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SUMMARY WITH CRITICAL APPRAISAL

Multidisciplinary Treatment Programs for Patients with Chronic Non-Malignant Pain: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Context and Policy Issues

Chronic pain is a common disorder that can result in considerable disability leading to substantial psychosocial and socioeconomic consequences.[1] The prevalence of chronic pain in Canada varies between 16% and 40%.[2,3] The variability is likely due to differences in the definitions used for chronic pain, sample populations surveyed, and the survey methodologies.[2] In Canada, the estimated direct costs to the health care system for chronic pain are estimated to be over six billion dollars and the indirect costs resulting from job losses and sick days are estimated to be over 37 billion dollars annually.[3] In the United States, the 2010 estimates of cost of pain to society ranged between 560 and 635 billion dollars annually, considering both direct and indirect costs.[4] This annual cost of pain was found to be greater than the 2010 annual cost estimates for heart disease (309 billion dollars), cancer (243 billion dollars), and diabetes (188 billion dollars).[4]

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage" according to the International Association for the Study of Pain.[5] Chronic pain is defined as pain that persists for more than three months.[6] It is associated with disorders, such as osteoarthritis, low back pain, fibromyalgia, headaches, and neuropathy.[1] Long-lasting pain results in changes in pain perceptions and threshold levels, coping abilities, social and professional activities, and significantly affects one's quality of life.[7] Considering the multi-dimensional aspect of chronic pain, it appears that a single treatment modality may not be sufficient for the optimal management of chronic pain.

There is growing interest in multimodal approaches, such as a multidisciplinary treatment program (MTP). MTP encompasses medical therapy, behavioral therapy, physical reconditioning and education and involves a multidisciplinary team.[5] There appears to be some variations in the definition of multidisciplinary treatment. Multidisciplinary treatment can be defined as including at least three of the following categories: psychotherapy, physiotherapy, relaxation techniques, medical treatment, patient education, or vocational therapy.[8] Multidisciplinary treatment can also entail a physical component (e.g., exercise programs) and at least one other element from psychological, social and occupational dimensions. As well, the program must be delivered by at least two healthcare professional of different professional backgrounds.[8,9] Various terminologies have been used for multidisciplinary treatment, such as interdisciplinary treatment, multimodal treatment, and inter-professional.

It is important to assess the evidence regarding the clinical effectiveness and cost-effectiveness of multidisciplinary treatment programs to assist in objective decision making in pain management. A 2011 CADTH Rapid Response report [10] assessed MTPs for adults with chronic, non-malignant pain. The results indicated that MTPs were effective in pain reduction, improving biopsychosocial standing and could reduce use of prescription pain medication; however, the evidence on cost-effectiveness was limited.

The purpose of this report is to review the comparative clinical effectiveness and cost-effectiveness of multidisciplinary treatment programs for patients with chronic, non-malignant pain in outpatient settings. Additionally, this report aims to review the evidence-

based guidelines regarding multidisciplinary treatment programs for patients with chronic, non-malignant pain in outpatient settings.

Research Question

1. What is the clinical effectiveness of multidisciplinary treatment programs for patients with chronic, non-malignant pain in outpatient settings?
2. What is the cost-effectiveness of multidisciplinary treatment programs for patients with chronic, non-malignant pain in outpatient settings?
3. What are the evidence-based guidelines regarding multidisciplinary treatment programs for patients with chronic, non-malignant pain in outpatient settings?

Key Findings

The evidence suggests that the multidisciplinary management of chronic non-malignant pain showed modest improvement for specific outcomes measured. No relevant cost-effectiveness studies of multidisciplinary treatment programs, for patients with chronic, non-malignant pain in outpatient settings, were identified. Three guidelines recommended multidisciplinary treatment for management of chronic non-malignant pain under specific circumstances.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, Canadian and major international health technology agencies, as well as a focused Internet search. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between October 1, 2011 and May 25, 2017.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients (any age) with chronic, non-malignant pain in outpatient settings
Intervention	Multidisciplinary treatment or multidisciplinary treatment programs for managing chronic pain (may also be called multi-professional, multimodal, interdisciplinary, inter-professional), including multidisciplinary primary care teams

Comparator	Q1 & Q2: Alternative treatments or programs for pain management, or usual care; no treatment; waitlist; placebo Q3: No comparator necessary
Outcomes	Q1: Clinical benefits and harms (e.g., pain, physical function, social function [including return to school or work], emotional and psychological functioning (e.g., anxiety, depression, sleep), health-related quality of life, opioid use, opioid prescribing practices) Q2: Cost-effectiveness outcomes (e.g., incremental cost per QALY or health benefit gained, health care resource utilization) Q3: Evidence-based guidelines and recommendations, including: types of patients for whom multidisciplinary treatment programs are recommended; structure or organization of the treatment programs; recommended care providers or specialties involved in treatment programs
Study Designs	Health technology assessments (HTA), systematic reviews (SR), meta-analyses (MA), randomized controlled trials (RCT), non-randomized studies (NRS), economic valuations, and evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to October 2011. Studies on subacute pain, pain less than months, acute whiplash, were excluded. Further, studies in which it was unclear if patients had chronic pain or studies that included surgical interventions as comparators were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews were critically appraised using AMSTAR,[11] randomized and non-randomized studies were critically appraised using Downs and Black checklist,[12] and guidelines were assessed with the AGREE II instrument.[13] Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 482 citations were identified in the literature search. Following the screening of titles and abstracts, 446 citations were excluded, and 36 potentially relevant reports from the electronic search were retrieved for full-text review. Five potentially relevant publications were retrieved from the grey literature search. Of these 41 potentially relevant articles, 25 publications were excluded for various reasons, while 16 publications met the inclusion criteria and were included in this report. These comprised two systematic reviews,[9,14] six RCTs,[15-21] three non-randomized studies, [22-25] and three evidence-based guidelines.[8,26,27] One RCT was described in two reports[17,18] and one non-randomized study was described in two reports.[22,23] No relevant economic studies were identified. Appendix 1 describes the PRISMA flowchart of the study selection.

Additional references of potential interest are provided in Appendix 7.

Summary of Study Characteristics

Summary of the characteristics of the included systematic reviews, clinical studies and guidelines are presented below and details are available in Appendix 2, Tables 2 to 5.

Study Design

Two systematic reviews,[9,14] six RCTs,[15-21] three prospective non-randomized studies,[22-25] and three guidelines[8,26,27] were included. Information from the systematic reviews which was relevant for this review is presented here.

Country of Origin

One systematic review[9] was published in 2014 by the Cochrane Collaboration. This systematic review included 41 studies conducted in various countries: Europe, North America, Iran and Australia; the majority was conducted in Europe. The second systematic review[14] was published in 2016 by the Agency of Healthcare Research Quality (AHRQ) and included the above systematic review and one additional RCT.

Of the six RCTs, one RCT[17] was published in 2016 from Norway, one RCT[16] was published in 2015 from the US, one RCT[15] was published in 2013 from Canada, two RCTs were published in 2012, one each from Spain[19] and Italy,[21] and one RCT was published in 2011 from China.[20]

Of the three non-randomized studies, one study[24] was published in 2013 from Switzerland, one study[22] was published in 2012 from Sweden, and one study[25] was published in 2011 from Spain.

Of the three guidelines, one guideline[26] was published in 2017 from Canada, one guideline[27] was published in 2015 from Canada, and one guideline[8] was published in 2013 from the UK.

Patient Population

One systematic review[9] included 6,858 patients with chronic low back pain; the sample size in the individual RCTs ranged from 20 to 542, mean age in the range from 40 to 45 years, and a variable proportion of females. The second systematic review[14] besides including the above mentioned systematic review included an additional RCT involving 20 patients with a mean age of 58 years, and 55% were female.

Of the six RCTs, three RCTs[15,16,20] were on chronic pain, one RCT[21] was on chronic low back pain, one RCT[17] was on musculoskeletal pain, and one RCT[19] was on fibromyalgia. The number of patients ranged between 63 and 284, mean age ranged between 36 to 58 years, and proportion of females ranged between 10% to 91% in five RCTs[15-17,19,21] and these details were not reported in one RCT.[20]

Of the three nonrandomized studies, one study[24] was on chronic low back pain, one study[22] was on musculoskeletal pain, and one study[25] was on fibromyalgia. In these three studies[22,24,25] the number of patients ranged between 45 and 296, mean age ranged between 39 to 51 years, and proportion of females ranged between 47% and 100%.

Of the three guidelines, two guidelines[8,26] were on chronic non-malignant pain, and one guideline was on chronic low back pain.

Interventions and Comparators

The systematic reviews[9,14] compared multidisciplinary treatment with usual care, physical treatment, or a waitlist.

The six RCTS compared various forms of multidisciplinary treatments with other forms of treatment. They include usual care,[16,19,21] mindfulness based stress reduction (MBSR),[20] brief intervention (BI),[17] and waitlist.[15]

The three non-randomized studies compared various forms of multidisciplinary treatments with other forms of treatment. They include usual care,[25] standard rehabilitation,[22] and muscle reconditioning program (MRP).

Outcomes

Pain and disability or function were reported in all systematic reviews, RCTs and non-randomized studies. Other outcomes reported included health related quality of life (HRQoL)[9,15,19,21,25] healthcare service utilization,[15,17] medication use, [15,16] and return to work (RTW) status.[9,22,24] Various outcome measures were used. They include Brief Pain Inventory (BPI), Spanish pain coping questionnaire (CAD-R)Center for Epidemiological Studies Depression Scale (CES-D), Dallas Pain Questionnaire (DPQ), Fibromyalgia Impact Questionnaire (FIQ), Graded Chronic Pain Scale (GCPS), Hospital Anxiety and Depression Scale (HADS), Hopkins Symptom Checklist (HSCL), Multidimensional Pain Inventory (MPI), Norwegian Function Scale (Norfunk), Numeric Rating Scale (NRS), Oswestry Disability Index (ODI), Profile of Mood Status (POMS), Roland Morris Disability Scale (RMDS), Rosenberg Self-Esteem Scale (RSES), Short form Health Survey (SF-12, SF-36) having a physical component (PCS) and a mental component (MCS), Subjective Health Complaints (SHC), State-Trait Anxiety Inventory (STAI), and Visual Analog Scale (VAS). Details of these outcome measures are available in Appendix 6, Table 11.

All three guidelines provided recommendations regarding multidisciplinary treatments.

Summary of Critical Appraisal

The critical appraisal of the included systematic reviews, RCTs, non-randomized studies, and guidelines are presented below and details are available in Appendix 3, Tables 6 to 8.

Both systematic reviews[9,14] were well conducted. The objective, inclusion and exclusion criteria were stated; a comprehensive literature search was undertaken, article selection was described and was done in duplicate. Further, data extraction was done by one reviewer and checked by a second reviewer, and meta-analyses were conducted. In one systematic review,[9] the studies were of variable quality. The additional RCT included in the second systematic review[14] was judged to be of good quality. In one systematic review[9] conflict of interest was not presented, and the second systematic review[14] mentioned that the authors had no conflicts of interest.

In all the six included RCTs[15-17,19-21] the study objectives inclusion and exclusion criteria, patient characteristics, intervention, and outcomes were described. Randomization was described in five RCTs[15-17,19,20] and appeared to be appropriate. In one RCT,[21] the randomization method was unclear. Withdrawals varied between 13% and 40%; hence, this could impact findings, but it was unclear in which direction. Intention-to-treat analysis was conducted in two RCTs,[16,20] unclear in one RCT,[15] and not conducted in three RCTs.[17,19,21]

Conflicts of interest were mentioned in four RCTs,[16,17,19,20] and no issues were apparent. In two RCTs,[15,21] conflicts of interest were not mentioned.

In all the three included non-randomized studies,[22,24,25] the objective, inclusion and exclusion criteria, patient characteristics, interventions, and outcomes were described. Withdrawals were less than 10% in one study,[25] between 31% and 32% in another study but was similar in both treatment groups, and were unclear in one study.[24] Conflicts of interest were mentioned in two studies,[24,25] and no issues were apparent. They were not mentioned in one study.[22]

In all three included guidelines,[8,26,27] the scope and purpose were described, the guideline development group had relevant expertise, a systematic review to identify evidence was conducted and recommendations were graded. In two guidelines,[8,26] patient input was sought, the document was externally reviewed, and a policy for updating the guideline was in place but was unclear in one guideline.[27] Conflicts of interest were not mentioned in any of the guideline reports.

