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Which Remote Rehabilitation Interventions Work Best for Chronic Musculoskeletal Pain and Depression? A Bayesian Network Meta-Analysis

OBJECTIVE: To evaluate the effectiveness of remote rehabilitation interventions for people living with chronic musculoskeletal pain and depression.

DESIGN: A systematic review with network meta-analysis (NMA) of randomized controlled trials.

LITERATURE SEARCH: We searched the Cochrane Central Register of Controlled Trials, CINAHL, EMBASE, LILACS MEDLINE, PSYNDEX, and PsycINFO databases from inception to May 2023.

STUDY SELECTION CRITERIA: Randomized controlled trials that evaluated the effectiveness of remote rehabilitation interventions in people with chronic musculoskeletal pain and depression.

DATA SYNTHESIS: We used Bayesian random-effects models for the NMA. Effect estimates were comparisons between rehabilitation interventions and waitlist. We performed a sensitivity analysis based on bias in the randomization process, large trials (>100 patients per arm) and musculoskeletal condition.

RESULTS: Fifty-eight randomized controlled trials involving 10 278 participants (median sample size: 137; interquartile range [IQR]: 77–236) were included. Interactive voice response cognitive behavioral therapy (CBT; standardized mean difference [SMD] -0.66, 95% credible interval [CrI] -1.17 to -0.16), CBT in person (SMD -0.50, 95% CrI -0.97 to -0.04), and mobile app CBT plus exercise (SMD -0.37, 95% CrI -0.69 to -0.02) were superior to waitlist at 12-week follow-up for reducing pain (> 98% probability of superiority). For depression outcomes, Internet-delivered CBT and telecare were superior to waitlist at 12-week follow-up (SMD -0.51, 95% CrI -0.87 to -0.13) (> 99% probability of superiority). For pain outcomes, the certainty of evidence ranged from low to moderate. For depression outcomes, the certainty of evidence ranged from very low to moderate. The proportion of dropouts attributed to adverse events was unclear. No intervention was associated with higher odds of dropout.

CONCLUSION: Interactive voice response CBT and mobile app CBT plus exercise showed similar treatment effects with in-person CBT on pain reduction among people living with chronic musculoskeletal pain and depression had over 98% probability of superiority than waitlist control at 12-week follow-up. Internet-delivered CBT and telecare had over 99% probability of superiority than waitlist control for improving depression outcomes at 12-week follow-up. *J Orthop Sports Phys Ther 2024;54(6):361-376. Epub 26 February 2024. doi:10.2519/jospt.2024.12216*

KEY WORDS: *chronic musculoskeletal pain, depression, mental health comorbidities, network meta-analysis, rehabilitation interventions, systematic review*

Pain is the primary driver of global disability.[95] Chronic musculoskeletal pain, defined as pain lasting for more than 3 months, imposes an immense personal and economic burden and affects over 30% of the global population.[95] Even when adjusted for higher instances of depression, suicide, and opioid use, chronic musculoskeletal pain corresponds to reduced life expectancy.[26] Depression is common in individuals with chronic musculoskeletal pain, and it impacts their quality of life and treatment outcomes.[53,68,75] Patients living with both conditions have complex needs due to high rates of persistent physical and mental health symptoms, issues around inadequate pain relief and risks with opioid use, frequent lack of access to primary care, 80% unemployment rates, and complicated family/social relationships.[64,65] A personalized, multimodal, treatment approach is required, integrating physical, cognitive, and social treatments delivered by a multidisciplinary team.[32,89]

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Prior to the COVID-19 pandemic, some patients living with chronic musculoskeletal pain and depression were provided intensive multimodal face-to-face outpatient or inpatient treatment programs, whereas others languished on waitlists due to a lack of system capacity.[21] In Canada, in 2017–2018, the median wait time was around 5.5 months; some people waited up to 4 years for access to multidisciplinary pain care.[21] Despite the disruption to health services caused by the pandemic, remote interventions and telemedicine are promising for managing chronic musculoskeletal pain, offering advantages in terms of accessibility, convenience, and potential cost effectiveness.[23,55,61,87] A recent network meta-analysis (NMA) has suggested that Internet-delivered cognitive behavioral therapy (CBT) was associated with greater reduction in depressive symptoms when compared with usual care or waitlist.[55] However, it is unclear how people with concurrent chronic musculoskeletal pain and depression would respond.

Previous systematic reviews have documented the effectiveness of remote interventions in pain and depression outcomes for treating chronic musculoskeletal pain.[23,61,87] However, the reviews used a pairwise meta-analysis, which allows for comparison of only two groups,[23,61] and did not differentiate between the mode of delivery and the type of interventions and they did not examine the individual components of these interventions.[87]

To provide a more comprehensive analysis, we aimed to assess the effectiveness of remote rehabilitation interventions in comparison to sham, traditional, or alternative virtual treatments in patients with concurrent chronic musculoskeletal pain and depression using NMA.

METHODS

We followed the reporting guidelines from Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA, extension for NMA).[52] Our protocol was registered in PROSPERO database (CRD42022292395).

Search Strategy

We searched the Cochrane Central Register of Controlled Trials, CINAHL, EMBASE, LILACS MEDLINE, PSYNDEX, and PsycINFO databases from inception to May 2023. A combination of search terms was used including "pain management", "musculoskeletal diseases", "behavior and behavior mechanisms", "anxiety disorders", "trauma and stressor related disorders", "depression", "telemedicine", "telerehabilitation", and "remote or virtual rehabilitation". The full search strategy can be found in **SUPPLEMENTAL FILE 1**. To identify additional eligible studies, we reviewed the reference lists of all included trials, searched clinical trial registries (ClinicalTrials.gov, Australian New Zealand Clinical Trials Registry, WHO International Clinical Trials Registry Platform, and UMIN Clinical Trials Registry) for trials in progress, and examined the reference lists of previously published systematic reviews.

Eligibility Criteria

Eligible studies were randomized controlled trials of remote rehabilitation interventions. The interventions included therapeutic programs delivered through virtual or remote platforms, encompassing psychological therapies based on principles such as CBT for pain control or exercise modalities such as aerobic or resistance training targeted at pain management or self-management interventions focusing on educational and strategic empowerment for managing chronic conditions.[15] The interventions could also involve a combination of therapeutic modalities (eg, CBT coupled with exercise or exercise combined with education).[15]

Eligible trials had to include at least one treatment arm with a remotely/virtually delivered intervention compared to an alternative (sham, nonintervention, face-to-face treatment or alternative virtual/remote intervention). Patients had chronic musculoskeletal pain and at least 60% of participants had depressive symptoms, or the analysis was stratified into separate groups based on depression status. Chronic musculoskeletal pain refers to pain that lasts for more than 3 months as defined by guidelines such as The ACTTION-American Pain Society Pain Taxonomy (AAPT)[35,38] and The IASP classification of chronic pain for ICD-11.[68] Depression was established by specified cutoffs on self-report scales or diagnostic interviews. We excluded observational studies, reviews and systematic reviews, editorials, and letters to the editor.

Study Selection and Data Extraction

Two investigators (PB TVP) independently assessed eligibility in a two-stage process (title/abstracts and full texts) using Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia.[28] Disagreements at the title/abstract stage underwent a full review. Disagreements at the full-text stage were resolved via consensus. Data extraction was completed independently by pairs of researchers (PB, TVP, DVP, MCT) using a standardized, piloted, web-based data management tool for systematic reviews (Ragic), accompanied by a codebook. We extracted trial design, trial size, population characteristics, intervention components, virtual and remote platforms that were used, dose, and treatment duration. Potential mediators extracted were patient characteristics such as mean age, sex, and duration of symptoms/follow-up. We did not need to contact any corresponding authors to clarify or request additional information.

Outcomes

The primary outcome of interest was pain intensity, and secondary outcomes were depression scores and treatment discontinuation rates. The primary and secondary outcomes were extracted and analyzed at 12-week follow-up. For trials with different follow-up lengths, we extracted data from the closest timepoint to 12-week (± 4 weeks) follow-up for both outcomes. If a trial reported more than

one outcome measure for pain intensity or depression scores, we prioritized the scale that was reported as the primary outcome of interest. Treatment discontinuation rate was assessed in the form of any-cause dropouts/withdrawals.

