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US ASSOCIATION FOR THE STUDY OF PAIN

PUBLISHED BY
ELSEVIER

The Journal of Pain, Vol xxx, No. xxx (xxxx), xxxx: pp xxx–xxx
Available online at www.jpain.org and www.sciencedirect.com

Review Article

The Effectiveness of Interventions for Improving Chronic Pain Symptoms Among People With Mental Illness: A Systematic Review

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Abstract: **Chronic pain (CP) and mental illness (MI) are leading causes of years lived with disability and commonly co-occur. However, it remains unclear if available interventions are effective in improving pain outcomes in patients with co-existing CP and MI. This systematic review synthesised evidence for the effectiveness of interventions to improve pain outcomes for people with comorbid CP and clinically diagnosed MI. Ten electronic databases were searched from inception until May 2023. Randomised controlled trials (RCTs) were included if they evaluated interventions for CP-related outcomes among people with comorbid CP and clinically diagnosed MI. Pain-related and mental health outcomes were reported as primary and secondary outcomes, respectively. 26 RCTs (2,311 participants) were included. Four trials evaluated the effectiveness of cognitive-behavioural therapy, 6 mindfulness-based interventions, 1 interpersonal psychotherapy, 5 body-based interventions, 5 multi-component interventions, and 5 examined pharmacological-based interventions. Overall, there was considerable heterogeneity in sample characteristics and interventions, and included studies were generally of poor quality with insufficient trial details being reported. Despite the inconsistency in results, preliminary evidence suggests interventions demonstrating a positive effect on CP may include cognitive-behavioural therapy for patients with depression (with a small to medium effect size) and multi-component intervention for people with substance use disorders (with a small effect size). Despite the high occurrence/burden of CP and MI, there is a relative paucity of RCTs investigating interventions and none in people with severe MI. More rigorously designed RCTs are needed to further support our findings.**

Perspective: ***This systematic review presents current evidence evaluating interventions for CP-related and MH outcomes for people with comorbid CP and clinically diagnosed MI. Our findings could potentially help clinicians identify the most effective treatments to manage these symptoms for this vulnerable patient group.***

Received June 27, 2023; Received in revised form October 26, 2023; Accepted November 1, 2023
The current systematic review was conducted in accordance with PRISMA guidelines and pre-registered on PROSPERO (CRD42021279211). Supplementary data accompanying this article are available online at www.jpain.org and www.sciencedirect.com.
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1526-5900/$36.00
https://doi.org/10.1016/j.jpain.2023.11.004

Key words: *Chronic pain, Intervention, Mental illness, Pain symptoms, Mental health outcomes*

Chronic pain (CP) and mental illness (MI) are individually leading causes of years lived with disability.[1] The global prevalence of CP is more than 30%.[2] In England, approximately 1 in 6 people aged 16 years and above experience symptoms of a MI (eg, depression and anxiety), and approximately 2% and .7% have a diagnosis of bipolar disorder and psychotic disorder, respectively.[3]

Pain and MI tend to co-occur. Pain has been found to affect about 33% of people with serious MI (SMI), for example, bipolar disorders and schizophrenia,[4] and up to 50% of those with a common mental disorder (eg, depression and anxiety).[5] People with MI are at least twice as likely to have CP versus the general population.[6] Perhaps this is not surprising since people with MI (particularly SMI) have substantially poorer physical health,[7] with many of these conditions being associated with pain.[8] Given the diagnostic overshadowing noted in the assessment and treatment of physical health conditions in people with MI,[9,10] it is likely that pain may also be underestimated.

Numerous (inter)national guidelines illustrate that non-pharmacological interventions (eg, physical activity [PA] and psychological therapy) are an important first step before considering pharmacotherapy.[11] Despite not having a primary focus on pain reduction, cognitive-behavioural therapy (CBT) has the largest evidence base to date with a small effect on symptoms including pain interference and depression in CP patients.[12] Acceptance and commitment therapy (ACT), a newer form of CBT, has also demonstrated a small to large effect on outcomes such as pain interference in CP.[13] Despite the high co-existence of CP and MI, no guidelines exist to address their co-occurrence. Previous research has suggested an inadequate referral or lack of access to pain management services among people with pain and comorbid MI, particularly for those with SMI.[14,15] Additionally, patients tend to be less responsive to mental health (MH) treatments if they are also experiencing comorbid pain and vice versa.[16] Therefore, it is important to improve our understanding of treatments for people with comorbid pain and MI, the safety of these options, and how these should be delivered, we may then further advance the development of a new treatment pathway for CP for this population.

To date, several recent systematic reviews have investigated pain management interventions for pain reduction in the general population with CP. For example, Thapa and colleagues[17] found a moderate effect of pharmacist-delivered interventions (eg, medication review and multidisciplinary team pain management) on pain intensity reduction. In their meta-analysis, Williams and colleagues[12] demonstrated a smaller yet sustained effect of CBT on pain intensity than other pain-related outcomes such as disability. Exercise interventions and PA (eg, aerobic experience, strength training, and yoga) have also been examined, and a small-to-medium effect has been found for outcomes including pain severity and quality of life (QoL), although inconsistency in findings was also noted.[18] It is also important to note that studies included in these meta-analyses tend to be small in nature, had short follow-up time, and are at high risk of bias due to confounding factors. Therefore, the interpretation of results is constrained by the overall low quality of the studies included. Additionally, despite these recently published meta-analyses, to the best of our knowledge, no systematic review has investigated evidence of pain management interventions for people with comorbid MI and CP specifically. To address this knowledge gap, this systematic review aims to comprehensively evaluate RCTs investigating the effectiveness of pharmacological and non-pharmacological interventions on pain among people with CP and clinically diagnosed MI.

Methods

The current systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and pre-registered on PROSPERO (CRD42021279211).

Inclusion Criteria

Type of Study

This systematic review included randomised controlled trials (RCTs), including feasibility RCTs, reporting data on the effectiveness of interventions on pain symptoms or pain-related interference in people with MI. No restrictions were determined on publication dates, country of origin or language. Papers published in English, Mandarin/Cantonese and Italian were screened by 2 independent reviewers. Papers published in Mandarin/Cantonese and Italian were first being translated by reviewer Ruimin Ma (RM) and Eugenia Romano (ER) (given these languages are their native languages), respectively. Consensus was then reached only if both reviewers agreed. For papers published in other languages and deemed to be potentially eligible based on the abstract, authors were contacted for further information.

Participants

People with a diagnosis of persistent/chronic non-cancer pain (either self-reported or clinically diagnosed pain that lasts for at least 3 months) and a clinical diagnosis of MIs (eg, by DSM-5 or ICD-10 criteria or any other validated methods of clinically diagnosing people as mentally ill) were included, including depression, bipolar disorder, schizophrenia spectrum disorders, eating disorders of all

types, substance use disorders (SUD) of all types, personality disorders of all types, anxiety and stress-related disorders. Studies that included people with autistic spectrum disorders, intellectual disability, dementia or any other organic illnesses were excluded. Studies of cohorts with only screened MH symptoms, rather than diagnoses, were also excluded (eg, including on the basis of an MH symptom scale, such as Beck's Depression Inventory and Patient Health Questionnnaire-2).

Interventions

This systematic review required inclusion of evaluated interventions which were designed to improve pain intensity, pain-related interference and/or MH symptoms, including any pharmacological interventions (eg, analgesics such as paracetamol, opioids), non-pharmacological interventions (eg, exercise, social prescribing), psychological interventions (eg, CBT, acceptance- and mindfulness-based interventions [MBIs]) and self-management interventions (eg, educational programmes on how to self-manage pain) delivered in any format (eg, Internet- or mobile-based interventions, in person or remote interventions). Surgical/invasive pain management interventions, including spinal cord stimulation, were excluded.

Comparison

Trials, where the control group received treatment-as-usual, waiting-list control, no treatment or placebo (in case of medication), and any active treatments, were eligible.

Outcomes

Studies reporting pain outcomes including pain (including intensity/severity), pain interference with life/activities of daily living and pain-related disabilities, as well as MH symptoms captured by recognised and validated scales were eligible for inclusion. Pain-related (eg, pain intensity and interference) and MH outcomes (eg, depressive severity) were reported as primary and secondary outcomes, respectively, for this review. Tertiary outcomes collected included cognition (any recognised metric), lifestyle (eg, changes in PA, smoking, nutrition), social outcomes (eg, ability to work), QoL and adverse events. End-of-treatment outcomes, short-term (ie, <6 months), mid-term (≥ 6 and <12 months), and long-term (≥ 12 months) follow-up outcomes were reported separately.

Search Strategy

Ten published and unpublished evidence databases were systematically searched from inception till September 15, 2022. An updated search was conducted in May 2023 to capture any eligible papers published within the past year. These included: Medline, PsycINFO, Embase, Web of Science, PEDro, CINAHL, WHO Clinical Trial Registry, ClinicalTrials.gov, ISRCTN and CENTRAL. Four groups of search terms were used: 1) mental disorders (eg, depression, anxiety, bipolar disorders, schizophrenia); 2) interventions (eg, analgesics, pain killers, exercise, mindfulness, physiotherapy); 3) trials (eg, RCTs, clinical trial); and 4) pain (eg, CP, back pain, osteoarthritis). For search terms included in the search, please see Appendix 1. Reference lists of included studies and relevant systematic reviews were hand-searched.

Data Extraction

Two reviewers (RM and ER) independently reviewed all titles, abstracts and full-texts. Inter-rater reliability between reviewers was good (95% and above). The final list of included papers was only confirmed when both reviewers agreed. Any disagreements between the 2 reviewers were resolved in consultation with a third independent reviewer (BS). For any potentially eligible papers with missing full text, any unclear and missing data, corresponding authors were conducted. Data of included papers were extracted by 1 reviewer (RM) and checked by another independent reviewer (BS) using a standardised form developed for the review. These included items related to study settings, publication year, inclusion criteria of the participants, the nature of the intervention, outcomes of CP and MI, and secondary outcomes of interest.

Quality Assessment

The Template for Intervention Description and Replication checklist and the Cochrane Risk of Bias Tool (RoB2) were used to assess the reporting of intervention and the quality of each paper. For each included paper, all 4 domains of RoB2 were assessed, including selection bias (ie, bias due to randomisation process), performance bias (bias due to deviations from intended interventions), attrition bias (ie, bias due to missing outcome data), measurement bias (ie, bias in the measurement of the outcome) and reporting bias (ie, bias in selection for reported result). Each included paper was assessed by 2 independent reviewers (RM and ER). For each paper, a final decision on the study quality was made only if both assessors agreed. If there were any disagreement, a third independent assessor (BS) was consulted to gain consensus.

Synthesis Plan

Given the heterogeneity in samples and intervention types, meta-analysis was deemed to be inappropriate. A narrative synthesis was therefore conducted based on the principles from the Economic and Social Research Council's Guidance on the Conduct of Narrative Synthesis in Systematic Reviews.[19] Based on the patient characteristics of the included trials, 4 main categories were generated, and results were reported separately: 1) trials that included participants with depressive disorders; 2) trials that included participants with anxiety and stress-related disorders; 3) trials that included participants with comorbid depression and anxiety; and 4) trials that included participants with SUD.

Results

The search results are displayed in Fig 1. From 34,006 records, 26 RCTs were eligible and included.

