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Review Article

Interventions for Depressive Symptoms in People Living with Chronic Pain: A Systematic Review of Meta-Analyses

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Abstract

Objective. This review investigated the effectiveness of clinical interventions on depressive symptoms in people with all types of chronic pain. **Methods**. We searched seven electronic databases and reference lists on September 15, 2020, and included English-language, systematic reviews and meta-analyses of trials that examined the effects of clinical interventions on depressive outcomes in chronic pain. Two independent reviewers screened, extracted, and assessed the risk of bias. PROSPERO registration: CRD42019131871. **Results**. Eighty-three reviews were selected and included 182 meta-analyses. Data were summarized visually and narratively using standardized mean differences with 95% confidence intervals as the primary outcome of interest. A large proportion of meta-analyses investigated fibromyalgia or mixed chronic pain, and psychological interventions were most commonly evaluated. Acceptance and commitment therapy for general chronic pain, and fluoxetine and web-based psychotherapy for fibromyalgia showed the most robust effects and can be prioritized for implementation in clinical practice. Exercise for arthritis, pharmacotherapy for neuropathic pain, self-regulatory psychotherapy for axial pain, and music therapy for general chronic pain showed large, significant effects, but estimates were derived from low- or critically low-quality reviews. **Conclusions**. No single intervention type demonstrated substantial superiority across multiple pain populations. Other dimensions beyond efficacy, such as accessibility, safety, cost, patient preference, and efficacy for non-depressive outcomes should also be weighed when considering treatment options. Further effectiveness research is required for common pain types such as arthritis and axial pain, and common interventions such as opioids, anti-inflammatories and acupuncture.

Key words: Depression; Chronic Pain; Systematic Review; Umbrella Review; Meta-Analysis; Effectiveness

Introduction

Chronic pain (CP) is a common and disabling group of health conditions defined as pain that persists or recurs for longer than 3 months [1]. CP affects approximately 20% of North American adults [2, 3]. Mental illness comorbidities like major depressive disorder (MDD) are disproportionately prevalent in people with CP, with rates ranging from 18% to 85% in various care settings [128]. This stands in stark contrast to the much lower 12-month prevalence for MDD in the general US population of 8–10% [5, 6]. In many cases, the comorbid prevalence of CP and MDD may also be underestimated and complicated by the common and overlapping

symptomatology between these two conditions [7] as well as from effects of treatments such as medications.

CP and MDD are known to exacerbate one another. CP increases the frequency and duration of depressive episodes [8]. Likewise, MDD contributes to significantly lower mental and physical quality of life in people with CP [9, 10] and may also intensify and reduce capacity to tolerate pain in pain populations [11, 12]. Overall, people living with the comorbidity report poorer well-being and functionality compared to those living with CP alone [9, 13]. Recent studies have also found that the development of chronic pain and depression are associated with changes in neuroplasticity in overlapping regions of the brain [14]. The cyclical and interactive nature of this comorbidity presents unique challenges that may not be sufficiently accounted for in clinical guidance for treatment of MDD alone. Meta-analyses for MDD treatments outside of the CP population may over- or underestimate treatment effects within the CP population. For example, psychotherapies and antidepressant medications could have synergistic effects on both MDD and CP, and thus greater overall effectiveness for people living with this comorbidity compared to those living with MDD alone. However, we also know that the effects of medications on mood can be hampered by severe and prolonged pain [4]. Furthermore, treating chronic pain is already complicated by analgesic polypharmacy [15–17], but the addition of antidepressants and anxiolytics can further complicate treatment by reducing the analgesic efficacy of opioids [18] and increasing the overall burden of adverse effects [19, 20].

Given the high coprevalence, significant effects on overall quality of life, and challenges extrapolating evidence for MDD treatment in the general population to people living with pain, there is an evident need to synthesize the effects of commonly used CP interventions on depressive symptoms. This need for synthesis is further highlighted by the scant available guidance in clinical practice guidelines—one national guideline cited only a single randomized controlled trial for its single recommendation for MDD management in CP [21].

In the last decade, there have been more primary studies of interventions for improving depression in CP (e.g., [22]), and there has been a corresponding proliferation of systematic reviews examining psychological, physical and pharmacological interventions for CP [23–25], many of which report depressive symptom outcomes. However, there have been no reviews focused on capturing the effects of all clinical interventions on depressive symptoms among patients with all types of CP. The majority of existing reviews have focused on specific interventions (e.g., psychological therapies) [26, 27] or specific types of CP (e.g., low-back pain) [28, 29]. Investigating the effects across all interventions and CP types will allow for comparisons across groups and allow for the identification of areas of under- and overinvestigation.

To better understand how existing interventions commonly used for people with CP may beneficially or negatively affect depressive symptoms, we conducted a systematic review of systematic reviews synthesizing any intervention in any type of CP that included a meta-analysis of depressive symptom outcomes. We developed a protocol guided by the Joanna Briggs Institute (JBI) recommendations [30] (PROSPERO registration: CRD42019131871).

Our primary research questions were: 1) What clinical interventions demonstrate an effect on depressive symptoms in CP? 2) What are the effects of clinical interventions for depressive symptoms in CP and how do effects vary across interventions and pain types ?

Methods

Data Sources and Search Strategy

We searched MEDLINE, EMBASE, PsycINFO, CINAHL, AMED, the Cochrane Database of Systematic Reviews and the JBI Database of Systematic Reviews and Implementation Reports from inception to March 14, 2019, with an update September 15, 2020. Findings from a small subset of reviews focused specifically on mind-body interventions and based only on the initial search from March 2019 have been reported elsewhere [31].

We initially developed the search strategy for MEDLINE and included a combination of controlled vocabulary and keywords for the concepts of "chronic pain" and "depression," then limited to a validated "systematic review" filter [32]. The search was validated against relevant studies previously identified for inclusion, peer-reviewed as per PRESS guidelines [33], and adapted for the remaining databases (See Supplemental File 1 for MEDLINE Search Strategy). We identified additional records through hand-searching references of ten overviews of systematic reviews [26–29, 34–39] and included reviews.

Study Selection

Population

We included systematic reviews that examined adults with CP, defined as pain of any etiology, involving any body part lasting $\geq$3 months [41] (and present $\geq$15 days per month for chronic persistent headache [40]. We only included diseases with pain as a primary and necessary symptom (e.g., arthritis, but not chronic fatigue). We excluded pediatric populations ($\geq$50% of sample size $<$18 years of age) and cancer or end-of-life pain [42]. Formal MDD diagnosis was not an inclusion criterion.

Intervention and Comparator

We included reviews of any kind of clinical intervention intended to address CP or a related aspect of CP. Interventions did not need to be explicitly developed for improving pain or depression in CP populations. No

limitations were used for comparator type (e.g., placebo, usual care, active). We excluded reviews of nonclinical interventions such as public health interventions.

Outcomes

We only included studies that reported quantitative syntheses of depressive symptoms using validated scales. Although there is no accepted list of validated scales for depressive symptoms in CP, expected scales included, but were not limited to, the Beck Depression Inventory, and the Hamilton Depression Rating, Montgomery-Asberg Depression Rating, and Centre for Epidemiological Studies Depression scales. Reviews lacking depression-specific outcomes (e.g., mental health, "mood") were excluded, as were reviews that only reported surrogate (e.g., physiological) outcomes. Other outcomes such as pain or function were not evaluated in this systematic review.

Study Design

We included completed, published reviews that synthesized efficacy or effectiveness studies using experimental designs and included a meta-analysis of depression outcomes across multiple studies. We excluded non-intervention reviews or reviews that only included a narrative synthesis. Only the most up-to-date reviews of duplicate publications were included.

We did not set limits in terms of outcome timeframe, context, or setting of reviews or their synthesized primary studies. We only included records published in English.

After removing duplicates, we calibrated screening using a random set of 50 records, which were screened independently by all the screeners (A.S., K.L., D.C., C.C., O.P., and D.R.). All calibration screening discrepancies were discussed until consensus on screening decisions were reached. We then conducted title and abstract screening and full-text review independently and in duplicate (A.S., K.L., D.C., C.C., O.P., and D.R.) and conflicts were resolved by consensus or by a third author. We contacted systematic review authors to clarify record details as needed.

Data Extraction and Quality Appraisal

We collected the following data: review details (citation, objectives, type of review, funding source, lead author country), target population (CP type, age, gender), number of included participants (total, intervention and control), intervention and comparator, primary study types, settings and contexts, search dates, nondepression outcomes reported, instrument for primary study quality, details of primary studies in depression syntheses (number, study type, depression symptom outcome scale, outcome timeframe, full study citation), depression synthesis outcome (effect size, confidence interval, measure of heterogeneity, *P* values of overall effect), methods of synthesis, and any additional comments. Outcome timeframe was categorized as short (immediately post-treatment), medium (<1 year post-treatment), or long (≥1 year post-treatment).

Prior to data extraction, two authors (D.C., A.S.) independently piloted a data extraction form on two reviews. We extracted data using the finalized form independently and in duplicate (A.S., K.L., D.C., C.C., O.P., G.M., D.R.). Inconsistencies and conflicts were resolved through consensus or by a third reviewer. We contacted authors for important missing information.

