Multidisciplinary-based Rehabilitation (MBR) Compared With Active Physical Interventions for Pain and Disability in Adults With Chronic Pain

A Systematic Review and Meta-analysis

*Máire-Bríd Casey, BSc (Physio), MMT, MISCP,**
Keith M. Smart, PhD, MSc, BSc (Hons) Physio, MISCP,†
*Ricardo Segurado, PhD, BA (Mod), PG, DIP,**
*and Catherine Doody, PhD, MSc, Dip Physio, Dip TP**

Downloaded from http://journals.lww.com/clinicalpain by /vrlaEfGK95nDAe9qHNHTodTYFkO9cv0vhuINdv9d8uuNc3Smxx+5ZadO9L/bRekNudV4Js7EEreoNuCl3L0B4SIE2hh2rHjoWNIKSd0Y223gSQgQ3NCk1tdBunhdrrhnp0lwfylhkxUP7xGw//NQ== on 10/12/2020

Objective: This systematic review and meta-analysis examined the effectiveness of multidisciplinary-based rehabilitation (MBR) in comparison with active physical interventions for adults with chronic pain.

Materials and Methods: The review was conducted in line with the recommendations provided in the Cochrane Handbook for Systematic Reviews and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A total of 8 electronic databases were searched from inception to November 2018. Only randomized controlled trials were eligible for inclusion. In total, 31 trials were identified, and most studies involved patients with chronic low back pain (25 trials). The main outcomes considered were pain intensity and disability at short-term follow-up ($\leq$3 mo after treatment), medium-term follow-up ($>$3 and $<$12 mo), and long-term follow-up ($\geq$12 mo). The quality of the evidence was assessed according to the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach

Results: A total of 27 studies were included in the meta-analysis. Statistically significant differences in favor of MBR were found for pain intensity and disability at short-term follow-up (standardized mean difference = 0.53 and 0.50) and long-term follow-up (standardized mean difference = 0.56 and 0.77), but the quality of the evidence was low. There was no significant difference between MBR and active physical interventions in the medium-term follow-up.

Conclusions: Overall, the results suggest that MBR may lead to greater improvements in pain intensity and disability compared with active physical interventions, and the effects appear to be sustained in the long term. However, these findings should be interpreted with caution in light of the low quality of the evidence, with all but one trial judged to be at high risk of bias. Further research is required to assess the effectiveness of MBR for people with chronic pain conditions other than low back pain.

Key Words: multidisciplinary-based rehabilitation, physical intervention, chronic pain

(*Clin J Pain* 2020;36:874–886)

Chronic pain is defined as pain that persists or recurs for $>$3 months and is now viewed as a disease in its own right.[1] The prevalence of chronic pain is high, with 19% of adults in Europe reported to experience chronic pain of moderate to severe intensity.[2] A recent survey of 1204 Irish people found that 1 in 3 people met the criteria for a diagnosis of chronic pain, and over 80% of those reported $>$1 pain site.[3] The financial effect of chronic pain is substantial, with the mean cost of treating chronic pain estimated at €5665 per patient, extrapolated to a total of €5.34 billion annually or 2.86% of Irish GDP in 2008.[4]

Chronic pain is widely considered to be a biopsychosocial phenomenon, affecting a person's physical and emotional state, in addition to their ability to participate in social and work activities.[2,5,6] The SIGN clinical guidelines for the management of chronic pain advocate a biopsychosocial approach to treatment.[7] The National Institute for Health and Care Excellence (NICE) has been commissioned by the Department of Health in England to develop an up-to-date clinical guideline on chronic pain.[8] This guideline, due to be published in 2020, will be used alongside other NICE guidelines related to specific conditions that are known to cause pain, such as low back pain (LBP) and sciatica[9] and osteoarthritis.[10] Specific guidelines for the management of fibromyalgia (FM) are also available.[11] There is considerable overlap within the various guidelines in terms of treatment recommendations for chronic pain conditions. These recommendations include supported self-management, advice on staying active, and exercise therapy of many forms. Referral for combined physical/psychological programmes or multidisciplinary-based rehabilitation (MBR) is also advocated.[7,9,11] MBR is a coordinated approach to pain management, usually delivered to groups by a team of health care professionals from disciplines such as pain medicine, nursing, psychology, physiotherapy, and occupational therapy.[12] The British Pain Society guidelines for pain management programmes report a preference for longer, more intensive interventions where possible,[13] but positive results have also been reported

Received for publication October 17, 2019; revised May 24, 2020; accepted July 22, 2020.
From the *School of Public Health, Physiotherapy and Sports Science, University College Dublin; and †Physiotherapy Department, St Vincents University Hospital, Dublin, Ireland.
Supported by the Health Research Board, Dublin, Ireland Grant reference HPF-2016-1685. The Health Research Board were not involved in any part of the design, execution, or interpretation of this study.
The authors declare no conflict of interest.
Reprints: Máire-Bríd Casey, BSc (Physio), MMT, MISCP, School of Public Health, Physiotherapy and Sports Science, University College Dublin, Belfield, Dublin 4, Ireland (e-mail: maire-brid.casey@ucdconnect.ie).
Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website, www.clinicalpain.com.
Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.
DOI: 10.1097/AJP.0000000000000871

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

following abbreviated pain management programmes.[14] Systematic reviews investigating MBR for LBP have provided moderate to strong evidence to support the effectiveness of MBR, in comparison with usual care and physical interventions.[15–17] However, one of these systematic reviews noted that the effects of MBR compared with usual care or physical interventions were modest, and the authors recommend that clinicians consider the monetary costs and time involved before referring patients with chronic LBP for MBR.[16] A subsequent systematic review found no clinically significant differences in pain or disability outcomes in a comparison of physical, behavioral/psychologically informed, and combined interventions for nonspecific spinal pain.[18]

Previous systematic reviews comparing MBR with physical interventions have defined physical interventions broadly to include both active treatments, such as exercise and physical activity, and passive modalities, such as manual therapy and electrotherapy modalities.[16,18] Exercise and physical activity interventions have been reported to improve pain, disability, and quality of life in chronic pain conditions.[19,20] Clinical guidelines recommend exercise of any form, with no evidence to support one particular type of exercise over the other.[7,11] The revised EULAR guidelines for FM also advocate exercise as the only therapy-based intervention with a strong evidence base.[11] In addition to the positive effects on pain, physical function, and well-being, the authors also refer to the availability, safety, and relatively low cost of exercise interventions.

In contrast, there is a lack of evidence to support the provision of passive physical interventions for treatment of chronic pain. The NICE guideline for the management of LBP and sciatica includes a specific recommendation that passive physical therapies such as acupuncture, electrotherapy, traction, and orthotics should not be offered. This guideline also suggests that manual therapy only be offered as part of a package that includes exercise with or without psychological therapy.[9] This systematic review will compare MBR with physical interventions, which include an active component such as exercise or physical activity and may additionally include passive therapies. Interventions that feature only passive therapies will be excluded.

A small number of systematic reviews have considered the evidence for MBR related to chronic pain conditions other than LBP or neck pain. Karjalainen and colleagues[21,22] found few high-quality studies and little evidence to support MBR for FM and musculoskeletal pain or for neck and shoulder pain among working-age adults. A subsequent systematic review and meta-analysis involving patients with FM reported that multicomponent therapy was effective in reducing pain and fatigue immediately after treatment when compared with a waiting list control, relaxation, treatment as usual, and education, but the effects were not sustained in the longer term.[23] To our knowledge, a systematic review examining the evidence for MBR compared with active physical interventions in chronic noncancer pain conditions has not been conducted in recent years. This systematic review and meta-analysis will build on previous reviews of MBR by including patients with a wide variety of chronic pain conditions such as chronic spinal pain, FM, persistent widespread pain, whiplash-associated disorder, and complex regional pain syndrome and in addition will compare MBR with evidence-based active physical interventions only.

MATERIALS AND METHODS

Protocol and Registration

The systematic review was registered on the Prospero database PROSPERO 2018 CRD42018117824 (www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42018117824).

Study Design

The systematic review and meta-analyses were conducted in accordance with the Cochrane Handbook for Systematic Reviews, and the results are reported according to the guidelines included in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Search Methods for Identification of Studies

Electronic search strategies were developed in conjunction with an academic medical librarian for each electronic database. The following databases were searched from inception to November 9, 2018: Cochrane Central Register of Controlled Trials (CENTRAL), clinicaltrials.gov, CINAHL, Embase, MEDLINE Ovid, PEDRO, PsychINFO, and Scopus. References were exported to Endnote, and duplicates were removed using the Endnote software. The remaining references were checked manually, and residual duplicates were removed. The search terms are listed in Supplemental Digital Content 1 (Search strategy, http://links.lww.com/CJP/A680). In addition to the electronic searches, the reference lists of previous relevant systematic reviews[16,18] were scanned, and further studies were identified and included.