Overview of Studies

Table 1 and Appendix 2 present the characteristics of the included 26 studies. These were grouped by MH diagnosis. Of the 26 trials, 2,311 participants were recruited in total, with approximately a similar proportion of male (47%) and female (57%) participants being included (of the 25 studies that reported such information). Of the 17 studies that reported information on ethnicity/race, the majority of the participants were from a White ethnic and non-Hispanic background. The majority of studies (n = 20) involved fewer than 100 participants. All trials were conducted between 1985 and 2023, with the majority of the trials being conducted in the US (n = 18), 2 in Germany, and 1 trial each in Belgium, Spain, Australia, Canada, China, and South Korea. Four trials in total included CBT,[20–23] six evaluated MBIs (eg, mindfulness-based cognitive or

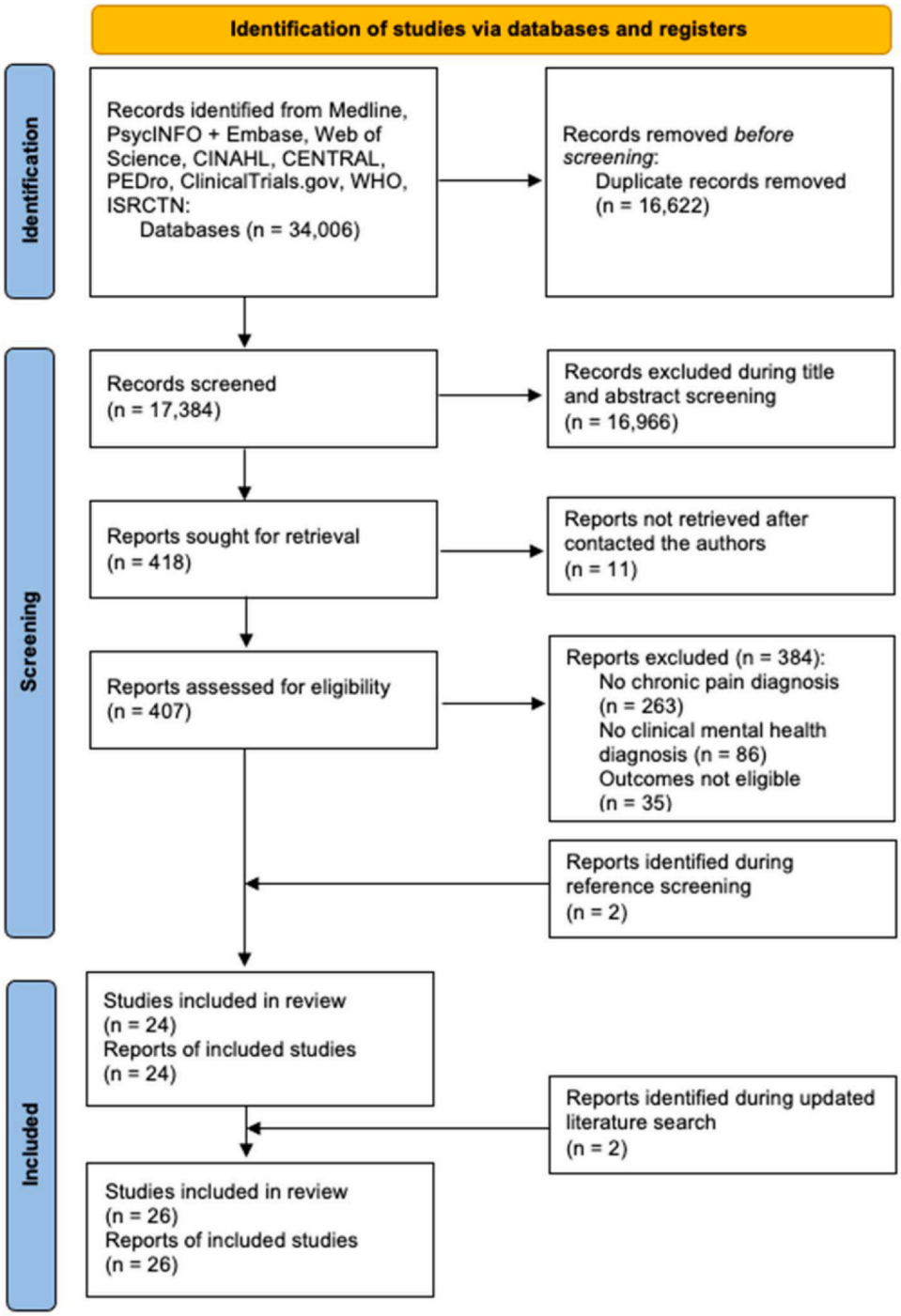

Figure 1. PRISMA 2020 flowchart for study selection. Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table 1. Study Characteristics of Included Studies

Author (publication year)	Number of participants Participants' characteristics (age, gender, ethnicity/race)	Treatment characteristics		Outcomes	
		Intervention type	Duration	Chronic pain outcome	Mental health outcome
Depression					
Body-based intervention					
Liao et al, (2023)	Total sample n = 47 Depression-Pain group (n = 23): Mean (SD) age 48 (15.42) years Male n = 4 (17%); Female n = 19 (83%) Pain-Depression group (n = 24): Mean (SD) age 48.05 (15.51) years Male n = 10 (50%); Female n = 10 (50%) No report on ethnicity /race	Depression-Pain acupuncture group vs Pain-Depression acupuncture group	24 sessions over 12 weeks, and a 2-week washout period	– The BPI	– The HAM-D – The BDI-II – Treatment response – Complete remission
Cognitive behavioural therapy (CBT)-based intervention					
Baumeister et al, (2020)	Total sample n = 209 Mean (SD) age 49.9 (9.36) years Male n = 84 (40%); Female n = 125 (60%) eSano BackCare-D group (n = 104): Mean (SD) age 50.3 (9.39) years Male n = 44 (42%); Female n = 60 (58%) TAU group (n = 105): Mean (SD) age 49.6 (9.36) years Male n = 40 (38%)' Female n = 65 (62%) No report on ethnicity/race	eSano BackCare-D +TAU vs TAU	6 regular and 3 optional weekly sessions with each session last approximately 54 min	– A NRS for pain intensity – The ODI – The PSEQ	– The clinician-rated structured HAM-D-17 – The HAM-D depression severity – QIDS-C_{16} – PHQ-9
Martin et al, (2015)	Total sample n = 66 Mean (SD) age 40.64 (13.41) years Male n = 17 (26%); Female n = 49 (74%) CBT group (n = 36): Mean (SD) age 40.19 (12.89) years Male n = 9 (25%); Female n = 27 (75%) RPC group (n = 30): Mean (SD) age 40.83 (14.32) years Male n = 8 (27%); Female n = 22 (73%) No report on ethnicity/race	CBT + RPC vs RPC alone	12 weekly sessions with each last 50 min	– Diary recording of pain using a scale from 0 (no headache) to 5 (an intense incapacitating headache)	– The BDI-II – The BAI PHQ-9
MBI					
de Jong et al, (2016)	Total sample n = 31 Mean (SD) age 49.45 (10.58) Male n = 8 (26%); Female n = 23 (74%) Caucasian n = 28(90%); African-American n = 3 (10%) Hispanic n = 1 (3%); Non-Hispanic n = 26 (84%) MBCT group (n = 19): Mean (SD) age 50.06 (11.68) years Male n = 4 (23%); Female n = 15 (77%) Hispanic n = 1 (6%); Non-Hispanic n = 15 (77%) Unknown/Not reported n = 3 (18%) African-American n = 1 (6%); Caucasian n = 18 (94%) TAU group (n = 12): Mean (SD) age 51.67 (10.08) years Male n = 4 (33%); Female n = 8 (67%) Non-Hispanic n = 12 (100%) Caucasian n = 10 (83%); African-American n = 2 (17%)	MBCT+ TAU vs TAU	8 weekly programme with each session last 2 h	– PCS	– QIDS-C_{16}

Table 1 (*Continued*)

Author (publication year)	*Number of participants Participants' characteristics (age, gender, ethnicity/race)*	*Treatment characteristics*		*Outcomes*	
		Intervention type	*Duration*	*Chronic pain outcome*	*Mental health outcome*
de Jong et al, (2018)	Total sample n = 40 Male n = 10 (25%); Female n = 30 (75%) White n = 36 (90%); African-American n = 4 (10%) Hispanic n = 2 (5%); Non-Hispanic n = 34 (85%) Not reported n = 4 (10%) MBCT group (n = 26): Mean (SD) age 51.3 (11.9) years Male n = 5 (19%); Female n = 21 (81%) White n = 24 (92%); African-American n = 2 (8%) Hispanic n = 1 (3.8%); Non-Hispanic n = 21 (81%) Not reported n = 4 (15%) Waitlist group (n = 14): Mean (SD) age 49.9 (11.1) years Male n = 5 (36%); Female n = 9 (64%) White n = 12 (86%); African-American n = 2 (14%) Hispanic n = 1 (7%); Non-Hispanic n = 13 (93%)	MBCT vs waitlist	MBCT consists of an 8-week programme with each session lasts 2 h.	– The BPI-SF – The VAS	– The QIDS-C_{161} – The HRSD – The BAI
Interpersonal psychotherapy					
Poleshuck et al, (2014)	Total sample n = 61 Mean (SD) age 36.7 (8.9) years Female= 61 (100%) African-American/Black n = 40 (66%); White/Caucasian n = 10 (16%) Hispanic n = 8 (13%); Biracial n = 2 (3%); Native American n = 1 (2%) IPT-P group (n = 33): Mean (SD) age 36.3 (8.2) years Female n = 33 (100%) African/American n = 22 (67%); White/Caucasian n = 3 (9%) Hispanic n = 6 (18%); Biracial n = 1 (4%) E-TAU group (n = 28): Mean (SD) age 37.1 (9.8) years Female n = 28 (100%) African/American n = 18 (64%); White/Caucasian n = 7 (25%) Hispanic n = 2 (7%); Biracial n = 1 (3%); Native American n = 1 (3%)	IPT-P vs E-TAU	16 weekly sessions	The Multidimensional Pain Inventory (MPI)	– The clinician-rated HRSD – The BDI
MCI					
Aragonès et al, (2019)	Total sample n = 328 DROP group (n = 167): Mean (SD) age 61.4 (10.2) years Male n = 29 (17%); Female n = 138 (83%) Usual care group (n = 161): Mean (SD) 59.3 (10.1) years Male n = 27 (17%); Female n = 134 (83%) Not reported on ethnicity/race	DROP programme vs usual care	Unclear duration Care manager contacted participant monthly during the first 3 months, and then every 3 months for up to 1 year The psychoeducational programme included 9 weekly sessions within the first 3-month, each lasts 2 h	– The BPI	– The 20-item version of the HSCL

Table 1 (*Continued*)

Author (publication year)	*Number of participants Participants' characteristics (age, gender, ethnicity/race)*	*Treatment characteristics*		*Outcomes*	
		Intervention type	*Duration*	*Chronic pain outcome*	*Mental health outcome*
Schlicker et al, (2020)	Total sample n = 76 Mean (SD) age 50.78 (7.85) years Male n = 21 (28%); Female n = 55 (72%) Get.Back group (n = 40): Mean (SD) age 51.3 (8.60) years Male n = 14 (35%); Female n = 26 (65%) Waitlist group (n = 36): Mean (SD) age 50.1 (7.00) years Male n = 7 (19%); Female n = 29 (81%) Not reported on ethnicity/race	Get.Back vs waitlist	Get.Back consisted of 7 weekly modules with each last 45–60 min	– A pain severity NRS – A categorical pain intensity rating – The ODI – The PSEQ	– CES-D – QIDS-C_{16} – The Hamilton Anxiety and Depression Scale – The MDQ
Pharmacological intervention					
Hameroff et al, (1985)	Total sample n = 60 Doxepin group (n = 30): Mean (SD) age 48.9 (2.4) years Male n = 17 (57%); Female n = 13 (43%) Placebo group (n = 30): Mean (SD) age 48.4 (2.0) years Male n = 15 (50%); Female n = 15 (50%) Not reported on ethnicity/race	Doxepin vs placebo	6 weeks	– The VAS	– The HAM-D – The CGI
McIntyre et al, (2014)	Total sample n = 120 Mean (SD) age 51 (10) years Male n = 4 (3%); Female n = 115 (97%) Quetiapine XR group (n = 61): Mean (SD) age 52 (9) years Male n = 1 (2%); Female n = 60 (98%) RPC group (n = 59): Mean (SD) age 50 (10) years Male n = 3 (5%); Female n = 56 (95%) Not reported on ethnicity/race	Quetiapine fumarate extended release (quetiapine XR) vs placebo	8 weeks	– The BPI – The BPI-S – The BPI-I	– The 17-item HAM-D – The CGI-S of Depression The HAM-A
Onghena et al, (1993)	Total sample n = 35 Mean age 45.1 years Male n = 13 (37%); Female n = 22 (63%) Group A n = 8 Group B n = 8 Group C n = 11 Group D n = 8 No report on ethnicity/race	Mianserin vs placebo	12 weeks	– The CCP – The MPQ – The VAS	– DSM-III-R – The HRSD – The BDI
Anxiety or stress-related disorders					
Body-based intervention					
Park et al, (2015)	Total sample n = 31 CE group (n = 15): Mean (SD) age 57.5 (6.7) years Male n = 13 (87%); Female n = 2 (13%) Conventional physical therapy group (n = 16): Mean (SD) age 62.8 (7.9) years Male n = 12 (75%); Female n = 4 (25%) Not reported on ethnicity/race	CE vs conventional physical therapy	Both interventions were conducted 3 times per week for 6 weeks	– The VAS	– The SCL-90-R – The HSCL-25

