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Cost-effectiveness of Multidisciplinary Interventions for Chronic Low Back Pain

A Narrative Review

Anonnya R. Chowdhury, MIDEC, Petra L. Graham, PhD,† Deborah Schofield, PhD,‡ Michelle Cunich, PhD,§||¶ and Michael Nicholas, PhD**

Objective: Chronic musculoskeletal pain in adults is a global health and economic problem. The aim of this paper was to systematically review and determine what proportion of multidisciplinary approaches to managing chronic musculoskeletal pain are cost-effective.

Materials and Methods: The EconLit, Embase, and PubMed electronic databases were searched for randomized and nonrandomized economic evaluation studies of nonpharmaceutical multidisciplinary chronic pain management interventions published from inception through to August 2019.

Results: Seven studies comprising 2095 patients were included. All studies involved diverse multidisciplinary teams in one or more of the study arms. All studies involved chronic (both chronic and subacute) low back pain and were economic evaluations from either a societal or health care perspective. Two of the 3 studies that reported on a multidisciplinary pain intervention compared with nonmultidisciplinary intervention concluded favorable cost-effectiveness based on cost per quality adjusted life years gained, 1 study was not found to be cost-effective. Cost-effectiveness of the multidisciplinary intervention of interest was also not established by another 3-arm study. Two studies compared 2 multidisciplinary interventions; neither of these could definitively declare cost-effectiveness. The remaining study indicated the intervention by a multidisciplinary team was more effective but at a higher cost. None of the included studies used decision models to estimate long-term health outcomes and cost-effectiveness of multidisciplinary programs.

Discussion: There are few studies on the cost-effectiveness of multidisciplinary chronic pain management interventions. This study encourages additional rigorous economic evaluations of multidisciplinary models for chronic pain management. Economic evaluations that enable extrapolating costs and effects of multidisciplinary programs beyond the time horizon of clinical trials may be more informative for clinicians and health administrators.

Key Words: chronic pain, multidisciplinary intervention, economic evaluation, cost-benefit analysis, cost-effectiveness analysis, cost-utility analysis

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From the *Pain Management Research Institute, Sydney Medical School; §Charles Perkins Centre, Faculty of Medicine and Health (Central Clinical School), The University of Sydney; †Department of Mathematics and Statistics, Macquarie University; ‡Centre for Economic Impacts of Genomic Medicine (GenIMPACT), Macquarie Business School, Macquarie University, Sydney; ||Sydney Institute for Women, Children and their Families, Sydney Local Health District; and ¶Sydney Health Economics Collaborative, Sydney Local Health District, Camperdown, NSW, Australia.

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Reprints: Anonnya R. Chowdhury, MIDEC, Pain Management Research Institute, Sydney Medical School, The University of Sydney, Sydney, NSW 2065, Australia (e-mail: acho5019@uni.sydney.edu.au).

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The Global Burden of Disease Study (2018) estimated that chronic pain was the leading cause of years lived with disability in high and high-middle income countries.[1] The clinical, psychological and social effects of chronic musculoskeletal pain as well as the higher health care expenditure, carer costs, and lost productivity represent a significant burden to the worldwide economy.[2–6] In Australia the direct (medical) and indirect (productivity, carer costs, lost taxes, and extra welfare payments) cost of chronic pain is estimated to be > \$73 billion while the estimated reduction in quality of life is valued at \$66.1 billion.[7]

Although complete resolution of symptoms is rare with available treatments for chronic pain conditions, many approaches for treating and managing chronic pain have been described. In the main, rehabilitative approaches have been the most widely endorsed as they typically focus more on improving function and quality of life through enhanced self-management rather than symptom relief.[8–12] Typically, these approaches are conducted by a multidisciplinary team of health professionals who attempt to address identified physical, psychological, and social factors that may contribute to the experience and impact of chronic pain.[13–16] This requires health care staff to work in a collaborative, interdisciplinary manner, with the patient playing an active role. The disciplines involved typically include physiotherapists, physicians, clinical psychologists, nurses, and rehabilitation advisors.[17] Not surprisingly, such multidisciplinary approaches can require significant resources and organizational support for their implementation and, as such, clinicians, researchers, and administrators have called for economic evaluations to determine whether such interventions are cost-effective.[13,18]