Eligibility Criteria

Only randomized controlled trials (RCTs) published as full text in the English language in peer-reviewed journals were included. Studies including adults (18 y of age and older) with chronic noncancer pain (defined as pain persisting for 12 wk or more) were eligible. Studies were excluded if they pertained to specific pain conditions such as inflammatory conditions (including rheumatological disorders or spondyloarthropathy), clearly diagnosed radiculopathy, infection (including human immunodeficiency virus), neoplasm, metastasis, fracture, headache, or migraine. Studies that included individuals with major psychiatric or substance misuse disorders were also excluded.

Studies were required to examine the effectiveness of MBR compared with an active physical intervention. There is some inconsistency in the definition of MBR interventions for chronic pain.[7] We applied the same definition of MBR that was used in a previous Cochrane review related to MBR for LBP.[16] The previous review defined MBR as an intervention that included a physical component (eg, exercise or physiotherapy) and at least one other element that was psychological, social, or occupational. In addition, the intervention must have been delivered by a team comprising at least 2 clinicians from different professional backgrounds. For the purpose of this review, an active physical intervention was defined as one that involved some form of exercise or physical activity. Studies featuring interventions that combined exercise with passive treatments (eg, manual therapy, massage, chiropractic and osteopathic treatment, electrotherapy modalities, and acupuncture) were included, but studies examining only passive physical interventions were excluded. Studies featuring either group or individual therapies were included, but it was required that the MBR

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

and active physical interventions were delivered face to face. Online or telephone-based interventions were excluded.

Clinical Outcomes

The outcomes considered in the systematic review were pain intensity and disability, assessed using patient-reported outcome measures. Outcomes were considered as short-term (up to 3 mo posttreatment), medium-term (> 3 and <12 mo) and long-term (12 mo or more). When a study measured outcomes at a variety of timepoints, the closest timepoint to 3 months (for short-term), 6 months (for medium-term), and 1 year (for long-term) was chosen for inclusion in the meta-analysis.

Selection of Studies

Two independent reviewers screened titles and abstracts of all studies. The full texts of potentially eligible studies were sourced and screened by 2 reviewers (M.-B.C. and K.M.S. or C.D.) to further determine eligibility. Disagreements were resolved by discussion and consensus or by consultation with a third reviewer (K.M.S. or C.D.). Original study authors were e-mailed when clarification was required. Reasons for the exclusion were documented by both reviewers.

Assessment of Risk of Bias

Risk of bias was assessed by 2 reviewers independently using Version 2 of the Revised Cochrane Risk of Bias Tool.[24] Two reviewers (M.-B.C. and K.M.S. or C.D.) independently assessed risk of bias for each included study. The Cochrane Risk of Bias tool assesses risk of bias in 5 domains:

(1) Risk of bias arising from the randomization process.
(2) Risk of bias due to deviations from the intended interventions (*effect of assignment to intervention*).
(3) Risk of bias due to missing outcome data.
(4) Risk of bias in measurement of the outcome.
(5) Risk of bias in selection of the reported result.

Each item was scored as having a high risk of bias, low risk of bias, or some concerns. As both of the outcomes to be assessed in this review were patient-reported outcome measures (pain intensity and disability), the risk of bias tool was applied to each individual study, rather than each individual outcome. Any disagreements regarding judgments were resolved by discussion and consensus. An overall risk of bias judgment score was provided for each study according to the Revised Cochrane Risk of Bias Tool guidance.[24]

Quality Assessment

The overall quality of the evidence was assessed using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach.[25] GRADE defines the quality of the evidence as the extent to which one can be confident that the point estimate of effect is correct. The quality assessment was performed by 2 reviewers (M.-B.C. and K.M.S.) independently based on the 5 domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias. To ensure consistency of GRADE judgments, the following criteria were applied to each domain for the 6 comparisons: (1) risk of bias: quality was downgraded by one level if > 20% of the participants were from trials that had been deemed to be at high risk of bias; (2) inconsistency: we downgraded once if heterogeneity was statistically significant and the I^2 statistic was > 40%; (3) indirectness: the quality rating was downgraded once if > 50% of participants were outside the target group; (4) imprecision: we downgraded once if there were < 400 participants in the comparison; (5) publication bias: funnel plots were examined for comparisons that included 10 studies or more, and the quality rating was downgraded if there is substantial asymmetry indicating publication bias. An overall GRADE rating was agreed for each comparison in the meta-analysis. The following definition was applied in relation to the quality of the evidence[26]: (1) high quality: we are very confident that the true effect lies close to that of the estimate of the effect; (2) moderate quality: we are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; (3) low quality: our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect; and (4) very low quality: we have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Data Extraction

Data from each study were extracted by 2 reviewers (M.-B.C. and K.M.S. or C.D.) independently using a customized data extraction tool in the form of an MS Excel spreadsheet. The following data were extracted: (1) study characteristics: number of participants, sex, age, and chronic pain condition; (2) characteristics of the interventions for both MBR and active physical interventions: type of intervention (group vs. individual), dosage, and description of content of interventions; (3) outcome measures: details of the patient-reported outcome measures used to assess pain intensity and disability; (4) length of follow-up; and (5) summary of findings.

Similarities in the outcome measures used, the subjects included, and the interventions allowed a meta-analysis to be performed, incorporating the majority of the included studies. Group means, SDs, and sample sizes were extracted and analyzed for each follow-up timepoint. If outcomes were incompletely reported or unclear, authors were contacted via e-mail. Some studies did not report raw data but displayed it in graph format only. Where possible, these authors were contacted via e-mail with a request to provide the raw data. In cases where authors were uncontactable, a web-based tool was used to extract the data from the graphs (https://automeris.io/WebPlotDigitizer/). A number of studies reported only median and interquartile range scores. Under the assumption of normality of the underlying distribution, the median was substituted for the mean and the width of the interquartile range was used as an approximation of 1.35 times the SD as per the Cochrane guidelines.[27] If the SD was not given, it was calculated from the SE or confidence intervals when these were available. Where these data were unavailable, we used the SD for the same measure at baseline, or follow-up, as a substitute. Where neither the baseline nor follow-up SD were reported, we substituted the SD from the same measure used in another study within the same comparison. If no estimate was possible using the aforementioned methods, the data were not used in the meta-analysis.

A number of studies contained > 1 eligible intervention or control group. For these studies, to avoid double counting which would have biased the meta-analysis, the outcome measure data for the eligible interventions were pooled to create one effect size for the study. For example, in the studies by Bendix and colleagues,[28,29] 2 MBR interventions that were both eligible for inclusion were merged using the formulae for combining groups from the Cochrane handbook.[27] Details related to sources of data for each study outcome in the 6 comparisons are reported in

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Supplemental Digital Content 2 (Sources of data for meta-analysis, http://links.lww.com/CJP/A681).

Synthesis of Results

The treatment effects of MBR were compared with active physical interventions for pain intensity and disability. In the included studies, a variety of outcome measures were reported for both pain intensity and disability outcomes, and for this reason, the standardized mean difference (SMD) rather than the mean difference was calculated.[30] If >1 measure of pain intensity or disability was used in a study, then the one considered to be the primary outcome or the one considered most similar to outcome measures used in other included studies was chosen for inclusion in the meta-analysis (eg, Numerical Rating Scale and Visual Analog Scale were considered similar outcome measures as they both require the rating on an 11-point severity scale). Heterogeneity between studies was assessed graphically with forest plots and funnel plots and statistically with the χ^2 test and I^2 statistic. The level of heterogeneity was interpreted according to the latest version of the Cochrane Handbook for Systematic Reviews of Interventions, which provides the following rough guidance related to the I^2 statistic: "0% to 40%: might not be important; 30% to 60%: may represent moderate heterogeneity; 50% to 90%: may represent substantial heterogeneity; and 75% to 100%: considerable heterogeneity."[30] A random-effects model was applied for all analyses. All analyses were conducted in Review Manager (RevMan) software (version 5.3).[31]

Publication Bias

Publication and reporting biases were assessed visually using funnel plots, when a minimum of 10 studies were included in the meta-analysis as recommended in the Cochrane handbook.[32]

Additional Analyses

A subgroup analysis was conducted including only studies that related to LBP. A sensitivity analysis was also conducted to check the effect of each individual study on the pooled result by repeating the meta-analysis systematically excluding each individual study.