Summary of Findings

What is the clinical effectiveness of multidisciplinary treatment programs for patients with chronic, non-malignant pain in outpatient settings?

Findings are summarized below and details are available in Appendix 4, Table 9.

Chronic pain, chronic low back pain, or musculoskeletal chronic pain

Pain, and function or disability:

A systematic review by Kamper et al.[9] investigated multidisciplinary biopsychosocial rehabilitation (MBR) for chronic low back pain. Moderate to low quality evidence showed that in the long term, MBR was more effective than usual care in reducing pain and disability. The range of improvement across all time points was approximately equivalent to 0.5 to 1.4 units on the NRS (scale 0 to 10) for pain and 1.4 to 2.5 points on the RMDS (scale 0 to 24) for disability. Moderate to low quality evidence showed that in the long term, MBR was more effective than physical treatment for pain and disability. The range of improvement across all time points was approximately equivalent to 0.6 to 1.2 units on the NRS (scale 0 to 10) for pain and 1.2 to 4.0 points on the RMDS (scale 0 to 24) for disability. In the short term (i.e., up to three months), patients on MBR had improvement in pain (very low quality evidence) and disability (low quality evidence) compared to those on wait list. The estimates were 1.7 points on NRS for pain and 2.9 points on RMDS for disability.

The systematic review by Chou et al.[14] summarized findings from the systematic review by Kamper et al.,[9] which is presented above, and also included an additional RCT relevant for this report. Findings from this RCT are presented here. This RCT showed that, compared with usual care, multidisciplinary intervention resulted in greater improvements in pain and disability, which were consistent with the findings from the systematic review.

The RCT by Bair et al.[16] on Veterans with chronic pain found that there were statistically significant between group differences favouring stepped care compared with usual care.

The RCT by Brendbekken et al.[17] compared multidisciplinary intervention with standard treatment referred to as brief intervention for adult patients with chronic musculoskeletal pain. By 12 months, improvements in pain and functional ability were found in both groups compared to baseline, but there were no significant differences between the groups.

The RCT by Paolocci et al.[21] compared Back School Program (BSG), a multidisciplinary treatment, with medical assistance in adults with chronic non-specific low back pain. Statistically significant improvements with respect to baseline were found with BSG for pain and disability but not with the control group.

The RCT by Wong et al.[20] involved adult patients with chronic pain and compared mindfulness based stress reduction (MBSR) with multidisciplinary intervention. Statistically significant improvements in pain intensity were observed in both the MBSR and the multidisciplinary treatment groups. Overall, there were no statistically significant differences in outcomes between the two groups.

Quality of life (QoL), anxiety, and depression:

The systematic review by Kamper et al.[9] showed significant effects with respect to SF-36 (MCS), catastrophizing, and fear avoidance favouring multidisciplinary treatment compared with usual care and no significant between group difference for SF-36 (PCS). Also, this systematic review showed no significant between group differences with respect to SF-36, depression or anxiety for multidisciplinary treatment compared with physical treatment.

The pilot RCT by Angeles et al.[15] on adult patients with chronic pain found no statistically significant differences in the mean change in scores for the SF-36 physical or mental summary scores between the interprofessional treatment (referred by the authors as early intervention [EI]) group and the group waiting treatment (referred to as delayed intervention [DI] group) (Appendix 4 Table 12).

The RCT by Brendbekken et al.[17] showed that by three months there were improvements in anxiety and depression in both the multidisciplinary and standard care groups but the improvements in the standard care group were smaller. By 12 months, however, improvements were similar in both groups.

The RCT by Paolocci et al [21] showed that there were statistically significant improvements in QoL with multidisciplinary treatment compared to baseline but there was no difference in the control group (i.e., medical treatment).

The RCT by Wong et al.[20] showed that there were improvements in QoL (i.e., SF-12, MCS and PCS) in both the multidisciplinary and MBSR groups compared to baseline but there was no significant between-group difference. There was no statistically significant difference between the groups with respect to anxiety (i.e., STAI) and depression (i.e., CES-D, POMS)

With respect to QoL, anxiety, and depression, there appears to be improvements with multidisciplinary treatments but the difference compared with control treatments were not always significant.

Healthcare resource use:

The systematic review by Kamper et al.[9] showed that there was no significant difference with respect to health care visits in the long term for multidisciplinary treatment compared to physical treatment.

The RCT by Angeles et al.[15] showed that there were no significant differences with respect to clinic visits, early refill of opioid medication, or increase in dose of opioids for interprofessional treatment compared to wait list.

The RCT by Brendbekken et al.[17] showed that by three and 12 months, the multidisciplinary treatment group had statistically significantly less general practitioner consultations compared with the standard care group. There were no significant differences between the groups with respect to consultation with other therapists.

Work status:

With respect to work related outcomes, the systematic review by Kamper et al.[9] showed that multidisciplinary treatment was more effective compared with physical treatment, with respect to work related outcomes, but there was no difference compared with usual care.

The RCT Brendbekken et al.[18] showed that, during the first seven months of follow up, patients in the multidisciplinary treatment group had a higher probability of partial return to work (RTW) compared with the patients in the standard care group. However, during 12 and 24 months of follow up, full-time RTW was not statistically significantly different between the groups.

The RCT by Wong et al.[20] showed that there was no difference in terms of sick leave days for multidisciplinary treatment compared to MBSR.

Adverse events:

Reporting of adverse events was sparse across the studies. The systematic review by Kamper et al.[9] mentioned that one study reported that there were no adverse effects with multidisciplinary treatment and it was unclear if adverse events were recorded for the control group (i.e., usual care).

Fibromyalgia

The RCT by Martin et al.[19] compared interdisciplinary intervention (IT) with standard pharmacological care in adults with fibromyalgia. Compared with standard care, interdisciplinary intervention resulted in statistically significant improvements in QoL, pain, and physical function, as assessed using FIQ. There was no statistically significant between group difference with respect to changes in anxiety and depression symptoms assessed using HAD or coping assessed using CAD-R. After twelve months the IT group maintained statistically significant improvements in QoL, pain, physical functioning, and anxiety and depression symptoms.

The prospective non-randomized study by Carbonell-Baeza et al.[25] involved women with fibromyalgia with widespread pain greater than three months and compared multidisciplinary treatment with usual care. They conducted a post-hoc analysis and demonstrated that there were statistically significant improvements in several outcomes in the multidisciplinary treatment group, whereas there was statistically significant worsening in some outcomes in the usual care group.

What is the cost-effectiveness of multidisciplinary treatment programs for patients with chronic, non-malignant pain in outpatient settings?

No relevant cost-effectiveness studies of multidisciplinary treatment programs for patients with chronic, non-malignant pain in outpatient settings were identified.

What are the evidence-based guidelines regarding multidisciplinary treatment programs for patients with chronic, non-malignant pain in outpatient settings?

The guidelines are summarized below and details are available in Appendix 5, Table 10. One Canadian guideline[26] recommended a formal multidisciplinary program for patients with chronic non-cancer pain who were using opioids and experiencing serious challenges in tapering. A second Canadian guideline[27] recommended the referral of patients significantly affected by chronic low back pain and with no improvement with primary care management to a multidisciplinary chronic pain program.

The SIGN guideline[8] recommended that a pain management program (i.e., multidisciplinary biopsychsocial treatment) should be considered for patients with chronic pain.

Limitations

Multidisciplinary interventions used in the studies were of different types, and the definition of multidisciplinary treatment varied; the comparators were also variable, so comparisons between studies were difficult.

The reporting of adverse events was sparse. No relevant study on chronic pain in the pediatric population was identified.

Three studies were non-randomized, and the potential for selection bias cannot be ruled out. In one non-randomized study,[23] patients who were likely to benefit from multidisciplinary treatment were given the treatment and the others were considered for standard rehabilitation.

No relevant economic studies were identified.

Conclusions and Implications for Decision or Policy Making

Two systematic reviews,[9,14] six RCTs,[15-21] three prospective non-randomized studies,[22-25] and three guidelines[8,26,27] were included. No relevant economic study was identified.

Overall, the multidisciplinary management of chronic non-malignant pain appears to be promising. However, the effect is modest. Several different outcome measures were used, and a statistically significant difference between multidisciplinary treatment and control treatment was not always observed for all outcome measures.

The three guidelines recommended multidisciplinary treatment for management of chronic non-malignant pain under specific circumstances.

Improvements with multidisciplinary treatment appear to be modest and need to be balanced against time and resource requirements.[9] Also, logistical issues, such as difficulty in attending sessions due to having to take time off work, availability for the scheduled sessions, conflicting appointments need to be considered.[15] Furthermore, some patients may find it difficult to tolerate prolonged sitting during the sessions.[15]

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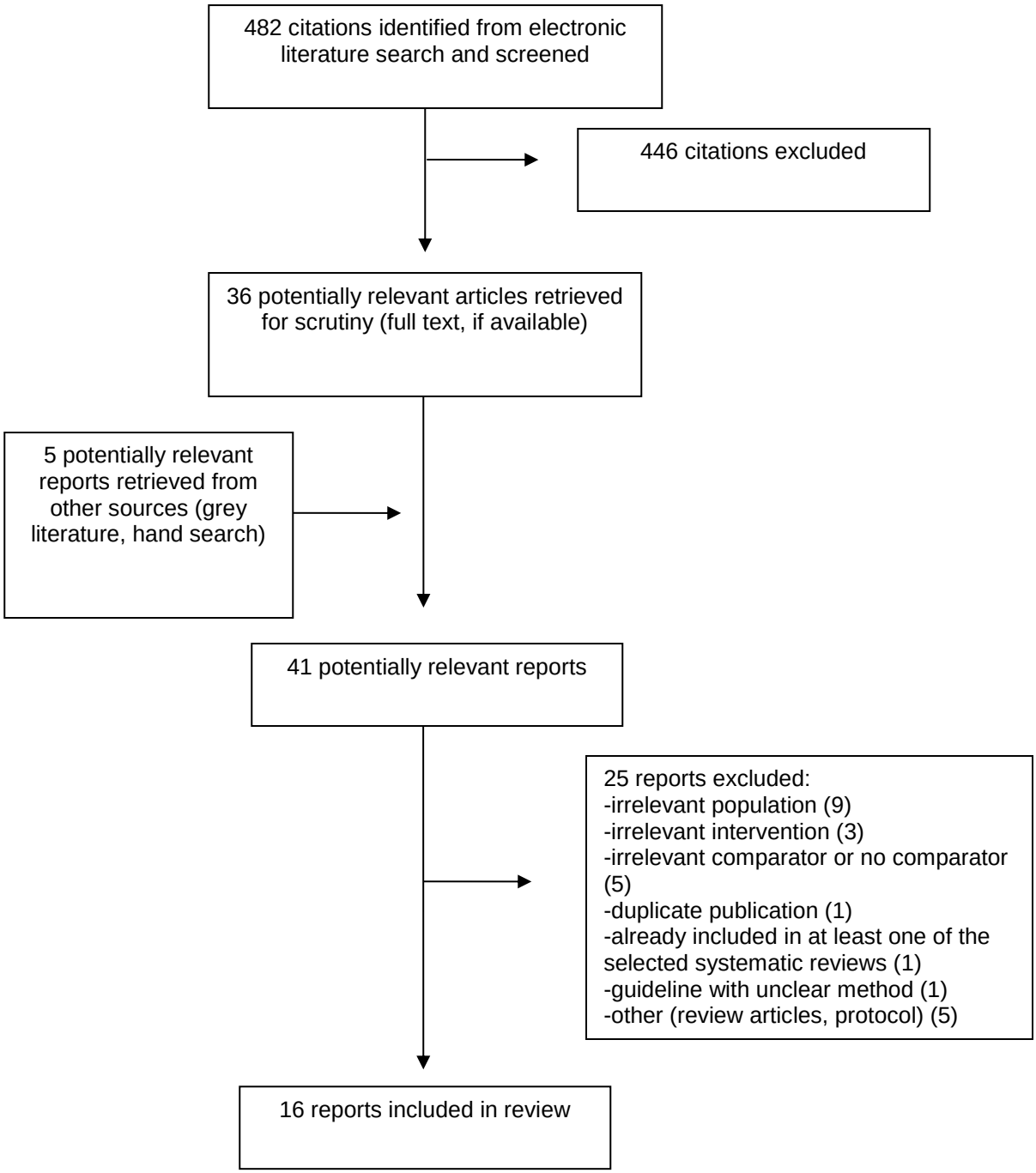
Abbreviations

