamus, left striatum, right
559 striatum, left insula, right insula, right primary somatosensory cortex, anterior cingulate
560 cortex, right middle frontal gyrus, and right premotor cortex in hypnotic state compared to
561 wakefulness condition (Vanhaudenhuyse et al., 2014). Additional research reported that
562 structural properties and activation of the anterior cingulate and frontal regions differ across
563 levels of suggestibility, i.e. tending to positively respond to hypnotic induction (Jensen et al.,
564 2017; Jensen and Patterson, 2014), which may highlight the greater pain relief observed at a
565 high rather than a low level of hypnotic suggestibility (Thompson et al., 2019). The cortical
566 areas involved in the pain matrix are mirrored with those identified as playing a major role in
567 pain modulation (Jensen and Patterson, 2014; Vanhaudenhuyse et al., 2014). Pain matrix
568 potentially provides a neural basis for hypnotic analgesia.
569

570 *Quality of evidence*

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

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

587

588 *Limitations*

589 The current systematic review and meta-analysis has several limitations. First,
590 although, as previously shown in experimental pain (Thompson et al., 2019), hypnotic
591 suggestibility could substantially impact hypnosis efficacy, the 9 RCTs included in this
592 review did not discriminate, with regard to pain relief, between high and low hypnotic
593 suggestibility patients. The moderate to large evidence of hypnosis efficacy reported in our
594 meta-analysis could nonetheless be strengthened in high suggestibility patients and weakened

595 in low hypnotic suggestibility patients presenting with chronic musculoskeletal and/or
596 neuropathic pain. Hypnotic suggestibility has shown to be improved by training and practice
597 (Patterson and Jensen, 2003), and should be included in future research to address this issue.
598 Second, as medication intake was used primarily to treat pain in chronic pain patients,
599 modification in its usage could influence clinical outcomes. Hypnosis treatment can be
600 considered as an added value to manage pain when no modification of medication intake
601 occurs (Ardigo et al., 2016; Jensen et al., 2020). Nevertheless, one study reported a potential
602 double impact of hypnosis treatment by reporting clinical outcome improvement and
603 medication intake reduction (Gay et al., 2002). Third, while hypnosis efficacy has been
604 observed in young (Hosseinzadegan et al., 2017; Razak et al., 2019) and older adults (Ardigo
605 et al., 2016; Billot et al., 2020b; Dumain et al., 2021; Gay et al., 2002), there is no evidence to
606 determine the influence of age on hypnosis efficacy. **Fourth, the very limited available data on**
607 **depression, anxiety, quality of life, and sleep quality do not provide robust evidence about the**
608 **effects of hypnosis on these outcomes. Fifth,** we were unable to report evidence of hypnosis
609 efficacy over a long-term period. Finally, the heterogeneity of the study should be considered
610 when interpreting our results, which need to be confirmed in future well-designed studies.

611

612 *Clinical implications, recommendations and future studies*

613 This systematic review and meta-analysis has several clinical implications. Hypnosis
614 may be considered as an effective complementary to medication for in management of
615 chronic musculoskeletal and neuropathic pain. Hypnosis could be offered by a practitioner
616 (e.g., psychologist, physiotherapist, nurse) during hospitalization (Ardigo et al., 2016; Gay et
617 al., 2002; Paredes et al., 2019; Razak et al., 2019; Tan et al., 2015) or at home (Billot et al.,
618 2020b; Dumain et al., 2021), and could also be provided as self-practice though audio-tape
619 recording (Brugnoli et al., 2018; de la Vega et al., 2019; Eason and Parris, 2019). This

620 systematic review and meta-analysis showed that a minimum of 8 sessions are needed in
621 order to observe significant clinical effect. Furthermore, the benefits of hypnosis treatment on
622 pain relief have got to be assessed in a long-term follow-up period, the objective being to
623 determine the time frame effects (Dumain et al., 2021; Jensen et al., 2008, 2005). Hypnosis
624 approach could also be combined with virtual reality to potentiate efficacy (Rousseaux et al.,
625 2020a, 2020b; Thompson et al., 2010) particularly in low hypnotic suggestibility patients. In
626 addition, hypnosis treatment focusing on a combination of pain, psychological distress and
627 functional capacity could offer overall health-related benefits by reducing kinesiophobia (fear
628 of movement), catastrophizing (imagining the worst possible outcome of an action or event),
629 psychological distress and sleep disorders (Grégoire et al., 2018; Luque-Suarez et al., 2019;
630 Vanhauzenhuysse et al., 2018).