Table 1 (*Continued*)

Author (publication year)	*Number of participants Participants' characteristics (age, gender, ethnicity/race)*	*Treatment characteristics*		*Outcomes*	
		Intervention type	*Duration*	*Chronic pain outcome*	*Mental health outcome*
Swann (2019)	Total sample n = 9 TRE group (n = 5): Mean (range) age 47.2 (32–62) years Male n = 2 (40%); Female n = 3 (60%) Caucasian n = 3 (60%) Hispanic n = 1 (20%); Non-Hispanic n = 4 (80%) Prefer not to say n = 1 (20%) PMR group (n = 4): Mean (range) age 54.3 (36–73) years Male n = 1 (25%); Female n = 3 (75%) Caucasian n = 3 (75%); Other n = 1 (25%) Non-Hispanic n = 4 (100%)	TRE vs self-practice of PMR	4 weeks	– The DVPRS – The ODI Version 2.0	– The DES-B-Modified – The PCL-5
MCI					
McGeary et al, (2022)	Total sample n = 103 FORT-A group (n = 50) Mean (SD) age 43.7 (11.0) years Male n = 41 (82%); Female n = 9 (18%) Asian n = 1 (2%); Native Hawaiian/Pacific Islander n = 1 (2%); Black or African-American n = 5 (10%); White n = 36 (72%); Other n = 7 (14%) PMR group (n = 53): Mean (SD) age 43.7 (9.4) years Male n = 40 (75%); Female n = 13 (25%) American Indian/Alaskan Native n = 2 (4%); Asian n = 1 (2%); Black of African-American n = 16 (30%); White n = 28 (53%); Other n = 5 (9%)	FORT-A vs TAU	18–720 min of intervention over 3 weeks	– The ODI	– A structured TLFB interview for opioid use
Pharmacological intervention					
Dadabayeve et al, (2020)	Total sample n = 41 CP+PTSD ketamine group (n = 11): Mean (SD) age 45.3 (11.18) years Male n = 7 (64%); Female n = 4 (36%) Caucasian n = 11 (100%) CP+PTSD ketorolac group (n = 10): Mean (SD) age 40.1 (9.73) years Male n = 6 (60%); Female n = 4 (40%) Caucasian n = 9 (90%) CP ketamine group (n = 10) Mean (SD) age 43.5 (9.65) years Male n = 9 (90%); Female n = 1 (10%) Caucasian n = 9 (90%) CP ketorolac group (n = 10) Mean (SD) age 52.9 (8.61) years Male n = 9 (90%); Female n = 1 10%) Caucasian n = 10 (100%)	Ketamine vs Ketorolac	4 h	– The VAS – The BPI-SF	– The IES-R – The CADSS

Table 1 (*Continued*)

Author (publication year)	*Number of participants Participants' characteristics (age, gender, ethnicity/race)*	*Treatment characteristics*		*Outcomes*	
		Intervention type	*Duration*	*Chronic pain outcome*	*Mental health outcome*
Comorbid depression and anxiety					
MBI					
Dindo et al, (2020)	Total sample n = 32 ACT group (n = 20): Mean (SD) age 37.7 (6.3) years White n = 9 (42%); African-American n = 4 (21%) Hispanic/Latino n = 4 (21%); Other n = 3 (15%) TAU group (n = 12): Mean (SD) age 34.7 (5.8) years White n = 5 (42%); African-American n = 2 (17%) Hispanic/Latino n = 3 (25%); Other n = 2 (17%) Not reported on gender	Acceptance and Commitment Therapy (ACT) workshop vs Treatment-as-usual (TAU)	1-day ACT workshop lasts 5 h	– The BPI	– The PCL-C – The DASS-21
Substance misuse disorder					
CBT-based intervention					
Barry et al, (2019)	Total sample n = 40 Mean (SD) age 38.1 (11.3) years Male n = 25 (63%); Female n = 15 (37%) White n = 34 (85%) CBT group (n = 21): Mean (SD) age 38.4 (12.1) years Male n = 14 (67%); Female n = 7 (33%) White n = 17 (81%) MDC group (n = 19): Mean (SD) 37.7 (10.6) years Male n = 11 (58%); Female n = 8 (42%) White n = 17 (90%)	CBT vs MDC	CBT consisted of 12 weekly sessions, each session lasts 30–45 min MDC included 4 weekly sessions, each session lasts 15–20 min	– The BPI-I	– Urine toxicology testing for opioid use – Maximum consecutive number of weeks of abstinence from nonmedical opioids use
Wilson et al, (2018)	Total sample n = 60 Mean (SD) age 44.3 (12.0) years Male n = 34 (56%) men; Female n = 26 (44%) Black/African-American n = 4 (7%); Native American or American Indian n = 8 (13%); White/Caucasian n = 47 (78%) Hispanic n = 1 (2%) CPMP group (n = 31): Mean (SD) age 45.5 (12.4) years Male n = 16 (52%); Female n = 15 (48%) Black/African-American n = 2 (7%); Native American or American Indian n = 4 (13%); White/Caucasian n = 24 (77%) Hispanic n = 1 (3%) Waitlist group (n = 29): Mean (SD) age 42.9 (11.7) years Male n = 16 (55%); Female n = 13 (45%) Black/African-American n = 2 (7%); Native American or American Indian n = 4 (14%); White/Caucasian n = 23 (79%)	CPMP vs waitlist attention control	2 h of programme use each week for 8 weeks	– The BPI – The PSEQ	– The PHQ-9 – The GAD-7 – The COMM – The ARSW

Table 1 (*Continued*)

Author (publication year)	*Number of participants Participants' characteristics (age, gender, ethnicity/race)*	*Treatment characteristics*		*Outcomes*	
		Intervention type	*Duration*	*Chronic pain outcome*	*Mental health outcome*
MBI					
Cooperman et al, (2021)	Total sample n = 30 Mean (SD) age 50.4 (8.8) years Male n = 15 (50%); Female n = 15 (50%) Black/African-American n = 16 (53%); White n = 11 (37%) Hispanic n = 6 (20%) MORE+ TAU group (n = 15): Mean (SD) age 47.9 (8.7) years Male n = 7 (47%); Female n = 8 (53%) Black/African-American n = 7 (47%); White n = 7 (47%) Hispanic n = 3 (20%) TAU group (n = 15): Mean (SD) age 52.9 (8.4) years Male n = 8 (53%); Female n = 7 (47%) Black/African-American n = 9 (60%); White n = 4 (27%) Hispanic n = 3 (20%)	MORE + TAU vs TAU	8 weekly sessions with each session last 2 h	– The RAND SF-36 pain subscale	– The PACS – The CES-D – The BAI
Garland et al, (2019)	Total sample n = 30 MORE group (n = 15): Mean (SD) age 47.9 (8.7) years Male n = 7 (47%); Female n = 8 (53%) White n = 7 (47%); Black/African-American n = 7 (47%) Hispanic n = 3 (20%); Other n = 1 (7%) TAU group (n = 15): Mean (SD) age 52.9 (8.4) years Male n = 8 (53%); Female n = 7 (47%) White n = 4 (27%); Black/African-American n = 9 (60%) Hispanic n = 3 (20%)	MORE vs TAU	8 weekly sessions with each last 2 h	– A NRS for pain intensity	– An NRS – Event-contingent ratings of opioid craving – Capacity to self-regulate opioid craving with an NRS
Vowles et al, (2020)	Total sample n = 35 Mean (SD) age 50.5 (10.5) years Male n = 30 (86%); Female n = 5 (14%) Non-Hispanic White n = 18 (51%); Latinx n = 10 (29%); Native American n = 6 (17%); Other n = 1 (3%) Integrated intervention group (n = 17): Mean (SD) age 48.3 (11.6) years UC group (n = 18): Mean (SD) age 53.3 (8.6) years No separate reporting on gender and ethnicity/race for intervention and control groups	ACT + MBRP + UC vs UC	12 weekly sessions with each session last 90 min	– The PROMIS-PI short form – The PROMIS Pain Behaviour short form – An NRS for pain intensity	– The COMM

Table 1 (*Continued*)

Author (publication year)	*Number of participants Participants' characteristics (age, gender, ethnicity/race)*	*Treatment characteristics*		*Outcomes*	
		Intervention type	*Duration*	*Chronic pain outcome*	*Mental health outcome*
Body-based intervention					
Uebelacker et al, (2019)	Total sample n = 40 Yoga group (n = 20): Mean (SD) age 43 (10.7) years Male n = 11 (55%); Female n = 9 (45%) Black/African-American n = 2 (10%); White n = 16 (80%); Other/More than one n = 2 (10%) Hispanic/Latino n = 3 (15%) HE group (n = 20): Mean (SD) age 44 (10.8) years Male n = 6 (30%); Female n = 14 (70%) White n = 17 (85%); Other/More than one n = 3 (15%) Hispanic/Latino n = 1 (5%)	Hatha yoga vs health education	Both interventions included 12 weekly sessions	– The BPI-I	– An NRS for depression and anxiety
Wiest et al, (2015)	Total sample n = 51 Mean (SD) age 40 (12.1) years Male n = 24 (47%); Female n = 27 (53%) White n = 39 (76%) Massage + TAU group (n = 27): Mean (SD) age 40 (13.5) years Male n = 13 (48%); Female n = 14 (52%) White n = 18 (67%) TAU group (n = 24): Mean (SD) age 39 (10.5) years Male n = 11 (46%); Female n = 13 (54%) White n = 21 (88%)	Massage + TAU vs TAU	8 weekly Swedish massage sessions with each session last 50 min	– An NRS for pain intensity	– The HADS – Substance use from EMR
MCI					
Ilgen et al, (2016)	Total sample n = 129 Mean (SD) age 51.7 (9.5) years Male n = 115 (89%); Female n = 14 (11%) White n = 76 (59%); Others n = 53 (41%) ImPAT group (n = 65): Mean (SD) age 51.7 (9.2) years Male n = 58 (89%); Female n = 7 (11%) White n = 35 (54%); Others n = 30 (46%) SPC group (n = 64): Mean (SD) age 51.7 (9.8) years Male n = 57 (89%); Female n = 7 (11%) White n = 41 (64%); Others n = 23 (36%)	ImPAT vs SPC	Both conditions involved 10 weekly sessions with each session lasts 1 h	– An NRS for pain intensity – The 18-item WHYMPI – The cold-pressor task for pain tolerance	– The TLFB interview for days of any alcohol and drug use
Ilgen et al, (2020)	Total sample n = 510 Mean (SD) age 34.8 (10.3) years Male n = 264 (52%); Female n = 246 (48%) White n = 389 (76%) ImPAT group (n = 255): Mean (SD) age 36.2 (10.3) years for men, 32.9 (8.8) for women Male n = 133 (52%); Female n = 122 (48%) White n = 188 (74%) SPC group (n = 255): Mean (SD) age 34.9 (12.0) years for men, 35.3 (9.6) for women Male n = 131 (51%); Female n = 124 (49%) White n = 201 (79%)	ImPAT vs SPC	Both conditions included 8 1-h group sessions over the course of 4 weeks	– An NRS for pain intensity – The 18-item WHYMPI – The ischaemic pain task for pain tolerance	– The TLFB interview for any alcohol or drug use

Table 1 (*Continued*)