AHRQ	Agency for Healthcare Research and Quality
BI	brief intervention
BPI	Brief Pain Inventory
CAD-R	Spanish pain coping questionnaire
CES-D	Center for Epidemiological Studies Depression Scale
DPQ	Dallas Pain Questionnaire
FIQ	Fibromyalgia Impact Questionnaire
GCPS	Graded Chronic Pain Scale
GRADE	Grading Recommendation Assessments, Development and Evaluation
HADS (or HAD)	Hospital Anxiety and Depression Scale
HSCL-25	Hopkins Symptom Checklist-25
ISIVET	Interdisciplinary Structured Interview with a Visual Educational Tool
MBSR	mindfulness based stress reduction
MCS	mental composite score
MI	multidisciplinary intervention
MPI	multidimensional pain inventory
Norfunk	Norwegian Function Assessment Scale
NRS	numeric rating scale
ODI	Oswestry Disability Index
OEF	Operation Enduring Freedom
OIF	Operation Iraqi Freedom
OND	Operation New Dawn
PCS	physical composite score
PSYMEPHY	coordinated psychological, medical, educational, and physiotherapeutic components
POMS	profile of mood status
QoL	quality of life
RCT	randomized controlled trial
RMDS	Roland Morris Disability Scale
RSES	Rosenberg Self-Esteem Scale
SC	stepped care
SF-12	Short Form Health Survey -12
SF-36	Short Form Health Survey Questionnaire
SHC	Subjective Health Complaints inventory
SIGN	Scottish Intercollegiate Guidelines Network
SMD	standardized mean difference
STAI	State-Trait Anxiety Inventory
TOP	Toward Optimized Practice
WI	Waddell Index

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Systematic Reviews

Author, Year, Country	Type and Number of Primary Studies Included Aim	Population characteristics	Comparison	Outcome
Chou,[14] 2016, USA,	1 SR (Kramer et al.[9] described in the later section, and 1 additional RCT were relevant for this report Aim: Broad focus. To investigate pharmacological and non-pharmacological therapies for acute and chronic low back pain. Only studies relevant for this report are described here	Adults with chronic low back pain Characteristics of the patients in the additional RCT. Mean age (years): 59 in MT, 57 in UC % Female: 70% in MT, 40% in UC. Pain duration (months): 15 in MT, 14 in UC	This systematic review included the systematic review by Kamper et al.[9] which is discussed in the later section, and an additional RCT which is presented here. Additional RCT - MT: Multidisciplinary rehabilitation (exercise and CBT) vs UC: usual care (passive spinal mobilization and exercise)	Pain, function Outcome measures: ODI, NRS, SF-36
Kamper,[9] 2014, Cochrane Back and Neck Group	41 RCTs (33 conducted in Europe, 3 from North America, 3 from Iran, and 2 from Australia) Aim: To assess effectiveness of MBR for patients with chronic LBP	Adult patients with non-specific chronic LBP N = 6858 (sample sizes ranged from 20 to 542). Average age in the studies (years): 40 t0 45. Gender balance varied in the studies. Average duration of symptoms usually > 1 year.	MBR vs usual care (16 studies), MBR vs physical treatment (19 studies), MBR vs surgery (2 studies), MBR vs wait list (4 studies). (In the above 41 studies, there were 12 studies that also compared two MBR programs)	Pain, disability or functional status, work status, adverse events. Findings presented as SMD, OR

LBP = low back pain; MBR = multidisciplinary biopsychosocial rehabilitation; RCT = randomized controlled trial

Table 3: Characteristics of Included Clinical Studies

Author, Year, Country	Study Design	Population characteristics	Comparison	Outcome, Follow-up
Randomized Controlled Trials				
Angeles,[15] 2013, Canada	RCT Setting: two clinic sites of MFHT	Adult patients with chronic non-cancer pain. (Chronic pain: musculoskeletal or neuropathic pain lasting at least 6 months)	Early intervention [EI] vs control (waiting list i.e. delayed intervention [DI]) Intervention: 2h group sessions once per week for 8 weeks. The curriculum was developed and facilitated by an	Pain, function, QoL, medication use, clinic visits Outcome measure: SF-36 Study period = 8 months

Author, Year, Country	Study Design	Population characteristics	Comparison	Outcome, Follow-up
		N = 63 (29 early intervention, 34 control) Age: ≥ 18 years. 51% in the age range: 40 to 50 years. % Female: 63% % with pain ≥15 years: 47%	occupational therapist and a social worker, both well experienced. Physicians, pharmacists, dieticians, and physiotherapists were involved as resource persons for specific sessions. Group sessions included education on pain and medication management; mindfulness relaxation techniques; cognitive reflection; and physical activation techniques	
Bair,[16] 2015, USA	RCT. Block randomized in groups of 8. Assessors were blinded to treatment allocation	Veterans from OEF/OIF/OND with chronic pain (> 3 months duration) and at least moderately disabling. Pain associated with cervical or lumbar spine or an extremity. N = 24i (121 in stepped care [SC], 120 in usual care [UC]) Age (mean ± SD) (years): 36.4±10.1 in SC, 38.2 ± 10.5 in UC. %Female: 10% in SC, 13% in UC. Majority with back pain: 53% in SC, 62% in UC	Stepped care (intervention group) vs. usual care. Stepped care (SC): Step 1 involved optimization of analgesic therapy, and education which included pain information and self-management strategies. Step 2: Analgesic therapy and self-management strategies were continued and a CBT program was added. Interventions were delivered by two nurse care managers (NCMs) trained in these areas. The NCMs met weekly with physician investigators and a supervising psychologist to review care of the intervention group. There were biweekly telephone contacts between the patient and the NCM. Usual care (UC): Patients received educational material on musculoskeletal pain. They were cared for by their treating physician. Care included medication, clinic visits, specialty referrals, and other usual care. Pharmacological and non-pharmacological treatments for pain were allowed.	Pain, disability, analgesic use Outcome measure: BPI, GCPS, RMDS Study period: 9 months

Author, Year, Country	Study Design	Population characteristics	Comparison	Outcome, Follow-up
Brendbekken,[17] 2016, Norway; Brendbekken,[18] 2017, Norway	RCT No blinding to treatment of therapist or patient. Setting: out-patient clinic	Adult with musculoskeletal pain. (The authors mentioned it was reasonable to assume that the study population consisted of chronic and more complex cases as they were sick listed on average for 147 days and were referred by their GPs to specialists). Low back pain, neck pain, widespread pain/fibromyalgia, or shoulder pain N = 284 (141 in MI, 143 in BI) Age (mean) (years): 41.3 % Female: 54% Majority with low back pain: 40%	Multidisciplinary intervention (MI) vs brief intervention (BI) MI: The team comprised a social worker, a physician, and a physiotherapist. The ISIVET method was used by the 3 therapists. This assessment tool comprised two figures, a manual, a table for the rehabilitation plan and list of possible rehabilitation initiatives. It is used to evaluate working conditions and QoL. BI: A physician and a physiotherapist were involved. The basic principal of BI is the non-injury model which emphasizes lack of any objective signs of injury and non-directive communication.	Pain, function, symptoms and use of health care services, work status. Outcome measure: HADS, HSCL-25, Norfunk, SHC Follow up: 12 months. RTW (follow up 24 months)
Martin,[19] 2012, Spain;	RCT Setting: Outpatient hospital pain management unit.	Adults with fibromyalgia (chronic pain > 6 months). N = 180 (90 in each group), 110 (54 in IT+ 56 control) completed the study For the 110 patients Age (mean ± SD) (years): 50.2 ± 9.3 % Female: 91% Years since onset of pain (mean ± SD): 14.1 ± 10.0	IT vs control IT: PSYMEPHY including also standard pharmacological treatment. Control: Standard pharmacological treatment PSYMEPHY: Interdisciplinary treatment that combines coordinated psychological, medical, educational, and physiotherapeutic components. Standard pharmacological treatment: tricyclic antidepressant, an analgesic, and an opioid central analgesic.	Pain, function, symptom Outcome measure: FIQ, HADS, CAD-R Follow up: 6 months

Author, Year, Country	Study Design	Population characteristics	Comparison	Outcome, Follow-up
Paolucci,[21] 2012, Italy	RCT (mentioned as single blind but unclear who was blinded) Setting: Ambulatory rehabilitative university center	Adults with chronic non-specific low back pain 73 were randomized but 23 were then excluded due to various reasons (such as no sufficient answer to MMPI-II or refusal to take MMPI-II test) and 51 completed N = 51 (29 in treatment group [BSG], 21 in control group [CG]). Each group was subdivided according to presence (ES) or absence (NES) of elevation in MMPI-II scale scores Age (mean ± SD) (years): 58± 13 for BSG-NES, 60±16 for BSG-ES; 56±13 for CG-NES, 58± 15 for CG-ES % female: 55% in BSG, 71% in CG	Multidisciplinary back school program (BSG) vs control (CG). BSG was an intensive four weeks intervention carried out by a multidisciplinary professional team and comprised education and exercise. CG had medical treatment self-administered during the study period under physician supervision similar to the BSG group. Physicians were instructed not to start any new therapies	Pain, disability, HRQoL, Outcome measure: SF-36, VAS, ODI Follow up: 6 months after treatment end
Wong,[20] 2011, China	RCT Assessors were blinded to treatment allocation. Setting: community based clinics, hospitals and community service centers.	Adults with chronic pain (persisted ≥ 3 months at moderate to severe level) N = 99 (51 in MBSR, 48 in MI) Age (mean ± SD) (years): 47.9 ± 7.8 % Female: NR Majority (85%) with pain > 1 year	MBSR vs MI MBSR involved clinical psychologist. There were three elements: (i) material related to mindfulness, relaxation, meditation, yoga and the body-mind-connection; (ii) experimental practice of meditation and yoga; and (iii) group activities MPI involved experienced nurse, registered physiotherapist and	Pain, function, HRQoL, Outcome measure: POMS, CES-D, STAI, SF-12 Follow up: 6 months

Author, Year, Country	Study Design	Population characteristics	Comparison	Outcome, Follow-up
			registered dietician. MPI consisted of educational instructions on pain management, instructions on exercise, and advice on healthy diet and weight control	
Non randomized studies				
Merrick,[23] 2013, Sweden; Merrick[22], 2012, Sweden	Prospective longitudinal study Setting: Pain rehabilitation clinic at the Umeà University hospital in Sweden	Adults with disabling chronic musculoskeletal pain. N = 296 (220 in rehabilitation plan [RP]; 76 in multimodal rehabilitation program [MMR]) For 210 in RP and 75 in MM,. Age (mean ± SD) (years): 38.9 ± 10.5 in RP; 39.2 in MMR, % Female: 62% in RP; 76% in MMR. For 172 in RP and 61 in MMR, Years with chronic pain (mean ± SD): 6.2 ±6.4 in RP; 5.2 ± 5.0 in MMR	Multimodal rehabilitation program (MMR) vs rehabilitation plan (RP) MMR: It was based on cognitive behavioral principles. It included physical therapy (exercise, relaxation, and body-awareness training); occupational therapy (ergonomics); information regarding reactions to chronic pain; training in coping strategies; and education in pain management. It was a 4-week outpatient program. MMR was given to patients considered suitable for MMR. RP: It included team assessment of the patient's pain condition and working capacity; and suggestions recommendations for further investigations and treatment. For patients who were assessed as likely to benefit with treatment by one professional only (such as physiotherapist, psychologist, occupational therapist) and/or did not satisfy the criteria for the MMR program, an individual rehabilitation program was presented.	Pain, disability, sick leave Outcome measure: MPI Follow up: 1 year