We used the AMSTAR 2 quality appraisal tool to assess the risk of bias of included reviews. This 16-item checklist is widely used, comprehensive, has clear guidance on appropriate use, and is designed specifically for systematic reviews of healthcare interventions [43]. We completed the checklist [44] independently and in duplicate (A.S., K.L., D.C., C.C., O.P., and D.R.). Conflicts in scoring were resolved by consensus between raters or by a third rater. As recommended by developers, we reported an overall confidence in the review results as high, moderate, low, or critically low, determined by the matrix of responses. Ratings were not used as an inclusion criterion.

Data Synthesis and Analysis

Our principal summary measure was the synthesized effect size and 95% confidence interval (CI) for the depression outcome, which we described using Cohen's Effect Size (<0.2 = trivial, 0.2 to 0.49 = small, 0.5 to 0.79 = medium, ≥0.8 = large) [45]. Negative effect sizes indicated a reduction in depressive symptoms in response to the intervention evaluated, whereas positive effect sizes indicated either a worsening of depressive symptoms or that the comparator was more effective in reducing depressive symptoms. Some reviews reported positive effect size as improvement in depressive symptoms, and so such effects were converted to negative effects to align with the majority of reviews. We described, compared and contrasted results using visual and narrative approaches [30]. Data across studies were compared in terms of review quality, CP types, interventions, comparators, outcome timeframes, and the included underlying primary studies. Narrative results focused on moderate- and high-quality reviews (see Supplementary Data for study-by-study findings).

In order to visualize the breadth of the included literature and relationships between the included reviews and the primary studies they synthesized for depression outcomes, we created a network visualization using Gephi (software version 0.9.2) and Adobe Illustrator. We displayed each included systematic review and the primary trials they synthesized. Nodes (circles) represented reviews in grey and primary trials in blue and green, and the inclusion of trials in syntheses was represented by edges (connecting lines). Trial node size and color reflect the number of times it was synthesized in reviews (blue =

synthesized in one review; green = synthesized in two or more reviews; size = number of times synthesized). The size of review nodes reflected the number of trials that it synthesized. Reviews are considered as "overlapping" when they synthesize the same trial(s), which is visualized by edges connecting to the same trial node(s). We established pain type groups based on included populations reported in the reviews. Intervention types were also grouped based on descriptions reported in the reviews. In cases where reviews did not clearly define the intervention, we considered the described intervention components as well as the review's network connection with other reviews that more clearly defined interventions.

Results

Search Results

Our search yielded 8,435 unique records, which were screened by title and abstract, leaving 496 for full-text review. Initially, 106 records were included. During data extraction, two updated reviews were identified: one replaced a review that was initially included; the other was added in addition to the original review, as different syntheses were conducted. In total, we excluded 25 studies during data extraction, leaving 83 included reviews (Figure 1). Full-text- and data extraction-level exclusion reasons are included in Supplementary Data.

Included reviews were published from August 1987 to December 2020 and synthesized depression outcomes from 459 unique primary studies published from January 1981 to November 2018 (Table 1). Reviews were most commonly conducted by researchers in Germany (24%, n = 20) and the United Kingdom (18%, n = 15). Thirty-five (42%) reviews were conducted by six distinct groups of authors. Thirty-five (42%) reviews included depressive symptoms as a primary outcome.

A total of 182 meta-analyses were extracted. Fibromyalgia (31%, n = 56), and mixed or unspecified chronic pain (30%, n = 55), inactive comparators (29%, n = 53), and short outcome timeframes (36%, n = 65), were most common. Sample sizes ranged from 24 to 6,478 participants (mean = 646) as reported in 81% (n = 147) of the meta-analyses. Forty-two percent of meta-analyses (n = 77) were extracted from reviews funded by the government, 3% (n = 5) were funded by industry, and 27% (n = 49) did not report funding details.

Quality Appraisal

Reviews were rated high- (12%, n = 10), moderate- (16%, n = 13), low- (24%, n = 20), and critically low quality (48%, n = 40). The most common critical quality issues were: no list of reasons for excluded full-text articles (Question 7 [Q7]; 54%, n = 45); no investigation of causes of heterogeneity (Q11; 28%, n = 23); and no investigation of publication bias or discussion of its impacts (Q15; 28%, n = 23). The most common non-critical quality issues included: no explanation of included study designs (Q3; 92%, n = 76); no description of included study funding details (Q10; 83%, n = 69); and no account for risk of bias in when interpreting/discussing results (Q12; 35%, n = 29).

Pain and Intervention Types

We identified eight pain types. Since some reviews aggregated types of pain differently in their meta-analyses, some of these pain types overlap:

1. Arthritis (osteoarthritis, rheumatoid arthritis, and ankylosing spondylitis)
2. Axial (chronic low back and neck pain)
3. Fibromyalgia
4. Chronic headache
5. Musculoskeletal (when conditions like osteoarthritis and fibromyalgia were studied together and could not be disaggregated)
6. Neuropathic
7. Orofacial (primarily temporomandibular joint disorder)
8. Mixed or unspecified

We identified 13 types of interventions (Table 2).

Network Visualization

Across the 83 reviews, fibromyalgia (35%, n = 29), mixed CP (28%, n = 23), and arthritis (16%, n = 13) were the most common pain types evaluated, and psychological (45%, n = 37), pharmacological (18%, n = 15), and mind-body (15%, n = 12) were the most common intervention types (Figure 2). See Supplementary Data for detailed Network Visualization; Captions include instructions to view.

The network visualization provides a representation of the current landscape surrounding interventions for depression in people with chronic pain. Many included reviews synthesized the same primary articles and this overlap created multiple networks of connected reviews. Within these networks, distinct subgroups formed based on both pain type and intervention type.

Main Network (Psychological)

The largest network included 37 (45%) reviews of psychological interventions with a variety of subtypes (Table 2). One high-quality review [77] comparing ACT in mixed chronic pain against inactive comparators over medium outcome timeframes reported the largest significant point estimate (SMD −0.71 [95% CI −1.09 to

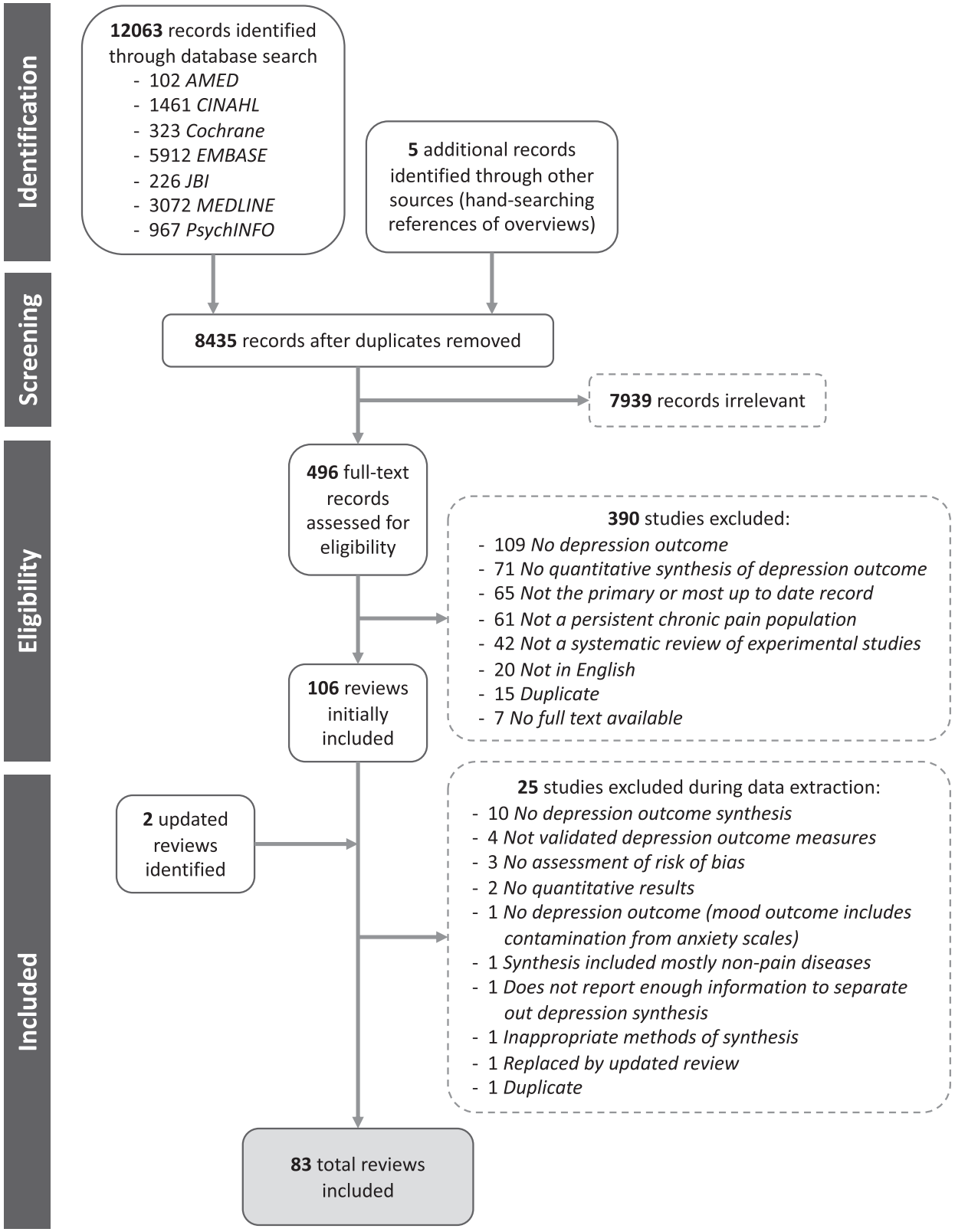

Figure 1. PRISMA flow diagram.