Risk of Bias

We used the Cochrane Risk of Bias tool (version 2) to assess the risk of bias in included trials. Two reviewers (GN and DVP) independently assessed each study resolved disagreements by consensus.[48] We used the Cohen's kappa to calculate the level of agreement among reviewers.

Data Analysis

Throughout the analysis, we used the waitlist group as the reference group. Results of variables with nonnormal distributions were presented as median (interquartile range [IQR]). Categorical variables were presented as numbers (percentages). A Bayesian random-effects NMA model was used.[33] For continuous outcomes, we used the normal likelihood and an identity link. For binary outcomes, we used the binomial likelihood and the logit link. Effect sizes of continuous outcomes (pain and depression) were summarized as standardized mean differences (SMDs, Cohen's *d*) of mean change scores, along with 95% credible intervals (95% CrIs) and presented in caterpillar plots. An SMD < 0 indicates a more favorable outcome response in the intervention compared to the control group. For binary outcomes (treatment discontinuation), summary results were presented as odds ratios (ORs) with 95% CrI, with an OR > 1 representing higher odds of the event among patients who received the intervention than those who received the comparison. Vague priors were employed throughout the analyses.

We estimated the heterogeneity of treatment effects estimated via the posterior median between-trial variance, τ^2, and interpreted the magnitude of the heterogeneity as previously described.[27]

We checked inconsistency by fitting both consistency and inconsistency models and calculated the deviance information criterion (DIC). A smaller DIC value indicates a better fit of the model to the data. Mean ranks with 95% credible intervals provided a hierarchy of the best treatments.

We fitted all models in OpenBUGS (Linux version, 3.2.3) using three Markov chain Monte Carlo chains. Convergence was assessed using Brooks–Gelman–Rubin R statistic and trace plots. Additional model diagnostics included visual inspection of autocorrelation plots and the posterior densities. Posterior estimates were based on the median (2.5th and 97.5th percentiles) of three chains of 50 000 each, totalling 150 000 simulations after a burn-in period of 10 000 iterations. We assessed transitivity by inspecting trials in terms of patient characteristics (age, sex, and baseline pain value); study design and methods; patient's condition; study setting (eg, outpatient and chronic care); and follow-up time across studies.

If 10 or more trials were available for the same comparison, we examined publication bias through funnel plot asymmetry via Egger's test (for continuous outcome) or Harbord's test (for binary outcomes). Non-Bayesian analyses were performed in Stata (version 16, College Station, TX, USA). We performed a sensitivity analysis based on "low risk of bias" in the randomization process, large trials (>100 patient per arm), and musculoskeletal condition that were defined a priori as potential moderators.

We used the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach to assess the certainty of evidence for direct, indirect, and network comparisons.[54,78]

RESULTS

Our search identified 4108 records. After removing duplicates, we screened 3291 references resulting in 119 publications for full-text review. Of these, 58 trials (10 278 participants) were eligible (**FIGURE1**). None of the included trials were quasi-randomized. Reasons for exclusion are provided in **SUPPLEMENTAL FILE 2**. Fifty-five trials (10 002 participants, median sample size: 152 [IQR: 76 to 239]) contributed pain outcomes, 39 trials (6226 participants, median sample size: 118 [IQR: 69 to 228]) contributed depression outcomes, and 52 trials (9980 participants, median sample size: 152 [IQR: 79 to 244]) contributed treatment discontinuation rate outcomes. A detailed analysis of each of the included studies' arms can be seen in **TABLE**. **FIGURE 2** displays the geometry of the network for pain outcomes. **FIGURE 3** displays the corresponding geometry of the network for depression. **FIGURE 4** displays the corresponding geometry of the network for treatment discontinuation rates. CBT, either as a stand-alone treatment or in combination with exercise-based rehabilitation was the most frequently investigated intervention (52 trials) with six modes of delivery; in person, telephone-based CBT (tele-CBT), mobile app CBT, Internet-delivered CBT (guided and unguided), virtual reality (VR) CBT, and interactive voice response CBT.

The mean age of participants was 53 years (IRQ: 47 to 62), the mean average percentage of female participants was 64%, and the median average baseline pain on a 10-cm scale was 5.4 (IQR: 4.8-5.9; **TABLE**). Most participants had chronic musculoskeletal pain due to osteoarthritis (20 trials, 4387 patients), low back pain (6 trials, 668 patients), fibromyalgia (4 trials, 242 patients), and rheumatoid arthritis (1 trial, 133 patients). The remaining 27 trials included mixed populations of patients with different types of chronic musculoskeletal pain. These conditions varied both in location (neck pain with or without radiculopathy, back pain, low back pain, upper back pain, knee pain, hip pain with or without sciatica, shoulder pain) and in etiology (fibromyalgia, noncancerous, spinal stenosis, degenerative disk, and injury related) and, herein, referred to as "Chronic Pain" in **TABLE**.

The detailed intervention components of all the delivered interventions were reported in 14 (24%) out of 58 studies.

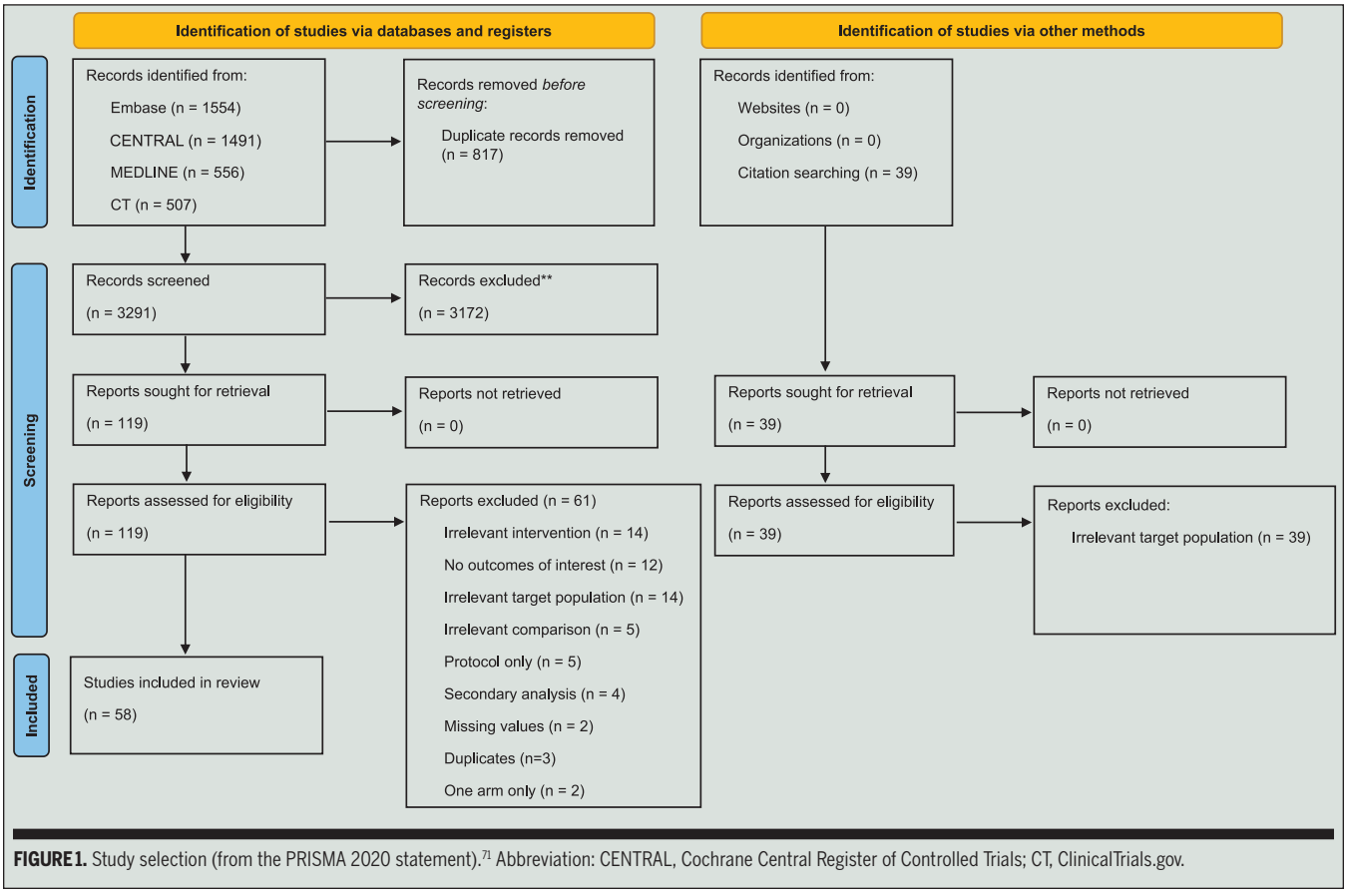

FIGURE 1. Study selection (from the PRISMA 2020 statement).[71] Abbreviation: CENTRAL, Cochrane Central Register of Controlled Trials; CT, ClinicalTrials.gov.