Author (publication year)	Number of participants Participants' characteristics (age, gender, ethnicity/race)	Treatment characteristics		Outcomes	
		Intervention type	Duration	Chronic pain outcome	Mental health outcome
Pharmacological intervention					
Neumann et al, (2013)	Total sample n = 54 Mean (SD) age 38.3 (9.7) years Male n = 29 (54%); Female n = 25 (46%) White n = 46 (85%) BUP/NLX group (n = 26): Mean (SD) age 39.0 (10.9) years Male n = 17 (65%); Female n = 9 (35%) White n = 20 (77%) MET group (n = 28): Mean (SD) age 37.7 (86) years Male n = 12 (43%); Female n = 16 (57%) White n = 26 (93%)	Sublingual buprenorphine/naloxone vs oral methadone tablets	Both treatments lasted 6 months SL buprenorphine dose was 4–16 mg/1–4 mg/day PO methadone tables dose was 10–60 mg/day All doses were divided 1–4 times daily	– An NRS for pain rating	– Self-reported drug use – Self-reported alcohol use – Monthly urine samples

Abbreviations: ACT, acceptance and commitment therapy; CE, cervical exercise; CCP, classification of chronic pain; CBT, cognitive-behavioural therapy; DSM-III-R, diagnostic and statistical manual of mental disorders; EMR, electronic medical record; CPMP, chronic pain management programme; ImPAT, improving pain during addiction treatment; IPT-P, interpersonal psychotherapy for depressed patients with pain; MDD, major depressive disorder; MDC, methadone drug counselling; MBI, mindfulness-based intervention; MBRP, mindfulness-based relapse prevention; MBCT, mindfulness-based cognitive therapy; MORE, mindfulness-oriented recovery enhancement; MCI, multi-component intervention; NRS, numeric rating scale; PCS, pain catastrophizing scale; PCL-5, post-traumatic stress disorder checklist for DSM-; PMR, PMR, progressive muscle relaxation; RPC, routine primary care; TRE, self-practice of trauma releasing exercises; SPC, supportive psychoeducational control; ARSW, the adjective rating scale for withdrawal; INEP, the assessment of negative effects of psychotherapy; BAI, the beck anxiety inventory; BDI-II, the beck depression inventory; BPI, the brief pain inventory; BPI-I, the brief pain inventory-interference; BPI-S, the brief pain inventory-severity; BPI-SF, the brief pain inventory-short form; CES-D, the center for epidemiological studies depression scale; CADSS, the clinician-administered dissociative state scale; COMM, the current opioid misuse measure; DVPRS, the defence and veterans pain rating scale; DASS-21, the depression anxiety and stress scale; EQ-5D, the EuroQoL; GAD, the general anxiety disorder scale; HAM-A, The Hamilton Anxiety Rating Scale; HAM-D, The Hamilton Depression Scale; HRSD, The Hamilton Rating Scale for Depression-17; HSCL, The Hopkins Symptom Checklist; HADS, the hospital anxiety and depression scale; IES-R, the impact of event scale-revised; MPQ, The McGil Pain Questionnaire; MDQ, the mood disorder questionnaire; NRS, the neurotoxicity rating scale; ODI, The Oswestry Disability Index; ODI, The Oswestry Low Back Pain Disability Questionnaire; PSEQ, the pain self-efficacy questionnaire; PHQ, the patient health questionnaire; PCAS, the penn alcohol craving scale; PCL-C, The Post-traumatic Stress Disorder Checklist-Civilian Version; The PROMIS-PI, PROMIS Pain Interference; QIDS-C_{16}, The Quick Inventory of Depressive Symptomatology—Clinician Rated; DES-B, The Severity of Dissociative Symptoms-Adult/Brief Dissociative Experiences Scale; SCL-90-R, The Symptom Checklist-90-revised; TLFB, timeline followback; VAS, the visual analogue scale; The WHYMPI, West Haven-Yale Multidimensional Pain Inventory; TAU, treatment-as-usual; UC, usual care.

recovery therapy),[24–30] 1 involved interpersonal psychotherapy,[31] 5 examined body-based interventions (interventions involving exercise or mind-body PA),[32–36] 4 included multi-component interventions (MCIs; interventions combining different treatment options; eg, CBT plus psychoeducation; CBT plus acceptance-based pain management approaches),[37–40] and 5 were pharmacological-based interventions (eg, pain relief or antidepressants).[41–45] Nine trials compared interventions with a different active treatment group (with one trial being a crossover trial comparing a sequence of 2 treatments consecutively), the remainder compared their intervention group with a control group: 11 included treatment-as-usual (usual care) group, 3 involved waiting-list group, and 3 included placebo group. The overall quality of included studies is low with only 2 trials being judged as having a 'low risk of bias' and the majority of the trials included less than 100 participants. Therefore, there is a scarcity of rigorous evidence as to the effectiveness of interventions aimed at improving pain and MH outcomes for people with comorbid pain and MH problems. For detailed quality assessment, Fig 2 displays domain-specific risk of bias and overall risks for all included studies.

Interventions in patients with depression

Of the 11 trials that included patients with depression, 3 implemented pharmacological-based intervention,[41–43] two included interventions with multiple components,[37,38] two involved MBIs,[24,25] two included cognitive-behavioural therapy-based (CBT-based) intervention,[21,22] one included body-based intervention[32] and 1 involved interpersonal psychotherapy (IPT).[31] The duration of interventions ranged from 6 to 16 weeks. Details of pain-related, MH and tertiary measures and outcomes, grouped by MH diagnoses, are presented in Table 1. According to RoB2 criteria, one trial was judged to have 'low concerns,[32] four trials to have 'some concerns',[21,31,37,38] and 6 to have 'high risk of bias.[21,24,25,41–43] In terms of the quality of included studies, more recent studies (ie, published in the last 5 years) are less likely to be subject to lack reporting on domains being assessed, but relatively older studies tend to lack of reporting on randomisation process, which subject them to high risk of selection bias. Overall, majority of trials have risks of poor blinding of trial personnel (ie, outcome assessors and intervention personnel) and participants or lack of reporting on such information, and a few studies also lack of reporting on how they handled missing data (Fig 2).

Five trials reported end-of-treatment outcomes,[24,25,32,42,43] and 4 trials included a pain severity scale with 2 out of which reporting positive changes in pain,[32,42] the remaining 3 failed to find any statistically significant changes following interventions. Of the 5 trials that included an outcome measure for depression severity, 3 of them also found improved depressive symptoms at post-intervention.[24,32,42] Two studies involved a scale for anxiety,

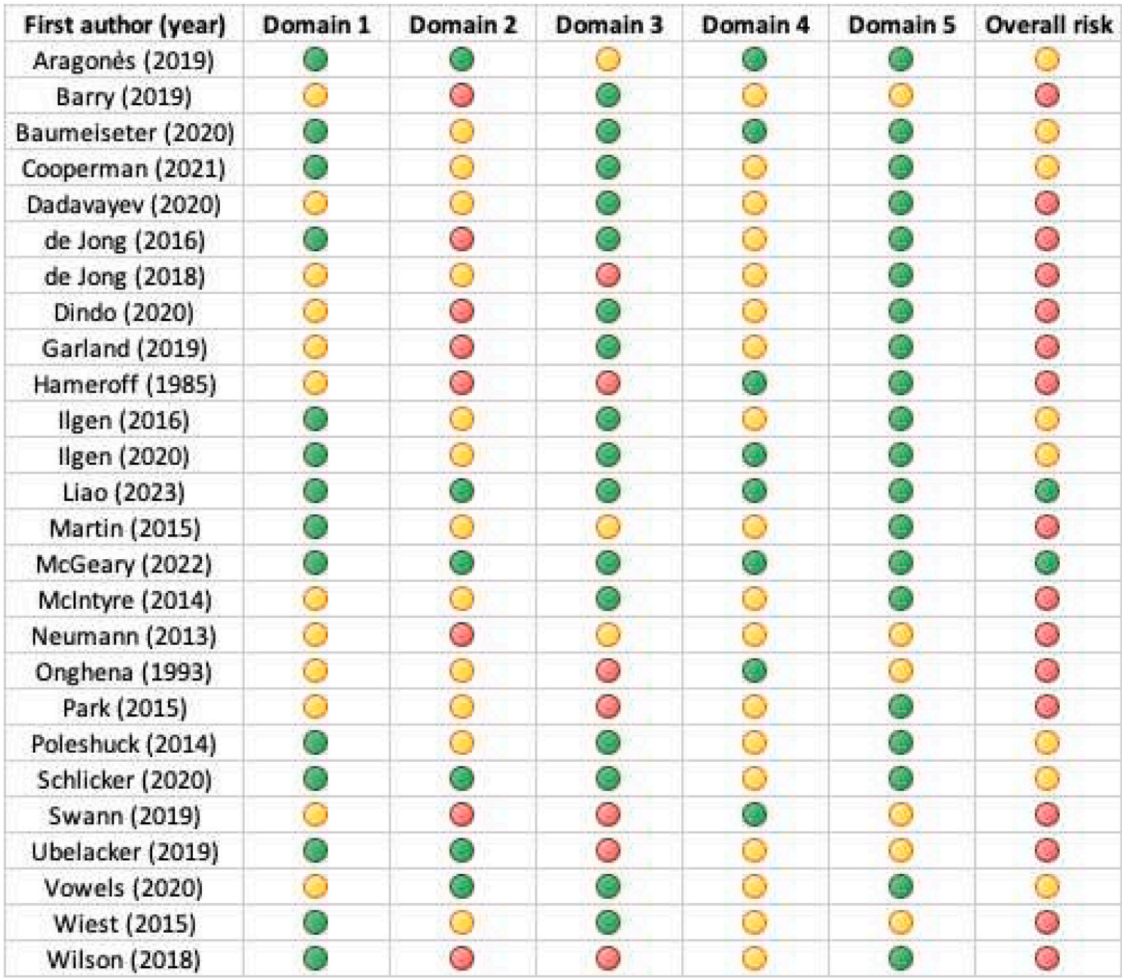

Figure 2. Results of risk of bias assessment, based on version 2 of the Cochrane Risk-of-bias tool (RoB2). Domain 1: bias arising from the randomisation process. Domain 2: bias due to deviations from intended interventions. Domain 3: bias due to missing outcome data. Domain 4: bias in the measurement of the outcome. Domain 5: bias in selection for reported result. Colour green = low risk of bias. Colour yellow = some concerns. Colour red = high risk of bias.

one reported improved anxiety symptoms,[42] and the other trial found no significant time x treatment interaction. Only one study included a pain catastrophising scale and a moderate effect[46] was reported.[24] Of the 2 trials that included short-term follow-up outcomes,[22,41] both only found a statistically significant positive effect of intended interventions on outcomes at post-treatment, not at follow-up: moderately improved pain severity and largely improved depressive symptoms were reported; and of the one trial including a measure of anxiety, moderately improved anxiety symptoms were reported.[22] Of the 3 trials that included mid-term follow-up outcomes,[21,31,38] only one found a small effect on pain intensity at post-treatment and this effect was sustained at follow-up,[21] with no signficiant between-group difference on pain severity and other pain-related outcomes (eg, pain interference and self-efficacy) was found at either post-treatment or follow-up. All 3 trials also reported positive changes on depression severity. Only one study included an anxiety scale, with improved symptoms being reported at both post-treatment and at 6-month follow-up.[38] Only one trial reported long-term follow-up outcomes,[37] with this multidimensional intervention only yielding a small effect on depression severity at 12-month follow-up, favoring the intervention group, and no significant effect on pain severity.

Other tertiary outcomes were examined in 8 out of 11 trials. Improved QoL was reported in 5 out of 6 trials.[21,22,25,32,42] Additional improvements in illness impact, social interactions,[42] as well as interpersonal sensitivity and ambivalence[31] were found, but these outcomes were only reported in 1 RCT. Only 6 trials included adverse events (AEs) as an outcome[21,25,32,38,42,43]: one reported no serious AEs,[32] two found none of the AEs reported were related to the intended intervention,[21,25] three reported AEs associated with the intervention,[38,42,43] two of which were pharmacological. Please see Table 2 and Appendix 3 for detailed and supplementary results, respectively, as well as Table 3 for positive outcomes reported by follow-up time. The Template for Intervention Description and Replication checklist for each included RCT is presented in Appendix 4.