Protocol Deviations

A small number of modifications were made to the study methods, following publication of the systematic review protocol on PROSPERO. These are presented in Supplemental Digital Content 3 (Deviations from protocol, http://links.lww.com/CJP/A682).

RESULTS

Study Selection

The trial identification process is summarized in Figure 1. The electronic database search yielded 7508 records, and additional searching via relevant systematic reviews yielded an additional 9 records. After removal of duplicates, 5124 were screened

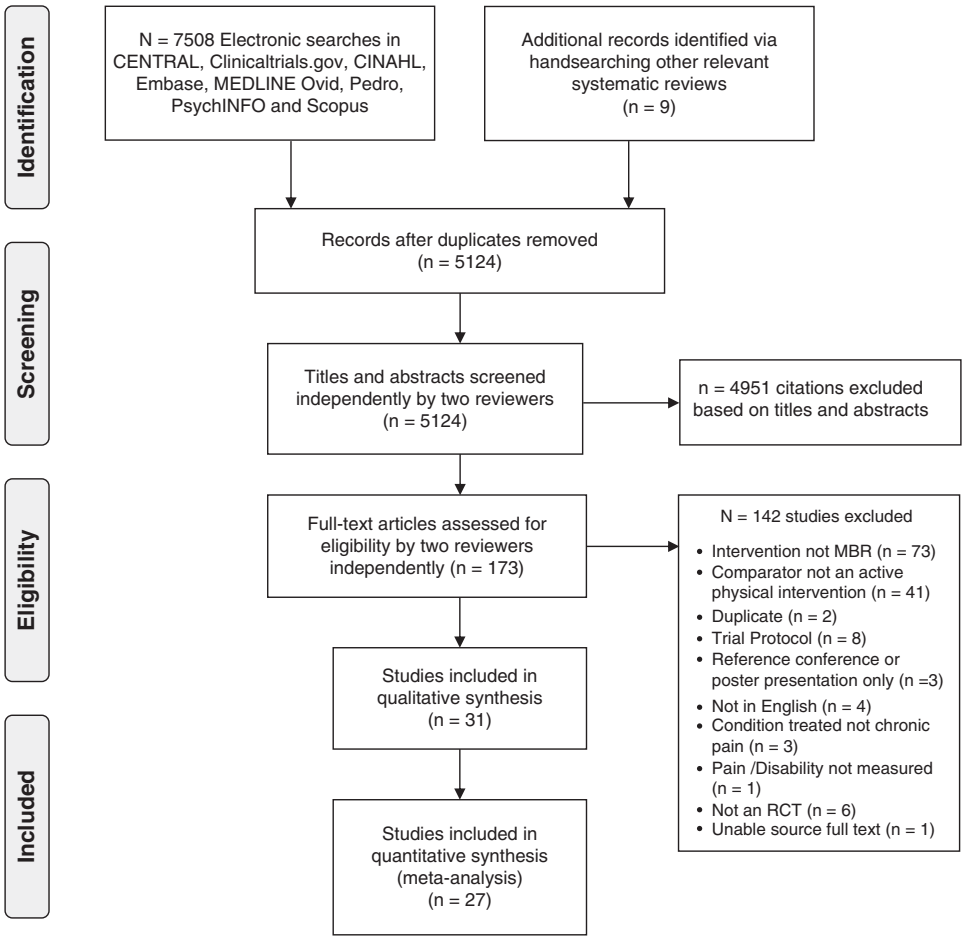

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart. MBR indicates multidisciplinary-based rehabilitation; RCT, randomized controlled trial.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

independently by 2 reviewers based on title and abstracts. A further 4951 records were excluded, leaving 173 to be screened by full text. Of these, 141 studies did not fit the eligibility criteria for this review. The most common reasons for exclusion were that the interventions studied did not fit the criteria to be defined as MBR (n = 73) or an active physical intervention (n = 41). A final total of 31 records met the selection criteria. Of these, 3 studies reported follow-up data in separate papers.[28,29,33–38]

Study Characteristics

Characteristics of the included studies are presented in Supplemental Table 1 (Supplemental Digital Content 6, http://links.lww.com/CJP/A692).[28,29,33–61] Sample sizes of the included studies ranged from 20 to 459 participants, and the mean age of study participants ranged from 40 to 61 years. A total of 25 studies included patients with chronic LBP,[28,29,33–41,44–48,50–52,54,55,57–60] 1 with generalized osteoarthritis,[42] 1 with neck pain,[53] 1 with late whiplash disorder,[56] 1 with nonspecific musculoskeletal disorders,[49] 1 with FM,[61] and 1 with complex regional pain syndrome.[43] A description of the interventions, including content and duration, is provided in Supplemental Table 1 (Supplemental Digital Content 6, http://links.lww.com/CJP/A692).[28,29,33–61]

Risk of Bias

Apart from 1 trial,[42] all of the reviewed studies were classified as having an overall high risk of bias. Regarding the individual domains, only 2 studies were deemed to be at a high risk of bias arising from the randomization process. However, 39% (n = 12/31 studies) were considered to have a high risk of bias owing to deviations from the intended interventions, and 47% (n = 15/31) were judged to be at high risk in the category related to missing outcome data. Blinding of participants and treatment providers is difficult in studies involving the complex interventions in the review, and this is reflected in the high number of trials (59%, n = 19/31) that were judged to be at high risk of bias owing to measurement of the outcome. In the final domain related to selection of the reported result, 1 trial was judged to be at high risk of bias. Details related to risk of bias judgments are displayed in Table 1.

Synthesis of Results

Of the 31 studies, 27 were included in the meta-analysis. Two studies were excluded as they were the only studies to report follow-up data at 2 and 5 years after intervention.[33,34] One study did not report data for either pain or disability for the intervention groups relevant to this review, and therefore, the study was excluded from the meta-analysis.[56] There were queries in relation to the accuracy of data reported in 1 paper, as the results described in the text did not appear to correlate with data reported in the table.[59] Attempts were made to contact the author for clarification, but no response was received and the study was excluded. One study did not report data for disability; therefore, only data for pain were included in the meta-analysis.[49]

Pain Intensity Outcomes

A variety of measures were used to assess pain intensity (Supplemental Table 1, Supplemental Digital Content 6, http://links.lww.com/CJP/A692).[28,29,33–61] Statistically significant differences in pain intensity were found in favor of MBR at short-term (19 studies, n = 2361; SMD = −0.53; 95% confidence interval [CI]: −0.88 to −0.19; $I^2 = 93\%$; $P = 0.002$) and long-term (14 studies, n = 1727; SMD = −0.56; 95% CI: −1.02 to −0.11; $I^2 = 95\%$; $P = 0.02$) (Fig. 2). There was no significant difference between MBR and active physical interventions in the medium-term (10 studies; n = 1068; SMD = −0.20; 95% CI: −0.37 to −0.03; $I^2 = 39\%$; $P = 0.02$) (Fig. 2). The quality of the evidence based on the GRADE framework was judged to be low for pain intensity at short-term and long-term follow-up and moderate at medium-term follow-up (Table 2).

Disability Outcomes

As was the case with measurement of pain intensity, a wide variety of scales were used to assess disability outcomes across the studies (Table 1). Statistically significant differences were found for disability in favor of MBR, at short-term (18 studies; n = 2587; SMD = −0.50; 95% CI: −0.79 to −0.20; $I^2 = 92\%$; $P = 0.001$) and long-term follow-up (15 studies; n = 2040; SMD = −0.77; 95% CI: −1.23 to −0.31; $I^2 = 96\%$; $P = 0.001$), but not at medium-term follow-up (8 studies; n = 886; SMD = −0.14; 95% CI: −0.29 to 0.01; $I^2 = 10\%$, $P = 0.07$) (Fig. 3). The quality of the evidence based on the GRADE framework was judged to be low for disability at short-term and long-term follow-up and moderate at medium-term follow-up (Table 3).

Heterogeneity

Significant heterogeneity was found in the estimates for pain intensity and disability at short-term and long-term follow-up, with I^2 statistics in excess of the threshold of 75%, representing "considerable heterogeneity."[30] Moderate heterogeneity was observed in the estimate for pain at medium-term follow-up (I^2 statistic = 39%). Funnel plots were generated for these 5 estimates, which included the minimum of 10 studies as recommended by the Cochrane Collaboration for the inspection of publication, reporting, and other biases (Funnel plots, Supplemental Digital Content 4, http://links.lww.com/CJP/A683).[32] Some of the funnel plots showed slight tendencies toward asymmetry.