The number of sessions, duration, intensity, or dose were adequately reported in 17 (29%) out of the 58 trials. Only seven trials described both the intervention components and the dose and duration of the intervention. A detailed analysis of the reporting of each component for each study is summarized in **SUPPLEMENTAL FILE 3** using the TiDiER checklist.[50]

SUPPLEMENTAL FILE 4 displays the risk of bias assessment for each domain. No trial was at overall low risk of bias. Thirty-four trials (59%) had a low risk of bias arising from the randomization process, 45 trials (78%) for missing outcome data, 48 trials (83%) for bias in the measurement of the outcomes and 50 trials (86%) for bias in the selection of the reported result. No trials were at low risk of bias for deviations from the intended intervention. Cohen's kappa for the ROB-2 was very high (0.96). **SUPPLEMENTAL FILES 5** and **6** display the assessment of publication bias for pain and depression outcomes, respectively. We did not detect any publication bias as illustrated in the funnel plots.

Assessing Transitivity

We summarized characteristics across direct comparisons for both pain intensity and depression outcomes from all included trials. Most of the trials were set in outpatient settings and focused on chronic musculoskeletal pain and osteoarthritis. Most of the trials reported participant mean ages ranging from 59 to 65.3 years; a subset of trials included a younger demographic, mean ages between 47.4 and 50.5 years. Regarding sex distribution, a considerable number of trials showed female participation exceeding 65%, others reported low proportions of female participants—as low as 3.1%. The median average baseline pain on a 10-cm standardized scale was 5.4 (IQR: 4.8–5.9), suggesting a moderate pain intensity in the examined populations. The trial designs, predominantly parallel, featured a wide range of sample sizes (from as few as 39 participants up to 866 participants). Intervention durations spanned up to 12 weeks across varying comparisons involving the same therapeutic approaches. Our analysis supports the validity of the transitivity assumption.

Pain

Fifty-five trials (n = 10 002 participants; 20 interventions) reported treatment effects for pain intensity. Interactive voice response CBT (SMD = -0.66, 95% CrI, -1.17 to -0.16, posterior probability of superiority > 99%), CDB in person (SMD = -0.50, 95% CrI, -0.97 to -0.04, posterior probability of superiority > 98%), mobile app CBT plus exercise (SMD = -0.37, 95% CrI, -0.69 to -0.02, posterior probability of superiority > 98%), and Internet CBT guided (SMD = -0.21, 95% CrI, -0.42 to 0.01,

TABLE CHARACTERISTICS OF THE INCLUDED STUDIES

Study	Outcome	Study Design	Population	Pain Duration	Mean Age	N	% of Females	Pain at Baseline (standardized, 0-to-10)	Intervention	Control	Arm 3
Aburizik 2013[1]	Depression	Parallel	Chronic pain	Not reported	64.4	83	6%		Tele CBT	Usual care	Tele education
Allen 2010[4]	Pain	Parallel	Osteoarthritis	mean time from onset: 16 years	60.1	515	81.9%	5.9	Tele CBT & education & exercise	Usual care	Tele education
Allen 2016[6]	Pain, depression	Parallel	Osteoarthritis	mean time from onset: 14 years	61.1	300	9.3%	5.1	Tele CBT & education & exercise	Usual Care	NA
Allen 2017[2]	Pain, depression	Cluster	Osteoarthritis	mean time from onset: 10 years	63.9	257	72%	4.2	Tele CBT & exercise	Usual care	NA
Allen 2018[3]	Pain, depression	Parallel	Osteoarthritis	mean time from onset: 13 years	65.3	350	71.7%	3.1	Internet exercise	Usual care	Waitlist
Allen 2019[5]	Pain, depression	Parallel	Osteoarthritis	mean time from onset: 13 years	59	248	49.2%	5.5	Tele CBT	Usual care	NA
Ang 2013[8]	Pain, depression	Parallel	Fibromyalgia	≥ 3 months, mean time from onset: 12 years	47.4	39	97.4%	6.3	Tele CBT	Tele education	NA
Barone Gibbs 2018[9]	Pain	Parallel	Chronic pain	>3 years	51.5	27	77.8%	4.6	Tele CBT & exercise	Waitlist	NA
Baumeister 2020[10]	Pain, depression	Parallel	Chronic pain	≥ 6 months	49.9	210	59.5%	1.8	Internet CBT guided	Usual care	NA
Bennell 2017[11]	Pain	Parallel	Osteoarthritis	time from onset: < 2 year: 30%; 2-10 years: 50%; >10 years: 20%;	62.3	169	62.7%	5.7	Tele CBT	Usual care	NA
Bennell 2022[12]	Pain, depression	Parallel	Osteoarthritis	≥ 3 months	65.4	239	57.7%	5.9	Tele CBT & education & exercise	Internet education	NA
Berman 2009[13]	Pain, depression	Parallel	Chronic pain	Not reported	65.8	78	87.2%	5.3	Internet CBT unguided	Waitlist	NA
Blixen 2004[14]	Pain, depression	Parallel	Osteoarthritis	median (IQR) time from onset: intervention 6.5 (2-18) years; control: 10 (2-30) years	70.8	32	37.5%	6.3	Tele education	Usual care	NA
Boselie 2018[16]	Pain, depression	Parallel	Chronic pain	≥ 3 months				6.5	Internet CBT & telecare	Waitlist	NA
Bossen 2013[17]	Pain, depression	Parallel	Osteoarthritis	mean time from onset: 2.8 years	62	199	64.8%	5.2	Internet exercise	Waitlist	NA
Brattberg 2007[18]	Depression	Parallel	Chronic pain	≥ 6 months	47.3	60	90%		Internet CBT unguided	Usual care	NA
Buhrman 2004[19]	Pain, depression	Parallel	Chronic pain	≥ 3 months (mean time from onset: 10 years)	44.6	56	62.5%	4.1	Internet CBT & telecare	Waitlist	NA
Buhrman 2011[7]	Pain, depression	Parallel	Chronic pain	≥ 3 months (mean time from onset: 12 years)	43.2	54	68.5%	5.5	Internet CBT guided	Waitlist	NA
Carmody 2013[22]	Pain, depression	Parallel	Chronic pain	mean time to onset: 17.5 years	67.7	98	3.1%	8.4	Tele CBT	Tele education	NA
Carpenter 2012[24]	Pain	Parallel	Low back pain	≥ 6 months	42.5	141	83%	5.5	Internet CBT unguided	Waitlist	NA
Chiauzzi 2010[25]	Pain, depression	Parallel	Chronic pain	≥ 3 months	46.1	199	67.3%	5.4	Internet CBT unguided	Internet education	NA
Crotty 2009[29]	Pain, depression	Parallel	Osteoarthritis	Not reported (waitlist for surgery)	67.5	152	60.5%	7.9	Tele education	Usual care	NA
Dear 2018[31]	Pain, depression	Parallel	Chronic pain	> 6 months	50	213	79.8%	5.9	Internet CBT unguided	Usual care	NA
Fanning 2017[36]	Pain	Parallel	Chronic pain	≥ 3 months	70.2	28	78.6%	7	Tele education	Waitlist	NA
Ferwerda 2017[37]	Depression	Parallel	Rheumatoid Arthritis	Not reported	56.4	133	63.9%	..	Internet CBT guided	Usual care	NA
Friesen 2017[39]	Pain, depression	Parallel	Fibromyalgia	≥ 3 months; mean time from onset: 9 years	48	60	95%	5.9	Internet CBT & telecare	Usual care	NA
Garcia 2015[43]	Pain, depression	Parallel	Fibromyalgia	≥ 3 months	50.5	61	100%	5.4	VR CBT	Usual care	NA

(Table continues on next page.)