Table 2. Results of Included Studies

Author (publication year)	*Chronic pain outcome*	*Mental health outcome*
Depression		
Body-based intervention		
Liao et al, (2023)	From baseline to week 6, both pain- and depression-specific acupoints decreased BPI (ES = .855), and the pain-specific acupoints contributed to significantly greater reduction in the BPI than depression-specific acupoints (P = .008) From Week 8 to Week 14,both pain- and depression-specific acupoints decreased BPI (ES = .386), but no significant change was found between pain- and depression-specific acupoints	From baseline to week 6, both pain- and depression-specific acupoints decreased HAM-D (ES = .483) and BDI-II (ES = .604), but no significant between-group differences between pain- and depression-specific acupoints From Week 8 to Week 14, both pain- and depression-specific acupoints decreased HAM-D (ES = .332) and BDI-II (ES = .470), but no significant changes were found in the HAM-D score between pain- and depression-specific acupoints. The pain-specific acupoints contributed to a greater reduction in BDI-II scores than depression-specific acupoints (P = .048)
CBT-based intervention		
Baumeister et al, (2020)	ITT analysis at T1: the intervention group had significantly higher pain self-efficacy (β = .33, 95 CI .15, .51, P < .001), but lower – pain intensity (β = –.32, 95% CI –.57, –.06, P = .01) – pain-related disability (β = –.31, 95% CI –.47, –.15, P < .001) ITT analysis at T2: the intervention group showed significantly higher pain self-efficacy (β = .24, 95 CI .02, .46, P = .03), but no significant between-group differences in – pain intensity (β = –.14, 95% CI –.43, .15, P = .33) – pain-related disability (β = –.17, 95% CI –.35, –.01, P = .06)	ITT analysis at T1: no significant between-group difference for HAM-D (β = –.19, 95% CI –.43, .05, P = .12), but significant and favour the intervention group for – QIDS (β = –.27, 95% CI –.52, –.01, P = .04) – PHQ-9 (β = –.40, 95% CI –.61, –.19, P < .001) ITT analysis at T2: the intervention group demonstrated a non-significantly between-group difference for – HAM-D (β = –.14, 95% CI –.40, .12, P = .28) – QIDS (β = –.22, 95 CI –.49, .05, P = .10)
Martin et al, (2015)	Significant and greater decrease on mean daily headache ratings from baseline to post-treatment by 47.1% in the CBT group compared to 1.9% in the RPC group [F (2,106) = 4.17, 95% CI .01, .13, P = .02]. Although no significant differences between the 2 groups at baseline, mean daily headache ratings were significant at post-treatment: (P = .04, d = .66, 95% CI .33, .99). Men demonstrated a significant larger reduction in mean daily headaches compared to women t (16) = 2.30, P = .004, d = 1.21, 95% CI .08, 2.31	From baseline to post-treatment, significant and greater decrease on – the BDI-II by 57.1% in the CBT group, compared to 13.4% in the RPC group [F (1,87) = 24.39, 95% CI .08, .36, P < .001] – the PHQ-9 by 61.5% in the CBT group compared to 27.8% in the RPC group [F (1,87) = 12.42, 95% CI .02, .26, P = .001] – the BAI by 49.9% in the CBT group compared to 13.9% in the RPC group [F (1,61) = 15.55, 95% CI .05, .36, P < .001] Although no significant differences between the 2 groups at baseline, outcomes were significant at post-treatment: – the PHQ-9 (P < .001, d = 1.16, 95% CI .58, 1.74) – the BDI-II (P < .001, d = 1.82, 95% CI .91, 2.73) – the BAI (P = .03, d = .68, 95% CI .34, 1.02)
MBI		
de Jong et al, (2016)	No significant group-by-time interaction effect [F (1,27) = 1.15, P = .29, η2p = .04] on pain catastrophising. The main effect of time showed a trend towards significance [F (1,270 = 3.60, P = .069, η2p = .12) A large and significant decrease on pain catastrophising in the MBCT group [t (16) = –2.23, d = –.56, P = .04], and a small and nonsignificant decrease in the AUT group [t (11) = –.57, d = –.17, P = .58]	MBCT has a positive effect on depression severity A significant indirect effect of group on depression through the MAIA subscale Not Distracting (a_1 X b_1 = –3.58, 95% CI –8.88, –.36). A significant direct effect of group on depression (c' = 4.82, P = .05) independent of Self-Regulation and Not Distracting
de Jong et al, (2018)	For the ITT sample, no significant time x treatment interaction for – the VAS [F (1,38) = .09, P = .77] – the BPI-I [F (1,32) = .11, P = .74]	For the ITT sample, clinical improvement measured by the QIDS-C_{161} and $HRSD_{17}$ was greater in the MBCT group than the waitlist control group, however, the between-group differences were not significant on either QIDS-C_{161} [F (1,38) = 1.31, P = .26] and $HRSD_{17}$ [F (1,38) = .50, P = .48] No significant time x treatment interaction for anxiety [F (1,33 =2.32, P = .14]

Table 2 (*Continued*)

Author (publication year)	*Chronic pain outcome*	*Mental health outcome*
Interpersonal psychotherapy		
Poleshuck et al, (2014)	No significant between-group difference on – pain severity (estimate = –.49, SE = –.30, $P > .05$) – pain interference (estimate = .33, SE = –.20, $P > .05$) at post-treatment	At post-treatment, compared to E-TAU, the IPT-P group had significantly lower – adjusted depression scores (estimate = 2.13, SE = 1.05 $P < .05$ for HRSD; estimate = 3.89, SE = 2.19, $P < .05$ for BDI) – occurrence of MDD (estimate = .19, SE = .10, $P < .05$)
MCI		
Aragonès et al, (2019)	No significant between-group difference at any timepoints on pain severity, pain interference and pain response rates	The severity of depression decreased in both groups over the follow-up period. Better results at 12 months in the DROP group than the usual care group with a between-group difference of –.23 (d = .32, 95% CI .08, .56, $P = .02$)
Schlicker et al, (2020)	No significant between-group difference from baseline to post-treatment on – pain intensity ($F_{1,76} = 3.76$, $P = .06$, d = .23, 95% CI –.22, .68) – pain-related disability ($F_{1,76} = .15$, $P = .35$, d = .02, 95% CI –.42, .47) – pain-related self-efficacy ($F_{1,76} = .02$, $P = .43$, d = .11, 95% CI –.33, .56) No significant between-group difference from baseline to 6-month follow-up on – pain intensity ($F_{1,76} = .03$, $P = .42$, d = .21, 95% CI –.24, .66) – pain-related disability ($F_{1,76} = .11$, $P = .36$, d = .14, 95% CI –.30, .59) – pain-related self-efficacy ($F_{1,76} = .57$, $P = .22$, d = .23, 95% CI –.21, .68)	Significant reductions on the CES-D from baseline to post-treatment in both the Get.Back ($t_{40} = 5.82$, $P < .001$, d = .84, 95% CI .39, 1.30) and the waitlist group ($t_{36} = 3.86$, $P < .001$, D = .64, 95% CI .17, 1.12), with significant between-group difference and a small between-group effect size favouring the Get.Back group ($F_{1,76} = 3.62$, $P = .03$, d = .28, 95 CI –.17, .74). At post-treatment no significant between-group difference on QIDS-SR16 ($F_{1,76} = 1.24$, $P = .13$, d = .16, 95% CI –.28, .62), but Get.Back group demonstrated greater reduction in anxiety than the waitlist group ($F_{1,76} = 10.45$, $P = .001$, d = .14, 95% CI –.31, .60). A within-group effect size d = .81 in the Get.Back group (95% CI .36, 1.28, $t_{40} = 5.40$, $P < .001$) vs d = .18 in the waitlist group (95% CI –.27, .65, $t_{36} = 1.26$, $P = .21$) Significant reductions on the CES-D from baseline to 6-month follow-up in both Get.Back ($t_{40} = 5.99$, $P < .001$, d = .98, 95% CI .51, 1.46) and waitlist group ($t_{36} = 4.99$, $P < .001$, d = .94, 95% CI .43, 1.45) Significant between-group difference on anxiety at 6-month follow-up ($F_{1,76} = 2.94$, $P = .047$, d = .38, 95% CI –.07, .83), but no significant between-group difference on – the CES-D ($F_{1,76} = 1.50$, $P = .11$, d = .10, 95% CI –.34, .46) – the QIDS-SR16 ($F_{1,76} = 1.93$, $P = .08$, d = .23, 95% CI –.21, .69)
Pharmacological intervention		
Hameroff et al, (1985)	Pain severity scores were better in the doxepin group versus the placebo group at week 6 Percentage time pain felt was lower in the doxepin group than the placebo group at week 4 and 6. It was also lower in the doxepin group at week 4 and 6 versus baseline	Global Assessment scores were constant in both groups and did not improve significantly in the placebo group. The doxepin group were improved versus the placebo group at week 1, 2, 4, and 6. The doxepin group at week 6 were significantly improved versus baseline. Placebo group at week 6 was also improved versus baseline No significant between-group difference on depression. The doxepin group had better depression scores than the placebo group at week 2, 4, and 6. The placebo group demonstrated some improvement at week 6 versus baseline. The doxepin group had significant improvement at 1, 2, 4, and 6 versus baseline, these patients' depression score at week 6 were below the entry level for depression

Table 2 (*Continued*)

Author (publication year)	*Chronic pain outcome*	*Mental health outcome*
McIntyre et al, (2014)	From baseline to Week 8, compared to the placebo group, Quetiapine XR group demonstrated significant improvement in – the BPI total score (mean change Quetiapine XR vs placebo –2.1 vs –.3, $P = .007$, adjusted difference mean = –1.6, 95% CI –2.8, –.5) – the BPI-S (mean change Quetiapine XR vs placebo –.5 vs .2, $P = .036$, adjusted difference mean = –.6, 95% CI –1.2, 0) – the BPI-I (mean change Quetiapine XR vs placebo –1.6 vs –.6, $P = .008$, adjusted difference mean = –1.0, 95% CI –1.7, –.2)	At Week 8, the mean change in the HAM-D from baseline was significantly higher in the quetiapine XR group than the placebo group (Quetiapine XR vs placebo –10.0 vs –5.8, $P = .001$, adjusted difference mean = –3.7, 95% CI –.59, –1.5) From baseline to Week 8, significantly greater mean change was found in the Quetiapine XR group than the placebo group in – the HAM-A (Quetiapine XR vs placebo –9.4 vs –6.3, $P = .02$, adjusted difference mean = –2.8, 95% CI –5.2, –.5) – the CGI-S of Depression (Quetiapine XR vs placebo –1.4 versus –.7, $P = .01$, adjusted difference mean = –.6, 95% CI –1.0, –.2)
Onghena et al, (1993)	No significant pain reduction at any timepoint compared to T1 was found in Group B.	No significant antidepressant effect and no effect on anxiety at any timepoint compared to T1 was found in Group B.
Anxiety and stress-related disorders		
Body-based intervention		
Park et al, (2015)	Both CE (mean difference: –4.3, $P < .05$) and control group (mean difference –1.0, $P < .05$) had significant change on the VAS from baseline to post-treatment There was a significantly greater change of the VAS in the CE group (4.26 [2.21]) than the control group (1.00 [1.19], $P = .00$, d = 1.8, 95% CI 1.9, 4.6)	From baseline to post-treatment, both CE and control group had significant change on – the SCL-90-R (CE mean difference: –9.4, $P < .05$; control mean difference –4.3, $P < .05$) – the HSCL-25 (CE (mean difference: –5.3, $P < .05$; control mean difference –1.8, $P < .05$) A significant change from baseline to post-treatment on anxiety was found in the CE (mean difference: –3.1, $P < .05$) but not in the control group (mean difference –1.3, $P < .05$) Greater change was found in the CE group than the controls on – the SCL-90-R (CE 9.40 [5.22]; control (4.33 [4.70]), $P = .009$, d = 1.0, 95% CI –8.8, –1.4 – the HSCL-25 (CE 6.33 [5.21]; control 2.8 [2.93]), $P = .03$, d = .8, 95% CI –6.7, –.4 No significant between-group difference on anxiety (3.06 [2.32] for the CE group vs 1.26 [3.26] for the control group, $P = .092$, d = .6, 95% CI 3.9, .3)
Swann (2019)	From baseline to post-training, both groups showed – more pain, with the TRE group increased by .80 (SD = 1.92, $P = .45$) and the PMR increased by .50 (SD = 1.00, $P = .73$) – increased pain disability, with the TRE group increased by .20 (SD = 1.79, $P = .19$) and the PMR increased by .75 (SD = 4.03, $P = .87$), No significant between-group difference in either outcome From baseline to post-self-practice, the TRE groups showed slightly more pain (mean difference = .60, SD = 2.41, $P = .60$), but no overall change in pain disability	From baseline to post-training, both groups showed decreased PTSD symptoms, with the TRE group decreased by 3.80 (SD = 4.82, $P = .59$) and the PMR decreased by 7.50 (SD = 8.66, $P = .15$), no significant between-group difference was found ($P = .44$) From baseline to post-self-practice, the TRE group showed decreased PTSD symptoms (mean difference = –10.20, SD = 10.96, $P = .23$)
MCI		
McGeary et al, (2022)	No significant main effect of time ($P = .61$) or group*time interaction ($P = .76$) Compared to TAU, FORT-A group demonstrated significantly lower pain-related disability at post-treatment ($P = .002$), 6- ($P = .002$) and 12-month follow-up ($P = .014$), with an aggregated collapsed adjusted mean different of –9.1 (95% CI –14.4, –3.7), $P = .001$ across all follow-ups	FORT-A group had higher pretreatment opioid counts than the TAU group. both groups demonstrated a liner decrease in opioid use from post-treatment to 12-month follow-up with a significant effect of time ($P = .001$). no significant effects of treatment arm ($P = .51$) or treatment*time interaction was found ($P = .87$)