Economic evaluations consider both the costs and health outcomes of alternative treatment options. They are categorized as either a cost-effectiveness analysis (CEA) where the outcomes are reported in natural units, for example, health outcomes such as an improvement on a pain scale achieved at a cost explained in monetary terms, cost-utility analysis (CUA) where outcomes are reported as quality-adjusted life-years (QALYs) gained and costs are measured in monetary units, or a cost-benefit analysis (CBA) where outcomes and costs are reported in monetary terms (see the Glossary).

Systematic reviews of economic evaluation studies in chronic pain have been undertaken but appear to have focused on single discipline interventions such as pharmaceutical[19] or single pain sites such as lower back.[20] A 2001 review by Thomsen et al[14] found that methodological issues precluded any conclusions regarding economic effectiveness. Instead, they recommended the application of standard costing methods and health outcome measures so that information used in decision-making for prevention and treatment of chronic pain could be more comparable across the different treatments.

The current review uses complete economic evaluation studies of multidisciplinary interventions for chronic musculoskeletal pain management to identify the proportion of cost-effective multidisciplinary interventions.

MATERIALS AND METHODS

Inclusion Criteria

Economic evaluations (cost-effectiveness, cost-utility, and cost-benefit studies) of multidisciplinary interventions for adult (18 y of age and older) chronic (> 12 wk) musculoskeletal (eg, neck, shoulder, arm, back, or leg) pain management. Studies were only included if they (1) reported one or more of the incremental cost-effectiveness ratio (ICER), the cost effectiveness (CE) plane, or the cost-effectiveness acceptability curve (CEAC), see Glossary; and (2) reporting of any outcome measures relating to pain, disability, quality of life, or return to work. Only English language papers were included in this review.

Studies involving pharmaceutical or surgical intervention were excluded as they primarily address pain relief rather than rehabilitation, and essentially entail the patient playing a passive role (with treatments being applied to them by skilled professionals), rather than the more active role played by patients undergoing a rehabilitation approach.

Identification and Selection of Studies

The EconLit, EMBASE, and PubMed electronic databases were searched for relevant studies published from inception through to August 2019. The search strategy, defined by 2 investigators (A.R.C. and M.C.), combined MeSH terms (arm pain, neck pain, shoulder pain, back pain, leg pain, and chronic pain) with text words (cost-effectiveness, cost-benefit, cost-utility, multidisciplinary, and interdisciplinary) to capture economic evaluations of interventions in chronic musculoskeletal pain. Conference proceedings and review articles were excluded. Abstracts and titles of the studies identified through the database search were screened independently and then together by 2 investigators (A.R.C. and D.S.) to identify full-text articles for detailed review.

Data Extraction and Synthesis

Two investigators (A.R.C. and P.L.G.) independently extracted study characteristics including year of publication, country, study design, intervention(s), effectiveness, and cost-effectiveness measures using a standardized form. Differences in extracted data were resolved by consensus.

Cost-effectiveness is calculated from measures of both effectiveness (efficacy) and economic cost. Effectiveness measures extracted were derived from health outcome measures such as the visual analogue scale[21,22] and bothersomeness of pain[23,24] to measure bodily pain, the 12-item Short-Form Survey (SF-12)[25] and EQ-5D, a standardized health-related quality of life measure with 5 dimensions[26] to measure several aspects of a person's health (eg, pain, functioning and mental well-being) and often used in evaluations because they are disease-generic and can be used to ascertain utilities, Fear Avoidance Belief Questionnaire (FABQ)[27] and Pain Self-Efficacy Questionnaire (PSEQ)[28] to measure psychological contributors to chronic pain conditions and the Roland and Morris Disability Questionnaire (RMDQ)[29] and Quebec Back Pain Disability Scale (QBPDS)[30,31] to evaluate disability associated with the condition and return-to-work outcomes. Different types of costs, such as direct costs comprising of the health care resources used in the intervention and indirect health care costs (eg, out of pocket costs associated with pain relief medications and travel costs for patients receiving the intervention), and other indirect costs (eg, productivity losses) were also measured.