−0.33]); three RCTs; 109 participants. One synthesis of four RCTs with 437 participants from a moderate-quality review [51] reported a significant medium effect of reducing depressive symptoms for web-based psychotherapy in fibromyalgia with mixed comparators across all timeframes (SMD −0.51 [95% CI −0.87 to −0.15]). This was larger than for in-person CBT where the only meta-analysis from a high-quality review [50]

Table 1. Included review characteristics (83 reviews; 182 syntheses)

Reviews							Syntheses			
First Author, Year	Country	Pain Type	Intervention Type	Funding	Dep. Prim. Outcome	AMSTAR2 Quality	Intervention Subtype	Comparator	Outcome Timeframe	SMD (95% CI)*
Aggarwal, 2019 [46]	UK	OF	PSY (Self)	NR	Yes	Crit L	PSYCH	Usual Care	ML	−0.41 (−0.68 to −0.13)*
							PSYCH	Usual Care	ML	−0.32 (−0.5 to −0.15)*
							PSY CBT	Usual Care	ML	−0.27 (−0.49 to −0.05)*
Ball, 2017 [47]	UK	CX	MB	PF	No	Crit L	Meditation	Mixed	NR	−0.31 (−0.52 to −0.1)*
Bawa, 2015 [48]	UK	CX	MB	Gov	No	Crit L	Meditation	Inactive	S	−0.18 (−0.49 to 0.14)
							Meditation	Mixed	S	−0.12 (−0.3 to 0.05)
							Meditation	Active	S	−0.05 (−0.28 to 0.18)
Berdal, 2015 [49]	Norway	CX	PSY (MDC)	Gov	Yes	Low	PSY MDC	Usual Care	M	−0.02 (−0.22 to 0.19)
							PSY MDC	Usual Care	M	−0.01 (−0.56 to 0.54)
Bernardy, 2017 [50]	Germany	FM	PSY	None	Yes	High	PSY ACT	Usual Care	S	−0.91 (−1.95 to 0.13)
							PSYCH	Mixed	S	−0.43 (−0.62 to −0.24)*
							PSY CBT	Mixed	S	−0.34 (−0.48 to −0.21)*
							PSY EDU	Mixed	S	−0.1 (−0.3 to 0.1)
Bernardy, 2019 [51]	Germany	FM	PSY (Web)	None	Yes	Mod	PSY WEB	Mixed	SML	−0.51 (−0.87 to −0.15)*
Boehm, 2014 [52]	Germany	FM	CAM	Gov, PF	No	Crit L	CAM	Mixed	M	−0.18 (−0.6 to 0.24)
Buhrman, 2016 [53]	Sweden	CX	PSY (Web)	NR	No	Low	PSY WEB	Mixed	S	−0.27 (−0.38 to −0.16)*
Bujak, 2019 [54]	USA	CX	PSY (MDC)	None	No	Crit L	PSY MDC	NR	SM	−0.84 (−0.93 to −0.73)*
Cao, 2010 [55]	China	FM	CAM	Gov, PF	No	Crit L	CAM	Active	M	−0.55 (−0.73 to −0.38)*
Carnes, 2012 [56]	UK	MSK	PSY (MDC)	Gov	Yes	Crit L	PSY MDC	Mixed	ML	−0.25 (−0.47 to −0.03)*
							PSY MDC	Mixed	SM	−0.15 (−0.28 to −0.03)*
							PSY MDC	Mixed	L	−0.04 (−0.26 to 0.18)
Caruso, 2019 [57]	Italy	NP	PHARM	NR	Yes	Mod	Antidepressants	Inactive	M	−0.11 (−0.2 to −0.02)*
							Antidepressants	Inactive	M	−0.11 (−0.21 to −0.01)*
							Antidepressants	Inactive	M	−0.19 (−0.57 to 0.18)
							Antidepressants	Inactive	M	−0.08 (−0.19 to 0.03)
							Antidepressants	Inactive	M	−0.08 (−0.43 to 0.28)
Courtois, 2015 [58]	Belgium	FM	MB	NR	No	Crit L	Meditation	Mixed	NR	−0.25 (−0.47 to −0.03)*
Davari, 2020 [59]	Iran	NP	PHARM	None	No	Crit L	Gabapentinoids	Inactive	NA	−0.99 (−1.08 to −0.89)*
Dixon, 2007 [60]	USA	AR	PSY	Gov, PF	No	Crit L	PSY CBT	Mixed	S	−0.21 (−0.36 to −0.05)*
Eccleston, 2014 [61]	UK	CX	PSY (Web)	Gov	Yes	Crit L	PSY WEB	NR	M	−1.03 (−3.18 to 1.12)
							PSY WEB	NR	M	−0.53 (−1.84 to 0.78)
							PSY WEB	Mixed	S	−0.26 (−0.87 to 0.36)
							PSY WEB	NR	S	−0.19 (−0.35 to −0.04)*
Fiest, 2017 [62]	Canada	AR					CAM+PHARM	Gov	Yes	Mod
CAM+PHARM	Mixed	M	−0.49 (−1.07 to 0.1)							
							CAM+PHARM	Inactive	M	−0.21 (−1.27 to 0.85)
Foster, 2007 [63]	UK	AR	PSY (Edu)	NR	No	Mod	PSY EDU	Mixed	M	−0.22 (−0.34 to −0.09)*
Garza-Villarreal, 2017 [64]	Mexico	CX	Music	None	No	Low	Music Therapy	Mixed	NR	−0.82 (−1.08 to −0.56)*
Glombiewski, 2010 [65]	Germany	FM	PSY	PF	Yes	Crit L	PSYCH	Active	S	−0.56 (−0.93 to −0.19)*

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Reviews							Syntheses			
First Author, Year	Country	Pain Type	Intervention Type	Funding	Dep. Prim. Outcome	AMSTAR2 Quality	Intervention Subtype	Comparator	Outcome Timeframe	SMD (95% CI)*
							PSYCH	Inactive	S	−0.44 (−0.66 to −0.21)*
							PSYCH	Mixed	ML	−0.34 (−0.46 to −0.22)*
							PSYCH	Mixed	S	−0.33 (−0.45 to −0.2)*
Glombiewski, 2013 [66]	Germany	FM	PSY (Self)	NR	Yes	Mod	PSY Self	NR	M	−0.8 (−2.11 to 0.51)
Haugmark, 2019 [67]	Norway	FM	PSY (ACT)	Gov	Yes	Crit L	PSY ACT	Mixed	S	−0.49 (−0.85 to −0.12)*
							PSY ACT	Mixed	M	−0.48 (−0.77 to −0.19)*
Häuser, 2009a [68]	Germany	FM	EX (EDU; MDC)	Uni	Yes	Crit L	EX	Mixed	S	−0.67 (−1.08 to −0.26)*
Häuser, 2009b [69]	Germany	FM	PHARM	Gov, PF, Uni	No	Crit L	SSRIs	Inactive	S	−0.37 (−0.66 to −0.07)*
							Antidepressant	Inactive	S	−0.26 (−0.39 to −0.12)*
							SNRIs	Inactive	S	−0.26 (−0.42 to −0.1)*
Häuser, 2009c [70]	Germany	FM	PHARM	Ind	No	Crit L	Gabapentinoids	Inactive	S	−0.03 (−0.14 to 0.09)
Häuser, 2010a [71]	Germany	FM	EX	NR	No	Low	EX	Mixed	ML	−0.44 (−0.88 to 0.01)
							EX	Mixed	S	−0.32 (−0.53 to −0.12)*
Häuser, 2010b [72]	Germany	FM	PHARM	Ind	No	Crit L	Duloxetine	Inactive	NR	−0.27 (−0.39 to −0.16)*
							Milnacipran	Inactive	NR	−0.11 (−0.19 to −0.04)*
							Gabapentinoids	Inactive	NR	0.01 (−0.07 to 0.1)
Henschke, 2010 [73]	Australia	AX	PSY (MDC)	Gov, Uni	No	Low	PSY B	Active	M	−0.49 (−1.07 to 0.09)
							PSY B	Active	S	−0.24 (−0.76 to 0.27)
							PSYCH	Inactive	S	−0.24 (−0.52 to 0.05)
							PSY B	Inactive	S	−0.11 (−0.67 to 0.44)
							PSY MDC	Active	M	−0.1 (−0.69 to 0.5)
							PSY B	Active	L	−0.01 (−0.57 to 0.55)
							PSY B	Active	M	0.02 (−0.32 to 0.35)
							PSY MDC	Active	S	0.02 (−0.53 to 0.57)
							PSY B	Active	L	0.07 (−0.27 to 0.41)
							PSY B	Active	S	0.25 (−0.07 to 0.58)
							PSY B	Active	M	0.31 (−0.19 to 0.81)
							PSY B	Active	S	0.42 (0.01 to 0.82)*
Hilton, 2017 [74]	USA	CX	MB	Gov	No	Low	Meditation	Mixed	NR	−0.15 (−0.26 to −0.03)
Hoffman, 2007 [75]	USA	AX	PSY (Self; MDC)	NR	Yes	Crit L	PSY Self	Inactive	S	−0.81 (−1.52 to −0.11)*
							PSY CBT	Inactive	S	−0.34 (−1.19 to 0.51)
							PSY MDC	Mixed	S	−0.31 (−0.71 to 0.1)
							PSY CBT	Active	S	0.41 (−0.01 to 0.83)
Hou, 2016 [76]	Taiwan	FM	Brain Stim	Gov, Uni	Yes	Low	rTMS	Inactive	S	−0.38 (−0.61 to −0.15)*
							rTMS + TDCS	Inactive	S	−0.32 (−0.5 to −0.14)*
							TDCS	Inactive	S	−0.23 (−0.53 to 0.07)
Hughes, 2017 [77]	UK	CX	PSY	NR	No	High	PSY ACT	Inactive	M	−0.71 (−1.09 to −0.33)*
							PSY ACT	Inactive	S	−0.59 (−0.93 to −0.24)*
							PSY ACT	Mixed	S	−0.52 (−0.8 to −0.24)*