TABLE Characteristics of the included studies (continued)

Study	Outcome	Study Design	Population	Pain Duration	Mean Age	N	% of Females	Pain at Baseline (standardized, 0-to-10)	Intervention	Control	Arm 3
Garcia 2021[42]	Pain	Parallel	Low back pain	≥3 months; Time from onset: <1 year: 4%; 1-4 years: 29%; 5-10 years: 22%; > 10 years: 45%; > 5 years: 54%	51.5	179	76.5%	5.2	VR CBT	Placebo	NA
Hauser-Ulrich 2020[44]	Pain	Parallel	Chronic pain	Time from onset: 2-6 months: 7%; 6-12 months: 6%; 1-2 years: 16%; 2-5 years: 18%; > 5 years: 54%	43.7	102	80.4%	5.9	Mobile App CBT & exercise	Waitlist	NA
Hausmann 2018[45]	Pain	Parallel	Osteoarthritis	Not reported	64.2	360	23.6%	4.9	Tele education	Placebo	NA
Heapy 2017[46]	Pain, depression	Parallel	Chronic pain	> 3 months	57.9	125	22.4%	5.5	Interactive Voice Response CBT	CBT in person	NA
Herbert 2017[47]	Pain, depression	Parallel	Chronic pain	≥ 6 months	52	128	18%	6.1	Tele CBT	CBT in person	NA
Hinman 2020[49]	Pain	Parallel	Osteoarthritis	≥ 3 months	62.5	175	62.9%	6	Tele CBT & exercise	Tele education	NA
Hüppe 2019[51]	Pain, depression	Parallel	Chronic pain	Not reported	53.5	444	36.7%	4.5	Tele education & exercise	Usual care	NA
Kloek 2018[56]	Pain	Cluster	Osteoarthritis	time from onset: < 1 year: 20%; 1-5 years: 38%; >5 years: 42%;	63	208	67.8%	4.7	Internet education & exercise	Usual care	NA
Kroenke 2019[57]	Pain, depression	Parallel	Chronic pain	≥ 3 months	57.4	294	12.6%	5.9	Internet CBT & telecare	Internet CBT unguided	NA
Lin 2017[58]	Pain	Parallel	Chronic pain	≥ 6 months	51.7	302	84.1%	5.3	Internet CBT guided	Waitlist	Internet CBT unguided
Lorig 2002[59]	Pain	Parallel	Chronic pain	Not reported	45.5	421	71.3%	3.9	Internet education	Usual care	NA
Lorig 2008[60]	Pain	Parallel	Chronic pain	Not reported	53.4	866	90.2%	6.4	Internet CBT guided	Usual care	NA
McCurry 2021[62]	Pain, depression	Parallel	Osteoarthritis	Not reported	70.3	327	74.6%	4.6	Tele CBT	Tele education	NA
Mecklenburg 2018[63]	Pain	Parallel	Osteoarthritis	Not reported	46	155	36.8%	4.5	Mobile App CBT & exercise	Internet education	NA
Naylor 2008[66]	Pain	Parallel	Chronic pain	≥ 6 months; mean time from onset: 11 years	46	51	86.3%	5.8	Interactive Voice Response CBT	Usual care	NA
NCT01236196[94]	Pain, depression	Parallel	Chronic pain	≥ 12 months	35	39	17.9%	7.2	Tele CBT	Tele education	NA
Nelligan 2021[67]	Pain	Parallel	Osteoarthritis	≥ 3 months	59.5	206	61.2%	6.3	Internet education & exercise	Internet education	NA
O'moore 2018[69]	Pain, depression	Parallel	Osteoarthritis	Not reported	61.4	69	79.7%	4.7	Internet CBT unguided	Usual care	NA
Pariser 2005[73]	Pain, depression	Parallel	Osteoarthritis	time from onset: < 1 year: 6%; 1-5 years: 12%; 5-10 years: 25%; > 10 years: 42%	65	85	80%	5.7	Tele education & exercise	Home exercise	NA
Petrozzi 2019[76]	Pain, depression	Parallel	Low back pain	> 3 months; time from onset: >1 year: 5 %; 1-2 years: 13%; 2-5 years: 15% >5 years: 67%;	50.4	108	50%	5	Internet CBT unguided	Usual care	NA
Rini 2016[79]	Pain	Parallel	Osteoarthritis	≥ 3 months	67	113	80.5%	4.9	Internet CBT unguided	Waitlist	NA
Rutledge 2018a[82]	Pain	Parallel	Low back pain	≥ 6 months	53.3	66	37.9%	5.3	Tele CBT & exercise	Tele education	NA
Rutledge 2018b[81]	Pain, depression	Parallel	Low back pain	≥ 6 months	63.4	61	9.8%	4.9	Tele CBT	Tele education	NA
Sander 2020[83]	Pain, depression	Parallel	Chronic pain	≥ 6 months	52.8	295	62.4%	1.6	Internet CBT guided	Usual care	NA
Schlicker 2020[84]	Pain, depression	Parallel	Chronic pain	Not reported	50.8	76	72.4%	4.3	Internet CBT guided	Usual care	NA
Shebib 2019[86]	Pain	Parallel	Low back pain	Not reported	43	113	40.7%	4.6	Mobile App CBT & exercise	Internet education	NA

Smith 2019[88]	Pain, depression	Parallel	Chronic pain	> 3 months; time from onset: < 5 years: 41%; > 5 years: 59%	45	80	87.5%	5.3	Internet CBT & exercise	Usual care	NA
Thorsell 2011[90]	Pain, depression	Parallel	Chronic pain	>1 year	46	90	66.7%	8.1	Tele CBT	Tele education	NA
Trompetter 2015[92]	Pain, depression	Parallel	Chronic pain	≥ 6 months	70	238	75.6%	6.2	Internet CBT guided	Usual care	Internet education
Trudeau 2015[93]	Pain, depression	Parallel	Osteoarthritis	Not reported	49.9	228	68.4%	5.4	Internet CBT unguided	Usual care	NA
Williams 2010[96]	Pain, depression	Parallel	Fibromyalgia	≥ 3 months	50.5	118	94.9%	5	Internet CBT unguided	Usual care	NA

Abbreviation: CBT, cognitive behavioral therapy; NA, not applicable; VR, virtual reality.

posterior probability of superiority = 97%) were associated with the highest probabilities of being superior to waitlist control (**FIGURE 5**).

Interactive voice response CBT had the highest probability of being ranked the best intervention (58.6% posterior probability of being ranked the best), followed by CBT in person and mobile app mobile app CBT plus exercise at 36.4% and 20.3%, respectively (**SUPPLEMENTAL FILE 7**). **SUPPLEMENTAL FILE 8** outlines the relative effectiveness for pain intensity for all possible pairs of interventions. Remotely delivered CBT nodes had statistically comparable effects to in-person CBT on the head-to-head comparisons.

Sensitivity analysis of large trials only (average of ≥ 100 randomized participants per arm) showed evidence of superiority for Internet-delivered CBT (SMD -0.40, 95% CrI -0.75 to -0.05) with a 99% posterior probability of superior treatment effects on reducing pain outcomes compared to waitlist control (**SUPPLEMENTAL FILE 9**). Analyses based on low risk of bias in the randomisation process showed evidence of superiority with a probability >99% for two interventions: interactive voice response CBT (SMD -0.91, 95% CrI -1.57 to -0.24) and Internet education & exercise; (SMD -0.69, 95% CrI -1.19 to -0.16; **SUPPLEMENTAL FILE 10**).

We conducted a sensitivity analysis for patients with osteoarthritis only. Six remote interventions had more than 84% probability of superiority compared to waitlist control at 12-week follow-up in patients with osteoarthritis: tele CBT combined with education and exercise, tele CBT, Internet exercise, tele CBT and exercise, Internet education and exercise, and Internet CBT unguided. None of the interventions excluded the null threshold (**SUPPLEMENTAL FILE 11**).