Author, Year, Country	Study Design	Population characteristics	Comparison	Outcome, Follow-up
Steiner,[24] 2013, Switzerland	Prospective non-randomized study Setting: Patients were recruited from the tertiary rheumatology and rehabilitation center of Geneva University hospitals.	Adults with chronic low back pain. (Patients working outside the home had to be on sick leave). N = 45 (24 in multidisciplinary functional rehabilitation program [MFRP]; 21 in muscle reconditioning program [MRP]) Age (mean ± SD) (years): 39.9 ± 11.7 in MFRP, 41.1 ± 10.9 in MRP. % Female: 42% in MFRP; 52% in MRP Length of present episode ≥3 months: 87% in MFRP; 76% in MRP	Multidisciplinary functional rehabilitation program (MFRP) vs muscle reconditioning program (MRP) MFRP: It included cognitive behavioral components and work-related goals. This program was designed by a multidisciplinary team (rheumatologist, rehabilitation physician, pain specialist, psychiatrist, physical therapists, occupational therapists and a psychologist) for groups of four to six patients, and duration was over four weeks (with a total of 100 hours). Although treatments were given in groups, the type and intensity of the physical treatment and treatment goals were individualized. MRP: Therapy provided to groups of four to six patients. It included muscle reinforcement and stabilisation exercises, relaxation, proprioception sessions and water gymnastics, given over five half-days/week over three weeks (with a total of 46 hours). Also six hours of occupational therapy was provided. There was no individualization of therapy.	Pain, function, work status Outcome measures: DPQ, VAS Treatment duration was 4 weeks in MFRP and 3 weeks in MRP. Subsequently follow up (in months), mean (SD): 8.7 (2.9) in MFRP, and 8.8 (1.2) in MRP
Carbonell-Baeza,[25] 2011, Spain	Post-hoc analysis of a prospective non-randomized study Setting: unclear	Women with fibromyalgia with widespread pain lasting more than 3 months. N = 75. 65 completed the study (33 in multidisciplinary treatment [MT], 32 in usual care [UC])	Multidisciplinary treatment [MT] vs usual care [UC]). MT: Exercise (pool and land based) sessions with fitness specialist and physical therapist, and psychological-educational sessions with psychologist, with experience treating fibromyalgia patients.	Pain, function Outcome measures: FIQ, SF-36, HADS, RSES Treatment period: 12 weeks

Author, Year, Country	Study Design	Population characteristics	Comparison	Outcome, Follow-up
		Age (mean ± SD) (years): 50.0 ± 7.3 in MT, 51.4 ± 7.4 in UC. %Female: 100% Proportion of patients with >5 years since clinical diagnosis: 49% in MT, 50% in UC.	UC: Continued exercise and medication as usual	

BI = brief intervention; CAD-R = Spanish pain coping questionnaire; CES-D = Center for Epidemiological Studies Depression Scale; DPQ = Dallas Pain Questionnaire; FIQ = Fibromyalgia Impact Questionnaire; GCPS = Graded Chronic Pain Scale; HADS = Hospital Anxiety and Depression Scale; IT = interdisciplinary treatment; MBSR = mindfulness based stress reduction; MFHT = McMaster Family Health Team; MI = multidisciplinary intervention; MPI = multidimensional pain inventory; Norfunk = Norwegian Function Assessment Scale; NR = not reported; NRS = numeric rating scale OEF = Operation Enduring Freedom; OIF = Operation Iraqi Freedom; OND = Operation New Dawn; POMS = Profile of Mood Status; PSYMEPHY = psychological, medical, educational and physiotherapeutic components; QoL = quality of life; RCT = randomized controlled trial; RMDS = Roland Morris Disability scale; RTW = return to work; SC = stepped care; SD = standard deviation; SF-12 = short form health survey; SHC = Subjective Health Complaints inventory; STAI = State-Trait Anxiety Inventory, UC = usual care; VAS = visual analog scale

Table 4: Characteristics of Included Guidelines

First Author/ Group, Year, Country	Objective	Guideline Development Group, Target Users	Methodology
Busse[26] 2017, Canada	To provide guidance on the use of opioids for management of chronic non-cancer pain in adults	The guideline development group comprised multidisciplinary experts (researchers with expertise in pain, opioids, systematic reviews and guideline development; pain specialists; and regulators). Target audience: primary care physicians; specialists involved in management of chronic non-cancer pain; nurse practitioners;, regulatory agencies and policy makers. Secondary target: other healthcare professionals and patients.	Systematic review was conducted. GRADE system was used in formulating recommendations
TOP,[27] 2015, Canada	To help clinicians make evidence-informed decisions regarding care of patients with non-specific low back pain.	The guideline committee comprised multidisciplinary experts (clinicians of various backgrounds, physiotherapist, psychologist and occupational therapist. Target audience: Clinicians caring for patients with low back pain	Systematic review was conducted. Recommendations were categorized according to specific criteria
SIGN,[8] 2013 UK	To provide recommendations based on current evidence for best practice in the assessment and management of	The guideline development group comprised multidisciplinary experts (clinician, pain specialist, psychologist, neuropsychiatrist, general practitioner, nurse consultant, occupational therapist, pharmacist, patient representative, evidence and information specialist)	Systematic review was conducted. Recommendations were graded according to the SIGN system

First Author/ Group, Year, Country	Objective	Guideline Development Group, Target Users	Methodology
	adults with chronic non-malignant pain in non-specialist settings	Target audience: Healthcare professionals including general practitioners, pharmacists, anesthetists, rheumatologists, psychologists, psychiatrists, physiotherapists, occupational therapists, nurses, patients, caregivers and organizations interest in chronic pain.	

SIGN = Scottish Intercollegiate Guideline Network; TOP = Toward Optimized Practice

Table 5: Grade of Recommendations and Level of Evidence for Guidelines

Grade of Recommendations	Strength of Evidence
Busse[26] 2017, Canada	
Interpretation of strong and weak recommendation using the GRADE approach: For clinicians. Strong recommendation: "All or almost all individuals should receive the intervention. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences." p13 Weak recommendation: "Recognize that different choices will be appropriate for individual patients and that clinicians must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences." p13 For patients. Strong recommendation: "All or almost all informed individuals would choose the recommended course of action, and only a very small proportion would not." p13 Weak recommendation: "The majority of informed individuals would choose the suggested course of action, but an appreciable minority would not." p13 For policy makers. Strong recommendation: "The recommendation can be adopted as policy in most situations. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator." p13 Weak recommendation: "Policymaking will require substantial debate and involvement of various stakeholders." p13	Cochrane risk of bias tool was used

<table>
<tr><th>Grade of Recommendations</th><th>Strength of Evidence</th></tr>
<tr><td colspan="2">TOP,[27] 2015, Canada</td></tr>
<tr><td>“SUMMARY OF CRITERIA TO DETERMINE THE CATEGORIZATION OF RECOMMENDATIONS:

<table>
<tr><th>Category</th><th>Explanation</th></tr>
<tr><td>Do

√</td><td>●The Guideline Development Group (GDG) accepted the original recommendation, which provided a prescriptive direction to perform the action or used the term “effective” to describe it

●The GDG supplemented a recommendation or created a new one, based on their collective professional opinion, which supported the action

●A supplementary literature search found at least one systematic review presenting consistent evidence to support the action</td></tr>
<tr><td>Do Not Do

X</td><td>●The GDG accepted the original recommendation, which provided a prescriptive direction not to perform the action, used the term “ineffective” to describe it, or stated that the evidence does “not support” it

●The GDG supplemented a recommendation or created a new one, based on their collective professional opinion, which did not support the action

●A supplementary literature search found at least one systematic review presenting consistent evidence that did not support the action</td></tr>
<tr><td>Do Not Know

?</td><td>●The GDG accepted the original recommendation, which did not recommend for or against the action or stated that there was “no evidence”, “insufficient or conflicting evidence,” or “no good evidence” to support its use

●The GDG supplemented a recommendation or created a new one, based on their collective professional opinion, which was equivocal with respect to supporting the action

●A supplementary literature search found either no systematic reviews (“insufficient evidence to recommend for or against”) or at least one systematic review presenting conflicting or equivocal results or stating that the evidence in relation to the action was “limited,” “inconclusive,” inconsistent,” or insufficient” (“inconclusive evidence to recommend for or against”)</td></tr>
</table>
“ Page 25</td><td>NR</td></tr>
</table>

Grade of Recommendations	Strength of Evidence

SIGN,[8] 2013 UK

Grade	Explanation
A	"At least one meta-analysis, systematic review, or RCT rated as 1++, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results" 1st page
B	"A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+" 1st page
C	"A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++" 1st page
D	"Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+" 1st page

Level	Explanation
1++	"High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias" 1st page
1+	"Well conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias" 1st page
1-	"Meta-analyses, systematic reviews, or RCTs with a high risk of bias" 1st page
2++	"High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal" 1st page
2+	"Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal" 1st page
2-	"Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal" 1st page
3	"Non-analytic studies, eg case reports, case series" 1st page
4	"Expert opinion" 1st page

GDG = Guideline Development Group; NR = not reported; SIGN = Scottish Intercollegiate Guidelines Network; RCT = randomized controlled trial; TOP = Toward Optimized Practice

Appendix 3: Critical Appraisal of Included Publications

Table 6: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR

Strengths	Limitations
Chou,[14] 2016, USA	
• The objective was explicit. • The inclusion criteria were stated. • The exclusion criteria were stated • Multiple databases (Medline, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews). Also, hand searches of reference list of relevant studies. Trial registries were searched. Initial search was January 2008 to 2014. The start date was 2008 as a prior review was used to identify studies published prior to 2008. An update search was conducted in April 2015. • Study selection was described • Flow chart of study selection was provided • List of included studies was provided • List of excluded studies was provided • Article selection was done in duplicate • Data extraction was done by one reviewer and checked by a second reviewer • Quality assessment was done by two reviewers independently using AMSTAR for the systematic review and the Cochrane risk of bias tool for the RCT and quality was judged as good. Strength of evidence was assessed using AHRQ methods guide • Characteristics of the RCT were provided.. • Meta-analyses results from the included systematic review were presented • It was mentioned that there were no conflicts of interest	• Publication bias was not explored. The authors mentioned "We were unable to assess for publication bias using graphical or statistical methods to detect small sample effects; methodological limitations in the trials; heterogeneity in the interventions, populations, and outcomes addressed; and small numbers of trials for many comparisons. However, based on searches of reference lists, clinical trial registries, and peer review suggestions, we did not find evidence to suggest that unpublished trials would impact conclusions." p ES-40.
Kamper,[9] 2014, Cochrane Back and Neck Group	
• The objective was explicit. • The inclusion criteria were stated. • The exclusion criteria were stated • Multiple databases (Medline, Embase, Central, PsycInfo and CINAHL) were searched until January and March 2014. Also, hand searches of reference list of included and related studies • Study selection was described • Flow chart of study selection was provided • List of included studies was provided • List of excluded studies was provided • Article selection was done in duplicate • Data extraction was done by one reviewer and checked by a second reviewer • Quality assessment was done by two reviewers using Cochrane risk of bias tool. The studies met one to nine of the 12 criteria for low risk of bias. Thirteen of the 41 studies	• There was no mention of conflicts of interest

Strengths	Limitations
were judged to be of low risk of bias as they met six or more criteria. GRADE was used to determine the strength of evidence • Characteristics of the individual studies were provided. • Meta-analyses were conducted • Publication bias was explored using Funnel plot for comparisons with at least 10 included studies. The criteria was satisfied for the comparison MBR vs physical treatment for three outcomes. No substantial asymmetry was apparent in the plots.	

AHRQ = Agency for Healthcare Research and Quality, GRADE = Grading of Recommendation Assessments, Development and Evaluation.