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Reviews							Syntheses			
First Author, Year	Country	Pain Type	Intervention Type	Funding	Dep. Prim. Outcome	AMSTAR2 Quality	Intervention Subtype	Comparator	Outcome Timeframe	SMD (95% CI)*
							PSY ACT	Mixed	M	−0.52 (−0.9 to −0.14)*
							PSY ACT	Active	S	−0.35 (−0.67 to −0.02)*
Hurley, 2018 [78]	UK	AR	EX	PF	No	High	EX	Mixed	ML	−0.16 (−0.29 to −0.02)*
Jandaghi, 2019 [79]	Iran	CX	PSYCH	None	Yes	Crit L	PSYCH	Mixed	S	−1.52 (−1.89 to −1.15)*
							PSYCH	Mixed	M	−1.35 (−1.7 to −1)*
Kamper, 2014 [80]	Australia	AX	PSY (MDC)	Gov	No	Mod	PSY MDC	Inactive	SM	−0.21 (−0.59 to 0.18)
							PSY MDC	Active	M	−0.16 (−0.42 to 0.09)
							PSY MDC	Active	L	−0.05 (−0.4 to 0.3)
							PSY MDC	Active	SM	0.05 (−0.12 to 0.22)
Kelley, 2015 [81]	USA	MSK	EX	Gov	Yes	Mod	EX	Mixed	ML	−0.42 (−0.58 to −0.26)*
Khoo, 2019 [82]	Canada	CX	MB; PSYCH	None	No	Mod	Meditation	Mixed	NR	−0.49 (−1.89 to −0.1)*
							PSY CBT	NR	NR	−0.44 (−1.29 to −0.08)*
Knijnik, 2016 [83]	Brazil	FM	Brain Stim	NR	Yes	Low	rTMS	Inactive	M	−0.15 (−0.47 to 0.17)
Knittle, 2010 [84]	Netherlands	AR	PSY	NR	Yes	Crit L	PSYCH	Mixed	ML	−0.32 (−0.48 to −0.16)*
							PSYCH	Mixed	S	−0.23 (−0.39 to −0.06)*
Langhorst, 2013 [85]	Germany	FM	MB	NR	No	Low	MM	Mixed	NR	−0.49 (−0.76 to −0.22)*
							MM	Mixed	NR	−0.41 (−0.96 to 0.15)
							MM	Mixed	NR	−0.3 (−0.85 to 0.25)
Lauche, 2013a [86]	Germany	FM	MB	PF	No	Low	MM	Active	S	−0.4 (−1.07 to 0.27)
Lauche, 2013b [87]	Germany	FM	MB	PF	No	Mod	Meditation	Usual Care	L	−0.19 (−0.43 to 0.04)
							Meditation	Usual Care	S	−0.15 (−0.38 to 0.08)
							Meditation	Active	S	−0.13 (−0.4 to 0.15)
							Meditation	Active	L	−0.13 (−0.42 to 0.17)
Lauche, 2019 [88]	Australia	AR	MB	NR	No	Low	MM	Mixed	NA	−0.28 (−0.72 to 0.16)
							MM	Mixed	NA	−0.18 (−0.48 to 0.12)
Li, 2014 [89]	China	FM	Massage	None	Yes	Crit L	Massage	Mixed	S	−0.49 (−0.84 to −0.15)*
							Massage	Mixed	S	−0.38 (−0.67 to −0.08)*
Li, 2019 [90]	China	AX	MB	Gov	No	Crit L	MM	Active	S	−0.61 (−0.95 to −0.27)*
Liang, 2015 [91]	China	AR	EX	NR	No	Crit L	EX	Mixed	NR	−0.95 (−1.36 to −0.55)*
Martorella, 2017 [92]	USA	CX	PSY (Web)	NR	No	Low	PSY WEB	Mixed	SM	−0.33 (−0.66 to 0)
							PSY WEB	Active	SM	−0.09 (−0.28 to 0.09)
							PSY WEB	Active	M	−0.04 (−0.3 to 0.21)
Mehta, 2014 [93]	Canada	NP	PHARM	PF	No	Crit L	Gabapentinoids	Inactive	SM	−1.22 (−1.48 to −0.97)*
Mehta, 2019 [94]	Canada	CX	PSY (Web)	NR	Yes	Crit L	PSY WEB	Mixed	M	−0.64 (−0.8 to −0.48)*
							PSY WEB	Mixed	NR	−0.44 (−0.54 to −0.34)*
							PSY WEB	Mixed	NR	−0.42 (−0.55 to −0.29)*
Moman, 2019 [95]	USA	CX	PSY (Web)	NR	No	Crit L	PSY WEB	Mixed	S	−0.28 (−0.48 to −0.08)*
							PSY WEB	Mixed	M	−0.29 (−0.49 to −0.09)*
Morley, 1999 [96]	UK	CX	PSY (Self)	Gov	No	Crit L	PSY Self	Inactive	NR	−0.74 (−1.2 to −0.28)*
							PSY CBT	Inactive	NR	−0.38 (−0.69 to −0.07)*
							PSYCH	Inactive	NR	−0.36 (−0.59 to −0.13)*
							PSY B	Inactive	NR	0.03 (−0.15 to 0.21)

(continued)

Reviews							Syntheses			
First Author, Year	Country	Pain Type	Intervention Type	Funding	Dep. Prim. Outcome	AMSTAR2 Quality	Intervention Subtype	Comparator	Outcome Timeframe	SMD (95% CI)*
							PSY B	Active	NR	0.14 (−0.11 to 0.38)
							PSY CBT	Active	NR	0.14 (−0.08 to 0.36)
							PSYCH	Active	NR	0.14 (−0.04 to 0.32)
Mullen, 1987 [97]	USA	AR	PSY (Edu)	PF	Yes	Crit L	PSY EDU	Active	SML	−0.28 (−0.42 to −0.15)*
Naumann, 2014 [98]	Germany	FM	Water	PF, Uni	Yes	Mod	Balneo	Inactive	S	−0.87 (−1.82 to 0.08)
							Balneo	Inactive	ML	−0.31 (−0.59 to −0.03)*
							Hydro	Mixed	S	−0.19 (−0.89 to 0.5)
Niknejad, 2018 [25]	USA	CX	PSY	Gov, PF	No	Low	PSYCH	Mixed	S	−0.13 (NR)
							PSYCH	Mixed	M	−0.09 (NR)
							PSYCH	Active	ML	−0.01 (NR)
Nouged, 2020 [99]	USA	OF	Injection	None	No	Crit L	Injection	Active	M	−0.24 (−0.9 to 0.42)
							Injection	Active	M	−0.06 (−0.45 to 0.32)
Onakpoya, 2019 [100]	UK	NP	PHARM	Gov	No	High	Gabapentinoids	Inactive	NR	−0.06 (−0.26 to 0.13)
Riemsma, 2003 [101]	UK	AR	PSY (Edu)	Uni	Yes	Mod	PSY EDU	Mixed	S	−0.14 (−0.23 to −0.05)*
							PSY EDU	Mixed	ML	−0.09 (−0.21 to 0.02)
Roldán-Barraza, 2014 [102]	Germany	OF	PSY (MDC)	None	No	Mod	PSY MDC	Usual Care	M	−0.21 (−0.41 to 0)*
Shen, 2020 [103]	China	AR	PSY CBT	Gov, PF	Yes	Crit L	PSY CBT	Usual Care	NA	−0.48 (−0.27 to −0.07)*
Sielski, 2017 [104]	Germany	AX	PSY (Self)	Uni	No	Crit L	PSY Self	Inactive	NR	−0.69 (−1.14 to −0.24)*
							PSY Self	NR	M	−0.49 (−0.83 to −0.15)*
							PSY Self	NR	S	−0.4 (−0.52 to −0.27)*
							PSY Self	Active	NR	−0.26 (−0.48 to −0.04)*
Silva Guerrero, 2018 [105]	Australia	MSK	PSY (MDC)	NR	Yes	Low	PSY MDC	Mixed	M	−0.21 (−0.42 to 0)*
							PSY MDC	Mixed	L	−0.15 (−0.36 to 0.06)
Smith, 2013 [106]	UK	AR	PSY (Edu)	NR	No	Crit L	PSY EDU	Inactive	ML	0.02 (−0.11 to 0.14)
Sosa-Reina, 2017 [107]	Spain	FM	EX	Gov, Uni	Yes	Crit L	EX	Mixed	NR	−0.4 (−0.55 to −0.24)*
Stockings, 2018 [108]	UK	CX	Cannabis	Gov	No	Low	Cannabis	Inactive	NA	0.03 (−0.12 to 0.17)
Tang, 2015 [109]	UK	CX	PSY	Uni	No	Low	PSYCH	Mixed	S	−0.27 (−0.57 to 0.03)
							PSYCH	Mixed	ML	−0.08 (−0.47 to 0.3)
Üçeyler, 2013 [110]	Germany	FM	PHARM	Ind	No	High	PHARM	Inactive	S	−0.09 (−0.16 to −0.01)*
Urquhart, 2008 [23]	Australia	AX	PHARM	Uni	Yes	Crit L	PHARM	Inactive	SM	−0.06 (−0.33 to 0.21)
Veehof, 2016 [111]	Netherlands	CX	MB	NR	Yes	High	Meditation	Mixed	NR	−0.18 (−0.34 to −0.03)*
Vowles, 2020 [112]	Australia	CX	PSY (ACT)	None	Yes	Crit L	PSY ACT	NR	S	−0.52 (−0.76 to −0.29)*
							PSY ACT	NR	S	−0.81 (−0.97 to −0.66)*
							PSY ACT	NR	S	−0.72 (−0.85 to −0.58)*
							PSY ACT	NR	M	−0.35 (−0.55 to −0.15)*
							PSY ACT	NR	M	−0.66 (−0.78 to −0.53)*
							PSY ACT	NR	M	−0.57 (−0.69 to −0.44)*
Walitt, 2015 [113]	USA	FM	PHARM	Gov, PF	Yes	High	Fluoxetine	Inactive	S	−0.55 (−0.93 to −0.18)*
							SSRIs	Inactive	S	−0.39 (−0.65 to −0.14)*