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

638

639 *Conclusion*

640 The current meta-analysis showed, on the basis of 9 RCTs, evidence of effective
641 hypnosis treatment in view of managing pain intensity and pain interference with daily
642 activities in chronic musculoskeletal and neuropathic pain patients. This is the first time that
643 an efficacy threshold has been identified based on the number of sessions, showing that 8 or
644 more sessions should lead to moderate to large effects, and that fewer than 8 sessions should

645 yield little or no effect. All in all, these findings suggest that hypnosis treatment may
646 represent an effective and complementary approach to management of chronic pain. Further
647 research is needed to delineate the long-term relevance of hypnosis in clinical practice and to
648 determine the cost-utility of this approach.

649

650

651 **Funding**

652 This review did not receive any specific grant from funding agencies in the public,
653 commercial, or not-for-profit sectors.

654

655 **Conflicts of interest statement**

656 None.

657

658 **Acknowledgments**

659 We thank Jeffrey Arsham for his proofreading of the manuscript and his suggestions
660 regarding medical writing.

661 The authors would like to thank the CHU of Liège, the University of Liège, the Belgian
662 National Fund for Scientific Research (FRS-FNRS - Télévie), the Belgian Cancer Foundation
663 (2020-118), the Benoit Foundation and the Léon Fredericq Foundation.

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1117 Figure Legends

1118 Figure 1. Study selection flowchart.

1119 Figure 2. Forest plot of standardized mean differences (with 95% confidence intervals) and
1120 study weights for 9 pain intensity studies. The overall effect is plotted as a diamond. TE:
1121 Treatment Effect; se: Standard Error.

1122 Figure 3. Funnel plot of the effect sizes (Hedges'g) of the 9 studies included in the meta-
1123 analysis.

1124 Figure 4. Forest plot of standardized mean differences (with 95% confidence intervals) and
1125 study weights for 5 studies assessing the pain intensity outcome with a short-term follow-up.
1126 The overall effect is plotted as a diamond. TE: Treatment Effect; se: Standard Error.

1127
1128 Figure 5. Forest plot of Standardised Mean Differences (with 95% confidence intervals) and
1129 study weights for pain intensity studies with fewer than 8 sessions of hypnosis (upper panel),
1130 and with 8 sessions or more (lower panel). The overall effect is plotted as a diamond. TE:
1131 Treatment Effect; se: Standard Error.

1132 Figure 6. Forest plot of Standardised Mean Differences (with 95% confidence intervals) and
1133 study weights for 6 pain interference studies. The overall effect is plotted as a diamond. TE:
1134 Treatment Effect; se: Standard Error.

1135 Figure 7. The summary of risk of bias judgements for each study.

1136 Figure 8. The summary of risk of bias judgements presented as percentages across all
1137 included studies.

1138

1139 Table Legend

1140 Table 1. Main characteristics of the 9 included randomized control trials.

1141 Table 2. GRADE evidence profile.

1142 **Appendix A : Search strategies for databases used in the review**

1143 1. MEDLINE (PubMed):

1144 [Search date May 13th 2021]

1145 The search string was: (*chronic pain OR low back pain OR chronic widespread pain OR*
1146 *musculoskeletal pain OR persistent inflammation OR infection OR crystal deposition OR*
1147 *auto-immune disorder OR auto-inflammatory disorder OR osteoarthritis OR spondylosis OR*
1148 *musculoskeletal injury OR parkinson disease OR multiple sclerosis OR peripheral neurologic*
1149 *disease OR neuropathic pain OR trigeminal neuralgia OR peripheral nerve injury OR*
1150 *polyneuropathy OR postherpetic neuralgia OR radiculopathy OR spinal cord injury OR brain*
1151 *injury OR post-stroke pain*) AND hypnosis.

1152 **557 potential articles were retrieved.**

1153 2. Scopus

1154 [Search date May 13th 2021]

1155 The search string was: (*chronic pain OR low back pain OR chronic widespread pain OR*
1156 *musculoskeletal pain OR neuropathic pain*) AND hypnosis.

1157 **185 potential articles were retrieved.**

1158 3. PEDro

1159 [Search date May 13th 2021]

1160 The search string was:

- 1161 • *Substract & title : hypnosis*
- 1162 • *Therapy : \emptyset*
- 1163 • *Problem : pain*
- 1164 • *Body Part : \emptyset*
- 1165 • *Subdiscipline : \emptyset*
- 1166 • *Topic : chronic pain*
- 1167 • *Method : clinical trial*
- 1168 • *Match all search terms (AND)*

1169 **19 potential articles were retrieved.**

1170 4. CINAHL

1171 [Search date May 13th 2021]

1172 The search string was: (*hypnosis or hypnotherapy or hypnoses or hypnotism or*
1173 *hypnotherapies or hypnotic analgesia*) AND (*chronic pain OR low back pain OR*
1174 *musculoskeletal pain OR (inflammation or inflammatory) OR auto immune disease OR*
1175 *inflammatory disease OR osteoarthritis OR spondylosis OR musculoskeletal injury OR*
1176 *parkinson's disease OR multiple sclerosis OR peripheral neuropathy OR neuropathic pain*
1177 *OR peripheral neuropathy OR trigeminal neuralgia OR peripheral nerve injury OR*
1178 *polyneuropathy OR (postherpetic neuralgia or post-herpetic neuralgia) OR radiculopathy*
1179 *OR (spinal cord injury or sci) OR multiple sclerosis OR post stroke pain*).