Depression

Thirty-nine trials (n = 6226 participants; 17 interventions; **TABLE**) were included in the NMA for depression outcomes. The most frequent interventions were usual care (22 arms, 1770 participants), Internet CBT unguided (9 arms, 717 participants), and tele CBT (9 arms, 518 participants). **FIGURE 6** shows the effect estimates for depression outcomes ordered by the magnitude of the treatment effect. Internet-delivered CBT plus telecare (SMD -0.51, 95% CrI -0.87 to -0.13, posterior probability of superiority > 99%) and Internet-delivered CBT unguided (SMD -0.30, 95% CrI -0.64 to 0.04, posterior probability of superiority = 96%) were the interventions associated with the highest posterior probabilities of superiority compared to the waitlist group. Internet-delivered CBT plus telecare had the highest probability of being ranked the best intervention (46.5% posterior probability of being the best), followed by Internet-delivered CBT unguided and Internet-delivered CBT guided at 12.7% posterior and 12.3%, respectively (**SUPPLEMENTAL FILE 7**).

SUPPLEMENTAL FILE 8 outlines the relative effectiveness for depression outcomes for all possible pairs of interventions. Remotely delivered CBT nodes had similar effect sizes to in-person CBT based on the head-to-head comparisons. A sensitivity analysis for depression including only large trials is summarized in **SUPPLEMENTAL FILE 12**. A sensitivity analysis including only trials with a low risk of bias in the randomization process is summarized in **SUPPLEMENTAL FILE 13**. The results of the large trials analysis were statistically comparable to the ones of the main analysis (95% CrIs overlapped with main findings). Internet CBT plus telecare, Internet CBT unguided and Internet CBT guided, had >90% probability of being superior to waitlist control. The probabilities dropped to 74%, 60%, and 57% for Internet CBT & telecare, Internet CBT unguided and Internet CBT guided, respectively, when adjusting for bias in the randomization process. The credible intervals were wide and did not exclude the null threshold.

Discontinuing Treatment

Most studies did not report reasons for dropouts such as adverse and serious events. It was unclear what proportion of dropouts were attributed to adverse events (AEs). There was no evidence of

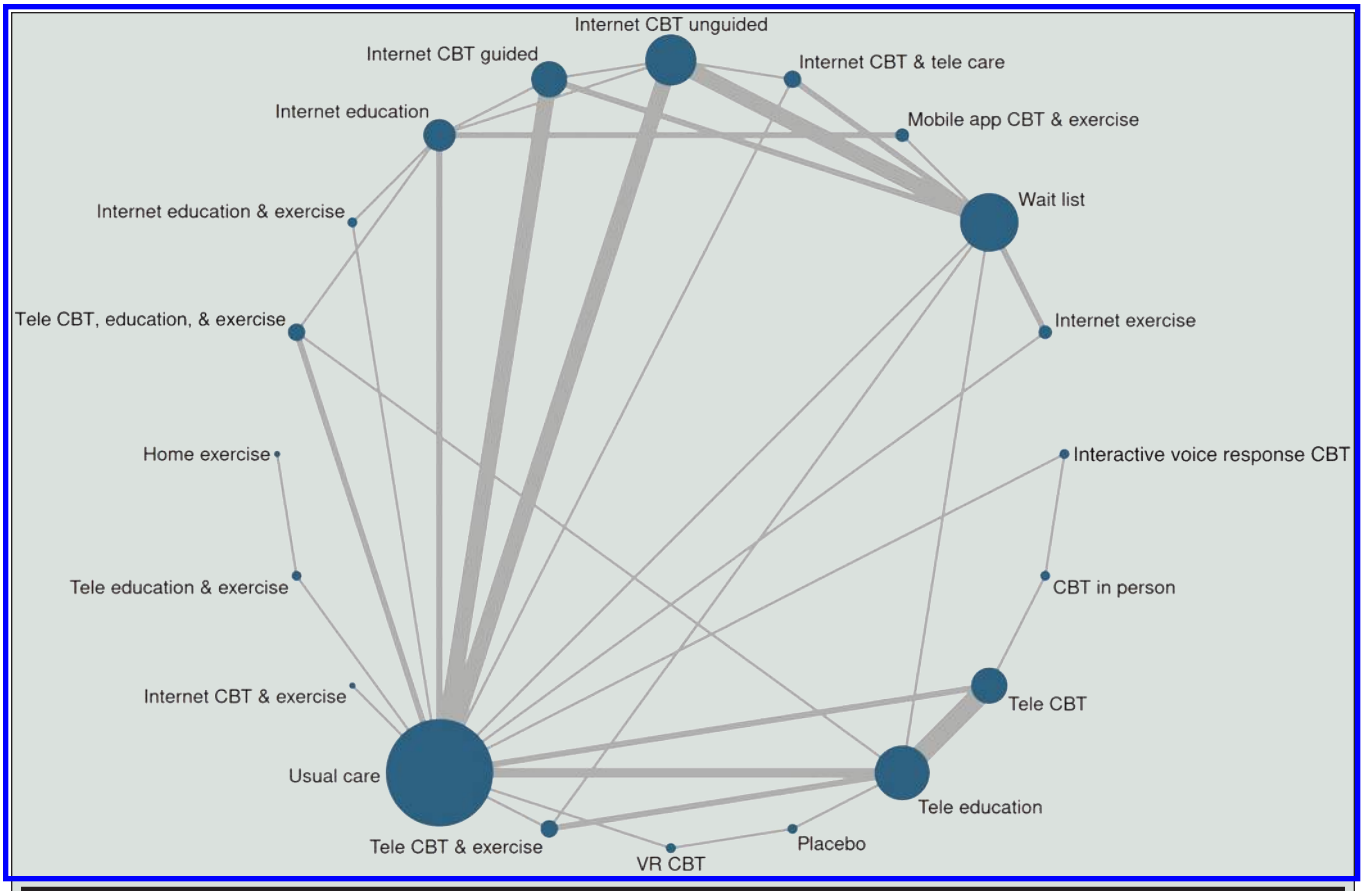

FIGURE 2. Network plot for pain outcomes. The lines connecting the nodes denote the available direct comparisons between treatments. The width of the lines is proportional to the number of trials comparing every pair of treatments. The size of every circle is proportional to the number of randomly allocated participants. Abbreviation: CBT, cognitive behavioral therapy; VR, virtual reality.

an association among the interventions with higher odds of dropouts (all credible intervals included the null effect). A detailed analysis of the dropouts per treatment node is summarized in **SUPPLEMENTAL FILE 14**. **SUPPLEMENTAL FILE 15** summarizes the odds of treatment discontinuation for all possible pairs of interventions. A sensitivity analysis for treatment discontinuation including only large trials is summarized in **SUPPLEMENTAL FILE 16**. A sensitivity analysis including only trials with a low risk of bias in the randomization process is summarized in **SUPPLEMENTAL FILE 17**. A sensitivity analysis for patients with osteoarthritis only is summarized in **SUPPLEMENTAL FILE 18**. Overall, all sensitivity analyses mirrored the findings from the main analysis, with all 95% credible intervals crossing the line of null effect.

Model Fit, Heterogeneity and Inconsistency Assessment

For both pain intensity and depression, the DIC was smaller in the consistency model than in the inconsistency model, indicating no major concerns with inconsistency (**SUPPLEMENTAL FILE 19**). The magnitude of τ^2 at 12 weeks indicated low statistical heterogeneity for pain intensity ($\tau^2 = 0.04$; 95% CrI, 0.01 to 0.08), depression ($\tau^2 = 0.01$; 95% CrI 0.001 to 0.09), and for dropouts ($\tau^2 = 0.41$; 95% CrI, 0.16 to 0.95).

Certainty of Evidence

For pain outcomes, the certainty of evidence ranged from low to moderate (**SUPPLEMENTAL FILE 20**). For depression outcomes, the certainty of evidence ranged from very low to moderate (**SUPPLEMENTAL FILE 21**). For treatment discontinuation rate, certainty of evidence ranged from very low to moderate (**SUPPLEMENTAL FILE 22**).

DISCUSSION

CBT interventions were associated with very high probability of improving pain intensity and depression at 12 weeks compared to waitlist control. The magnitude of the treatment effects for pain outcomes varied by delivery method. Interactive voice response, Internet, mobile, and telephone-delivered remote CBT interventions overlapped in credible intervals with in-person CBT. Interactive voice response and in-person CBT interventions were associated with moderate magnitudes of treatment effects compared to waitlist/control, but the evidence was derived from two small trials only.