Cost-effectiveness summary measures, such as the ICER and incremental cost-utility ratio (ICUR) and presence of a graphic that summarizes these measures, called the CEAC, were also extracted. These measures incorporate study-specific costs and a range of health outcomes and quality of life measures (such as the SF-12 and EQ-5D). These are not standardized comparable measures and so cannot be combined in a meta-analysis. As such, for this review, a narrative synthesis of the studies meeting the inclusion criteria was conducted.

In addition, whether a decision analytic model was included was investigated. Such models incorporate a time horizon longer than the intervention period and apply discounting to estimate costs, intended effects, unintended side effects such as additional physical, mental or economic costs,[32] and cost-effectiveness of an intervention. Thus, this systematic approach synthesizes the appropriate long-term evidence from randomized controlled trials (RCTs). This approach is important to enable clinicians and decision makers to make optimal choices under conditions of uncertainty.[33]

Assessment of Methodological Quality and Risk of Bias

The methodological quality of the economic evaluation of the studies was assessed independently by 2 reviewers (A.R.C., D.S.) using Drummond and colleagues' checklist.[34] This checklist comprises 10 yes/no questions evaluating key methodological areas (study design, data collection and analysis, and interpretation of results) as well as those specific to economic evaluations (such as reporting ICERs and CEAs) that must be considered in any well-executed economic evaluation study measuring both costs and health outcomes. Drummond's checklist provides no cut-point for determining acceptable or unacceptable quality. As such, for this study, any "no" responses were carefully examined to guide assessment of overall quality of the particular study.

Risk of bias was assessed by 2 reviewers (A.R.C., P.L.G.) using the Agency for Healthcare Research and Quality checklist.[35] This checklist explicitly assesses risk of selection, performance, attrition, detection, and reporting biases and includes design specific criteria for common study designs such as RCT or cohort studies using 14 yes/no questions. Higher proportions of positive responses were used as a proxy for better quality studies.

RESULTS

Flow of Studies Through the Review

A total of 2213 studies were identified through the initial search. After removing 123 duplicates, 2090 titles and abstracts were screened for inclusion. Of these, 30 full-text articles were assessed for eligibility with 7 included in the narrative synthesis. Figure 1 shows the flow diagram including details for studies excluded.

Characteristics of Studies Included

Table 1 summarizes characteristics of the 7 studies included in this review. Six studies were RCTs[36–41] and 1 was a cohort study.[42] Six of the included studies focused on chronic low back pain (CLBP),[36,37,39–42] and 1 on subacute and CLBP.[38] Multidisciplinary intervention was compared with a variety of other interventions including advice alone,[38] brief intervention of clinical examination,[37] or similar multidisciplinary treatment.[36] In all but 1 of the studies, physiotherapists were involved in all study arms; the study of Lambeek et al[39] only involved physiotherapists in the intervention arm of their trial. All of the included studies involved multidisciplinary teams that typically comprised psychologists, physiotherapists, pain specialist doctors, and occupational therapists in 1 or both arms of the studies.