1180 **330 potential articles were retrieved.**

1181

1182 5. Cochrane Library

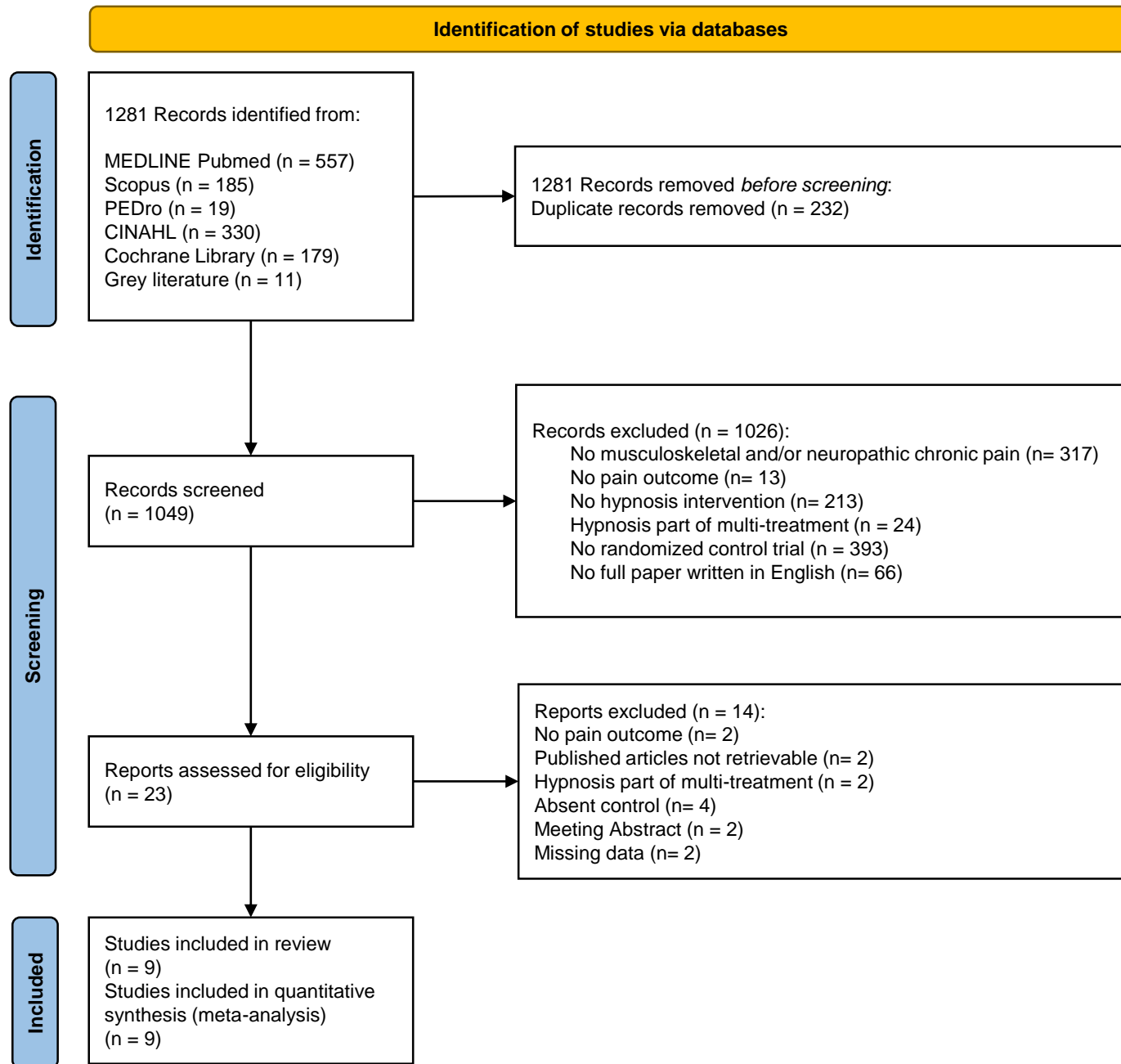
1183 [Search date May 13th 2021]