Table 7: Strengths and Limitations of Clinical Studies using Downs and Black checklist

Strengths	Limitations
Randomized Controlled Trials	
Angeles,[15] 2013, Canada	
• The objective was explicit • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. Details of the scoring system were not provided • Randomization was performed using the online Research Randomizer • Withdrawals were reported and were high but similar in both groups (34% in EI and 35% in DI) • *P*-values were reported for outcomes but not for baseline patient characteristics	• Unclear if there was blinding of assessor • Sample size calculation was conducted, but the sample size used was less than that calculated to detect a significant difference. However, the authors mentioned it was a pilot study to investigate if the research design could be used successfully and detecting a significant difference was not of primary interest. • Does not appear to be ITT analysis • Conflict of interest was not mentioned
Bair,[16] 2015, USA	
• The objective was explicit • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomization was performed using a computer generated randomization list • Assessor was blinded • Sample size was determined and appropriate number of patients were included • Withdrawals were reported and was less than 15% (11% in the stepped care group and 5% in the usual care group) • *P*-values were reported for outcomes but not for baseline patient characteristics • ITT analysis was conducted for the primary outcome (pain assessed by RMDS). Not specifically mentioned for the other outcomes but appears to be so from the data presentation. • Conflict of interest was reported. One author received honoraria from industry outside the submitted work; for the remaining 11 authors it was mentioned that no other disclosures were reported.	• There appears to be no major limitations

Strengths	Limitations
Brendbekken,[17] 2016, Norway; Brendbekken,[18] 2017, Norway	
• The objective was explicit • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomization was performed using a computer generated randomization list • Sample size was determined and the appropriate number was randomized • Return of questionnaires dropped to 60.3% in the multidisciplinary treatment group and 60.8% in the brief intervention (standard treatment) group • It was mentioned that there were no conflicts of interest	• No blinding • Does not appear to be ITT analysis • *P* values for between group differences were not reported
Martin,[19] 2012, Spain	
• The objective was explicit • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomization using a random number list made by using an electronic numbers generator • Sample size was determined and the appropriate number was randomized • Drop-outs were reported (21% [i.e. 15/71] in the control group, and 34% [i.e. 28/82] in the experimental group) • *P* values were reported • The authors mentioned that there were no conflicts of interest	• Unclear if there was any blinding • Does not appear to be ITT analysis
Paolucci,[21] 2012, Italy	
• The objective was explicit • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • The authors mentioned that concealed randomization was performed by sealed envelopes extracted every 15 patients	• Mentioned to be single blinded but it was unclear who was blinded • After randomization some patients were excluded as they did not provide sufficient answers to the MMPI-II test or refused MMPI-II, after that no drop-outs • Sample size determinations were not reported • Per protocol analysis not ITT • *P* values for between group differences were not reported • Conflicts of interest were not mentioned
Wong,[20] 2011, China	
• The objective was explicit • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Randomization was conducted using a predetermined random table of numbers generated electronically by Microsoft Excel. • Single blinded study; assessor was blinded	• Post-intervention questionnaire not returned at one or more time points was unequal in the two groups; 25% in MBSR group and 13% in MI group.

Strengths	Limitations
• Sample size was determined and almost appropriate numbers were used. Calculated sample size was 50 in each group, actual numbers were 51 in mindfulness based stress reduction group (MBRS) and 48 in multidisciplinary intervention (MI) group • Withdrawals were reported. Post-intervention questionnaire not returned at one or more time points was unequal in the two groups; 25% in MBSR group and 13% in MPI group. • ITT analysis was conducted • *P* values were reported • The authors mentioned that there were no conflicts of interest	
Non-randomized studies	
Merrick,[23] 2013, Sweden	
• The objective was explicit • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Drop outs were reported. Drop outs were those who did not complete the questionnaires. Dropout: 31% in RP; 32% in MMR • *P* values were reported	• Non-randomized study • Unclear if there was any blinding • Sample size determinations were not reported • Drop-out rates were high (> 30%) but similar in both groups • Only patients with available data were included in the analysis • Conflicts of interest were not mentioned
Steiner,[24] 2013, Switzerland	
• The objective was explicit • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • *P* values were reported • The authors mentioned that there were no conflicts of interest	• Non-randomized study, however patient characteristics appeared to be comparable • Unclear if there was any blinding • Sample size determinations were not reported • Unclear if there were any drop outs • Unclear if all patients were included in the analysis
Carbonell-Baeza,[25] 2011, Spain	
• The objective was explicit • The inclusion and exclusion criteria were stated • Patient characteristics, intervention and outcomes were described. • Drop-outs were reported (10% in MT, 6% in UC) • *P* values were reported • The authors mentioned that there were no conflicts of interest	• Post-hoc analysis of a non-randomized study • Unclear if there was any blinding • Sample size determinations were not reported • Results of per protocol analysis were presented. However it was reported that ITT analysis was also conducted and results were similar for most outcome measures except for two outcome measures the results were no longer statistically significant.

BI = brief intervention; DI = delayed intervention; ITT = intention-to-treat, MBSR = mindfulness based stress reduction; MI = multidisciplinary intervention

Table 8: Strengths and Limitations of Guidelines using AGREE II

Strengths	Limitations
Busse,[26] 2017, Canada	
• The scope and purpose were clearly stated. • The guideline development group had relevant expertise (clinical and research methodology) • A systematic review was conducted using appropriate methodology • Evidence was provided • Recommendations were graded using the GRADE approach • Patient preferences were considered • Resource implications appear to have been considered • The document was externally reviewed • Process was in place for updating guideline	• Conflict of interest was not presented explicitly but it was mentioned that a process was in place to manage conflicts of interest.
TOP,[27] 2015, Canada	
• The scope and purpose were clearly stated. • The guideline committee had relevant expertise (various clinical areas) • A systematic review was conducted • The sources of evidence were provided but the evidence was not described • Recommendations were graded using specific criteria	• Unclear if patient preferences were considered • Unclear if resource implications were considered • Unclear if the document was externally reviewed • Unclear if a policy was in place for updating the guideline • Conflict of interest was not presented
SIGN,[8] 2013, UK	
• The scope and purpose were clearly stated. • The guideline development group had relevant expertise (clinical and research methodology) • A systematic review was conducted using standard methodology • Evidence was provided • Recommendations were graded using the SIGN approach. • Patient representatives were included in the guideline development group • The document was externally reviewed • Process was in place for updating guideline	• Unclear if resource implications were considered • Conflict of interest was not presented explicitly but it was mentioned that the guideline development group and all members of the SIGN editorial board were required to make declarations of interest which are available on request

Appendix 4: Main Study Findings and Author's Conclusions

Table 9: Summary of Findings of Included Studies

<table>
<tr><th>Main Study Findings</th><th>Author's Conclusion</th></tr>
<tr><td colspan="2">Systematic Reviews</td></tr>
<tr><td colspan="2">Chou,[14] 2016, USA</td></tr>
<tr><td>This systematic review included the systematic review by Kamper et al.[9] which is discussed in the later section and an additional RCT (by Monticone et al.) which is presented here.

Multidisciplinary rehabilitation versus usual care
<table>
<tr><th>Outcome measure</th><th>Time point</th><th colspan="2">Score</th><th>P value</th></tr>
<tr><th></th><th></th><th>Multidisciplinary rehabilitation</th><th>Usual care</th><th></th></tr>
<tr><td>Oswesity disability index</td><td>Baseline</td><td>26</td><td>24</td><td>0.43</td></tr>
<tr><td></td><td>3 months</td><td>8</td><td>15</td><td>NR</td></tr>
<tr><td>Numeric rating scale (0 to 10)</td><td>Baseline</td><td>5</td><td>4</td><td>0.67</td></tr>
<tr><td></td><td>3 months</td><td>15</td><td>27</td><td>NR</td></tr>
<tr><td>Pain catastrophizing scale</td><td>Baseline</td><td>25</td><td>23</td><td>0.43</td></tr>
<tr><td></td><td>3 months</td><td>9</td><td>18</td><td>NR</td></tr>
<tr><td>SF-36 physical activity</td><td>Baseline</td><td>41</td><td>43</td><td>0.55</td></tr>
<tr><td></td><td>3 months</td><td>84</td><td>67</td><td>NR</td></tr>
</table></td><td>"A number of pharmacological and nonpharmacological noninvasive treatments for low back pain are associated with small to moderate, primarily short-term effects on pain versus placebo, sham, wait-list, or no treatment. Effects on function were generally smaller than effects on pain." p242
(Note: Note non-pharmacological treatment included multidisciplinary treatment)</td></tr>
<tr><td colspan="2">Kamper,[9] 2014, Cochrane Back and Neck Group</td></tr>
<tr><td>Systematic review involving adults with chronic low back pain
(Follow up: short [up to 3 months], medium [> 3months and< 12 months], and long [≥12 months])

MBR versus usual care
<table>
<tr><th>Outcome</th><th>Follow up period</th><th>No. of studies (No. of patients)</th><th>Effect measure</th><th>Effect size</th></tr>
<tr><td>Pain</td><td>Short</td><td>9 (879)</td><td>SMD (95% CI)</td><td>-0.55 (-0.83, -0.28)</td></tr>
<tr><td></td><td>Medium</td><td>6 (74)</td><td>SMD (95% CI)</td><td>-0.60 (-0.85, -0.34)</td></tr>
<tr><td></td><td>Long</td><td>7 (821)</td><td>SMD (95% CI)</td><td>-0.21 (-0.37, -0.04)</td></tr>
<tr><td>Disability</td><td>Short</td><td>9 (939)</td><td>SMD (95% CI)</td><td>-0.41 (-0.62, -0.19)</td></tr>
<tr><td></td><td>Medium</td><td>6 (786)</td><td>SMD (95% CI)</td><td>-0.43 (-0.66, -0.19)</td></tr>
<tr><td></td><td>Long</td><td>6 (722)</td><td>SMD (95% CI)</td><td>-0.23 (-0.40, -0.06)</td></tr>
<tr><td>QoL SF-36 PCS</td><td>Short</td><td>2 (144</td><td>MD (95% CI)</td><td>13.45 (-9.07, 35.96)</td></tr>
<tr><td></td><td>Medium</td><td>2 (144)</td><td>MD (95% CI)</td><td>7.41 (-4.99, 19.81)</td></tr>
<tr><td>QoL SF-36 PCS</td><td>Short</td><td>2 (144</td><td>MD (95% CI)</td><td>15.25 (2.05, 28.44)</td></tr>
<tr><td></td><td>Medium</td><td>2 (144)</td><td>MD (95% CI)</td><td>7.59 (1.69, 13.49)</td></tr>
</table></td><td>"Patients with chronic LBP receiving MBR are likely to experience less pain and disability than those receiving usual care or a physical treatment. MBR also has a positive influence on work status compared to physical treatment. Effects are of a modest magnitude and should be balanced against the time and resource requirements of MBR programs. More intensive interventions were not responsible for effects that were substantially different to those of less intensive interventions. While we were not able to determine if symptom intensity at presentation influenced the likelihood of success, it seems appropriate that only those people with indicators of significant psychosocial impact are referred to MBR." p3 of 136</td></tr>
</table>

Main Study Findings				Author's Conclusion

Catastrophising	Short	2 (99)	SMD (95% CI)	
	Long	2 (127)	SMD (95% CI)	-0.40 (-0.76,-0.05)
Fear avoidance	Short	2 (253)	SMD (95% CI)	
	Long	3 (371)	SMD (95% CI)	-0.29 (-0.49, -0.08)
Work	Short	2 (373)	OR (95% CI)	1.07 (0.60, 1.90)
	Medium	3 (457)	OR (95% CI)	1.60 (0.52, 4.91)
	Long	7 (1360)	OR (95% CI)	1.04 (0.73, 1.47)

Subgroup analyses for MBR versus usual care (outcome: pain, long term)

Subgroup	No. of studies (No. of patients)	Effect size, SMD([95% CI)
High baseline symptoms intensity (>60% on pain and disability scale	1 (119)	-0.11 (-0.47, 0.24)
Low baseline symptoms intensity (<60% on pain and disability scale	6 (702)	-0.23 (-0.42, -0.03)
High intervention intensity (>100 hours, daily contact)	2 (216)	-0.24 (-0.52, 0.04)
Low intervention intensity (<30 hours, non daily contact)	4 (447)	-0.31 (-0.50, -0.12)

Subgroup analyses for MBR versus usual care (outcome: disability, long term)

Subgroup	No. of studies (No. of patients)	Effect size, SMD (95% CI)
High baseline symptoms intensity (>60% on pain and disability scale	1 (119)	-0.49 (-0.85, -0.12)
Low baseline symptoms intensity (<60% on pain and disability scale	5 (603)	-0.17 (-0.34, -0.01)
High intervention intensity (>100 hours, daily contact)	1 (117)	-0.52 (-0.92, -0.13)
Low intervention intensity (<30 hours, non daily contact)	4 (447)	-0.22 (-0.41, -0.03)