Return to work was investigated as one of the main outcome measures by 3 studies.[37,39,40] Quality-adjusted life-years were calculated in 6 studies[36,38–42] by using outcome measure such as the 36-item Short Form Survey (SF-36),[36] or the shorter version, SF-12,[38,42] and EQ-5D[38,40,41] or EuroQoL.[39] Direct health care costs (eg, general practitioner, medical specialist) were identified by all 7 included studies although it was necessary to consult other publications[38,43–47] on these studies to determine some of the information. Informal care costs (such as home care, paid domestic work, help from partner or friends) were included by 3 studies.[36,39,41] Productivity loss was measured as an indirect cost by 6 studies.[36,37,39–42] Most studies used market price for cost analysis. Two studies did not present the unit

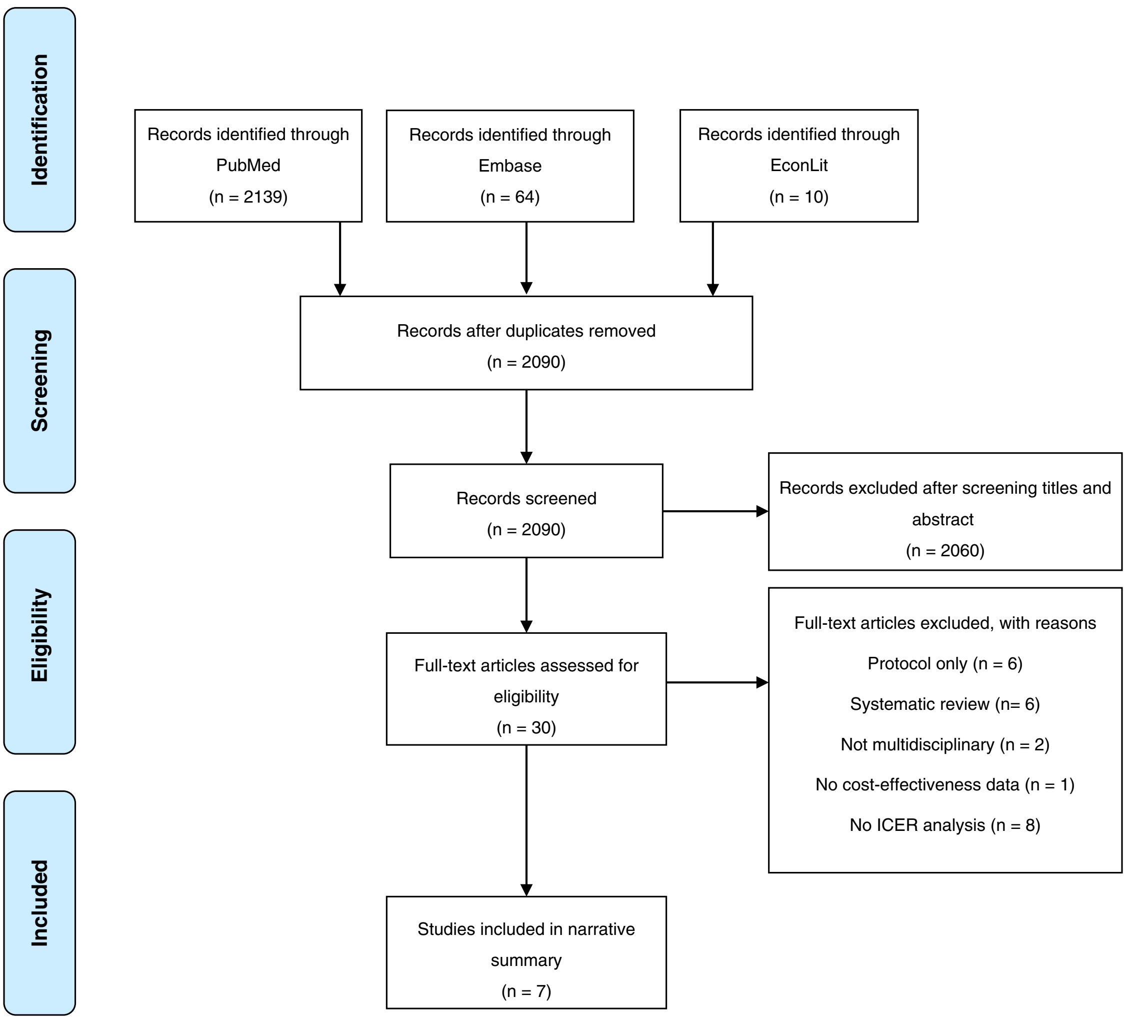

FIGURE 1. PRISMA flow chart of the study selection process. ICER indicates incremental cost-effectiveness ratio.