(continued)

Reviews							Syntheses			
First Author, Year	Country	Pain Type	Intervention Type	Funding	Dep. Prim. Outcome	AMSTAR2 Quality	Intervention Subtype	Comparator	Outcome Timeframe	SMD (95% CI)*
Walitt, 2016 [114]	Germany	FM	PHARM	PF	No	High	Quetiapine	Inactive	S	−0.39 (−0.74 to −0.04)*
Wang, 2017 [115]	China	NP	PHARM	NR	No	Crit L	Gabapentinoids	Inactive	NR	−1.18 (−2.02 to −0.34)*
Wang, 2020 [116]	China	FM	Music	Gov, PF	Yes	Crit L	Music	Mixed	NA	−0.34 (−0.55 to −0.03)*
Welsch, 2018a [117]	Germany	FM	PHARM	Gov, PF	No	Low	Mirtazapine	Inactive	NR	−0.67 (−1.44 to 0.1)
Welsch, 2018 b [118]	Germany	FM	PHARM	Gov, PF, Uni	No	High	Duloxetine	Inactive	NR	−0.25 (−0.34 to −0.17)*
							SNRIs	Inactive	NR	−0.16 (−0.21 to −0.11)*
							Milnacipran	Inactive	NR	−0.11 (−0.17 to −0.05)*
White, 2020 [119]	Australia	AR	PSY (Web)	Gov, Uni	Yes	Low	PSY WEB	Usual Care	NA	−0.44 (−0.91 to 0.02)
		FM					PSY WEB	Usual Care	NA	−0.67 (−1.18 to −0.17)*
		CX					PSY WEB	Usual Care	NA	−0.24 (−0.47 to −0.01)*
Wieland, 2017 [120]	USA	AX	MB	Gov	No	High	MM	Mixed	M	−0.22 (−0.68 to 0.25)
Williams, 2012 [24]	UK	CX	PSY	Gov	Yes	Low	PSY B	Usual Care	L	−0.65 (−2.07 to 0.77)
							PSY B	Usual Care	S	−0.53 (−1.42 to 0.35)
							PSY CBT	Usual Care	S	−0.38 (−0.57 to −0.18)*
							PSY CBT	Usual Care	L	−0.26 (−0.51 to 0)*
							PSY CBT	Active	L	−0.07 (−0.18 to 0.05)
							PSY CBT	Active	S	−0.05 (−0.19 to 0.09)
Yan, 2020 [121]	China	CX	Acupuncture	NR	Yes	Crit L	Acupuncture	Active	M	−0.7 (−1.23 to −0.17)*
Yu, 2019 [122]	China	NP	PHARM	NR	No	Crit L	Gabapentinoids	Inactive	NR	−0.34 (−0.55 to −0.12)*
Yu, 2020 [123]	China	NP	Brain Stim	Gov, PF	No	Mod	Brain Stim	Inactive	S	0.21 (−0.1 to 0.52)
		NP					Brain Stim	Inactive	M	0.62 (0.22 to 1.47)
Yuan, 2015 [124]	Brazil	FM	Massage	NR	Yes	Low	Massage	Inactive	S	−0.52 (−0.85 to −0.19)*
							Massage	Inactive	M	−0.37 (−0.7 to −0.04)*
Zhang, 2018 [125]	China	AR	PSY	Gov, PF, Uni	No	Crit L	PSYCH	Mixed	S	−0.42 (−1.05 to 0.21)

*Significant effect.

Dep = depression; Prim = primary; NR = not reported; SMD = standardized mean difference, CI = confidence interval. Pain type: AR = arthritis; AX = axial; CX = mixed chronic pain; FM = fibromyalgia; MSK = musculoskeletal; NP = neuropathic; OF = orofacial. Intervention type/subtype: ACT = acceptance and commitment therapy; B = behavioral; Balneo = balneotherapy; Brain Stim = brain stimulation; CAM = complementary and alternative medicine; CBT = cognitive behavioral therapy; EDU = education; EX = exercise; Hydro = hydrotherapy; MB = mind-body; MDC = multidisciplinary care; MM = mindful movement; PHARM = pharmacological; PSY/PSYCH = psychological; rTMS = repetitive transcranial magnetic stimulation; Self = self-regulatory; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TDCS = transcranial direct current stimulation; Web = web-based. Funding: Gov = government; Ind = industry; PF = private foundation; Uni = university. AMSTAR2 Quality: Crit L = critically low; Mod = moderate. Outcome timeframe: S=short timeframe (post-treatment); M=medium timeframe (post-treatment < 1 year), L=long timeframe (≥1 year).

Table 2. Intervention types, descriptions, and corresponding reviews

Intervention Type	Description	Corresponding Reviews
Psychological	Due to the large number and heterogeneity of psychological interventions, this group was further divided into eight subgroups, based on intervention components and methods of delivery that were investigated and synthesized by reviews	–
Acceptance and commitment therapy (ACT)*	Psychological therapies with acceptance and commitment therapy components. Some reviews also included acceptance-based and mindfulness-based interventions in syntheses with traditional ACT.	Bernardy 2017, Haugmark 2019, Hughes 2017, Vowles 2020
Behavioral therapy*	Psychotherapies explicitly described as "behavioral therapy"; largely syntheses that included a mix of therapies focused on behavioral change. Some reviews included operant therapy, respondent therapy, cognitive behavioral therapy, and biofeedback in their definition.	Henschke 2010, Morley 1999, Williams 2012
Cognitive behavioral therapy (CBT)*	Psychotherapies explicitly described as "cognitive behavioral therapy," or focused on changing cognitive activity to achieve other psychological changes.	Aggarwal 2019, Bernardy 2017, Dixon 2007, Hoffman 2007, Khoo 2019, Morley 1999. Shen 2020, Williams 2012
Educational	Interventions explicitly described as education programs; formal structured instructions largely on managing chronic pain symptoms. Some programs also included exercise, biofeedback, or psychosocial components in syntheses.	Bernardy 2017, Foster 2007, Mullen 1987, Riemsma 2003, Smith 2013
Multidisciplinary	Programs that involved psychotherapy combined with components from other intervention groups (education, exercise, physical therapy, self-management). This group was highly varied within syntheses as well as across reviews. All interventions included at least 2 components, one of which was educational or psychological in nature.	Berdal 2015, Bujak 2019, Carnes 2012, Henschke 2010, Hoffman 2007, Kamper 2014, Roldán-Barraza 2014, Silva Guerrero 2018
Self-regulatory	Interventions where patients learn to self-regulate physiological processes—most often through biofeedback.	Glombiewski 2013, Hoffman 2007, Morley 1999, Sielski 2017
Web-based	Psychologically-based programs or therapies delivered using non-face-to-face methods (via telephone, mobile device or computer), individually, in groups, or asynchronous self-guided programming.	Bernardy 2019, Buhrman 2016, Eccleston 2014, Martorella 2017, Mehta 2019, Moman 2019, White 2020
Mixed or unspecified	Multiple types of psychotherapies synthesized together or did not specify type of psychotherapy.	Aggarwal 2019, Bernardy 2017, Glombiewski 2010, Henschke 2010, Jandaghi 2019, Knittle 2010, Morley 1999, Niknejad 2018, Tang 2015, Zhang 2018
Pharmacological	Prescription medications, not including herbal supplements. Included primarily SSRIs, SNRIs, TCAs, and gabapentinoids.	Caruso 2019, Davari 2020, Hauser 2009b, Hauser 2009c, Hauser 2010b, Mehta 2014, Onakpoya 2019, Üçeyler 2013, Urquhart 2008, Walitt 2015, Walitt 2016, Wang 2017, Welsch 2018a, Welsch 2018b, Yu 2019
Mind-body	Interventions focused on the relationships among the brain, mind, body, and behavior, and their effect on health and disease. This group was further divided into two subgroups:	–
Meditation	Structured intervention focused on relaxation, consciousness, attention, and/or the body.	Ball 2017, Bawa 2015, Courtois 2015, Hilton 2017, Khoo 2019, Lauche 2013b, Veehof 2016
Mindful movement	Mind-body practice that involves exercise or movements with focused attention on breathing and movement of the body (e.g. yoga, tai chi).	Langhorst 2013, Lauche 2013a, Lauche 2019, Li 2019, Wieland 2017