Subgroup Analyses

Specific subgroup or sensitivity analyses had not been preplanned. However, owing to the high level of heterogeneity observed, a decision was made to conduct a subgroup meta-analysis including only patients with chronic LBP. For pain intensity, there were statistically significant differences in favor of MBR at short-term follow-up (14 studies; n = 1828; SMD = −0.47; 95% CI: −0.80 to −0.14; $I^2 = 90\%$; $P = 0.006$), at medium-term follow-up (8 studies; n = 902; SMD = −0.15; 95% CI: −0.28 to −0.01; $P = 0.04$), and at long-term follow-up (11 studies; n = 1274; SMD = −0.47; 95% CI: −0.92 to −0.03; $I^2 = 92\%$; $P = 0.04$). With respect to disability, a statistically significant difference was found at short-term follow-up (15 studies; n = 2115; $I^2 = 91\%$; $P = 0.001$; SMD = −0.52, 95% CI: −0.83 to −0.20) and long-term follow-up (12 studies; n = 1568; $I^2 = 96\%$; $P = 0.003$; SMD = −0.82, 95% CI: −1.35 to −0.28). No statistically significant difference was found for disability in this subgroup at medium-term follow-up (8 studies; n = 886; $I^2 = 10\%$; $P = 0.07$; SMD = −0.14; 95% CI: −0.29 to 0.01). Forest plots for LBP subgroup analysis are presented in Supplemental Digital Content 5 (LBP subgroup analysis, http://links.lww.com/CJP/A684). Subgroup meta-analyses of conditions other than LBP were not possible owing to an insufficient number of studies.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 1. Revised Cochrane Risk of Bias Scores for Included Studies

References	Domain 1: Risk of Bias Arising From the Randomization Process	Domain 2: Risk of Bias Due to Deviations From the Intended Interventions	Domain 3: Missing Outcome Data	Domain 4: Risk of Bias in Measurement of the Outcome	Domain 5: Risk of Bias in Selection of the Reported Result	Overall Risk of Bias
Alaranta et al[39]	++	++	+	++	++	+++
Bendix et al[29]	++	+++	+++	++	++	+++
Bendix et al[28]	+	+++	+++	++	++	+++
Bendix et al[33]	+++	+++	+++	++	++	+++
Bendix et al[34]	+++	+++	+++	++	++	+++
Bendix et al[40]	++	+	+++	++	++	+++
Christiansen et al[41]	+	+	+++	++	++	+++
Cuperus et al[42]	+	+	++	++	+	++
Den Hollander et al[43]	+	+	++	++	++	+++
Dufour et al[44]	+	+++	+++	++	++	+++
Härkapää et al[45]	++	++	+	+++	++	+++
Jousset et al[46]	++	+	+	++	++	+++
Kääpä et al[47]	+	++	+	+++	++	+++
Klaber Moffett et al[48]	+	+++	+++	+++	++	+++
Meyer et al[49]	+	+	+	+++	++	+++
Monticone et al[50]	+	+	+	+++	++	+++
Monticone et al[51]	+	+	+	+++	++	+++
Monticone et al[52]	+	+	+	+++	++	+++
Monticone et al[53]	+	+	+	+++	++	+++
Nicholas et al[54]	+	+++	+++	+++	++	+++
Paolucci et al[55]	+	++	+	++	+++	+++
Pato et al[56]	++	+++	+++	+++	++	+++
Roche et al[35]	++	+	+	+++	++	+++
Roche-Leboucher et al[36]	++	+	+++	+++	++	+++
Ronzi et al[57]	+	+++	+++	+++	+	+++
Sahin et al[58]	+	+	+	+++	++	+++
Smeets et al[37]	+	+	+	+++	+	+++
Smeets et al[38]	+	+	+	+++	+	+++
Schweikert et al[59]	++	+++	+++	+++	++	+++
Turner et al[60]	++	+++	+++	+++	++	+++
Van Eijk-Hustings et al[61]	+	+++	+++	+++	++	+++

+ indicates low risk of bias; ++, some concerns; +++, high risk of bias.

Sensitivity Analysis

A sensitivity analysis based on quality assessment was not conducted as all but 1 of the included studies were judged to be at high risk of bias. It was observed that 3 studies published by one research group reported effects in favor of MBR that appeared much larger than other studies.[50,52,53] When these studies were removed from the meta-analyses, the effect size for pain in the short-term decreased (SMD = −0.20), and no statistically significant difference was observed for pain in the long-term. Similarly, the effects on disability in the short-term and long-term decreased (SMD = −0.18 and −0.19, respectively). It was also notable that removal of these 3 studies reduced the heterogeneity substantially, in all of the comparisons that included these studies. For pain, the I^2 statistic decreased from 93% to 55% for short-term follow-up, and it reduced from 95% to 31% for long-term follow-up. Regarding disability, the I^2 statistic decreased from 92% to 54% at short-term follow-up, and it reduced from 96% to 0% for long-term follow-up.

Quality of the Evidence

The quality of the evidence started out as high for each of the 6 comparisons as only RCTs were included in this review. However, the quality rating was reduced by 1 level for each GRADE criterion not met in the comparison. As all of the included studies, apart from one,[42] were judged to be at a high risk of bias, quality was reduced by 1 level for all comparisons. Substantial heterogeneity (I^2 statistic > 50%) was observed in 4 of the 6 comparisons and therefore quality of the evidence was reduced by a further level in these comparisons (pain intensity and disability at both short-term and long-term follow-up). Indirectness was not an issue in this review owing to the specific inclusion criteria applied. None of the comparisons were downgraded due to imprecision, as sample sizes were considered sufficient (> 400).[62] Although slight tendencies toward asymmetry were observed in some of the funnel plots, this was not considered significant enough to warrant downgrading for publication bias (Funnel plots, Supplemental Digital Content 4, http://links.lww.com/CJP/A683). Overall, the quality of the evidence was graded as "low" for comparisons of pain intensity and disability at short-term and long-term follow-up. A grade rating of "moderate" was applied to both comparisons at medium-term follow-up (Tables 2, 3).

DISCUSSION

Summary of Evidence

A total of 31 studies were identified that met the criteria for inclusion in the systematic review and 27 of these were included in the meta-analysis. Overall, the results showed that MBR is significantly more effective than active physical interventions for reducing pain intensity and disability in