Table 2 (*Continued*)

Author (publication year)	*Chronic pain outcome*	*Mental health outcome*
Pharmacological intervention		
Dadabayeve et al, (2020)	There was significant diagnosis by medication interaction [F(1, 148)= 5.40, $P = .02$] with no significant difference on VAS between ketamine and ketorolac in the CP+PTSD group. Reduction on the BPI-P on Day 1 and Day 2 post-infusion was found in ketamine group, with higher scores returned on Day 7 in CP+PTSD group. No significant difference in pain score by medication was found in the CP+PTSD group ($P > .05$) Ketorolac was associated with greater score at baseline (M = 51.1, SD = 13.05) than subsequent timepoints in the CP+PTSD group (M = 25.75, SD = 18.42), t(22.87) = 4.66, $P < .01$	Two-way repeated measures ANOVAs (2 [ketamine, ketorolac] X 3[baseline, Day 1, Day 7]) demonstrated a significant main effect of time on PTSD in the CP+PTSD group: PTSD symptoms declined from baseline to Day-7 post-infusion in both medication groups, F (1,52) = 9.35, $P < .01$. There were no significant main effect of medication and no significant interaction between time and medication type (all $P > .05$). Significant decline in PTSD from baseline to Day 1 post-infusion [t(32.59) = 2.33, $P = .03$], and from baseline to Day 7 post-infusion [t(27.53) = 2.93, $P < .01$]. No significant symptom change from Day 1 to Day 7 post-infusion [t(31.75) = .92, $P = .37$] Ketamine and ketorolac infusion had less effect on dissociative symptoms in the CP+PTSD group than the CP group. In the CP+PTSD group, no significant difference was found between ketamine and ketorolac [t(169.98) = 1.228, $P > .1$]
Comorbid depression and anxiety		
MBI Dindo et al, (2020)	No significant between-group difference at 3-month follow-up in pain severity, mean difference = .12, 95% CI – 1.07, 1.32, d = .10, $P = .50$. TAU group demonstrated a greater reduction in pain interference than the ACT group, mean difference = 1.48, 95% CI – .36, 3.33, d = .78, $P = .03$	Compared to the TAU group, at 3-month follow-up, the ACT group demonstrated positive trends in the reduction of – anxiety, depression and/or stress (mean difference =–16.55, 95% CI –35.9,2.8, d = .68, $P = .09$) self-reported post-traumatic symptoms (mean difference = –5.1, 95% CI –17.1, 7.0, d = .33, $P = .39$]
Substance misuse disorder		
CBT-based intervention		
Barry et al, (2019)	No significant treatment group effects on – pain interference ($P = .27$) – pain intensity ($P = .25$) No significant treatment group by time effect on – pain interference ($P = .72$) – pain intensity ($P = .88$)	The proportion of participants abstinent from opioid use were higher in CBT than MDC group [Wald $\chi 2$ (1) = 5.47, $P = .019$] across baseline and the 3 assessment point, but were not significantly affected either by time ($P = .69$) or the interaction between groups and time ($P = .10$) The number of maximum consecutive weeks of abstinence from opioid use was higher for CBT (mean [SD] 6.1[4.2]) than MDC group (mean (SD) 3.9 [3.3]), t (38) = 1.831, $P = .06$
Wilson et al, (2018)	The treatment group had higher pain interference (B = 1.85, SE = .83, $P = .03$) but lower pain severity (B = 1.85, SE = .86, $P = .04$) at the end of treatment than the control group For the whole sample, pain self-efficacy did not change significantly over time, t (38) = –1.03, $P = .31$ No significant differences between the treatment and control group on self-efficacy when comparing at baseline [t (58) = –.48, $P = .63$], and post-treatment [t(37) = –1.44, $P = .16$], however, there is a positive trend favouring the CMPM group	The treatment group had higher depression (B = 10.57, SE = 2.94, $P = .001$) and opioid misuse (B = 13.03, SE = 6.06, $P = .04$) at the end of treatment than the control group No significant between group-difference on anxiety and withdrawal between the CPMP and control group

Table 2 (*Continued*)

Author (publication year)	*Chronic pain outcome*	*Mental health outcome*
MBI		
Cooperman et al, (2021)	From baseline to 16-week follow-up, the MORE group demonstrated significantly lower levels of pain at follow-up compared to the TAU group; primary analysis F (1,27.05) = 9.34, $P = .005$; sensitivity analysis (age, gender and duration of methadone treatment as covariates) F (1,24.26) = 8.29, $P = .008$ The MORE group reported significantly lower pain over time ($P = .01$), and the TAU group also reported higher pain but the result is not significant ($P = .74$)	From baseline to 16-week follow-up, compared to the TAU group, the MORE group demonstrated significantly lower levels of – opioid craving; primary analysis F (1,27.46) = 5.76, $P = .024$; sensitivity analysis F (1,24.35) = 6.95, $P = .014$ – depression; primary analysis F (1,24.82) = 7.14, $P = .013$; sensitivity analysis F (1,22.07)= 10.69, $P = .003$ – anxiety; primary analysis F(1,26.13)= 4.96, $P = .04$; sensitivity analysis F(1, 23.16)= 6.97, $P = .02$ The MORE group reported significantly lower opioid craving over time ($P = .01$), and the TAU group also reported lower opioid craving but the result is not significant ($P = .74$) Both groups reported increased depression over time, however, TAU group ($P < .001$) had a significantly greater increase than the MORE group ($P = .01$) The MORE group reported lower anxiety over time ($P = .78$), however. this result is not significant. The TAU group mean over time ($P = .046$) reported significantly higher anxiety over time
Garland et al, (2019)	Compared to the TAU group, the MORE group reported significantly greater decline in pain unpleasant (–13%) [Group X Time B = –.007 (SE = .003), $P = .025$], but no significant results on pain intensity ($P > .10$)	Compared to the TAU group, the MORE group reported significantly greater decreases in – opioid craving (–44%) [Group X time B = –.019 (SE = .005), $P < .001$] – opioid urge (–50%) [B = –.019 (SE = .005), $P < .001$]
Vowles et al, (2020)	At 6-month follow-up, the integrated intervention group demonstrated lower scores on – pain interference, – pain behaviour – usual pain intensity in the past week For pain interference and usual pain intensity, scores for the integrated intervention group decreased while the UC group increased between baseline and follow-up, with large effect sizes difference between the 2 groups at follow-up (pain interference d = .79; pain intensity d = 1.08) For pain behaviour, scores for the integrated intervention group reduced modestly but the UC remained stable with a small between group effect size at follow-up (d = .30)	The integrated intervention group demonstrated lower scores on current opioid use in the past week at follow-up For the UC group, COMM scores remained stable across the 2 assessment points, while the scores decreased for the integrated intervention group
Body-based intervention		
Uebelacker et al, (2019)	No significant between-group difference was observed on the BPI-I with a mean difference in change scores from pre-intervention to month 3 of –.08, $P = .94$, d = .03 (95% CI –.62, .69) The yoga group had larger within-subject reduction on their pain severity from pre- to post-intervention (–2.08, 95% CI –2.52, –1.64, $P < .001$). Between-group difference was significant (–1.11, 95% CI –1.76, –.47, $P < .001$). On average, the yoga group had a 2.08-point decrease in pain severity from pre- to post-intervention, the HE group had a .97-point decrease	The yoga group had larger within-subject reduction on their anxiety (.79, 95% CI –2.22, –1.36, $P < .001$) and sadness (–1.06, 95% CI –1.52, –.61, $P < .001$) from pre- to post-intervention. Between-group difference was significant (–.71, 95% CI –1.27, –.15, $P < .05$). On average, the yoga group had a 1.79-point decrease in anxiety from pre- to post-intervention, the HE group had a 1.07-point decrease
Wiest et al, (2015)	Massage group reported lower pain scores than the TAU group for Week 4 and 8 on all 3 NRS pain measures (pain in last 24 h, average pain in last week and worst pain last week), however, no significant between-group difference found at Week 12 For both groups, their scores for all 3 NRS measures were lower at Week 12 than baseline. Improvements at Week 4 and 8 in the massage group did not achieve clinical or statistical significance, except for worst pain measure at Week 8	The TAU group had slightly higher levels of anxiety and depression than the massage group from baseline to Week 12. Anxiety and depression remained stable during the study period No changes observed from baseline on urine drug screens. No significant difference found between massage and TAU group in urine drug screen through Week 12

Table 2 (*Continued*)

Author (publication year)	*Chronic pain outcome*	*Mental health outcome*
MCI		
Ilgen et al, (2016)	The ImPAT group demonstrated significantly lower pain intensity ratings across 3 time points than the SPC group [β(SE) = –.71 (.29), 95% CI –1.29, –.12, $P < .05$, d = .45]. Pain-related functioning was significant greater in the ImPAT than the SPC group (β[SE] = –.27 (.11), 95% CI .05, .49, $P < .05$, d = .36]. No significant results were found on pain tolerance between the 2 groups	The ImPAT group reported fewer days of alcohol use during the follow-up than the SPC group (β[SE] = –.77 [.29], 95% CI –1.34, –.20, $P < .05$, d = .59), but this effect was not seen in the difference between any versus no use. Alcohol use was relatively similar between the 2 groups at the 3-month follow-up but between-differences emerged at the 6- and 12-month follow-up No significant between-group difference was found on the days of drug use (β[SE] = .02 [.14], 95% CI –.25, .30, $P > .05$, d = 1.01). The changes from baseline were not significant between the 2 groups
Ilgen et al, (2020)	A significant time by condition interaction was found in women but not in men (β = .05, SE = .03) for pain intensity: There was a greater reduction in pain intensity among women in the ImPAT group than the SPC group over the follow-up period (β = –.11, SE = .03, 95% CI –.17, .05, $P = .001$), greater by .58 (95% CI –.07, 11.22, $P = .08$, d = –.22) Men in the ImPAT group demonstrated significantly greater pain tolerance than the SPC group over the follow-up (β = –.11, SE = .04, 95% CI .03, .16, $P = .004$), higher by .11 (95% CI .03, .18, $P = .004$, d = .40) at 3-month and by .07 (95% CI –.01, .19, $P = .11$, d = .25) at 12-month follow-up No significant between-group results were found for pain functioning across follow-up; men: β = –.01, SE = .02; women: β = –.01, SE = .02	No significant between-group results were found for alcohol or drug outcomes across follow-up
Pharmacological intervention		
Neumann et al, (2013)	All analyses were based on treatment completers (n = 13 in each treatment group) No significant between-group difference on the percentage change of pain from baseline ($P = .92$) A 2 × 2 analysis design [treatment (BUP/NLX, Methadone) x follow-up (baseline, 6-month follow-up)] found a main effect of follow-up F (df = 1) = 4.65, $P = .043$. Across both treatment groups, participants reported significantly less pain at the 6-month follow-up than at the baseline with a 12.75% reduction in pain with a medium effect size (d = .52)	All analyses were based on treatment completers (n = 13 in each treatment group) At the 6-month follow-up, 5 participants in the BUP/NLX group reported the use of opioids compared to none of the participants in the Methadone group ($P = .039$), no significant between-group difference found for positive urine for opioids (OR = .28, 95% CI .042, 1.878, $P = .371$), positive urine for cocaine ($P = .478$), positive urine for other drugs (OR = 1.0, 95% CI .197, 5.068, $P = 1.00$), self-reported alcohol use (OR = .41, 95% CI .060, 2.769, $P = .65$) and self-reported use of other drugs (OR = .41, 95% CI .087, 2.645, $P = .67$)