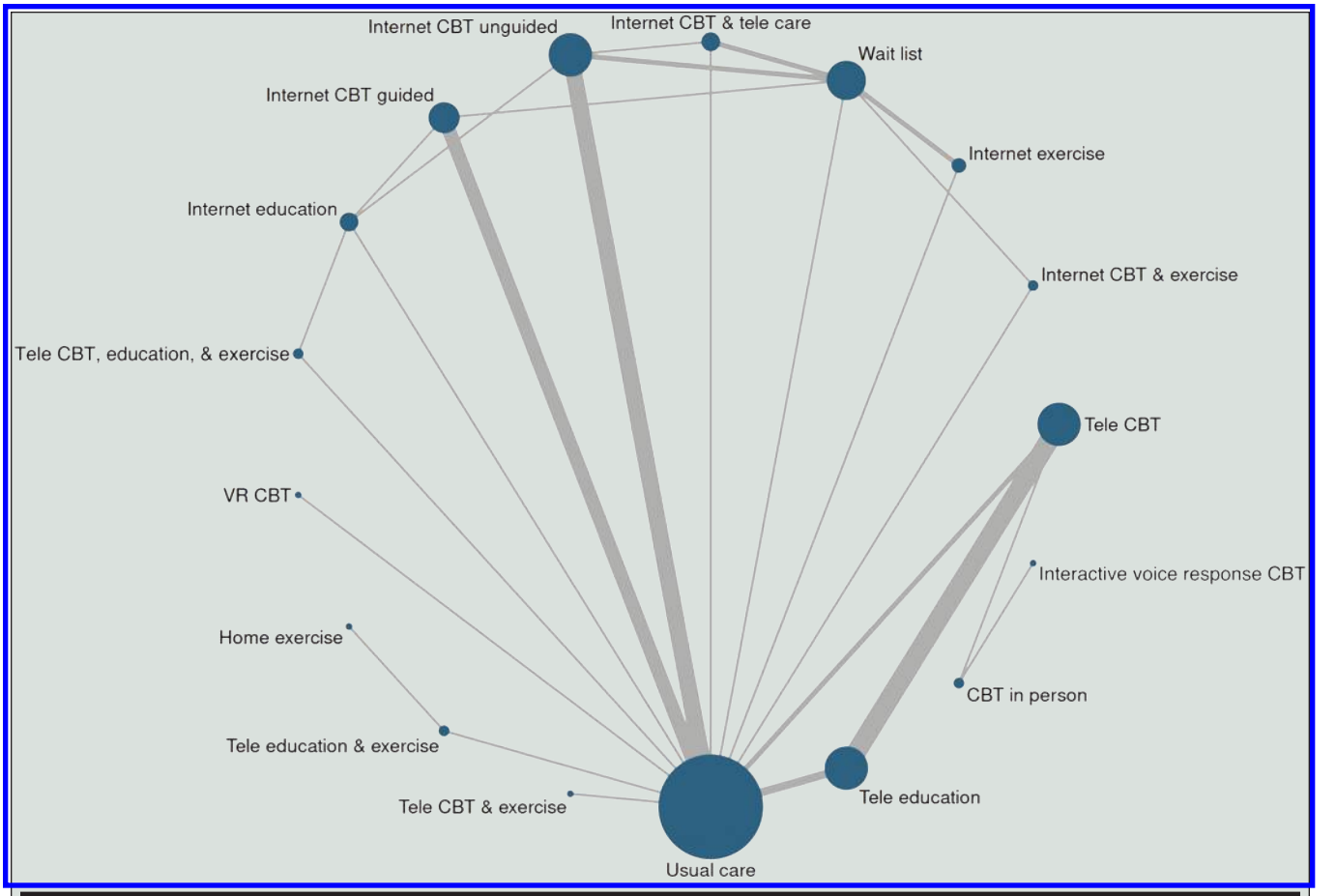

FIGURE 3. Network plot for depression outcomes. The lines connecting the nodes denote the available direct comparisons between treatments. The width of the lines is proportional to the number of trials comparing every pair of treatments. The size of every circle is proportional to the number of randomly allocated participants. Abbreviation: CBT, cognitive behavioral therapy; VR, virtual reality.

For depression outcomes after 12 weeks of follow-up, remote interventions such as Internet-delivered CBT guided, unguided, or CBT in combination with telecare had the highest probability of being the best treatment approach compared to waitlist/control. Analyses restricted to large trials or studies with a low risk of bias in the randomisation process corroborated the results from the main analysis. Only seven trials described the intervention components and the dose and duration of the intervention adequately enough for replication in clinical practice.

Strengths

As opposed to previous studies that either pooled all delivery methods together[30] or included only one delivery mode,[41,77,91] our NMA integrates all available randomized evidence on the effectiveness of remote rehabilitation interventions on pain and depression in one analysis. Integrating direct and indirect comparisons improves precision and allows for head-to-head comparisons with different delivery modes and interventions. The approach makes comparisons between the different interventions explicit and allows us to rank the different treatments in terms of their individual components, representing a more useful piece of information for decision-making by patients and practitioners. We also included an analysis of treatment discontinuation rate outcomes, focusing on any-cause dropouts/withdrawals, something that was not present in previous studies. The use of vague priors minimizes bias that could emerge from strong or misinformed priors and ensured that our findings were not influenced by any specific prior belief, making them broadly applicable.[34,70,85]

Limitations

Our analysis is contingent upon the integrity and the quality of the data upon which it is based on. No trial was at low risk of bias overall. Potential biases in the included studies in terms of the randomization process, deviations from intended interventions and missing outcome data could inflate the perceived efficacy of treatment effects. Patient blinding is an inherent limitation in nonpharmacological trials due to the nature of the interventions. It is