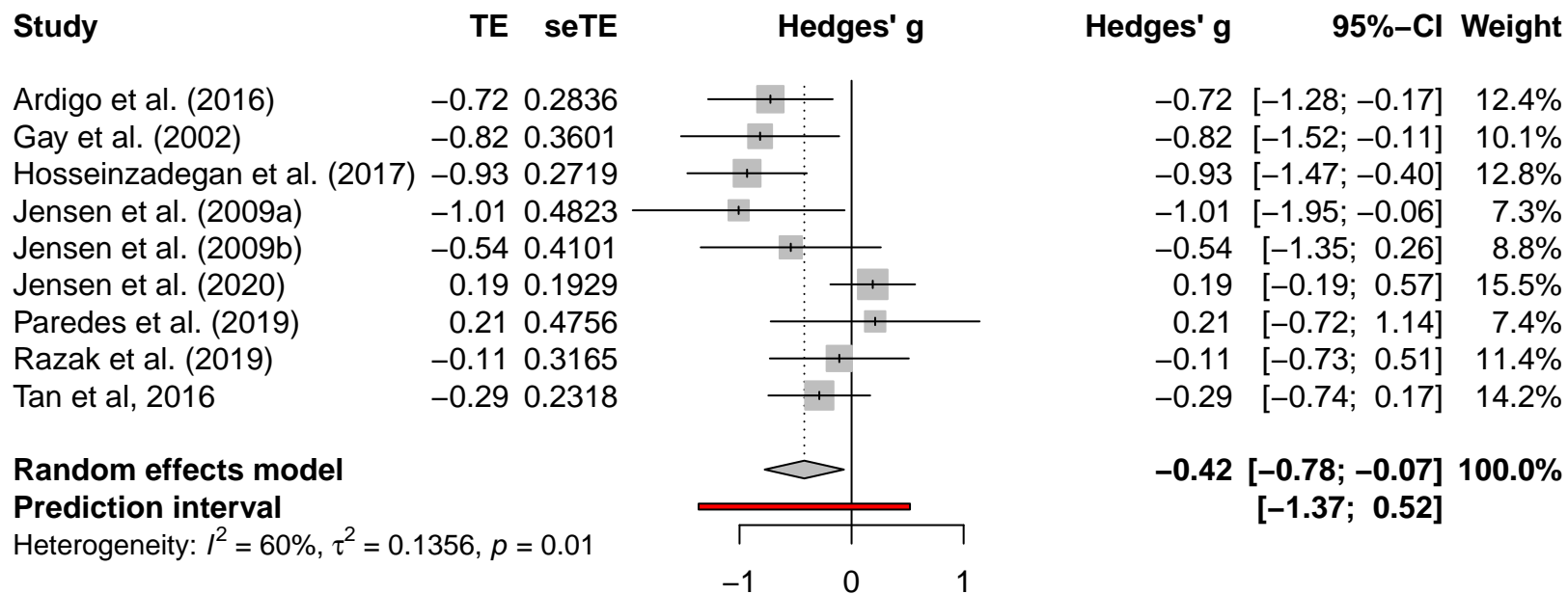
1184 The search string was: *(Hypnosis) AND (chronic pain OR low back pain OR chronic*
1185 *widespread pain OR Musculoskeletal Pain OR persistent inflammation OR infection OR*
1186 *crystal deposition OR auto-immune disorder OR auto-inflammatory disorder OR*
1187 *osteoarthritis OR spondylosis OR musculoskeletal injury OR Parkinson disease OR Multiple*
1188 *Sclerosis OR peripheral neurologic disease OR Neuropathic Pain OR trigeminal neuralgia*
1189 *OR peripheral nerve injury OR polyneuropathy OR postherpetic neuralgia OR radiculopathy*
1190 *OR spinal cord injury OR brain injury OR post-stroke pain).*
1191 **179 potential articles were retrieved.**