MBR versus physical treatment

Outcome	Follow up period	No. of studies (No. of patients)	Effect measure	Effect size
Pain	Short	12 (1661)	SMD (95% CI)	-0.30 (-0.54, -0.06)
	Medium	9 (531)	SMD (95% CI)	-0.28 (-0.54, -0.02)
	Long	9 (872)	SMD (95% CI)	-0.51 (-1.04, 0.01)
Disability	Short	13 (1878)	SMD (95% CI)	-0.39 (-0.68, -0.10)
	Medium	9 (511)	SMD (95% CI)	-0.21 (-0.48, 0.06)
	Long	10 (1169)	SMD (95% CI)	-0.68 (-1.19, -0.16)
QoL SF-36	Short	3 (568)	SMD (95% CI)	-0.04 (-0.34, 0.26)
	Medium	2 (342)	SMD (95% CI)	0.20 (-0.12, 0.51)

Main Study Findings					Author's Conclusion
Depression	Short	7 (911)	SMD (95% CI)	0.05 (-0.12, 0.22)	
	Medium	7 (411)	SMD (95% CI)	-0.16 (-0.42, 0.09)	
	Long	5 (506)	SMD (95% CI)	-0.05 (-0.40, 0.30)	
Anxiety	Short	2 (377)	SMD (95% CI)	-0.10 (-0.67, 0.47)	
	Medium	2 (51)	SMD (95% CI)	-0.40 (-1.80, 1.00)	
Work	Short	3 (379)	OR (95% CI)	1.60 (0.92, 2.78)	
	Medium	3 (221)	OR (95% CI)	2.14 (1.12, 4.10)	
	Long	8 (1006)	OR (95% CI)	1.87 (1.39, 2.53)	

Subgroup analyses for MBR versus physical treatment (outcome: pain, long term)

Subgroup	No. of studies (No. of patients)	Effect size, SMD(95% CI)
High baseline symptoms intensity (>60% on pain and disability scale	1 (90)	-3.41 (-4.07, -2.76)
Low baseline symptoms intensity (<60% on pain and disability scale	8 (782)	-0.15 (-0.37, 0.06)
High intervention intensity (>100 hours, daily contact)	5 (628)	-0.23 (-0.45, -0.01)
Low intervention intensity (<30 hours, non daily contact)	3 (140)	-1.25 (-3.64, 1.13)

Subgroup analyses for MBR versus physical treatment (outcome: disability, long term)

Subgroup	No. of studies (No. of patients)	Effect size, SMD (95% CI)
High baseline symptoms intensity (>60% on pain and disability scale	1 (90)	-5.32 (-6.21, -4.42)
Low baseline symptoms intensity (<60% on pain and disability scale	9 (1079)	-0.18 (-0.38, 0.03)
High intervention intensity (>100 hours, daily contact)	5 (823)	-0.18 (-0.42, 0.07)
Low intervention intensity (<30 hours, non daily contact)	3 (140)	-2.24 (-5.48, 1.00)

Randomized Controlled Trials

Angeles,[15] 2013, Canada

RCT involving adult patients with chronic pain.

Comparison of QoL (using SF 36 v2) between the early intervention group (EI) and the delayed (i.e. waiting) intervention (DI) group

Components of SF 36 v2	Mean change in score		*P* value
	EI, (N = 19)	DI, (N = 22)	
Physical components (summary)	-2.9	-3.0	0.98
- Role physical	-15.3	+3.4	0.01
- Physical functioning	-4.2	-7.3	0.66

"An interprofessional program in primary care for patients living with chronic pain may lead to improvements in quality of life and health resource utilization. The challenges to the feasibility of the program and its evaluation are recruitment and retention of patients, leading to the conclusion that the program, as it was conducted in the present study, is not appropriate for

Main Study Findings				Author's Conclusion
- Bodily pain	+9.2	-3.9	<0.01	this setting." p237
- General Health	-1.8	+0.3	0.76	
Mental components (summary)	+3.6	+3.6	1.00	
- Role emotional	+2.6	+3.7	0.92	
- Vitality	+4.0	+3.4	0.93	
- Mental Health	+3.0	+3.5	0.94	
- Social functioning	+3.2	+2.7	0.95	
+ indicates increase and – indicates decrease				

Healthcare utilization in the EI and DI groups

Item	EI	DI	*P* value
Clinic visits (mean ± SD)	2.34 ± 2.39	3.53 ± 2.60	0.08
Early refill of opioid medication (% patients)	7.7	25	0.08
Increase in dose of opioids (5 patients)	11.5	9.4	0.56

There was a statistically significant decrease in the number of clinic visits during the six month period following intervention compared to the six month period before intervention (*P* = 0.043)

Bair,[16] 2015, USA

RCT involving adults (Veterans) with chronic pain

Comparison of pain outcomes between the stepped care group and usual care group

Pain scale	Item	Pain outcome		*P* value
		Stepped care	Usual care	
RMDS score (range 0 to 24)	Baseline (mean ± SD)	14.0 ± 4.3	13.7 ± 4.7	0.62
	Change from baseline at 9 months (mean [95% CI])[a]	−3.7 (−4.5 to −2.8)	−1.7 (−2.6 to −0.9)	0.002
BPI pain interference subscale score (range: 0 to 10)	Baseline (mean ± SD)	5.4 ± 2.1	5.4 ± 2.4	0.86
	Change from baseline at 9 months (mean [95% CI])[a]	−1.7 (−2.1 to −1.3)	−0.9 (−1.2 to −0.05)	0.003
GCPS severity score (range 0 to 100)	Baseline (mean ± SD)	67.3 ± 12.1	65.1 ± 15.2	0.22
	Change from baseline at 9 months (mean [95% CI])[a]	−11.1 (−13.9 to −8.3)	−4.5 (−7.3 to −1.8)	0.001
[a]Estimates based on mixed effects model with repeated measurements				

Medication use: At study end (9 months) patients in the stepped care group were using more topical analgesics and patients in the usual care group were using more tricyclic antidepressants.

"A stepped-care intervention that combined analgesics, self-management strategies, and brief cognitive behavioral therapy resulted in statistically significant reductions in pain-related disability, pain interference, and pain severity in veterans with chronic musculoskeletal pain." p682

Main Study Findings	Author's Conclusion

Brendbekken,[17] 2016, Norway; Brendbekken,[18] 2017, Norway

RCT involving adults with chronic musculoskeletal pain

Effect on anxiety, depression and somatization with multidisciplinary intervention (MI) or standard intervention (brief intervention [BI])

Outcome	Time point (baseline or month)	MI		BI	
		Mean (SD)	Cohen's d[a]	Mean (SD)	Cohen's d[a]
HADS anxiety	Baseline[b]	5.59 (3.29)		5.51 (3.70)	
	3[c]	4.82 (3.34)[e]	0.27	5.74 (4.12)[e]	-0.02
	12[d]	4.53 (4.25)[e]	0.24	4.79 (4.08)[e]	0.28
HADS depression	Baseline[b]	4.58 (3.42)		4.50 (3.55)	
	3[c]	3.83 (3.35)[e]	0.32	4.86 (4.11)	−0.06
	12d[c]	3.71 (3.85)[e]	0.21	3.99 (3.65)[f]	0.23
HSCL somatization	Baseline[b]	2.01 (0.54)		1.95 (0.58)	
	3[c]	1.74 (0.49)[e]	0.63	1.87 (0.70)[f]	0.15
	12[d]	1.69 (0.57)[e]	0.61	1.73 (0.67)[e]	0.40

[a]Cohen's d for paired values. A negative Cohen's d indicates a worsened score with respect to baseline
[b]N = 139 in MI; N = 141 in BI
[c]N = 112 in MI, N = 95 in BI
[d]N = 85 in MI, N = 87 in BI
[e]*P* < 0.01 within each group compared with baseline
[f]*P* < 0.05 within each group compared with baseline

Effect on function with multidisciplinary intervention (MI) or standard intervention (brief intervention [BI]

Outcome	Time point (baseline or month)	MI		BI	
		Mean (SD)	Cohen's d[a]	Mean (SD)	Cohen's d[a]
Norfunk (all items)	Baseline[b]	1.44 (0.28)		1.44 (0.30)	
	3[c]	1.33 (0.29)[e]	0.43	1.40 (0.33)	0.10
	12[d]	1.32 (0.34)[e]	0.38	1.30 (0.29)[e]	0.51

[a]Cohen's d for paired values. A negative Cohen's d indicates a worsened score with respect to baseline
[b]N = 139 in MI; N = 141 in BI
[c]N = 112 in MI, N = 95 in BI
[d]N =85 in MI, N = 87 in BI
[e]*P* < 0.01 within each group compared with baseline

Effect on subjective health complaints (SHC) with multidisciplinary intervention (MI) or standard intervention (brief intervention [BI]

Outcome	Time period (baseline or month)	MI		BI	
		Mean (SD)	Cohen's d[a]	Mean (SD)	Cohen's d[a]
SHC (all items)	Baseline[b]	20.13 (9.38)		18.42 (9.39)	
	3[c]	16.12 (8.97)[e]	0.48	17.34 (10.51)[f]	0.16
	12[d]	15.71(10.22)[e]	0.42	15.25(10.44)[e]	0.42

[a]Cohen's d for paired values. A negative Cohen's d indicates a worsened score with respect to baseline
[b]N = 139 in MI; N = 141 in BI
[c]N = 112 in MI, N = 95 in BI
[d]N = 85 in MI, N = 87 in BI
[e]*P* < 0.01 within each group compared with baseline
[f]*P* < 0.05 within each group compared with baseline

"The results indicate that the new MI may represent an important supplement in the multidisciplinary therapeutic work in patients with chronic musculoskeletal pain and that visualization, shared decision and multidisciplinary assessment can reinforce the effect of treatment. The MI with the ISIVET should be applied in new studies to see if results could be reproduced or improved further." p10, Brendbekken, 2016 [17]

"A comprehensive MI focusing on work and psychosocial factors could not increase RTW at 12 months and 24 months in patients with chronic musculoskeletal pain, when compared to the effect of a less resource demanding BI. However, the MI hastened the return to work process through the increased use of partial sick leave during the first months of the follow-up, compared to the BI." p90, Brendbekken, 2017 [18]

Main Study Findings	Author's Conclusion

Use of healthcare services

Time period	Health service use	MI	BI	*P* value
3 months	% patients consulting GP	19.4	31.8	< 0.05
	Mean number of sessions	3.0	2.8	NR
12 months	% patients consulting GP	11.8	18.5	< 0.05
	Mean number of sessions	2.5	2.3	NR

Return to work (RWT) full time[18]

3 months 12 months	Number (%) patients full time RTW,		RR (95% CI)
	MI	BI	
12 months	63 (44.7)	64 (44.8)	1.10 (0.67 to 1.18)
24 months	60 (42.6)	52 (36.6)	1.25 (0.75 to 2.06)

Martin,[19] 2012, Spain

RCT involving adults with fibromyalgia and comparing interdisciplinary treatment (IT) with standard pharmacological care (CG)

Outcomes with IT compared with CG at six months follow-up

Outcome	Time point	Scores, mean (SD)		*P* value
		IT	CG	
FIQ - total	Baseline	76.28 (13.57)	76.23 (14.88)	NR
	6 months	70.33 (16.48)	76.81 (14.18)	NR
	Change from baseline	-5.95 (15.58)	0.58 (13.57)	0.04
FIQ - physical functioning	Baseline	5.47 (1.87)	5.40 (1.76)	NR
	6 months	5.19 (1.83)	5.92 (1.84)	NR
	Change from baseline	-0.27 (1.38)	0.52 (1.83)	0.01
FIQ - pain	Baseline	7.51 (1.97)	7.53 (2.19)	NR
	6 months	7.24 (2.17)	8.22 (1.62)	NR
	Change from baseline	-0.25 (2.31)	0.71 (2.06)	0.03
HAD - anxiety	Baseline	13.83 (3.39)	13.39 (3.45)	NR
	6 months	13.41 (4.31)	12.75 (4.55)	NR
	Change from baseline	-0.42 (3.62)	-0.64 (2.93)	0.72
HAD - depression	Baseline	10.63 (4.51)	10.57 (4.06)	NR
	6 months	9.77 (4.09)	10.2 (4.22)	NR
	Change from baseline	-0.85 (3.86)	-0.32 (2.39)	0.19
CAD-R, active coping	Baseline	31.32 (9.15)	32.09 (10.58)	NR
	6 months	33.76 (8.79)	31.98 (10.41)	NR
	Change from baseline	2.17 (7.40)	0.01 (8.18)	0.16
CAD-R, passive coping	Baseline	9.08 (6.56)	11.70 (7.81)	NR
	6 months	10.10 (6.83)	10.89 (7.86)	NR
	Change from baseline	0.77 (5.06)	-0.78 (5.15)	0.11

"An interdisciplinary treatment for FM was associated with improvements in quality of life, pain, physical function, anxiety and depression, and pain coping strategies up to 12 months after the intervention." pS-103

Main Study Findings	Author's Conclusion

Outcomes with interdisciplinary intervention (IT) up to 12 months of follow-up

Outcome	Scores, mean (SD) at			
	Baseline, (N = 82)	6 weeks (N = 70)	6 months, (N = 54)	12 months, (N = 58)[a]
FIQ, total	75.38 (13.93)	69.00 (17.46)[b]	70.33 (16.48)[b]	68.53 (17.82)[b]
FIQ, physical functioning	5.42 (1.99)	5.02 (2.03)[b]	5.19 (1.83)	4.90 (2.10)[b]
FIQ, pain	7.50 (2.11)	7.31 (2.13)	7.24 (2.17)	6.61 (2.13)[b, c, d]
HAD, anxiety	14.04 (3.30)	12.16 (4.33)[b]	13.41 (4.31)	12.43 (4.14)[b]
HAD, depression	10.71 (4.21)	8.51 (4.09)[b]	9.77 (4.09)[b, c]	9.21 (3.97)[b]
CAD-R, active coping	30.86 (9.55)	34.09 (8.24)[b]	33.77 (8.79)[b]	33.16 (9.54)
CAD-R, passive coping	9.59 (6.87)	10.29 (7.32)	10.10 (6.83)	8.49 (6.42)[c, d]

[a]Four patients were lost at 6 months but returned later.
[b]p< 0.05 compared to baseline; [c]p< 0.05 compared to 6 weeks; [d]p< 0.05 compared to 6 months.