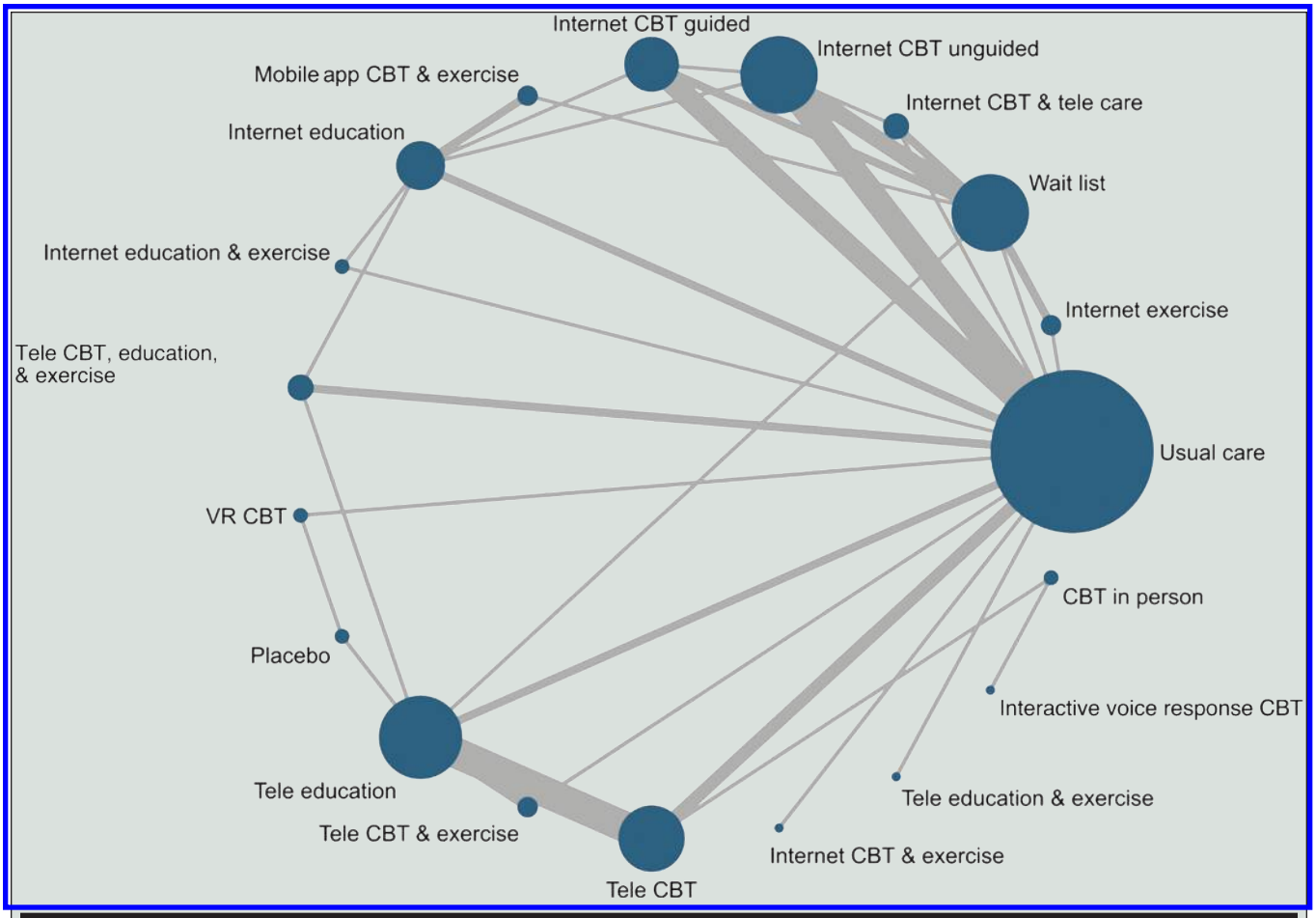

FIGURE 4. Network plot for treatment discontinuation. The lines connecting the nodes denote the available direct comparisons between treatments. The width of the lines is proportional to the number of trials comparing every pair of treatments. The size of every circle is proportional to the number of randomly allocated participants. Abbreviation: CBT, cognitive behavioral therapy; VR, virtual reality.

not surprising that no study was rated as low risk of bias overall. Most trials relied solely on estimates from intention-to-treat analyses, which might potentially lead to attenuated treatment effects. Furthermore, the scope of our analysis was specifically tailored to outcomes observed at 12-week follow-up meaning that the applicability of our findings to longer durations is uncertain.

Although our search was broad and conducted by an experienced librarian, we did not include all possible natural language terms, such as "cognitive behavioral therapy". Thus, due to the diversity of the interventions of interest, it is possible a few trials could have been missed, especially those published in languages other than English. However, the fact that most trials we included involved CBT (46 out of 58, 79%) is reassuring, indicating that our search was appropriately sensitive. Our sensitivity analysis per patient condition is limited to patients with OA. The limited number of trials for the rest of the patient conditions led to a disconnected network when we attempted to analyze them separately; hence, no further analysis was conducted. Lastly, the completeness and clarity of reporting the intervention components may pose another limitation, potentially influencing the interpretability and generalizability of our results.

Previous Evidence

Our findings build on and expand the current understanding of CBT interventions for chronic pain. While a recent systematic review has highlighted the benefits of in-person CBT in reducing pain intensity and stress in individuals with chronic pain (excluding headache),[20] our study emphasizes the potential of remote CBT. Our findings not only corroborate these observations regarding pain intensity and depression but also expand upon them.

We highlight the potential of remote CBT—delivered through modalities such as interactive voice response, Internet platforms, and mobile applications—to match the efficacy of its in-person counterpart, especially for individuals with chronic pain and depression. A previous smaller NMA on the comparative effectiveness of different remote modalities

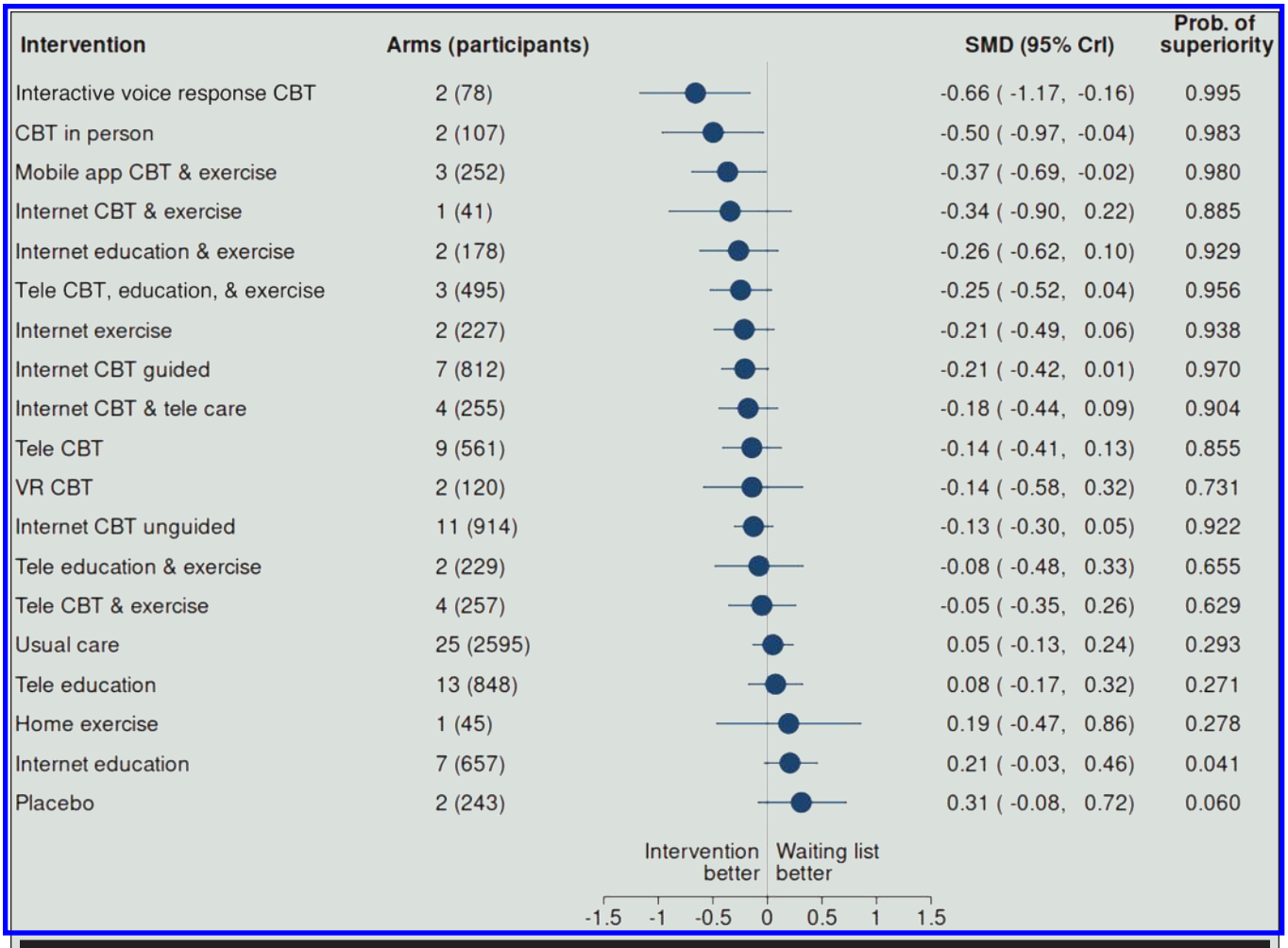

FIGURE 5. Treatment effect of interventions on pain intensity as compared to waitlist control. Interventions are ordered according to the treatment effect size on pain intensity at 12-week follow-up. Abbreviation: 95% CrI, 95% credible interval; CBT, cognitive behavioral therapy; Prob, probability; SMD = standardized mean difference; VR, virtual reality.

in people with chronic back pain was published in 2019 and included 30 trials with 5394 patients.[87] However, this analysis was based primarily on the modes of delivery of interventions, rather than focusing on the individual components of the rehabilitation interventions.[87] In contrast, our review includes 58 trials with 10 278 participants; we examined remote delivery methods across different types of interventions on pain, depression, and treatment discontinuation rate outcomes.

Clinical Implications

Clinicians may use our findings to improve access to digital health care for patients with chronic musculoskeletal pain and depressive symptoms. Remote rehabilitation interventions yield outcomes statistically comparable to tradition in-person CBT care in addressing pain and depression. This suggests that patients with chronic musculoskeletal pain and depressive symptoms might not solely rely on in-person care; they could benefit from remote care alternatives.[40] While guidelines[74] underscore the importance of telemedicine for such patients, implementation often faces challenges. Barriers stem from a scarcity of research, coupled with uncertainties surrounding treatment discontinuation rates associated with remote interventions.[74] Our review addresses this gap by presenting novel findings.