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

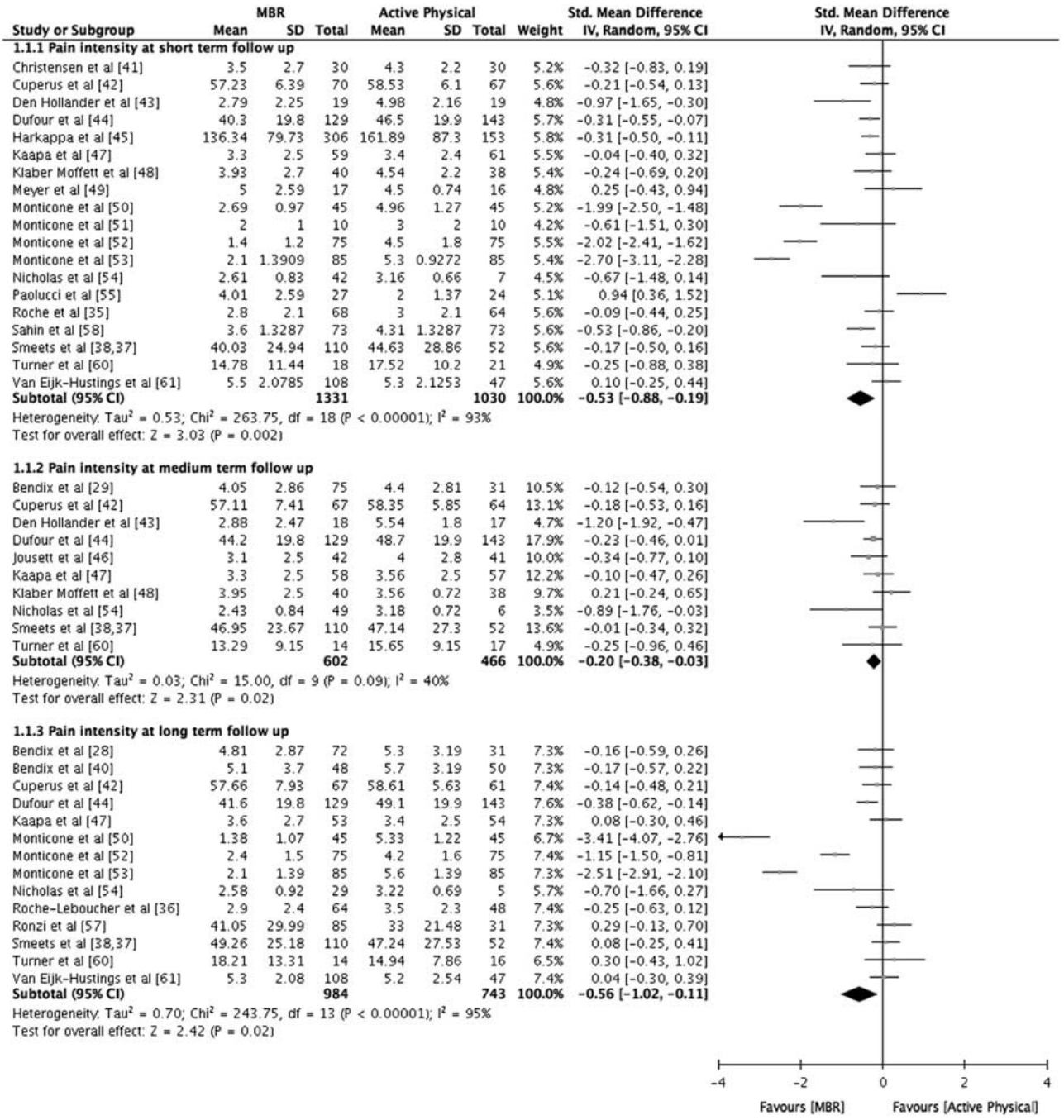

FIGURE 2. Effect of MBR versus active physical interventions on pain intensity. CI indicates confidence interval; MBR, multidisciplinary-based rehabilitation.

people with chronic pain, in both the short-term and long-term, but not in the medium-term. These findings must be interpreted in light of the overall quality of the evidence, which was determined to be low for the short-term and long-term comparisons and moderate for the comparisons at medium-term follow-up. Of the 31 studies, 30 were considered to be at an overall high risk of bias. A sensitivity analysis suggests that our findings were heavily influenced by 3 trials from one research group.

The studies that showed more promising effects in favor of MBR tended to feature individualized treatment with a cognitive-behavioral therapy component.[43,50,52–54] However, not all studies containing cognitive-behavioral therapy interventions resulted in large effects.[37–39,47,59] The studies by Monticone and colleagues,[50,52,53] which showed large positive effects in favor of MBR, included patients with a lower duration of chronic pain symptoms at baseline (mean duration of pain symptoms 1.85, 2.04, and 2.15 y) compared with other studies that showed no significant differences or smaller effects[37,38,60] (mean duration of pain at baseline, 4.7, 5, and 12.9 y, correspondingly). Longer pain duration has been identified as one prognostic factor that is associated with a less favorable outcome.[63] It is possible that people with chronic pain may have a better

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.
Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 2. GRADE Assessment of the Certainty of the Evidence: Pain Intensity

	Short-term Follow-up		Medium-term Follow-up		Long-term Follow-up	
Domain for Assessing Certainty of Evidence	**Results**	**Effect on Quality of Evidence Rating**	**Results**	**Effect on Quality of Evidence Rating**	**Results**	**Effect on Quality of Evidence Rating**
Risk of bias	18/19 trials judged to be at high risk of bias	Serious risk of bias: quality of evidence downgraded one level	9/10 trials judged to be at high risk of bias	Serious risk of bias: quality of evidence downgraded one level	13/14 trials judged to be at high risk of bias	Serious risk of bias: quality of evidence downgraded one level
Inconsistency	Considerable heterogeneity: I^2 statistic 93%	Quality of evidence downgraded one level	Low heterogeneity: I^2 statistic 39%	No effect on quality of evidence	Considerable heterogeneity: I^2 statistic 95%	Quality of evidence downgraded one level
Indirectness	Indirectness does not appear to be an issue. All included studies addressed the PICO	No effect on quality of evidence	Indirectness does not appear to be an issue. All included studies addressed the PICO	No effect on quality of evidence	Indirectness does not appear to be an issue. All included studies addressed the PICO	No effect on quality of evidence
Imprecision	Imprecision does not appear to be an issue. 2361 participants in this meta-analysis	No effect on quality of evidence	Imprecision does not appear to be an issue. 1068 participants in this meta-analysis	No effect on quality of evidence	Imprecision does not appear to be an issue. 1727 participants in this meta-analysis	No effect on quality of evidence
Publication bias	Funnel plot shows slight tendency towards asymmetry but not sufficient to warrant downgrading due to publication bias	No effect on quality of evidence	Funnel plot does not contain substantial asymmetry which would indicate presence of publication bias	No effect on quality of evidence	Funnel plot shows slight tendency towards asymmetry but not sufficient to warrant downgrading due to publication bias	No effect on quality of evidence
Final level of certainty rating	Low		Moderate		Low	

PICO indicates population, intervention, comparison, outcome.

response when MBR interventions are provided earlier, but further research is required to explore this theory. The findings of the sensitivity analysis indicate that 3 of the 4 studies published by the Monticone and colleagues' research group had a considerable effect on the overall results. This was noted in a previous systematic review,[16] which included one of these studies,[50] and the authors observed that removal of this study from the pooled analyses reduced the I^2 statistic substantially. It is notable that the studies by Monticone and colleagues[50–53] were considered to be of higher quality than most other included studies. They were judged to be at high risk of bias in only 1 of the assessed domains, which related to measurement of the outcome. Very few trials of complex interventions will be judged as low risk of bias in this domain due to the difficulty in blinding of participants and treatment providers.

The meta-analyses examining the effectiveness of MBR on pain intensity showed moderate improvements in comparison with active physical interventions at short-term and long-term follow-ups. In general, MBR programmes do not explicitly aim to change or reduce pain but instead focus on reducing disability and improving quality of life. It is of note that the meta-analysis showed no difference in the effect on pain intensity at the medium-term follow-up. However, the finding of a significant effect on pain intensity in the long-term may indicate that the positive effects of MBR on pain can be sustained.

Comparison With Previous Systematic Reviews

Our results are similar to those reported in 2 previous systematic reviews and meta-analyses conducted in relation to this topic in recent years.[16,18] The Cochrane review published by Kamper et al[16] compared the effectiveness of MBR to usual care, physical interventions, waiting list, and surgery, and they considered pain intensity, disability, and work outcomes (n = 41 trials). O'Keeffe et al[18] assessed the comparative effectiveness of physical, behavioral/psychological informed, or combined interventions for pain and disability in people with nonspecific chronic spinal pain (n = 24 trials). This discussion focused on the comparative effectiveness of MBR or combined interventions versus physical interventions for pain intensity and disability only. Similar to the current review, both Kamper et al[16] and O'Keeffe et al[18] reported statistically significant differences in favor of MBR or combined interventions versus physical interventions for low back and nonspecific spinal pain intensity and disability in the short-term and long-term.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