Paolucci,[21] 2012, Italy

RCT involving adults with chronic non-specific low back pain, comparing multidisciplinary treatment group (BSG) with control group (CG); groups further subdivided according to presence (ES) or absence (NES) elevation on MPPI-II scale scores

"These results suggest the Back School program has positive effects, even in terms of mental components of quality of life fin patients with scale elevation of MMPI-II. Probably these findings are due to its educational and cognitive-behavioural characteristics." p245

HRQoL: SF-36 (physical composite score [PCS])

Time point	Effect , median (interquartile range)			
	BSG-NES	BSG-ES	CG-NES	CG-ES
Baseline	39.1 (10.3)	41.2 (9.2)	46.1 (12.0)	40.4 (6.2)
Treatment end	42.3 (9.6)	41.1 (9.0)	46.6 (12.5)	40.0 (5.1)
3 months	45.3 (4.5)	45.9 (11.6)	42.8 (10.6)	41.1 (7.4)
6 months	45.0 (8.8)	46.7 (13.7)	46.3 (11.5)	39.6 (6.8)
P values (by Friedman's analysis)→	<0.001	0.003	0.938	0.816

HRQoL: SF-36 (mental composite score [MCS])

Time point	Effect , median (interquartile range)			
	BSG-NES	BSG-ES	CG-NES	CG-ES
Baseline	47.1 (14.6)	42.7 (15.3)	50.3 (7.3)	26.8 (18.9)
Treatment end	50.6 (17.0)	48.7 (8.8)	52.1 (6.4)	28.4 (19.6)
3 months	48.5 (19.9)	49.3 (10.9)	50.5 (10.7)	27.0 (17.1)
6 months	52.9 (7.7)	47.7 (11.4)	48.9 (18.5)	28.6 (23.7)
P values (by Friedman's analysis)→	0.079	0.016	0.525	0.347

Main Study Findings	Author's Conclusion

Disability (Oswestry disability index [ODI])

Time point	Effect , median (interquartile range)			
	BSG-NES	BSG-ES	CG-NES	CG-ES
Baseline	24	28	12	34
6 months	15.64	18.28	2.28	3.07
P values (by Friedman's analysis)→	0.001	< 0.001	0.516	0.381

Pain perception (Visual analog scale [VAS]))

Time point	Effect , median (interquartile range)			
	BSG-NES	BSG-ES	CG-NES	CG-ES
Baseline	6	7	7	8
6 months	23.17	23.40	1.35	3.17
P values (by Friedman's analysis)→	<0.001	<0.001	0.716	0.366

Wong,[20] 2011, China

RCT involving adults with chronic, comparing mindfulness based stress reduction (MBSR) with multidisciplinary intervention (MPI)

"This randomized, clinical trial showed that both MBSR and MPI programs reduced pain intensity and pain-related distress although no statistically significant differences were observed between the 2 groups and the improvements were small." p724

(Note MI = MPI)

Outcomes with IT compared with CG

Outcome	Score				*P* value[a]
	mean (SD)	Change from baseline, mean (SE)	mean (SD)	Change from baseline, mean (SE)	
	MBSR	MBSR	MI	MI	
Pain intensity					
- Baseline	6.55 (1.50)		6.76 (1.26)		
- 0 m post-tx	5.98 (1.63)	-0.57 (0.16)	6.15 (1.65)	-0.61 (0.22)	0.882
- 3 m post-tx	5.84 (1.49)	-0.71 (0.22)	5.85 (1.90)	-0.91 (0.27)	0.517
- 6 m post-tx	5.53 (1.94)	-1.02 (0.23)	5.79 (1.84)	-0.97 (0.29)	0.869
Pain related distress					
- Baseline	6.49 (2.12)		6.75 (1.81)		
- 0 m post-tx	6.12 (1.94)	-0.37 (0.23)	5.67 (1.88)	-1.08 (0.25)	0.046
- 3 m post-tx	5.70 (1.20)	-0.79 (0.24)	5.60 (1.93)	-1.15 (0.31)	0.324
- 6 m post-tx	5.34 (2.19)	-1.15 (0.30)	5.56 (1.85)	-1.19 (0.31)	0.910
SF-12, physical component					
- Baseline	35.27 (8.04)		32.46 (6.88)		
- 0 m post-tx	34.67 (8.56)	-0.59 (0.71)	31.79 (7.60)	-0.68 (0.74)	0.941
- 3 m post-tx	36.98 (9.34)	1.71 (0.86)	32.57 (7.83)	0.10 (0.84)	0.126
- 6 m post-tx	37.70 (10.19)	2.44 (0.90)	33.64 (8.56)	1.18 (0.85)	0.264
SF-12, physical component					
- Baseline	40.63 (11.21)			39.32 (9.16)	

Main Study Findings	Author's Conclusion

- 0 m post-tx	43.02 (9.84)	2.39 (1.01)	42.05 (11.52)	2.73 (1.32)	0.862
- 3 m post-tx	43.91 (10.92)	3.28 (1.58)	43.08 (11.55)	3.76 (1.32)	0.960
- 6 m post-tx	42.87 (11.27)	2.24 (1.57)	42.32 (10.30)	3.00 (1.37)	0.872

m = month; tx = treatment
[a]*P* value to test difference between groups using multilevel model analysis of outcome variables against time along with interactions between time and group.

Overall no statistically significant differences in outcomes betwee the MBSR and MPI groups were observed using various other outcome measures (such as STAI, POMS, and CES-D)

Non-randomized Studies

Merrick,[23] 2013, Sweden

Non-randomized prospective study involving adult patients with disabling chronic musculoskeletal pain

Comparison of results with RP and MMR (within group and between groups) using multidimensional pain inventory (MPI) part one tool

Outcome	Time point, or within group *P* value	Effect, mean (SD)		*P* value for RP vs MMR
		RP (N = 145)[a]	MMR (N = 51)	
Pain severity	Baseline	4.3 (0.9)	4.3 (0.9)	0.001
	1 year FU	3.9 (1.2)	3.1 (1.3)	
	P value	*<0.001*	*<0.001*	
Interference	Baseline	4.3 (1.1)	4.4 (0.9)	<0.001
	1 year FU	3.9 (1.4)	3.3 (1.5)	
	P value	*<0.001*	*<0.001*	
Life control	Baseline	2.9 (1.2)	3.0 (0.8)	0.021
	1 year FU	3.1 (1.2)	3.1 (1.2)	
	P value	*0.015*	*<0.001*	
Affective distress	Baseline	3.0 (1.5)	3.3 (1.2)	0.003
	1 year FU	3.0 (1.4)	2.5 (1.5)	
	P value	*0.982*	*0.003*	
Support	Baseline	4.3 (1.3)	4.3 (1.3)	0.688
	1 year FU	3.8 (1.2)	3.9 (1.3)	
	P value	*<0.001*	*0.003*	

[a]For RP group, N = 145 except for Life control N = 144

Sick leave

Outcome	Time point	Number of patients with outcome	
		RP (N = 140)	MMR (N = 51)
Full-time sick leave	Baseline	62	20
	1 year FU	35	12
Part-time sick leave	Baseline	34	15
	1 year FU	40	14
No sick leave	Baseline	44	16
	1 year FU	65	25

"The multimodal rehabilitation programme had long-term positive effects on sick leave and all Multidimensional Pain Inventory scales. However, a less intense intervention (rehabilitation plan) with follow-up in primary care can decrease levels of sick leave and improve some Multidimensional Pain Inventory scales. An interdisciplinary team assessment of patients with chronic pain seems to be useful for selecting which patients should undergo different rehabilitation interventions." p1049

Main Study Findings	Author's Conclusion
Over time, here were no significant between group differences with respect to sick leave status. **Sick leave**: Multiple logistic regression analyses showed that the variable "patients' positive expectation about work" was associated with the variable " no sick leave at one year follow up". When men and women were analyzed separately, the stepwise multiple regression analyses showed that the variable "no sick leave at one year follow up" was associated with the variable "patients' positive expectation about work" in case of women, and with the variable "low disability level" in case of men.	
Steiner,[24] 2013, Switzerland	
Non-randomized prospective study involving adult patients with chronic low back pain **Outcomes with MFRP and MRP after treatment compared to baseline values**	"In conclusion, despite the limitations and in the absence of higher quality evidence on this specific point, we feel that these results provide important information for practitioners and providers alike. MFRP in cLBP patients with severe disability in daily life activities seems to be more effective than a rehabilitation programme based predominantly on muscle reconditioning. Although more demanding for the team, more difficult to set up and with higher direct costs, there are elements (specifically concerning return to work rate) suggesting that these complex interventions could well be cost-effective and thus call for additional studies." p5 of 7

Outcome	Time point or *P* values for post treatment vs baseline	Score, mean (SD)	
		MFRP	MRP
DPQ – daily life activity	Baseline	59.5 (16.9)	62.3 (20.3)
	Post-treatment	44.8 (25.4)	58.8 (20.7)
	P values	0.002	NS
DPQ – work leisure	Baseline	61.0 (24.3)	65.5 (23.1)
	Post-treatment	42.2	56.4 (24.4)
	P values	0.001	NS
DPQ – anxiety-depression	Baseline	51.8 (28.8)	45.2 (26.9)
	Post-treatment	46.6 (30.7)	40.0 (24.9)
	P values	0.5	NS
DPQ - social	Baseline	38.3 (24.3)	39.5 (24.3)
	Post-treatment	38.5 (24.9)	39.0 (26.5)
	P values	NR	NR
Pain (VAS)	Baseline	5.9 (1.6)	5.9 (2.0)
	Post-treatment	4.5 (2.4)	5.1 (2.9)
	P values	0.01	NS

Impact on sick leave after treatment with MFRP and MRP

Outcome	Time point	Number (%) of patients with outcome		*P* values
		MFRP (N = 23)	MRP (N = 17)	
On sick leave	Baseline	23 (100)	17 (100)	0.08
	Post-treatment	5 (22)	9 (53)	
Of the 24 patients in the MFRP group, 23 were assessed for return to work as one was a housewife. Of the 21 patients in the MRP group, 17 were assessed for return to work as three were housewives and one had retired.				

Main Study Findings	Author's Conclusion

Carbonell-Baeza,[25] 2011, Spain

Non-randomized prospective study on women with fibromyalgia. Comparison between multidisciplinary treatment (MT) vs control (i.e. usual care [UC]).