We highlighted that remote CBT interventions, particularly when integrated with exercise targeting pain and depression outcomes offered clinical benefits in line with an in-person care. From a policy perspective, this is crucial, especially when a growing body of evidence suggests that digital health is cost effective and improves access to care.[80] However, it is essential for practitioners to tread carefully when translating our findings into real-world clinical settings. Across the 58 trials we examined, no serious AEs were reported. Yet, this might be influenced by incomplete or inconsistent reporting. Recent data have suggest a disparity in AEs reporting; only one out of nine psychotherapy

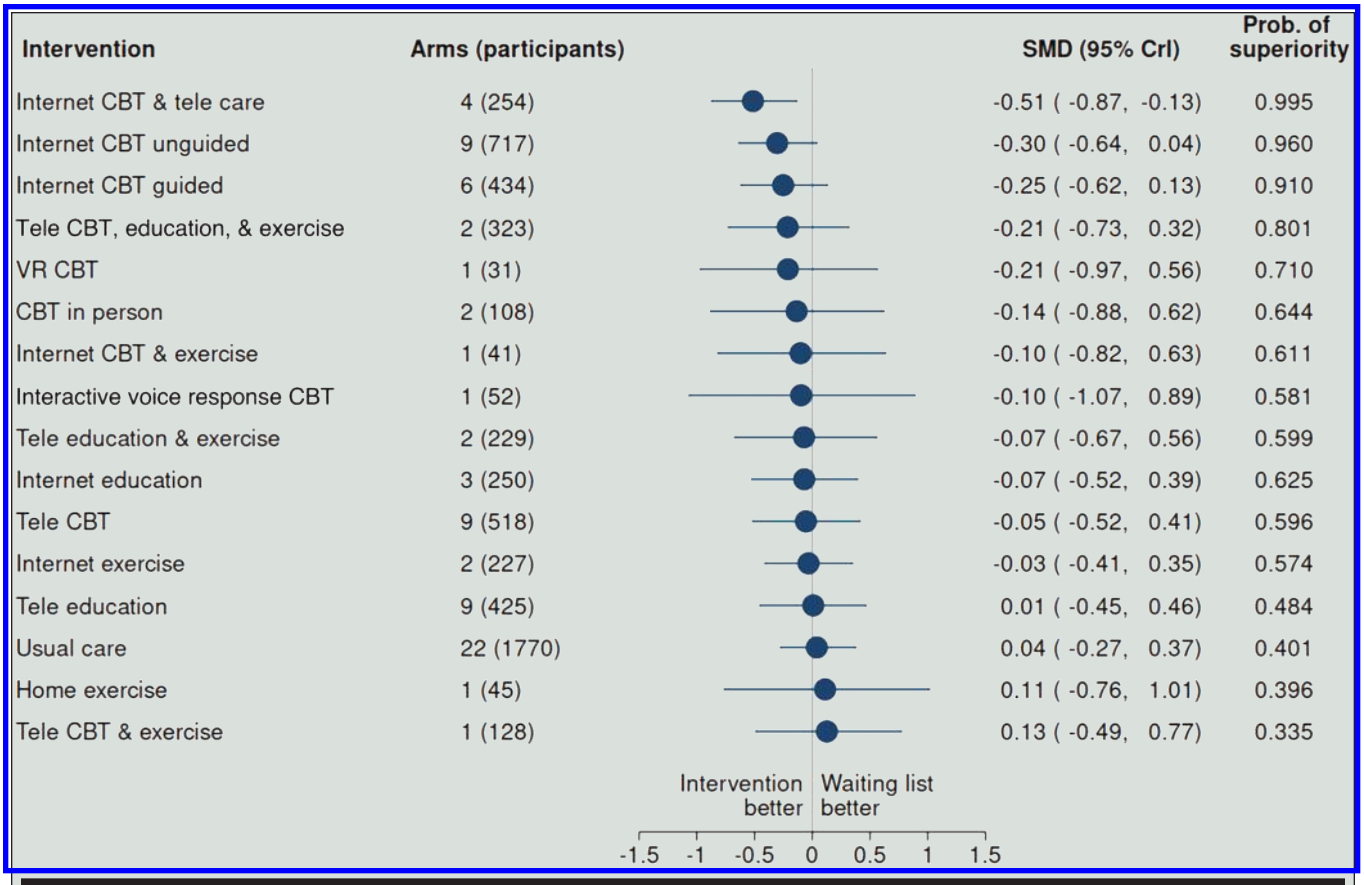

FIGURE 6. Treatment effect of interventions on depression levels as compared to waitlist control. Interventions are ordered according to the treatment effect size on depression levels at 12-week follow-up. Abbreviation: 95% CrI, 95% credible interval; CBT, cognitive behavioral therapy; Prob, probability; SMD = standardized mean difference; VR, virtual reality.

trials reported any information on AEs, in contrast to over 90% of pharmacological studies, with inadequacies in reporting the methodology for assessing AEs and the specific AEs that occurred.[72]

Implementing appropriate care may face challenges in clinical practice, given the poor descriptions of the components of the delivered interventions, such as the number of sessions, the dose, the duration, and the intensity of the intervention. The clinical interpretation of study results in the chronic pain field is often challenged by the subjective nature of pain reporting and the diverse pain aetiologies that are present in patients with chronic musculoskeletal pain. This diversity in underlying causes and symptoms can introduce complexities in the applicability of findings to specific patient populations, and more trials on specific population are warranted."

Future Studies

Future studies should adhere to stringent reporting guidelines, especially with the increasing prominence of telemedicine or remote interventions. For better clarity and replicability, a standardized approach should be adopted when describing intervention components. There is a need for future trials to incorporate longer follow-up periods and to report outcomes consistently across these extended durations. To ensure that clinicians and researchers are fully informed, it is essential to have a systematic approach to documenting and reporting AEs in future trials.

CONCLUSION

Internet and tele CBT were the most effective remote interventions for people with chronic musculoskeletal pain and depression and were associated with the highest probabilities of benefit regarding pain intensity and depression. ◉

KEY POINTS

FINDINGS: Internet and telecognitive behavioural therapy (CBT) were the most effective remote interventions for people with chronic musculoskeletal pain and depression. The interventions were associated with higher probability of improving pain and depression than waitlist control, and produced similar effects to in-person CBT.

IMPLICATIONS: Clinicians might adopt digital health interventions to improve access to effective care for people with chronic musculoskeletal pain and depression.

CAUTION: Our analysis was limited to 12-week follow-up, and therefore, clinicians that perform such interventions for a longer period might come across different results.

STUDY DETAILS

AUTHOR CONTRIBUTIONS: PB and JCM conceived the idea for the review. JCM was the nominated principal applicant on the grant funding this work, supervised staff and trainees, and led team meetings. PB and TVP designed, undertook the literature search, and coordinated the study. PB, JCM, GN, MCT, and DVP gave crucial intellectual input and provided critical revision for the initial protocol and database building. PB, GN, TVP, MCT, and DVP acquired data, screened records, extracted data, and assessed risk of bias. PB, TVP, and DVP wrote the first draft of the manuscript. All authors gave crucial feedback on the revised report and approved the final version of the manuscript. The guarantor (PB) accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. The corresponding author (PB) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

DATA SHARING: Data are available upon request. The guarantor (PB) is willing to examine all requests for the full data set after 2 years from the date of this publication.

PATIENT INVOLVEMENT: No patient was involved in this study.

ACKNOWLEDGEMENTS: *JCM was supported by the Canada Research Chair in Musculoskeletal Health Outcomes and Knowledge Translation, and the Dr. James Roth Research Chair in Musculoskeletal Measurement and Knowledge Translation. PB was supported by the Canadian Institutes of Health Research Doctoral award and the Arthritis Society Postdoctoral Fellowship Award with funding reference number 20-0000000016. TVP is funded by the Chevening Scholarship Program (Foreign and Commonwealth Office, United Kingdom). GN was supported by the Transdisciplinary Bone & Joint Training Award, the Collaborative Training Program in Musculoskeletal Health Research, Western University; and a CIHR Postdoctoral Fellowship Award.*

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