Abbreviations: ACT, acceptance and commitment therapy; CE, cervical exercise; CP, chronic pain; CBT, cognitive-behavioural therapy; CI, confidence interval; ES, effect size; FORT-A, functional orthopaedic rehabilitation treatment; ImPAT, improving pain during addiction treatment; ITT, intention-to-treat; IPT-P, interpersonal psychotherapy for depressed patients with pain; MDD, major depressive disorder; MDC, methadone drug counselling; MBCT, mindfulness-based cognitive therapy; MBI, mindfulness-based intervention; MORE, mindfulness-oriented recovery enhancement; MCI, multi-component intervention; nsCLBP, non-specific chronic low back pain; MRS, numeric rating scale; PTSD, post-traumatic stress disorder; PMR, progressive muscle relaxation; TRE, self-practice of trauma releasing exercises; SE, standard error; BAI, the beck anxiety inventory; BDI-II, the beck depression inventory; BPI, the brief pain inventory; BPI-I, the brief pain inventory -interference; BPI-S, the brief pain inventory-severity; CES-D, the center for epidemiological studies depression scale; CGI, the clinical global impression; CGI-S, the clinical global impression-severity; COMM, the current opioid misuse measure; DROP, the depression and pain; HRDS, The Hamilton Rating Scale for Depression-17; HSCL, The Hopkins Symptom Checklist; The HADS, hospital anxiety and depression scale; MAIA, the multidimensional assessment of interoceptive awareness; PHQ, the patient health questionnaire; QIDS-C_{16}, The Quick Inventory of Depressive Symptomatology—Clinician Rated; SCL-90-R, The Symptom Checklist-90-revised;VAS, the visual analogue scale; TAU, treatment-as-usual; UC, usual care.

Table 3. Studies With Positive Outcomes by Follow-up Time

	End-of-treatment	*Short-term follow-up*[*]	*Mid-term follow-up*[†]	*Long-term follow-up*[‡]
Improved pain outcomes				
Pain severity	Baumeister et al, (2020) Hameroff et al, (1985) Liao et al, (2023) Martin et al, (2015) McIntyre et al, (2014) Dadabayeve et al, (2020) Park et al, (2015) Ilgen et al, (2016) Ilgen et al, (2020) Neumann et al, (2013) Uebelacker et al, (2019) Wiest et al, (2015) Wilson et al, (2018)	Dadabayeve et al, (2020) Cooperman et al, (2021) Ilgen et al, (2016) Ilgen et al, (2020)	Ilgen et al, (2016) Ilgen et al, (2020) Vowles et al, (2020)	
Pain interference	McIntyre et al, (2014) Uebelacker et al, (2019) Wilson et al, (2018)	Cooperman et al, (2021) Dadabayeve et al, (2020) Dindo et al, (2020) Garland et al, (2019)	Vowles et al, (2020)	
Pain-related disability	Baumeister et al, (2020) McGeary et al, (2022)	McGeary et al, (2022)	McGeary et al, (2022)	McGeary et al, (2022)
Pain-related efficacy	Baumeister et al, (2020) Wilson et al, (2018)	Baumeister et al, (2020)		
Pain catastrophising	de Jong et al, (2016)			
Improved mental health outcomes				
Depression severity	Baumeister et al, (2020) de Jong et al, (2016) Hameroff et al, (1985) Liao et al, (2023) Martin et al, (2015) McIntyre et al, (2014) Poleshuck et al, (2014) Schlicker et al, (2020) Park et al, (2015) Uebelacker et al, (2019) Wiest et al, (2015) Wilson et al, (2018)	Baumeister et al, (2020) Cooperman et al, (2021) Wiest et al, (2015)	Schlicker et al, (2020)	Aragonès et al, (2019)
Depression response rate	Liao et al, (2023) McIntyre et al, (2014)			Aragonès et al, (2019)
Depression remission rate	Liao et al, (2023) McIntyre et al, (2014)	Baumeister et al, (2020)		
Anxiety severity	Martin et al, (2015) McIntyre et al, (2014) Schlicker et al, (2020) Park et al, (2015) Uebelacker et al, (2019) Wiest et al, (2015)	Cooperman et al, (2021) Wiest et al, (2015)	Schlicker et al, (2020)	
Anxiety remission rate	McIntyre et al, (2014)			
PTSD severity	Swann (2019)	Dadabayeve et al, (2020) Swann (2019)		
Alcohol or drug use/ craving	Wilson et al, (2018) McGeary et al, (2022)	Barry et al, (2019) Cooperman et al, (2021) Garland et al, (2019) Ilgen et al, (2016) McGeary et al, (2022)	Ilgen et al, (2016) McGeary et al, (2022) Vowles et al, (2020)	McGeary et al, (2022)

[*] < 6 months follow-up time.
[†] ≥6 and < 12 months follow-up time.
[‡] ≥12 months follow-up time.

Interventions in Patients With Anxiety or Stress-Related Disorders

Of the 4 trials in patients with anxiety or stress-related disorders, all involved people with post-traumatic stress disorder (PTSD). One trial implemented a pharmacological-based intervention,[44] one included a MCI,[29] and the other 2 included body-based interventions.[33,34] The duration of these interventions ranged from a single session to 6 weeks. In terms of bias, one trial was judged as 'low risk',[29] and the rest of the trials were considered as 'high risk'. Overall, all 3 trials are subject to participants selection bias and blinding of either participants or trial personnel or both. Information on how to handle missing data was not reported in 2 trials (Fig 2).

Of these 4 trials, one trial included only end-of-treatment outcomes,[33] and a large and very large effect was found on the reduction of pain severity and depressive symptoms, respectively, favoring the cervical exercise intervention group. Two trials included short-term follow-up outcomes: 1 of the 2 reported improved pain severity,[44] but the other surprisingly reported worse self-reported pain in the intervention from baseline to follow-up.[34] Both trials, however, reported improved PTSD severity. The remaining 1 trial[29] reported improved pain-related disability and decreased opioid use at all assessment points following the intervention.

Out of 2 trials including tertiary outcomes of interest, all reported some positive findings: significantly greater change of neck function,[33] along with decreased physical and emotional disturbances[34] were found. Although only investigated in 1 RCT, no AEs and well-tolerated medication responses were reported.[44]

Interventions in Patients With Comorbid Depression and Anxiety

Only 1 RCT included patients with both depression and anxiety: Dindo and colleagues[26] examined the effect of a one-day ACT workshop on pain severity and interference in patients with current major depression and anxiety disorder or PTSD. This study had a relatively short follow-up period of 3 months and a high risk of bias, mainly due to lack of reporting on randomisation process, and blinding of both participants and trial personnel (Fig 2). A large effect on pain interference among those receiving ACT compared to the control group was reported at follow-up. No significant results in pain severity, MH and tertiary outcomes were found.

Interventions in Patients With Substance Use Disorder (SUD)

Of the 10 trials in patients with a SUD, 8 involved people with opioid misuse disorder (OUD), and 2 included non-specific substance misuse. Two trials evaluated a CBT-based intervention,[20,23] three included a MBI,[27,28,30] one of which involved integrated MBI and ACT,[30] two examined a MCI,[39,40] one included a pharmacological-based treatment,[45] and 2 involved a body-based intervention.[35,36] The duration of these interventions ranged from 4 weeks to 6 months. Four trials were judged as having 'some concerns'[27,30,39,40] and 6 have 'high risk of bias'.[20,23,28,35,36,45] Four trials are subject to selection bias due to lack of reporting on randomisation process and 2 of which did not report information on allocation concealment. All trials lack of blinding, with almost all trials having issues with blinding of both participants and trial personnel. Information on missing data was not reported in 3 trials (Fig 2).

Of the 2 trials only reporting end-of-treatment outcomes,[23,35] both reported improved pain severity with a small-to-medium effect size. Of the MH outcomes examined, one of them only included measurement for anxiety but reported both within-and between-group reduction in anxiety symptoms.[35] The remaining trial included measures for depression and opioid misuse but reported both were worse in the CBT-based treatment group than the controls.[23] Of the 4 trials with a short-term follow-up,[20,27,28,36] two out of 4 studies reported statistically significant improvements in pain intensity in the intervention group,[27,36] however, this improvement was not sustained at follow-up for 1 trial.[36] The remaining 2 trials failed to find any significant treatment group effects on pain intensity. Trials from Cooperman and colleagues[27] and Wiest and colleagues[36] also included measures for depression and anxiety with both finding significant improvements in these outcomes. All 4 trials included drug screens, and reduced opioid craving post-treatment was also found in 3.[20,27,28] Of the remaining 4 trials with a medium-term follow-up,[30,39,40,45] although a small-to-medium effect on pain reduction from baseline to medium-term follow-up was reported in all, with 1 reporting a large ES,[30] one trial found this effect was only significant among women participants.[40] All 4 trials measured alcohol and drug use over time. Fewer days of alcohol use from baseline to follow-up was found in one[39] and less opioid use was also only reported in 1[28]

Function-related tertiary outcomes were examined in 2 trials,[27,45] but only 1 reported reduced physical and emotional limitations, as well as higher levels of well-being, vitality, and social functioning.[27] Of the all 3 trials recording AEs,[35,36,45] no severe AEs were reported related to the intervention.

Summary of Evidence for Intervention Types

Synthesising evidence from 4 trials included a CBT-based intervention,[20–23] it appears that this type of intervention has a positive effect on pain-related (particularly pain severity and pain-related efficacy) and MH outcomes (particularly depression severity and opioid use), at least for people with either depression or OUD till end-of-treatment period. However, 2 studies involving participants with OUD are small in nature (ie, less than 100) and are of high risk of bias due to issues such as lack of reporting on blinding and missing data, only inconclusive conclusion could be drawn on the effect of CBT in pain and opioid use for people with OUD. On the other hand, given one large study involving more than 200 participants with depression and of a moderate risk

of bias due to lack of blinding, there is a promising benefit of CBT on both pain and depression outcomes for people with depression.

In total, 6 trials evaluated an MBI, mostly among patients with OUD,[24–30] but all trials but one included a small sample size (ie, less than 50), which significantly undermine the statistical power of these studies. This type of intervention demonstrated a significant impact on pain-related (particularly pain intensity, pain interference) and MH (particularly opioid use) outcomes among those with an OUD diagnosis and this effect appears to be maintained at follow-up (both short- and mid-term follow-up). However, given the sample size (ie, less than 100 participants in total) and the moderate risk of bias of the 3 studies in people with OUD, a definite conclusion cannot be drawn for this population. Similarly, due to small samples and high risks of bias of trials involving participants with depression and those with comorbid depression and anxiety, the effectiveness of MBIs in pain and MH outcomes for these populations are inconclusive. Improved pain-related disability for people with PTSD was also found following a MBI, but given only one relatively large study (ie, over 100 participants) with a low risk of bias was included, this finding needs to be further verified.

Of the 4 trials that examined a body-based intervention,[33–36] no evident effect was reported on pain reduction and MH outcomes for people with PTSD. Both studies involving people with PTSD also included a small number of participants (ie, less than 50 in total) and are of high risk of bias due to issues with randomisation and lack of reporting on blinding and missing data, confidence in their findings is therefore significantly compromised. For people with OUD, body-based interventions appear to be more effective in reducing pain severity, anxiety, and depressive symptoms, at least till end-of-treatment period. However, these 2 trials evaluated 2 different types of intervention (yoga vs massage) and both have a high risk of bias due to issues with blinding and missing data handling, as well as small sample sizes (ie, less than 100 in total), existing evidence, therefore, does not support the benefit of either of these interventions in improving pain and MH outcomes for people with OUD.