Symptomatology using FIQ

Outcome	Group	Score, mean (SE)		*P* value, group effect	*P* value, time effect	*P* value, interaction effect
		Pre-treatment	Post-treatment			
FIQ-Total score	UC	70.5 (2.3)	74.7 (2.6)	0.122	0.435	<0.001
	MT[a]	72.5 (2.2)	63.3 (2.5)			
Physical function	UC	4.4 (0.3)	4.9 (0.4)	0.451	0.800	0.014
	MT	4.7 (0.3)	4.0 (0.3)			
Feel good	UC	8.5 (0.4)	8.8 (0.4)	0.133	0.035	0.072
	MT	8.3 (0.4)	7.4 (0.4)			
Pain	UC	7.3 (0.3)	8.0 (0.3)	0.179	0.514	0.015
	MT	7.4 (0.3)	7.0 (0.3)			
Fatigue	UC	8.3 (0.3)	8.7 (0.3)	0.032	0.892	0.001
	MT[b]	8.5 (0.3)	7.2 (0.3)			
Sleep	UC	8.1 (0.3)	8.2 (0.3)	0.989	0.763	0.010
	MT	8.7 (0.3)	7.6 (0.3)			
Stiffness	UC	7.7 (0.4)	8.0 (0.3)	0.463	0.317	0.001
	MT[a]	8.0 (0.3)	7.0 (0.3)			
Anxiety	UC	7.4 (0.4)	8.0 (0.4)	0.116	0.360	0.001
	MT[c]	7.4 (0.4)	6.3 (0.4)			
Depression	UC[b]	6.1 (0.5)	7.0 (0.5)	0.233	0.251	<0.001
	MT[b]	5.7 (0.6)	4.9 (0.6)			
P values presented above are before adjustment for multiple comparisons [a]*P*< 0.001, [b]*P*< 0.01, [c]*P*< 0.05, for post hoc analysis Pre *vs.* Post.						

Quality of life using SF-36

Outcome	Group	Score, mean (SE)		*P* value, group effect	*P* value, time effect	*P* value, interaction effect
		Pre-treatment	Post-treatment			
Physical function	UC	38.4 (3.2)	37.5 (2.7)	0.756	0.153	0.068
	MT	36.0 (3.2)	42.3 (2.7)			
Physical role	UC	4.3 (2.0)	2.0 (3.9)	0.088	0.606	0.001
	MT[b]	1.9 (2.0)	17.0 (3.8)			
Bodily pain	UC	21.1 (2.2))	21.3 (3.0	0.467	0.864	0.003
	MT[a]	17.5 (2.2)	29.6 (3.0)			
General health	UC	26.7 (2.7)	29.4 (3.0)	0.063	0.121	0.263
	MT	31.4 (2.7)	38.2 (3.0)			
Vitality	UC	17.7 (2.8)	18.0 (3.3)	0.133	0.740	0.003
	MT[a]	17.3 (2.7)	29.9 (3.2)			
Social functioning	UC[b]	42.9 (4.0)	35.0 (4.4)	0.487	0.925	<0.001
	MT[a]	33.5 (4.0)	52.1 (4.3)			
Emotional role	UC	33.3 (7.3)	37.5 (8.1)	0.792	0.726	0.108
	MT[a]	26.3 (7.2)	49.5 (8.0)			

"A 3-month low-moderate intensity multidisciplinary intervention improved fibromyalgia symptomatology and quality of life in women with fibromyalgia." pS-97

Main Study Findings							Author's Conclusion
Mental health	UC	45.7 (3.6)	44.8 (4.1)	0.502	0.346	0.008	
	MT[c]	44.4 (3.5)	53.1 (4.1)				
P values presented above are before adjustment for multiple comparisons [a]*P*< 0.001, [b]*P*< 0.01, for post hoc analysis Pre *vs.* Post.							

Other outcomes: No significant improvements were observed with the intervention for other outcome measures (HADS or RSES)

BPI = Brief pain inventory; CAD-R = Spanish pain coping questionnaire; CES-D = Centre for Epidemiological Studies Depression scale; CI = confidence interval; DPQ = Dallas Pain Questionnaire; FIQ = fibromyalgia impact questionnaire; FU = follow up; GCPS = Graded Chronic Pain Scale; HADS (or HAD) = Hospital Anxiety and depression scale; MBSR = mindfulness based stress reduction; MD = mean difference; MI = multidisciplinary intervention; Norfunk = Norwegian Function Assessment Scale; NR = not reported; NRS = numeric rating scale OR = odds ratio; POMS = profile of mood states; QoL = quality of life; RMDS = Roland Morris Disability scale; RR = risk ratio; RSES = Rosenberg Self-Esteem Scale; RTW = return to work; SC = stepped care; SD = standard deviation; SMD = standardized mean difference; STAI = state-trait anxiety inventory; UC =usual care; VAS = visual analog scale

Appendix 5: Guideline Recommendations

Table 10: Recommendations and related evidence

Evidence	Recommendations
Busse,[26] 2017, Canada	
In case of patients with chronic non-cancer pain who were using opioids and experiencing serious challenges in tapering, multidisciplinary tapering programs were likely to be successful in opioid cessation (from two studies, moderate quality evidence), however there was uncertainty with respect to pain and functional improvements (one study; very low quality evidence). In one study 76.5% (i.e.78/102) of patients, in mean of 22days successfully tapered off opioids, however, 31 patients reinitiated opioids within 12 to 24 months (moderate quality evidence) and in one study98 % (i.e. 99/101) of patients successfully tapered off opioids. One very low quality study with 102 patients showed, that pain was reduced from 7.1 (1.80) at baseline to 5.9 (2.3) at follow up and physical function improved from 26.1(7.7) at baseline to 27.8 (9.8) at follow up.	Formal multidisciplinary program was recommended for patients with chronic non-cancer pain who were using opioids and experiencing serious challenges in tapering (Strong recommendation). Further the following was mentioned: "Recognizing the cost of formal multidisciplinary opioid reduction programs and their current limited availability/capacity, an alternative is a coordinated multidisciplinary collaboration that includes several health professionals whom physicians can access according to their availability (possibilities include, but are not limited to, a primary care physician, a nurse, a pharmacist, a physical therapist, a chiropractor, a kinesiologist, an occupational therapist, an addiction specialist, a psychiatrist, and a psychologist)." p8
TOP,[27] 2015, Canada	
Source of evidence from two guidelines which had included systematic reviews	"Refer patient significantly affected by chronic low back pain and no improvement with primary care management to a multidisciplinary chronic pain program" p15 (Recommendation category: √)
SIGN,[8] 2013, UK	
One systematic review on non-specific musculoskeletal conditions showed that overall multidisciplinary programs were better than no treatment, standard medical treatment or unidisciplinary (e.g. physiotherapy or education) treatments. Patients with low back pain or fibromyalgia had greater benefits than those with chronic pain of diverse origins. (Level of evidence: 1++) Three systematic reviews on CLBP were identified. Two systematic reviews concluded that there was no demonstrable effect that multidisciplinary treatment reduces pain. However, the third systematic review found moderate evidence that in the short term, there was statistically significant reduction in pain with multidisciplinary treatment compared to no treatment (WMD, -9.47; 95% CI, -13.87 to -5.87) or other active treatment (e.g. physiotherapy; WMD, -11.55; 05% CI, -19,68 to -3.43). This systematic review found moderate quality evidence of no difference in the long term pain with multidisciplinary treatment compared to no treatment or active treatment. (Level of evidence: 1++)	"Referral to a pain management programme should be considered for patients with chronic pain." p5 Recommendation grade: C Note: the authors mentioned that multidisciplinary biopsychosocial treatment is also referred to as a pain management program.

CI = confidence interval; CLBP = chronic low back pain; SIGN = Scottish Intercollegiate Guidelines Network; TOP = Toward Optimized Practice; WMD = weighted mean difference

Appendix 6: Outcome Measures

Table 11: Description of outcome measures

Outcome measure	Description
BPI	Brief Pain Inventory: Interference subscale has seven items to assess interference resulting from pain; range 0 to 10, with higher scores indicating greater pain interference.[16]
CAD-R	Coping with chronic pain questionnaire: It includes 24 items grouped into two categories: active and passive coping. Responses are scored using a 5-point Likert scale; higher the value the more likely the patient uses the coping strategy.[19]
CES-D	Center for Epidemiological Studies Depression Scale: A higher CES-D score indicates greater depression[20]
DPQ	Dallas Pain Questionnaire: It explores four dimensions (daily life activities, work-leisure, anxiety-depression, and sociability) using 16 questions. The responses are scored on a Likert scale and computed as 0% (best) to 100%.[24]
FIQ	Fibromyalgia Impact Questionnaire: It assesses the impact of fibromyalgia (FM) on health related quality of life (HRQoL). The FIQ score ranges from 0 to 100, higher scores indicate greater impact of FM on HRQoL.[19]
GCPS	Graded Chronic Pain Scale: It has seven items to assess pain severity; scale range 0 to 100, higher scores indicate more severe pain[16].
HADS (also HAD)	Hospital Anxiety and Depression Scale: It is a 14 item tool used to screen for anxiety and depression in a non-psychiatric setting. A score of 0 to 7 indicates absence of anxiety or depression, a score of 8 to 100 indicates possible anxiety or depression, and a score of ≥11 indicates presence of anxiety or depression.[19]
HSCL	Hopkins Symptom Checklist: It consists of 25 items to assess common symptoms of anxiety, distress, and somatization. It uses a 4-point Likert scale from 0 (not at all) to 4 (very much/severe). A mean score <1.75 is within normal range, and ≥1.75 indicates psychological distress and in need of treatment.[17]
MPI	Multidimensional Pain Inventory: It has 3 parts, one psychological part and two behavioral parts. Responses are scored on a 7-point scale ranging from 0 to 6.[23]
Norfunk	Norwegian Function Scale: It uses 41 questions to assess four aspects of physical function and three aspects of psychological function. The responses are scored on a 4-point Likert scale from 0 (no problem) to 3 (not able to do the activity).[17]
NRS	Numeric Rating Scale: Scale range 0 to 10, with 0 indicating no pain/distress and 10 indicating pain/distress as bad as it could get.[20]
ODI	Oswestry Disability Index:
POMS	profile of mood status: Consists of 65 adjective rating scales assessing depression, anger, fatigue, vigor, tension, confusion, and total mood disturbance. Higher scores indicate greater depression, anger, fatigue, vigor, tension, confusion, and total mood disturbance.[20]
RMDS	Roland Morris Disability Scale: Morris Roland Disability Scale (RMDS) has 24 items to assess pain related disability; scale range 0 to 24, higher scores indicating severe pain related disability.[9,16]

Outcome measure	Description
RSES	Rosenberg Self-Esteem Scale: A tool to assess self-esteem. It consists of 10 items and scoring is on a 4-point Likert scale, with higher score indicating greater self esteem.[25]
SF-12	Short Form Health Survey -12: It has 12 items. Higher scores indicate better health.[20]
SF-36	Short Form Health Survey Questionnaire: It has 36 items and assesses physical and mental health. Each scale ran ges from 0 (worst health state) to 100 (best health state)[21]
SHC	Subjective Health Complaints: It has 29 items covering the most frequent subjective health complaints related to different body parts. Severity is scored on a 4-point Likert scale from 0 (not at all) to 3 (seriously).[17]
STAI	State-Trait Anxiety Inventory: State anxiety rellects a transitional emotional state, and trait-anxiety refers to a general tendency towards anxiety caused by perceived threats. Higher scores indicate more intense state-anxiety and trait-anxiety.[20]
VAS	Visual Analog Scale: It consists of a 10 mm line with one end labelled as “no pain” and one end labelled as “pain as bad as it could get”[21]

Appendix 6: Additional References of Potential Interest

Economic studies with alternate population, alternate comparator or no comparator

1. Evans JR, Benore E, Banez GA. The cost-effectiveness of intensive interdisciplinary pediatric chronic pain rehabilitation. J Pediatr Psychol. 2016 Sep;41(8):849-56.
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3. Jensen C, Nielsen CV, Jensen OK, Petersen KD. Cost-effectiveness and cost-benefit analyses of a multidisciplinary intervention compared with a brief intervention to facilitate return to work in sick-listed patients with low back pain. Spine. 2013 Jun 1;38(13):1059-67.
4. Johnsen LG, Hellum C, Storheim K, Nygaard OP, Brox JI, Rossvoll I, et al. Cost-effectiveness of total disc replacement versus multidisciplinary rehabilitation in patients with chronic low back pain: a Norwegian multicenter RCT. Spine. 2014 Jan 1;39(1):23-32.
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