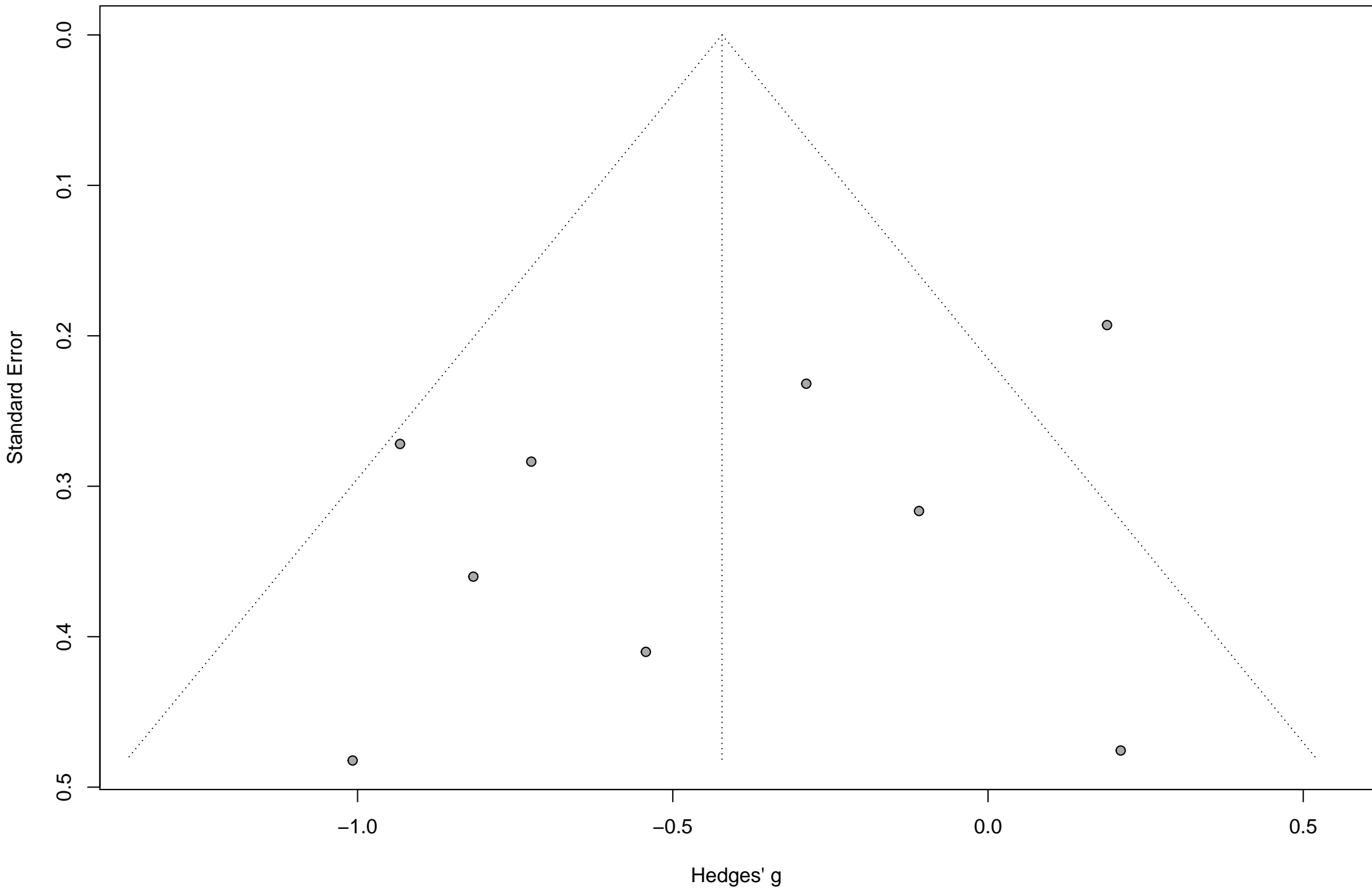
1192

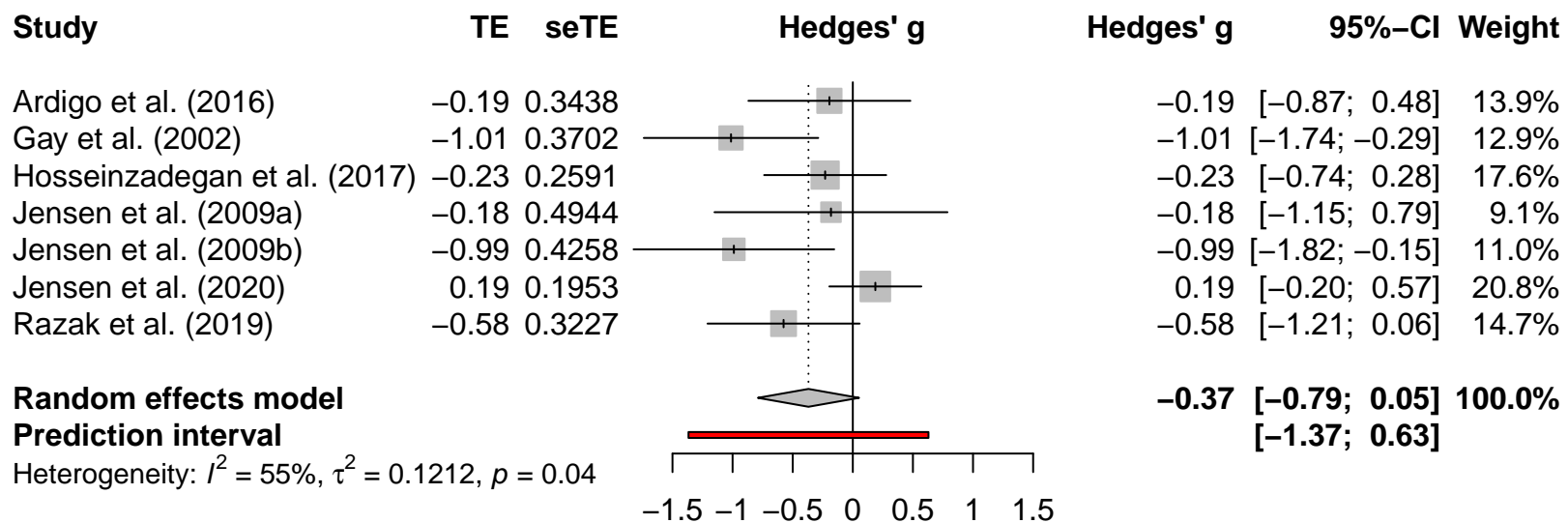
Appendix B

Author	Year	Title	Exclusionary ground
Ahmad et al.	2015	Hypnotherapy and acupressure 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
Ciaramella 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)
Gron Dahl 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
Vanhaudenhuyse et al.	2018	Psychological interventions influence patients' attitudes and beliefs about their chronic pain	Self-hypnosis treatment associated with self-learning care