Another 4 large trials included an intervention with multiple components.[37–40] No significant effect on pain for people with depression but reduced depressive and anxiety symptoms were evident following the intervention. For those with SUD, 2 large trials with moderate risk of bias (due to lack of blinding) support a sustained effect of multi-component interventions in improving pain intensity and tolerance at 12-month follow-up, although this effect may be moderated by gender. Lower alcohol use at follow-up was also reported.

Five trials in total implemented pharmacological-based intervention,[41–45] with only one trial including more than 100 participants. Patients with depression significantly benefited from pharmacological therapy received in terms of the severity of their pain, depression, and anxiety immediately following the intervention. However, these 2 trials examined different types of medications (antidepressants vs antipsychotics) and are both of high risk of bias due to lack of reporting on randomisation process and blinding, effectiveness of these medications on pain and MH outcomes for people with depression are therefore inconclusive. Although pain relief medication and treatment for OUD dependence also appear to be effective in pain reduction in people with PTSD and OUD, respectively, and this effect was sustained at the end of follow-up, these 2 trials only analysed a subset of participants (ie, less than 40 participants in total) and both also have a high risk of bias. Confidence in the effectiveness of these pharmacological-based interventions is therefore compromised.

Finally, with only one trial evaluating an IPT[31] and including a sample of less than 100, a conclusion could not be drawn regarding its effect on pain, and decreased depression appears to be the only positive outcome observed immediately after the intervention.

Discussion

To our knowledge, this is the first systematic review of RCTs investigating the effectiveness of interventions in pain outcomes in adults with clinically diagnosed MI and CP. There is a paucity of high-quality, adequately powered RCTs, largely due to a lack of information reporting on for example randomisation. This is further clouded by the absence of robust interventions commonly advocated in pain guidelines and trials in conditions commonly affected by painful comorbidities. Despite these caveats, there is some suggestive evidence that promising interventions include CBT for patients with depression and MCIs for SUD.

CBT is commonly recommended[11] for chronic primary pain, and it usually involves several components for pain intensity and distress,[47] for example, cognitive reappraisal addressing unhelpful pain-related thoughts.[12] However, the benefits of CBT appear to be small in the general population with pain.[12] Synthesising evidence from a large trial of a CBT-based intervention, this was concluded to have a positive post-treatment effect on pain severity, depression and QoL among people with depression. Evidence on its long-term effect however is lacking.

Limited evidence from small trials found positive short-term effects on pain for patients with OUD/SUD following MBIs and body-based interventions. Given the limited number of studies, the heterogenous intervention types involved and the limited robustness of evidence, definitive conclusions on the benefits of body-based interventions for OUD are precluded. MBIs originate from the Buddhist tradition and aim to cultivate mindfulness.[48] Systematic reviews in the general population support a small benefit of MBIs for pain reduction.[49] In this review, all but one of the MBI trials had small sample sizes, therefore there is a lack of sufficient power to support its efficiency.

Trials including an MCI are generally large in nature. These trials reported positive changes in pain intensity at post-intervention and follow-up, therefore suggesting its potential in reducing pain for patients with OUD/SUD. The challenge in managing co-existing OUD and CP has

been long recognised, mainly due to the complexity associated with opioid self-medication, CP symptoms, and psychopathology.[50] Given the nature of the comorbidity, MCIs could be an efficacious alternative.

Some but not all trials implementing pharmacological-based interventions have a positive immediate impact on pain and somatic symptoms in depression. Currently, antidepressants are not licensed for use in CP. Given their role in improving pain, sleep, and psychological distress,[11] some antidepressants, particularly selective serotonin reuptake inhibitors, are commonly used and were evaluated in some included trials. However, considering the quality of existing studies and its small evidence base, there is a need for further evidence to support their use.

Research Implications

As a multidimensional experience, CP can disrupt individuals' physical and MH, social roles, and emotional health.[51] Not only does CP interfere with daily activities, patients also experience significant role transitions and impaired social responsibilities.[52,53] Due to its invisibility, CP may also lead to fear of judgement and condescension from primary care providers[54] and isolation,[52] and these could be particularly true for patients with comorbid MI. The current review identifies an imperative need for rigorous RCTs to further understand the effectiveness of interventions, especially CBT, exercise and MCIs, for patients with comorbid CP and MI. Several research gaps were identified for future research.

First, only a minority of studies included AEs as an outcome, and evidence to date is inadequate to inform a comprehensive conclusion. Future trials should actively and systematically collect data on AEs, alongside other relevant outcomes (eg, perceived effect on pain, MH, and daily functions), to ensure interventions are well-tolerated by this patient group.

Second, there is a scarcity of trials including certain patient groups with high rates of comorbid CP and MI, despite people with SMI tend to have a high prevalence of pain,[14] a greater number of painful conditions, but low help-seeking behaviour for their pain.[4] A similar predicament is found in other patients (eg, eating disorders[55] and borderline personality disorder[56]). Future trials investigating pain strategies for people with these MIs are urgently required. In a similar vein, there is limited evaluation of non-pharmacological interventions including exercise/PA and physiotherapy, despite these interventions being key treatments for CP in the general population.[11] Therefore, there is also a pressing need to understand the effectiveness of these interventions and their mechanisms in improving pain and MH outcomes.

Third, evidence supporting the long-term effectiveness of potential interventions is lacking. For chronic conditions like CP, it is crucial to follow-up patients for a long period of time to detect differences between groups in mental and physiological outcomes, and subsequently help researchers determine long-term pain management solutions.

Clinical Implications

CP is a complex issue and is often the result of abnormal neural signalling with biopsychosocial contributions.[57] For people with comorbid CP and MI, this nature of CP is further complicated by MH problems, which are often accompanied by long-term physical conditions[7] that are associated with pain symptoms.[8] Therefore, there is an ongoing need for a multimodal treatment approach for people with CP[57] and those with comorbid CP and MI. However, current treatment guidelines fail to acknowledge the importance of addressing both issues. There is also a lack of understanding of treatment options with the potential to improve both pain and MH outcomes, given the limitations associated with current evidence-based pharmacological and non-pharmacological interventions. The current review fills this knowledge gap and identifies the promising potential for implementing CBT-based and MCIs for people with depression and SUD, respectively.

Given the lack of understanding of the complex comorbid nature of CP and MI, and over-reliance on medication prescribing among clinicians,[57] firstly there is an imperative need for early and accurate identification of MH patients who may present with CP symptoms. Considering the expertise of psychiatrists in potentially recognising the psychological, cognitive, and behavioural dimensions of CP,[58] integrating psychiatrists into the diagnosis and management of CP is vital for tackling the CP-MH interface.

Although CBT for pain aims to change behaviours that maintain pain and address persistent pain-related thoughts and feelings,[12] CBT was originally developed for depression. This may therefore explain the more desirable pain outcomes following CBT and subsequently improved depressive mood resulting from decreased pain in existing trials. Considering the relatively safe nature of CBT compared to existing pharmacological options, clinicians may consider delivering consistent CBT-based strategies to patients present with both pain and depressive symptoms.

There is a growing concern over the opioid prescription for CP, and this is particularly alarming for people with comorbid MH problems as this population is not only more likely to be prescribed with opioid[59] but also at a higher dose.[60] Utilising a multimodal treatment approach is therefore of a high priority, especially for those with SUDs given the high co-occurrence of CP and SUDs[61] and the high likelihood of opioid abuse among this patient group.[62] In line with the need for a more integrated approach,[57] MCIs including psychological and behavioural dimensions, and in some instances exercise/PA elements, may remain an effective and safe strategy to meet the complex needs of people with SUDs. The importance of MCIs should therefore be recognised in clinical settings, but its implementation will likely require a coherent collaboration between different interdisciplinary teams, such as physiotherapists, pain specialists, and psychiatrists.

Whilst this review is the first to provide a landscape understanding of the current state of pain treatments for

people with MI and CP and includes a wide range of potential treatments, a number of limitations should be considered. First, the review is limited by the small number of studies, the methodological flaws of many included RCTs, and the heterogeneity of intervention types and patient groups. Some interventions which are commonplace in the management of CP (eg, PA) had few RCTs. Further, no RCTs of patients with SMI were found. Second, search terms used in this review may prevent us from retrieving relevant trials of certain interventions. For example, this review used 'physiotherapy' for the literature search, therefore, trials using different terminology (eg, physical therapy), might have been missed. Third, although great effort was invested during literature searching and screening, including translating papers in Mandarin/Cantonese and Italian by the primary reviewers, this could have introduced bias and some trials in other languages may have been missed. Finally, insomnia was not included as an eligible MI. In line with the ICD-11, DSM-V and previous literature,[63] we considered insomnia as a sleep disorder. However, it is important to note that insomnia is common in people with CP and MI and many of the interventions that work for sleep could improve pain and MH symptoms (eg, CBT). Future research should consider the potential role of insomnia and its treatments on CP and MI symptoms.

Conclusions

To conclude, this review found inconsistent results on the effectiveness of both pharmacological and non-pharmacological interventions for CP management among patients with comorbid CP and clinically diagnosed MI. Despite the heterogeneity across trials and the overall low quality of synthesised evidence, the review noted some promising evidence supporting the use of CBT for patients with depression, and MCIs for SUD. There is a need for more rigorous and large-scale RCTs to provide a more accurate estimate.

The data that support the findings of this study are available from the corresponding author, RM, upon reasonable request.

Disclosures

This work was supported by the National Institute for Health Research (NIHR) Advanced Fellowship (NIHR301206, 2021–2026), hold by BS. BS is a co-investigator for an NIHR programme Grant Supporting physical activity and severe mental illness (SPACES).

RS is part-funded by: 1) the NIHR Biomedical Research Centre at the South London and Maudsley NHS Foundation Trust and King's College London; 2) an NIHR Senior Investigator Award; 3) the NIHR Applied Research Collaboration South London (NIHR ARC South London) at King's College Hospital NHS Foundation Trust; 4) the DATAMIND HDR UK Mental Health Data Hub (MRC grant MR/W014386).

WS is partly funded through the National Institute for Health Research (NIHR) Biomedical Research Centre at the South London and Maudsley NHS Foundation Trust and King's College London.

FG is in part supported by the National Institute for Health Research's (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London, the Maudsley Charity and the National Institute for Health Research (NIHR) Applied Research Collaboration South London (NIHR ARC South London) at King's College Hospital NHS Foundation Trust. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

The views expressed are those of the author(s) and not necessarily those of mentioned above, the NHS, the NIHR or any of the aforementioned.

Author Contributions

BS conceived the study, **BS and RM** developed protocol. **RM and ER** conducted the literature screening and quality assessment with support from BS. **RM** drafted the manuscript with support from BS and RS. All authors (BS, MA, TS, DV, WS, FG, RS, RM and ER) provided critical revisions and approved the final version.

Conflict of interest statement

BS is on the Editorial board of Ageing Research Reviews, Mental Health and Physical Activity, The Journal of Evidence Based Medicine and The Brazilian Journal of Psychiatry. BS has received honorarium from a co-edited a book on exercise and mental illness and advisory work from ASICS for unrelated work. BS has on a voluntary basis advised multiple charities on improving the physical health in SMI including Equally Well, Rethink Mental Illness and Mind in addition to government agencies including Public Health England and NHS England. BS has co-authored guidelines for the Lancet Psychiatry and World Psychiatric Association on the physical health of people with serious mental illness (SMI). BS has on an ad hoc basis lectured across several UK Universities on the physical health of people with SMI and on occasion (at the discretion of the University) received a standard hourly lecturer's fee and/or travel reimbursement.

RS declared research support in the last 3 years from Janssen, GSK and Takeda, and royalties received from Oxford University Press.

FG has received honoraria from Lundbeck, Otsuka and Sunovion, royalties from Oxford University Press, Springer Verlag and Wiley and is on the Editorial Board of BJPsych Open.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jpain.2023.11.004.

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