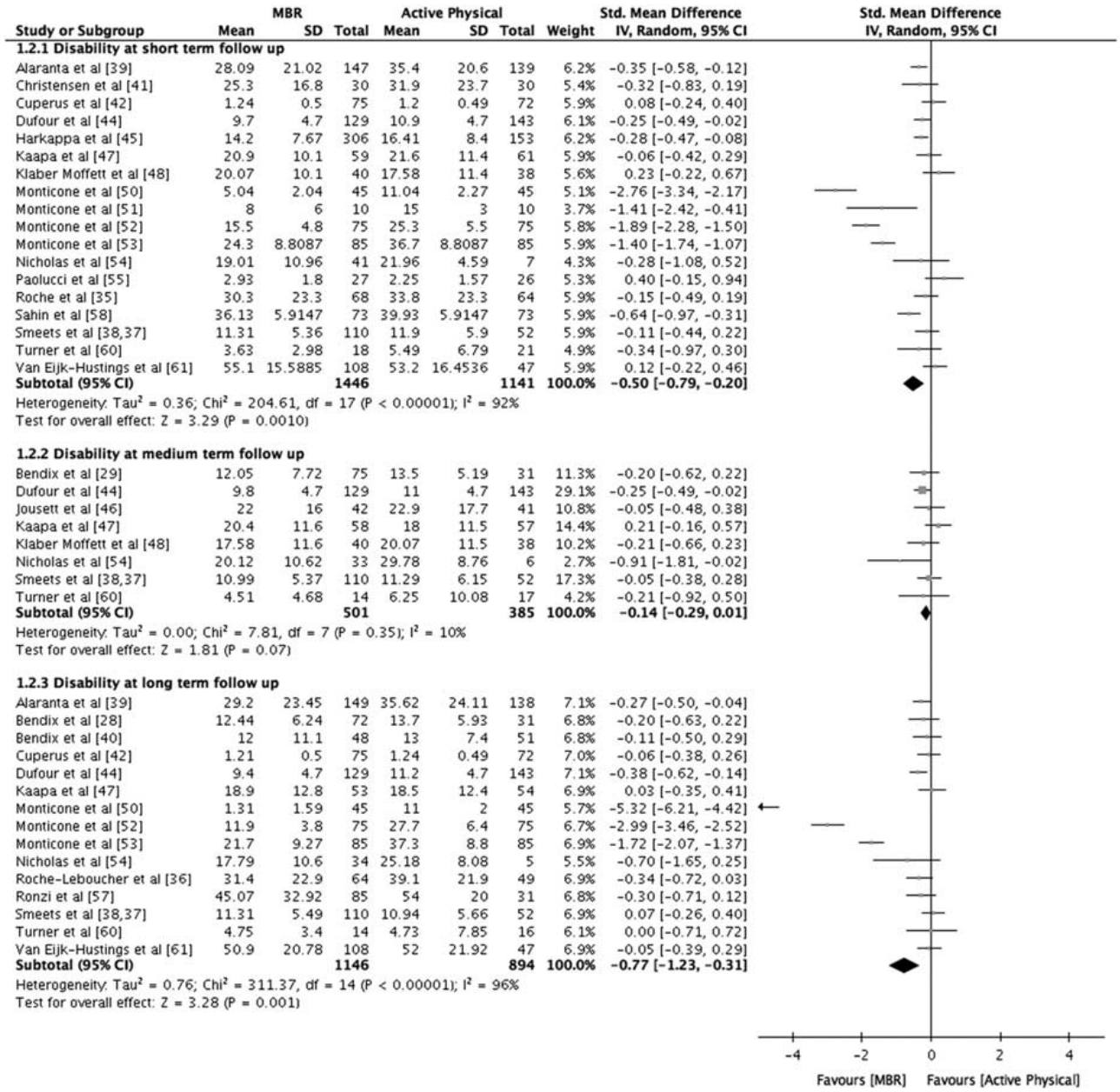

FIGURE 3. Effect of MBR versus active physical interventions on disability. CI indicates confidence interval; MBR, multidisciplinary-based rehabilitation.

O'Keeffe et al[18] also observed no statistical differences between combined and physical interventions in the medium term (n = 15 trials), but Kamper et al[16] reported a small significant difference for pain intensity in favor of MBR (SD = −0.28) at this timepoint (n = 9 trials). Both previous systematic reviews reported similar effects for pain intensity and disability in the short-term and long-term, in favor of MBR or combined interventions. The effects found in our meta-analyses for disability in the short-term were larger than those reported in these previous reviews, both of which reported smaller effects (SMD = 0.39[16] and 0.27[18]) compared with our result (SMD = 0.54). Similarly, our review reports a larger effect for disability in the long-term in favor of MBR (SMD = 0.77), in contrast with the effect found by O'Keeffe et al[18] (SMD = 0.25) and the effect reported by Kamper et al[16] (SMD = 0.68). Our subgroup meta-analysis, including only patients with LBP yielded similar results to both previous reviews, and as with the main analysis, a larger effect on disability was observed at long-term follow-up (SMD = 0.82).

The small effects on pain and disability noted in these previous reviews[16,18] prompted the authors to recommend due consideration of the associated cost, time, and resources before offering combined or MBR interventions to people with chronic spinal pain. Cost-effectiveness was not assessed in the current review, and neither of the previous reviews extracted data related to cost.[16,18] Although the effect sizes found in our review are slightly larger than these published previously, we also suggest that future research should be conducted to investigate which patients are most likely to benefit from these intensive MBR interventions. Few studies have investigated predictors of outcome for MBR interventions for chronic pain.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.
Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

TABLE 3. GRADE Assessment of the Certainty of the Evidence: Disability

	Short-term Follow-up		Medium-term Follow-up		Long-term Follow-up	
Domain for Assessing Certainty of Evidence	**Results**	**Effect on Quality of Evidence Rating**	**Results**	**Effect on Quality of Evidence Rating**	**Results**	**Effect on Quality of Evidence Rating**
Risk of bias	17/18 trials judged to be at high risk of bias	Serious risk of bias: quality of evidence downgraded one level	7/8 trials judged to be at high risk of bias	Serious risk of bias: quality of evidence downgraded one level	14/15 trials judged to be at high risk of bias	Serious risk of bias: quality of evidence downgraded one level
Inconsistency	Considerable heterogeneity: I^2 statistic 92%	Quality of evidence downgraded one level	Low heterogeneity: I^2 statistic 10%	No effect on quality of evidence	Considerable heterogeneity: I^2 statistic 96%	Quality of evidence downgraded one level
Indirectness	Indirectness does not appear to be an issue. All included studies addressed the PICO	No effect on quality of evidence	Indirectness does not appear to be an issue. All included studies addressed the PICO	No effect on quality of evidence	Indirectness does not appear to be an issue. All included studies addressed the PICO	No effect on quality of evidence
Imprecision	Imprecision does not appear to be an issue. 2587 participants in this meta-analysis	No effect on quality of evidence	Imprecision does not appear to be an issue. 886 participants in this meta-analysis	No effect on quality of evidence	Imprecision does not appear to be an issue. 2040 participants in this meta-analysis	No effect on quality of evidence
Publication bias	Funnel plot shows slight tendency toward asymmetry but not sufficient to warrant downgrading owing to publication bias	No effect on quality of evidence	Funnel plot was not generated as there are <10 studies in this comparison	Publication bias was undetected, therefore no effect on quality of evidence	Funnel plot shows slight tendency toward asymmetry but not sufficient to warrant downgrading owing to publication bias	No effect on quality of evidence
Final level of certainty rating	Low		Moderate		Low	

GRADE indicates Grades of Recommendation, Assessment, Development, and Evaluation; PICO, population, intervention, comparison, outcome.

In future, targeting these intensive interventions to the appropriate individuals, at the most appropriate time, could help maximize use of resources and cost-effectiveness.

Although the findings of these 3 reviews have some similarities, some important variations in the review methods should be noted. First, mainly owing to differences in the inclusion criteria, only 5 of the 22 studies included in the meta-analysis conducted by O'Keeffe et al[18] also feature in our review and meta-analysis. However, despite the largely different study pools, both meta-analyses found a statistically significant difference in favor of MBR. A number of factors related to the review methods may have contributed to the different effect sizes reported in the reviews. First, O'Keeffe and colleagues excluded studies with <12 weeks of follow-up, and they defined the short-term and medium-term follow-up time periods differently (short-term follow-up: 12 wk to <6 mo; medium-term follow-up: 6 mo to <12 mo; and long-term follow-up: 12 mo or more). The current review included studies that reported outcomes after intervention in the short-term follow-up comparisons. This may have contributed to the larger effect size seen for disability in the short-term, but it would not have influenced the difference observed at long-term follow-up. This particular finding may relate to the inclusion in our review of only combined interventions that were delivered by a multidisciplinary team of professionals. Indeed, Kamper and colleagues, who adopted similar inclusion criteria in their Cochrane review, noted a similar effect in favor of MBR versus physical interventions on disability at long-term follow-up (SMD = 0.68). The slightly larger effect on disability in the long term noted in our review (SMD = 0.77) may perhaps relate to the inclusion of further studies published since that review,[52,57] and/or the inclusion of studies related to conditions other than LBP,[42,53] particularly the study by Monticone et al,[53] which showed a very large effect in favor of MBR (SMD = 2.99) for chronic neck pain.