(continued)

Intervention Type	Description	Corresponding Reviews
Exercise	Programs that primarily included aerobic exercise, flexibility, stretching, endurance, and/or strength training.	Hauser 2009a, Hauser 2010a, Hurley 2018, Kelley 2015, Liang 2015, Sosa-Reina 2017
Brain stimulation	Noninvasive brain stimulation interventions.	Hou 2016, Knijnik 2016, Yu 2020
Massage therapy	Massage therapy that involved manipulation of the soft tissues in a systematic way—did not include Reiki or other manual therapy such as chiropractic, or spinal manipulation.	Li 2014, Yuan 2015
Water therapy	Therapies involving immersion in plain, mineral, or thermal water, sometimes with exercise components.	Naumann 2014
Music therapy	Listening to music, sounds, or rhythms, melodies, or chords. Included self- or instructor-chosen recorded music, group music, and group music and guided imagery.	Garza-Villarreal 2017, Wang 2020
Injections	Local anesthetic trigger point injections.	Nouged 2020
Complementary alternative medicine (CAM)	Herbal supplements, homeopathy, and eastern medicine.	Boehm 2014, Cao 2010
Combined CAM and pharmacological	One review synthesized trials investigating pharmacological interventions and herbal supplements together.	Fiest 2017
Cannabinoids	Cannabis extracts and synthetic cannabinoids.	Stockings 2018
Acupuncture	A therapeutic method of traditional Chinese medicine using needles to stimulate specific body points.	Yan 2020

*Interventions not investigated by entire reviews, but separated out in distinct meta-analyses within reviews, and cannot be displayed in the network visualization (Figure 2).

ACT = acceptance and commitment therapy; CAM = complementary alternative medicine; CBT = cognitive behavioral therapy; SSRIs = selective serotonin reuptake inhibitors; SNRIs = selective norepinephrine reuptake inhibitors; TCAs = tricyclic antidepressants.

including 1,181 participants across 18 RCTs reported a small effect (SMD −0.34 [95% CI −0.48 to −0.21]) over a short timeframe against mixed comparators (mostly for fibromyalgia). The remaining meta-analyses showed small to trivial effects or were of low- to critically low quality (Supplementary Data).

Main Network (Mind-Body, Exercise, Massage and Water Therapy)

The reviews of mind-body interventions examined effects in fibromyalgia and mixed chronic pain, while three unconnected reviews evaluated arthritis and axial pain. The largest significant effect of reducing depressive symptoms was from a moderate quality review [82] of meditation with mixed comparators synthesizing six RCTs with 658 participants (SMD −0.49 [95% CI −1.89 to −0.1]). Overall, mindful movement demonstrated small to medium effects with larger effects in axial pain than in fibromyalgia and also generally larger effects than meditation [31].

The exercise network only included reviews specific to fibromyalgia, arthritis, and musculoskeletal pain. The single meta-analysis of nine RCTs with 876 participants from a high-quality review [78] reported a small significant effect for exercise-based rehabilitation for arthritis (SMD −0.16 [95% CI −0.29 to −0.02]). The single meta-analysis of 29 RCTs with 2,449 participants from a moderate-quality review of musculoskeletal pain [81] reported a small but significant effect for mixed exercise interventions against mixed comparators over medium/long timeframes (SMD −0.42 [95% CI −0.58 to −0.26]).

Two low- and critically low-quality reviews [89, 124] investigated massage therapy in fibromyalgia. A moderate-quality review [98] investigated water-based interventions (balneotherapy and hydrotherapy) in fibromyalgia. The only meta-analysis here with a significant point estimate showed small effects on depressive symptoms for balneotherapy against inactive comparators at mixed medium/long outcome timeframes and included 205 participants from three RCTs (SMD −0.31 [95% CI −0.59 to −0.03]).

Pharmacological Network

There was no overlap between the main and pharmacological networks, meaning primary articles that were synthesized in the main network were not synthesized by any reviews in the pharmacological network and vice versa. The 16 reviews investigating pharmacotherapy showed a quality dichotomy: 53% were critically low, and 33% were high-quality. This network included the only three reviews reporting industry funding [70, 72, 110]. All pharmacological meta-analyses included only inactive comparators. Meta-analyses examined the

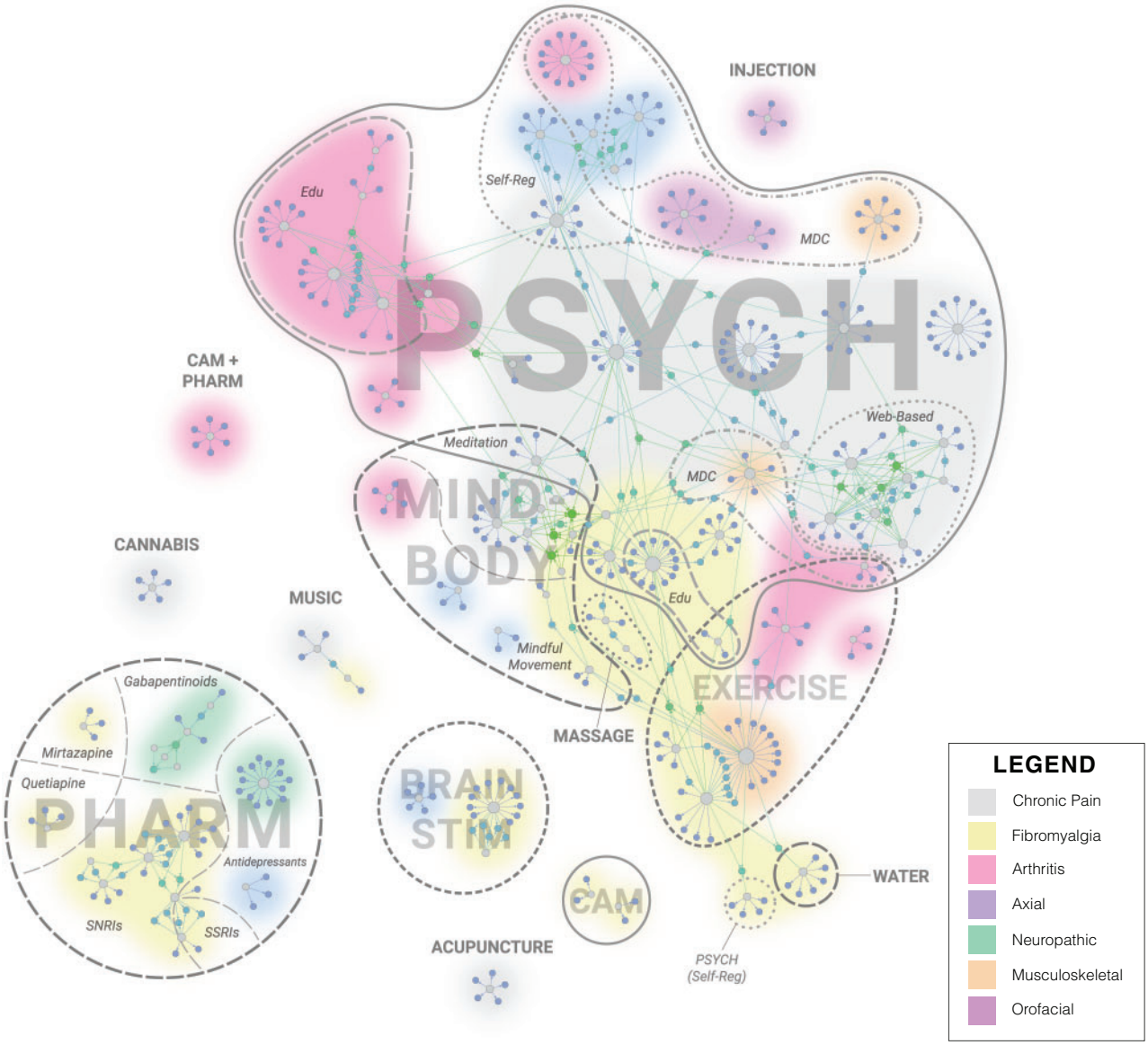

Figure 2. Network visualization of reviews and synthesized primary articles. CAM = complementary alternative medicine; BRAIN STIM = brain stimulation; EDU = education-based treatment; MDC = multidisciplinary care; PHARM= pharmacological therapy; PSYCH = psychotherapy; Self-Reg = self-regulatory treatment; SNRIs = selective-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; WATER = water-based therapy.

following medications (number of meta-analyses): antidepressants, including selective serotonin reuptake inhibitors (SSRIs; 3), selective serotonin-norepinephrine reuptake inhibitors (SNRIs; 9), tricyclic antidepressants (1), and mirtazapine (1); gabapentinoids (8), and quetiapine (1).