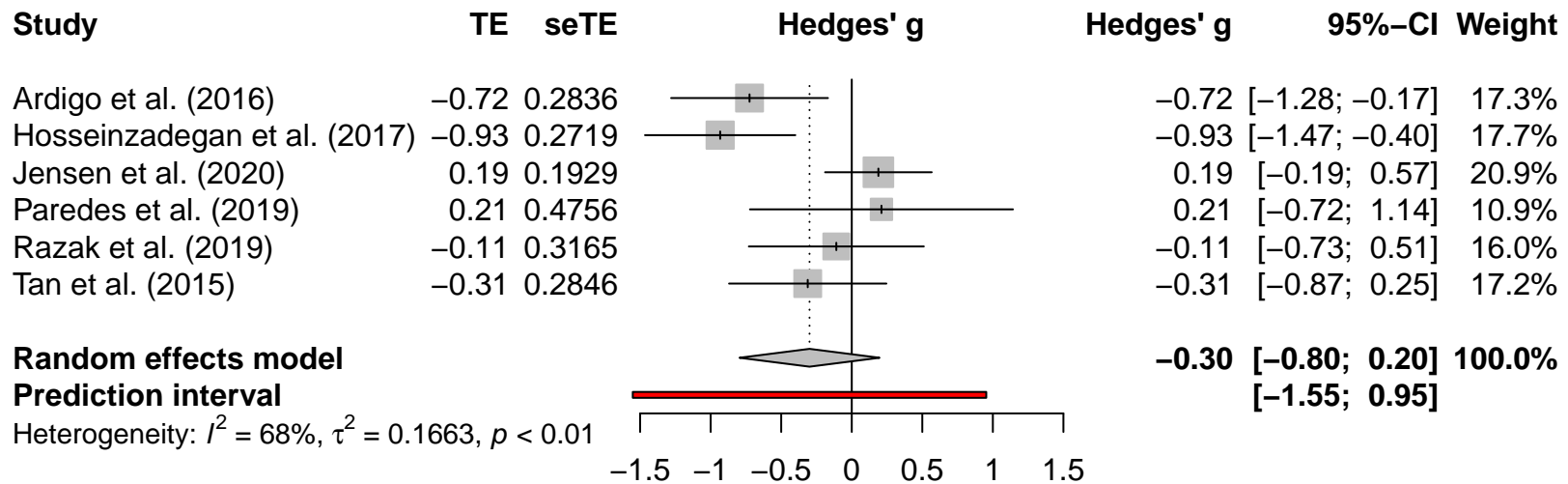




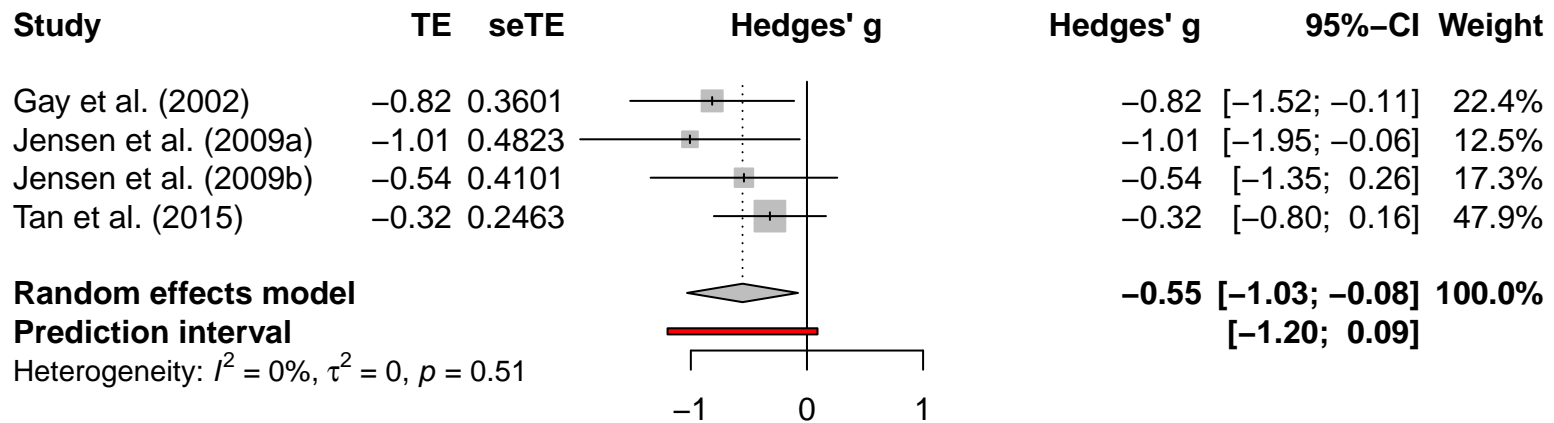


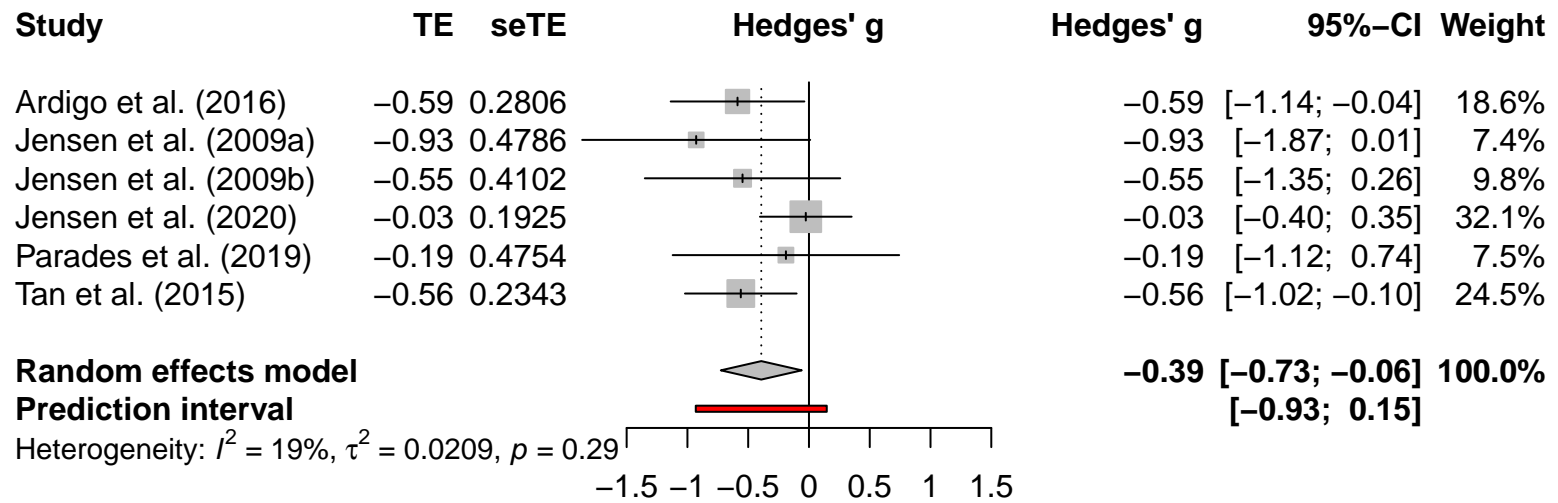


< 8 sessions



≥ 8 sessions





	D1a	D1b	D2	D3	D4	D5	Overall bias	
Ardigo et al. (2016)	!	+	+	+	+	+	!	+
Gay et al. (2002)	!	+	+	+	+	!	!	!
Hosseinzadegan et al. (2017)	+	+	+	+	+	+	+	-
Jensen et al. (2009a)	-	+	+	+	+	-	-	D1a Randomisation process
Jensen et al. (2009b)	+	+	+	+	+	-	-	D1b Timing of identification or recruitment of participants
Jensen et al. (2020)	+	+	+	+	+	+	+	D2 Deviations from the intended interventions
Paredes et al. (2019)	+	+	+	+	+	+	+	D3 Missing outcome data
Razak et al. (2019)	+	+	+	+	+	+	+	D4 Measurement of the outcome
Tan et al. (2015)	+	+	+	!	+	+	!	D5 Selection of the reported result