Our review is one of the few to include patients with a mix of chronic pain conditions, as opposed to LBP or spinal pain only.[16,18] However, it is difficult to compare the results of our review with previous research in relation to MBR for FM and other chronic pain conditions. The recent EULAR guidelines for the management of FM[11] base their recommendations related to MBR on a systematic review published 10 years ago.[23] This review included a meta-analysis of 10 RCTs and concluded that multicomponent therapy was effective in reducing pain (SMD = −0.37) and improving health-related quality of life (SMD = 0.59) in the short-term but not the long-term. However, these findings should

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

be interpreted in light of the wide range of comparator interventions featured in the review, including waiting list or usual care control groups, in addition to other treatments of lesser intensity such as relaxation and education. Considering the duration of time since publication of the last known systematic review related to MBR for FM, we were hopeful that our search would identify further RCTs that would add to the knowledge base in this area. However, only one trial concerning FM was found that met the criteria for inclusion in our review.[61] With respect to other types of chronic pain conditions, again few studies were eligible for inclusion, with only one study related to complex regional pain syndrome,[43] one for generalized osteoarthritis,[42] and one small study on nonspecific musculoskeletal conditions.[49]

Recommendations for Research

Although we set out to compare MBR with active physical interventions for all types of chronic pain conditions, few studies were identified that related to chronic pain conditions other than low back or neck pain. This is at odds with the current research, which reports that 80% of people with chronic pain are known to have pain in >1 site. Further trials including patients with FM and other types of chronic pain conditions are therefore needed.

The findings of our meta-analysis are similar to reports in previous systematic reviews,[16,18] with statistically significant improvements noted in favor of MBR at short-term and long-term follow-up but not at medium term. These findings support the inclusion of long-term follow-up in future studies. It is encouraging that moderate/large effects on pain intensity and disability appear to be maintained in the longer term. However, further studies are required to investigate which individuals with chronic pain conditions benefit most from these more intensive MBR interventions. Future studies should also include assessment of health care utilization and cost-effectiveness to optimize the use of health care resources.

Strengths and Limitations

This systematic review and meta-analysis provides an up-to-date assessment of the effectiveness of MBR compared with physical interventions for chronic pain. Our review differs from those published in recent years, as we included RCTs of all types of chronic pain conditions, and we limited the included studies to those that featured an active component within the control intervention arm. A relatively large number of studies ($n=27$) were included in the meta-analyses.

The review methods followed the most up-to-date Cochrane guidelines for systematic reviews of interventions, and quality of the evidence was assessed using the GRADE approach. The recently updated Cochrane Risk of Bias tool (RoB 2)[24] was used to assess risk of bias of the included studies.

There are a number of limitations with this systematic review that need to be acknowledged. First, there is no formal accepted definition for MBR, as has been noted in a previous review.[16] We adopted the same definition used by Kamper et al,[16] and likewise, we recognize that there is a possibility that if we had defined MBR differently, this may have led to the inclusion of different studies and perhaps different results. However, our review included few studies in common with the meta-analysis conducted by O'Keeffe and colleagues comparing combined and physical interventions, and the similar findings in both reviews add to the strength of evidence in favor of MBR interventions for chronic pain. Our results also need to be interpreted in light of the low to moderate quality of the evidence as determined using the GRADE framework and the significant heterogeneity present in most of the comparisons in the meta-analysis. It is likely that the variances in chronic pain populations, settings, interventions, and control groups led to this high level of heterogeneity. We also noted a high level of variation in the scales used to measure the outcomes of pain intensity and disability. Although we attempted to control for this by using the statistical method SMD, it would be preferable if there was greater standardization in the use of outcome measures in these studies. A further limitation was that we limited our search to include only studies published in the English language.

CONCLUSIONS

The results of this review provide low-quality evidence to suggest that MBR is more effective than active physical interventions for reducing pain intensity and disability in people with chronic pain, in both the short-term and long-term. As the benefits appear to be modest, other factors such as resource allocation should be considered before offering MBR programmes to people with chronic pain. Further research is required to assess the effectiveness of MBR for people with chronic pain conditions such as chronic widespread pain, FM, and complex regional pain syndrome and should include assessment of cost-effectiveness and long-term follow-up.

ACKNOWLEDGMENTS

The authors thank Dr Diarmuid Stokes, BA, DLIS, MSc (Econ), Liaison Librarian, Health Sciences Library, University College Dublin, Dublin, Ireland, for his assistance in developing the electronic search strategies.

REFERENCES

1. Treede RD, Rief W, Barke A, et al. A classification of chronic pain for ICD-11. *Pain*. 2015;156:1003–1007.
2. Breivik H, Collett B, Ventafridda V, et al. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain*. 2006;10:287–333.
3. Raftery MN, Sarma K, Murphy AW, et al. Chronic pain in the Republic of Ireland—Community prevalence, psychosocial profile and predictors of pain-related disability: results from the Prevalence, Impact and Cost of Chronic Pain (PRIME) study, Part 1. *Pain*. 2011;152:1096–1103.
4. Raftery MN, Ryan P, Normand C, et al. The economic cost of chronic noncancer pain in Ireland: results from the PRIME Study, Part 2. *J Pain*. 2012;13:139–145.
5. Adler R. Engel's biopsychosocial model is still relevant today. *J Psychosom Res*. 2009;67:607–611.
6. Engel GL. The need for a new medical model: a challenge for biomedicine. *Science*. 1977;196:129–136.
7. Scottish Intercolegiate Guidelines Network (SIGN). Management of chronic pain (SIGN publication no. 136); 2013. Available at: www.sign.ac.uk/assets/sign136.pdf. Accessed August 28, 2020.
8. National Institute for Health and Care Excellence (NICE). NICE Guideline: chronic pain: final scope; 2018. Available at: www.nice.org.uk/guidance/gid-ng10069/documents/final-scope. Accessed August 28, 2020.
9. National Institute for Health and Care Excellence (NICE). NICE Clinical Guideline [NG59]: Low back pain and sciatica in over 16s: assessment and management; 2016. Available at: https://www.nice.org.uk/guidance/ng59. Accessed August 28, 2020.
10. National Institute for Health and Care Excellence (NICE). NICE Clinical Guideline [CG177]: Osteoarthritis: care and management; 2014. Available at: www.nice.org.uk/guidance/cg177. Accessed August 28, 2020.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

11. Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis*. 2017;76:318–328.
12. Gatchel RJ, McGeary DD, McGeary CA, et al. Interdisciplinary chronic pain management past, present, and future. *Am Psychol*. 2014;69:119–130.
13. British Pain Society. Guidelines for pain management programmes for adults; 2013. Available at: www.britishpainsociety.org/static/uploads/resources/files/pmp2013_main_FINAL_v6.pdf. Accessed August 28, 2020.
14. Vowles KE, Witkiewitz K, Sowden G, et al. Acceptance and commitment therapy for chronic pain: evidence of mediation and clinically significant change following an abbreviated interdisciplinary program of rehabilitation. *J Pain*. 2014;15:101–113.
15. Guzman J, Esmail R, Karjalainen K, et al. Multidisciplinary bio-psycho-social rehabilitation for chronic low back pain. *Cochrane Database Syst Rev*. 2002;1:CD000963.
16. Kamper SJ, Apeldoorn AT, Chiarotto A, et al. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain: Cochrane systematic review and meta-analysis. *BMJ*. 2015;350:h444.
17. Scascighini L, Toma V, Dober-Spielmann S, et al. Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes. *Rheumatology*. 2008;47:670–678.
18. O'Keeffe MPH, Kennedy N, Conneely M, et al. Comparative effectiveness of conservative interventions for nonspecific chronic spinal pain: physical, behavioral/psychologically informed, or combined? A systematic review and meta-analysis. *J Pain*. 2016;17:755–774.
19. Häuser W, Thieme K, Turk DC. Guidelines on the management of fibromyalgia syndrome—a systematic review. *Eur J Pain*. 2010;14:5–10.
20. van Middelkoop MP, Rubinstein SMP, Verhagen APP, et al. Exercise therapy for chronic nonspecific low-back pain. *Best Pract Res Clin Rheumatol*. 2010;24:193–204.
21. Karjalainen KA, Malmivaara A, van Tulder MW, et al. Multidisciplinary rehabilitation for fibromyalgia and musculoskeletal pain in working age adults. *Cochrane Database Syst Rev*. 1999: CD001984.
22. Karjalainen KA, Malmivaara A, van Tulder MW, et al. Multidisciplinary biopsychosocial rehabilitation for neck and shoulder pain among working age adults. *Cochrane Database Syst Rev*. 2003:CD002194.
23. Häuser W, Bernardy K, Arnold B, et al. Efficacy of multicomponent treatment in fibromyalgia syndrome: a meta-analysis of randomized controlled clinical trials. *Arthritis Rheum*. 2009;61: 216–224.
24. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898.
25. Schünemann HJ, Higgins JPT, Vist GE, et al. Chapter 14: Completing 'Summary of findings' tables and grading the certainty of the evidence. Draft version (29 January 2019) for inclusion. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. London, UK: Cochrane; 2019:375–402.
26. Balshem H, Helfand M, Schunemann H, et al. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol*. 2011;64:401–406.
27. Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions [updated June 2017]*. London, UK: Cochrane; 2019.
28. Bendix AF, Bendix T, Lund C, et al. Comparison of three intensive programs for chronic low back pain patients: a prospective, randomized, observer-blinded study with one-year follow-up. *Scand J Rehabil Med*. 1997;29:81–89.
29. Bendix AF, Bendix T, Ostenfeld S, et al. Active treatment programs for patients with chronic low back pain: a prospective, randomized, observer-blinded study. *Eur Spine J*. 1995;4:148–152.
30. Deeks JJ, Higgins JPT, Altman DG. Chapter 10: Analysing data and undertaking meta-analyses (Draft version, 29 January 2019). In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. London, UK: Cochrane; 2019:241–284.
31. The Nordic Cochrane Centre. Review Manager (RevMan) (Computer Programme), Version 5.3. Copenhagen, Denmark: The Cochrane Collaboration; 2014.
32. Page MJHJ, Sterne JAC. Chapter 13: Assessing risk of bias due to missing results in a synthesis. Draft version (29 January 2019) for inclusion. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, eds. *Cochrane Handbook for Systematic Reviews of Interventions*. London, UK: Cochrane; 2019:349–374.
33. Bendix AE, Bendix T, Haestrup C, et al. A prospective, randomized 5-year follow-up study of functional restoration in chronic low back pain patients. *Eur Spine J*. 1998;7: 111–119.
34. Bendix AF, Bendix T, Labriola M, et al. Functional restoration for chronic low back pain. Two-year follow-up of two randomized clinical trials. *Spine*. 1998;23:717–725.
35. Roche G, Ponthieux A, Parot-Shinkel E, et al. Comparison of a functional restoration program with active individual physical therapy for patients with chronic low back pain: a randomized controlled trial. *Arch Phys Med Rehabil*. 2007;88:1229–1235.
36. Roche-Leboucher G, Petit-Lemanac'h A, Bontoux L, et al. Multidisciplinary intensive functional restoration versus outpatient active physiotherapy in chronic low back pain: a randomized controlled trial. *Spine*. 2011;36:2235–2242.
37. Smeets RJEM, Vlaeyen JWS, Hidding A, et al. Chronic low back pain: physical training, graded activity with problem solving training, or both? The one-year post-treatment results of a randomized controlled trial. *Pain*. 2008;134:263–276.
38. Smeets RJEM, Vlaeyen JWS, Hidding A, et al. Active rehabilitation for chronic low back pain: cognitive-behavioral, physical, or both? First direct post-treatment results from a randomized controlled trial. *BMC Musculoskelet Disord*. 2006;7:5.
39. Alaranta H, Rytokoski U, Rissanen A, et al. Intensive physical and psychosocial training program for patients with chronic low back pain. A controlled clinical trial. *Spine*. 1994;19:1339–1349.
40. Bendix T, Bendix A, Labriola M, et al. Functional restoration versus outpatient physical training in chronic low back pain: a randomized comparative study. *Spine (Phila Pa 1976)*. 2000;25: 2494–2500.
41. Christiansen S, Oettingen G, Dahme B, et al. A short goal-pursuit intervention to improve physical capacity: a randomized clinical trial in chronic back pain patients. *Pain*. 2010;149:444–452.
42. Cuperus N, Hoogeboom TJ, Kersten CC, et al. Randomized trial of the effectiveness of a non-pharmacological multidisciplinary face-to-face treatment program on daily function compared to a telephone-based treatment program in patients with generalized osteoarthritis. *Osteoarthritis Cartilage*. 2015;23: 1267–1275.
43. Den Hollander M, Goossens M, De Jong J, et al. Expose or protect? A randomized controlled trial of exposure in vivo vs pain-contingent treatment as usual in patients with complex regional pain syndrome type 1. *Pain*. 2016;157:2318–2329.
44. Dufour N, Thamsborg G, Oefeldt A, et al. Treatment of chronic low back pain: a randomized, clinical trial comparing group-based multidisciplinary biopsychosocial rehabilitation and intensive individual therapist-assisted back muscle strengthening exercises. *Spine (Phila Pa 1976)*. 2010;35: 469–476.
45. Härkapää K, Jarvikoski A, Mellin G, et al. A controlled study on the outcome of inpatient and outpatient treatment of low back pain. Part I. Pain, disability, compliance, and reported treatment benefits three months after treatment. *Scand J Rehabil Med*. 1989;21:81–89.
46. Jousset N, Fanello S, Bontoux L, et al. Effects of functional restoration versus 3 hours per week physical therapy: a randomized controlled study. *Spine (Phila Pa 1976)*. 2004;29:487–494.
47. Kääpä EH, Frantsi K, Sarna S, et al. Multidisciplinary group rehabilitation versus individual physiotherapy for chronic nonspecific low back pain: a randomized trial. *Spine (Phila Pa 1976)*. 2006;31:371–376.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

48. Klaber Moffett JA, Chase SM, Portek I, et al. A controlled, prospective study to evaluate the effectiveness of a back school in the relief of chronic low back pain. *Spine*. 1986;11:120–122.
49. Meyer K, Fransen J, Huwiler H, et al. Feasibility and results of a randomised pilot-study of a work rehabilitation programme. *J Back Musculoskelet Rehabil*. 2005;18:67–78.
50. Monticone M, Ferrante S, Rocca B, et al. Effect of a long-lasting multidisciplinary program on disability and fear-avoidance behaviors in patients with chronic low back pain: results of a randomized controlled trial. *Clin J Pain*. 2013; 29:929–938.
51. Monticone M, Ambrosini E, Rocca B, et al. A multidisciplinary rehabilitation programme improves disability, kinesiophobia and walking ability in subjects with chronic low back pain: results of a randomised controlled pilot study. *Eur Spine J*. 2014;23:2105–2113.
52. Monticone M, Ambrosini E, Rocca B, et al. Group-based task-oriented exercises aimed at managing kinesiophobia improved disability in chronic low back pain. *Eur J Pain*. 2016;20:541–551.
53. Monticone M, Ambrosini E, Rocca B, et al. Group-based multimodal exercises integrated with cognitive-behavioural therapy improve disability, pain and quality of life of subjects with chronic neck pain: a randomized controlled trial with one-year follow-up. *Clin Rehabil*. 2017;31: 742–752.
54. Nicholas MK, Wilson PH, Goyen J. Operant-behavioural and cognitive-behavioural treatment for chronic low back pain. *Behav Res Ther*. 1991;29:225–238.
55. Paolucci T, Zangrando F, Iosa M, et al. Improved interoceptive awareness in chronic low back pain: a comparison of Back school versus Feldenkrais method. *Disabil Rehabil*. 2017;39:994–1001.
56. Pato U, Di Stefano G, Fravi N, et al. Comparison of randomized treatments for late whiplash. *Neurology*. 2010;74:1223–1230.
57. Ronzi Y, Roche-Leboucher G, Bègue C, et al. Efficiency of three treatment strategies on occupational and quality of life impairments for chronic low back pain patients: is the multidisciplinary approach the key feature to success? *Clin Rehabil*. 2017;31:1364–1373.
58. Sahin N, Albayrak I, Durmus B, et al. Effectiveness of back school for treatment of pain and functional disability in patients with chronic low back pain: a randomized controlled trial. *J Rehabil Med*. 2011;43:224–229.
59. Schweikert B, Jacobi E, Seitz R, et al. Effectiveness and cost-effectiveness of adding a cognitive behavioral treatment to the rehabilitation of chronic low back pain. *J Rheumatol*. 2006;33: 2519–2526.
60. Turner JA, Clancy S, McQuade KJ, et al. Effectiveness of behavioral therapy for chronic low back pain: a component analysis. *J Consult Clin Psychol*. 1990;58:573–579.
61. Van Eijk-Hustings Y, Kroese M, Tan F, et al. Challenges in demonstrating the effectiveness of multidisciplinary treatment on quality of life, participation and health care utilisation in patients with fibromyalgia: a randomised controlled trial. *Clin Rheumatol*. 2013;32:199–209.
62. Ryan R, Hill S. Cochrane Consumers and Communication Group. How to GRADE the quality of the evidence, version 3.0; 2016. Available at: http://cccrg.cochrane.org/author-resources. Accessed August 28, 2020.
63. Green DJ, Lewis M, Mansell G, et al. Clinical course and prognostic factors across different musculoskeletal pain sites: a secondary analysis of individual patient data from randomised clinical trials. *Eur J Pain*. 2018;22:1057–1070.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2020 Wolters Kluwer Health, Inc. All rights reserved.