The three meta-analyses from high-quality reviews with the largest significant point estimates in reducing depressive symptoms evaluated fluoxetine (SMD −0.55 [95% CI −0.93 to −0.18]; three RCTs; 116 participants) [114], all SSRIs (SMD −0.39 [95% CI −0.65 to −0.14]; six RCTs; 244 participants) [114], and quetiapine (SMD −0.39 [95% CI −0.74 to −0.04]; three RCTs; 206 participants) [113] in fibromyalgia at short timeframes. Gabapentinoids demonstrated larger effects in patients with neuropathic pain than in those with fibromyalgia, although the two meta-analyses from high-quality reviews demonstrated trivial effects in both [100, 110]. All SSRI syntheses were conducted in fibromyalgia and had small to medium significant effect sizes. The SNRI syntheses demonstrated small to trivial significant effects.

Other Non-Networked Intervention Types

A variety of systematic reviews investigated brain stimulation [76, 83, 123], music [64, 116], complementary and alternative medicine (CAM; [52, 55, 62]), acupuncture [121], cannabis [108] and interventional therapy

[99]. The majority of these reviews were either of low- or critically low quality. One moderate-quality review [123] investigated the effects of brain stimulation in people with neuropathic pain and showed small to medium, nonsignificant effects on reducing depressive symptoms. The other moderate-quality review investigated the effects of herbal Chinese medicines combined with pharmacological interventions in people with arthritis [62] and reported small, non-significant effects.

Distribution of Effects by Pain Type

Fibromyalgia

The majority of fibromyalgia meta-analyses investigated the effects of pharmacological (26%), mind-body (18%), and mixed psychological (9%) interventions (Figure 3; Supplementary Data for detailed figure and plot of Effect Size by Intervention Type and Quality). This was the only pain type that included meta-analyses of massage therapy, water therapies and CAM. Among the high- and moderate-quality reviews, the meta-analyses with the largest significant point estimates showed medium effects of reducing depressive symptoms for fluoxetine (SMD, −0.55 [95% CI −0.93, −0.18]; three RCTs; 116 participants) [114], and web-based psychological therapies (SMD −0.51 [95% CI −0.87 to −0.15]; five RCTs; 437 participants) [51]. Meta-analyses specifically for gabapentinoids and milnacipran showed trivial effects.

Mixed or Unspecified Chronic Pain

The large majority of mixed CP meta-analyses investigated the effects of psychological interventions, including ACT (20%), web-based psychotherapies (18%), and mixed psychological (16%). Mind-body and cognitive behavioral interventions were also prominently represented (13%, each). Among moderate- and high-quality reviews, ACT was the most effective therapy (SMD −0.71 [95% CI −1.09 to −0.33]; three RCTs; 109 participants) [77] while mind-body (SMD −0.18 [−0.03 to −0.34]; nine RCTs; 622 participants [111] and SMD −0.49 [95% CI −1.89 to −0.1]; six RCTs; 658 participants [82]) and cognitive-behavioral therapies (SMD −0.44 [95% CI −1.29 to −0.08; nine RCTs; 761 participants [82]) demonstrated small effects.

Arthritis

The majority of arthritis meta-analyses investigated psychoeducation (22%) and mixed psychological (17%) interventions. Mind-body interventions, exercise, CBT, and CAM combined with pharmacological interventions were also represented (11%, each). The single synthesis from a high-quality review [78] included nine RCTs with 876 participants and reported a significant but small effect (SMD −0.16 [95% CI −0.29 to −0.02]) for exercise. The largest significant point estimates from moderate-quality reviews were reported for psychoeducation (SMD −0.22 [95% CI −0.34 to −0.09]; three RCTs; 1,426 participants [63] and SMD −0.14 [95% CI −0.23 to −0.05] 18 RCTs; 1,770 participants [101]).

Axial Pain

The majority of axial pain meta-analyses synthesized the effects of behavioral (31%), multidisciplinary (24%), and self-regulatory (17%) psychological, as well as mind-body (14%), interventions. No meta-analyses from high- or moderate-quality reviews reported significant effects on depressive symptoms in axial pain. A number of meta-analyses (largely behavioral psychological therapy) against active comparators (exercise, self-regulatory, and physical interventions) had positive effect sizes, suggesting that the comparators were more effective in reducing depressive symptoms (see Supplementary Data) [73, 75, 80].

Neuropathic

The 12 neuropathic pain meta-analyses investigated the effects of pharmacological interventions versus inactive comparators (83%) and brain stimulation (17%). Only one meta-analysis of four RCTs with 1,041 participants was from a high-quality review [100] and showed a trivial, nonsignificant effect for gabapentinoids (SMD −0.06 [95% CI −0.26 to 0.13]). Other syntheses of gabapentinoids from critically low-quality reviews found small to large non-significant effects. Meta-analyses of antidepressants from a moderate-quality review [57] found small effects.

Musculoskeletal

There were six musculoskeletal pain meta-analyses, all with mixed comparators, from three different systematic reviews. The only meta-analyses from a moderate-quality review [81] evaluated exercise across 29 RCTs with 2,449 participants and reported a significant small effect (SMD −0.42 [95% CI −0.58 to −0.26]).

Orofacial

There were six meta-analyses of interventions studying chronic orofacial pain from two reviews examining psychological interventions, and one investigating local anesthetic injections. Small but significant effects were reported for the psychological interventions versus usual care, while the reports for injections were small and non-significant. The only meta-analysis extracted from a moderate-quality review demonstrated that psychologically-based multidisciplinary care over medium timeframes had small effects (SMD −0.21 [95% CI −0.41 to 0.00]; four RCTs; 510 participants [102]).

Headache

Two chronic headache meta-analyses were extracted from a critically low-quality systematic review [61] and

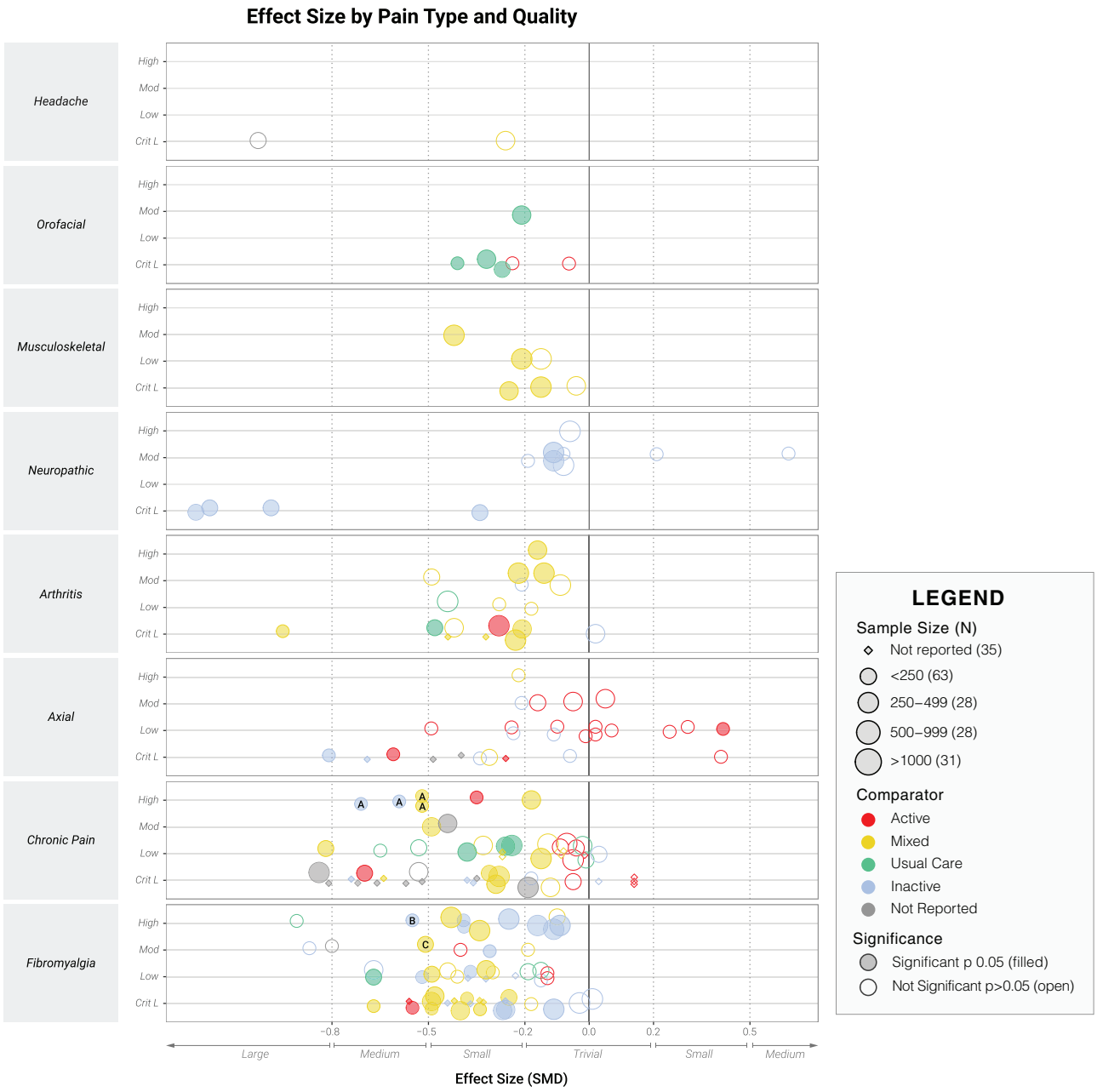

Figure 3. Effect size by pain type and quality. Size = sample size; color = comparator; fill = significance. Syntheses with significant effects from moderate- or high-quality reviews are labeled: A = Hughes 2017 (ACT); B = Walitt 2015 (Fluoxetine); C = Bernardy 2019 (Web-based). Two syntheses of very large effect from a critically low quality review of chronic pain (Jandaghi 2019) were excluded from the plot. Crit L = critically low; Mod = moderate; SMD = standardized mean difference.

both investigated the effects of web-based psychological interventions. Neither synthesis reported significant effects.