As percentage (intention-to-treat)

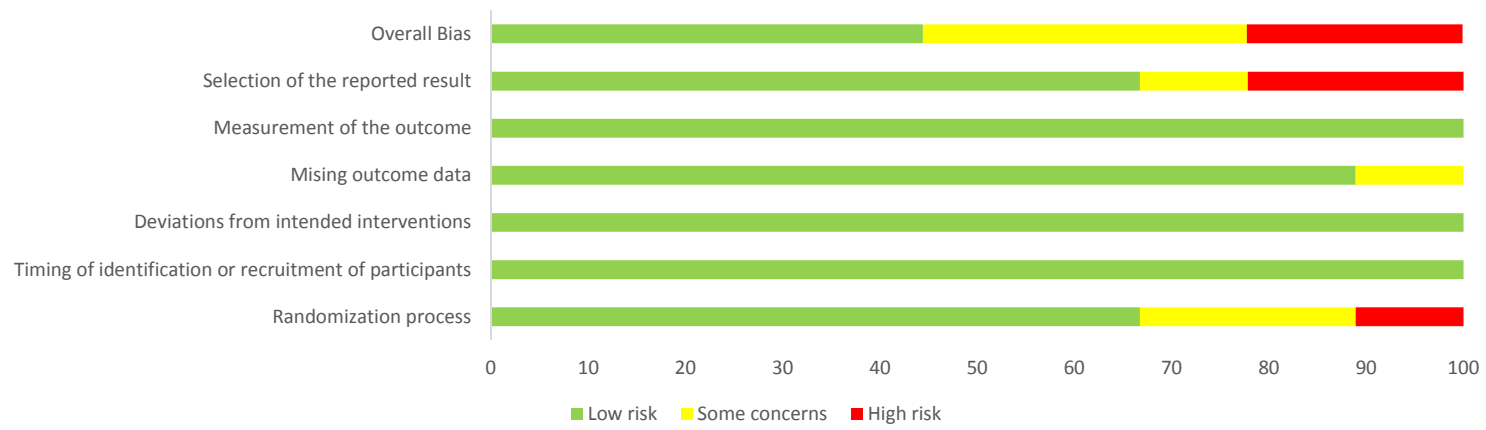


Table 1. Main characteristics of the 9 included randomized control trials.

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 Depression: HADS ^D Anxiety: HADS ^A	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 ^D Anxiety: HADS ^A	After intervention: ↓ BPI NRS, HG > CG ↓ BPI, HG = CG = HADS ^D = HADS ^A After 12 wks: = BPI NRS = BPI = HADS ^D = HADS ^A
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	<u>CG1</u> Relaxation 8 wks, 8 sessions, 30 min, 1/wk No self-intervention 12 and 26 wks <u>CG2</u> No intervention	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)	<u>MCP</u> : 9 low back pain, 7 overuse pain, 4 visceral pain <u>NCP</u> : 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 1session/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	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

				26 wks 52 wks			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 ± 9.48y HG: 8 (NR) CG: 10 (NR)	MCP: Heamarthrosis, heamatomas (irreversible muscles and joints damages) > 6 months	4 wks 4 sessions, 60min, 1/wk Self-hypnosis: taught and encouraged to practice	Medical treatment and standard care 4 wks	Pain intensity: NRS Pain interference: BPI Depression: HADS ^D Anxiety: HADS ^A	After intervention: = NRS ↓ BPI, HG > CG = HADS ^D = HADS ^A ↑ EQ-5D-5L, HG > CG ↑ A36 Hemofilia QoL, HG > CG Quality of life: EQ-5D-5L / A36 Hemofilia QoL	
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^{D/A}, 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).

Table 2. Grade evidence profile.

Number of studies	Study design	Quality assessment					Number of patients		Relative (95% CI)	Effect		Quality
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Hypnosis	control		Absolute (95% CI)		
Effectiveness of hypnosis on pain intensity after intervention												
9	randomised trials	not serious	serious ^a	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 ^a	not serious	serious ^b	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 ^c	not serious	serious ^b	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 ^c	not serious	serious ^b	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 ^c	not serious	serious ^b	none	142	189	-	SMD 0.37 SD lower (0.79 lower to 0.05 lower)		⊕⊕○○ Low

CI: confidence interval; **SMD:** standardised mean difference

Explanations

- Moderate heterogeneity and various treatments in control groups.
- A very small number of included studies.
- Various treatments in control groups.