Discussion

Summary of Findings

ACT for general chronic pain, and fluoxetine and web-based psychotherapy for fibromyalgia were the only interventions for which there was at least a medium, significant improvement in depressive symptoms as synthesized in moderate- to high-quality reviews. Exercise for arthritis, pharmacotherapy for neuropathic pain, self-regulatory psychological therapy for axial pain, and music therapy, ACT, and mixed psychotherapy for general chronic pain showed large significant effects, but these were derived from low- or critically low-quality reviews. The distribution and magnitude of effects for depressive symptoms are comparable to those of other important outcomes for chronic pain conditions such as a pain severity [34, 35] and anxiety [39]. There were no interventions synthesized in moderate- or high-quality reviews that demonstrated a large, significant effect for reducing depressive symptoms in chronic pain. Only one meta-

analysis examining long-term effects in a moderate-quality review showed trivial effects in psychologically focused multidisciplinary care [80]. Interventions commonly employed for the management of chronic pain such as opioids, anti-inflammatories, and chiropractic have not been meta-analyzed for their effects on depressive symptoms and should be considered for future syntheses. Reports on acupuncture and cannabis were also very limited.

For most pain types, the majority of syntheses showed trivial to small effects in reducing depressive symptoms. This trend appears to span across all quality levels and includes both significant and non-significant effects. One critically low-quality review from Iran [79] reported very large and significant effects for psychotherapy in mixed chronic pain, but suggested that cultural differences in pain perception and variations in study methods may have affected validity and observed magnitude of effect sizes which were out of keeping with the remainder of the reviews. In three reviews that investigated people with axial pain [73, 75, 80], several syntheses of psychological interventions reported positive effect sizes, demonstrating that the comparators (exercise, physiotherapy, and self-regulatory interventions), were more effective in reducing depressive symptoms than psychotherapy. This is similar to the findings of another umbrella review of interventions for neck pain which found that psychosocial interventions including psychoeducation were not beneficial across a number of outcomes [35]. In this review of reviews, we found that meta-analyses with active comparators generally showed smaller effects.

No trends were identified for reviews that included depressive symptoms as a primary versus secondary outcome. Three reviews of pharmacological interventions were the only ones to report industry funding and all reported trivial to small effects [70, 72, 110].

Implications of Findings

A broad range of interventions and methods of delivery have been investigated for addressing depressive symptoms in people with chronic pain. However, no single intervention type demonstrates substantial superiority across different pain populations. In fibromyalgia, fluoxetine and web-based psychotherapy show comparable medium effect sizes, and the latter can be prioritized in the context of physical distancing measures in response to the COVID-19 pandemic. In mixed chronic pain, ACT also showed medium effect sizes on depressive symptoms. For other pain types, this suggests that patients, clinicians and program planners should also consider other dimensions besides efficacy such as individual preference, intervention availability, safety, cost, and also efficacy for nondepressive outcomes when considering treatment and policy options. Nonspecific factors that are common across psychotherapies, such as warmth of the therapist, therapeutic alliance, and accurate empathy [126] may also play a role in reducing depressive symptoms when present in other interventions.

This also points to a need for further investigation and synthesis of interventions for improving depressive symptoms in pain types other than fibromyalgia and mixed chronic pain. This is despite the comparable prevalence of comorbid depression across pain types [127–130]. Likewise, the prevalence of axial and arthritic pain is significantly higher than fibromyalgia [131–133], which strongly suggests a misalignment between population health and clinical epidemiology priorities. This may in part be due to biases about mental illness comorbidities in different kinds of pain, as well as differences in standardized instruments across different pain types and the inclusion of variable depression measures [134].

Within fibromyalgia and generalized chronic pain, there is an opportunity for formal estimates of comparative efficacy, such as through network meta-analysis, and a need for further synthesis of depressive symptom effects as a distinct and important outcome. Many existing reviews either do not synthesize this outcome or subsume depression outcomes within a catch-all mental health or quality of life outcome, exemplified in a recent synthesis of acupuncture [135].

Large bodies of research have investigated psychological interventions, as well as mind-body, and pharmacological interventions. Future research should aim to study and synthesize other intervention types including exercise and massage therapy which show reasonable efficacy in the few lower quality reviews completed to date. Exercise shows beneficial effects for a variety of other non-depression chronic pain outcomes together with few adverse effects [28].

Looking outside of chronic pain, there is evidence that the combination of psychotherapy and pharmacotherapy can lead to large depression improvements with effects lasting up to 2 years post-treatment, suggesting that a combination approach in chronic pain populations merits further investigation [136]. As demonstrated by the network visualization, there has so far been no overlap between pharmacological systematic reviews and reviews of other kinds of interventions.

Limitations

Depressive symptoms were the focus of this review of meta-analyses since much existing literature does not specifically focus on MDD. Indeed, clinical trials across various fields often exclude people with comorbid mental illnesses including specifically those with more severe depression [137, 138]. As such, when applying these findings to people living with chronic pain and comorbid MDD, it is important to consider that changes in depressive symptoms in individuals with subthreshold symptomology may differ from those with MDD. Given the very high comorbid prevalence of MDD in chronic pain, further study and synthesis of outcomes specifically in

people with MDD is merited. Given identified challenges and controversies in translating standardized mean differences in depression outcomes to minimally important differences [139], we have not made attempts to interpret effect sizes in terms of clinically significant effects.

Intervention types were often not well-defined and often included overlapping components, making it challenging to aggregate meta-analyses by intervention type. We attempted to mitigate this by aggregating intervention types by review descriptions and augmenting this categorization using visual network analysis. However, these groupings may not perfectly distinguish between intervention types. Future systematic reviews in this area should provide detailed intervention descriptions, for example, by using recommended reporting checklists and guidelines [140, 141].

Pain types were grouped based on definitions provided by included reviews, which were inconsistent and varied in specificity. Some reviews included broader definitions of pain types compared to others, limiting our ability to create more distinct pain type groups in our evaluations. This heterogeneity was noted at the level of randomized controlled trials included in the meta-analyses, so disaggregation of the meta-analyses and then reaggregation based on specific pain types would be unlikely to resolve this challenge.

Comparator types varied across as well as within reviews, and at other times were unreported. Generally, as is to be expected, analyses against active comparators showed smaller effect sizes, however, inconsistencies in comparator reporting limit our ability to draw firm conclusions about treatment effects.

The AMSTAR 2 was used to appraise risk of bias, but the overall rating does not necessarily reflect the scientific rigor of the underlying primary evidence as AMSTAR 2 ratings are influenced by reporting practices of systematic reviewers. Given this, AMSTAR 2 ratings need to be taken into consideration when summarizing and interpreting results, but the evidence synthesized by reviews of low- or critically low quality should not be discounted altogether.

The scope of this review of meta-analyses did not consider the effects on other pain-relevant outcomes such as pain intensity, function or quality of life, which are also important to investigate in relation to depression in chronic pain [142]. However, these have been widely analyzed in a variety of other systematic reviews and umbrella reviews [143–146]. Finally, as a review of reviews, there may be important primary trials evidence that has not been captured in this synthesis. This would include primary trials published after the publication of the relevant review, trials that are studying unique interventions that are not easily synthesized with results of other trials, or trials that have otherwise not been captured by existing systematic reviews. For this and other reasons, it is important to note that an absence of evidence for a specific intervention does not imply an absence of effectiveness.

Conclusion

A wide variety of interventions have been meta-analyzed for effects on depressive symptoms on different kinds of chronic pain. The most common pain types were fibromyalgia and mixed chronic pain, and psychological interventions were most often examined. Acceptance commitment therapy, fluoxetine and web-based psychotherapy were the most promising interventions and can be currently prioritized for implementation in clinical practice. The majority of interventions showed small to trivial effects, and the only negative effects were demonstrated when interventions were compared against active controls. Effects on depressive symptoms so far have been under-synthesized in common pain interventions such as opioids and acupuncture. There is also a need for more assessment and synthesis of depression outcomes in common pain conditions such as arthritis and axial pain.

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Supplementary Data

Supplementary data are available at *Pain Medicine* online .

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