TABLE 1. Main Characteristics of Economic Evaluations of Pain Interventions

Study Design	Participants	Intervention	Intervention Team	Study Perspective, Cost Domain and Outcome Measures	Type of Economic Evaluation	Results
Goosens et al[36] (RCT)	N: 62 Female: 50% Age: 18-65 y Pain sites: LBP Pain duration: ≥ 3 mo	A (MD) = Exposure in vivo (EXP) (CBT, educational sessions) B (MD) = Graded activity —CBT 1 session psychological intake followed by 2 educational sessions	A = rehabilitation physician and a therapist mini-team (psychologists involved in almost every session) B = rehabilitation physician and a therapist mini-team	Societal perspective Costs: Health care costs Intervention cost Patient and family costs Production losses Currency: Euro (2014) Discounting: Not applied as slightly over 1 year time horizon Outcome measure: SF-36, QBPDS Follow-up = Baseline, before intervention, directly after intervention/at discharge month: 6, 12	CEA and CUA	No significant difference between A and B on disability and generic QoL ($P > 0.3$) but A and B both show improvement from baseline. Authors suggested A may be more cost-effective than B because of reduced cost and disability and improved quality of life
Jensen et al[37] (RCT)	N = 351 Female = 52% Age: 16-60 Pain sites: LBP Pain duration: Partly or fully sick listed for 4-12 wk due to pain	A = brief consultation and exercise B (MD) = multidisciplinary intervention (clinical examination+guidance)	A = rehabilitation doctor and physiotherapist B = social medicine specialist, rheumatology specialist (rehabilitation doctor), physiotherapist, social worker, and an occupational therapist	Societal perspective Costs: Direct health care costs: Outpatient and inpatient cost Primary sector cost Medicine cost Indirect costs: Tax paid sick leave compensation Currency: Danish Krone (Kr) 2009 Discounting: NA Outcome measure: Return to work, low back pain rating scale (score 0-60) and RMDQ (score 0-23), self-reported questionnaire on sick leave Follow-up = baseline month: 12	CEA and CBA	No evidence of a difference between A and B ($P > 0.05$). A more cost-effective than B. ICER was Kr 2,631 (€353) for 1 extra sick leave day implying intervention more expensive and less effective. B was effective only in special cases such as workers who are in a vulnerable position to lose their jobs ($P = 0.04$)
Lamb et al[38] (RCT)	N = 701 Female = 60% Age: ≥ 18 y Pain sites: LBP Pain duration: ≥ 6 mo	A = advice alone B (MD) = advice plus CBT	A = nurse or physiotherapist B = physiotherapists, psychologists, primary care nurses, and occupational therapists who were trained to deliver the program on a 2 d course	Health care perspective Costs: Total health care cost Intervention cost NHS resource utilization cost Currency: UK Pound (2008) Discounting: Not applied Outcome measures: PSEQ, RMDQ, SF-12, modified Von Korff, EuroQoL, Fear avoidance beliefs, Self-reported questionnaires	CEA and CUA	B significantly better than A on RMDQ, SF-12, and modified Von Korff Disability score outcomes ($P < 0.0001$). B more cost-effective than A. Gained 0.099 additional QALYs; incremental cost QALY was £1786

(*Continued*)

TABLE 1. (*continued*)

Study Design	Participants	Intervention	Intervention Team	Study Perspective, Cost Domain and Outcome Measures	Type of Economic Evaluation	Results
				completed by patients on benefit and satisfaction with the treatment Follow-up = baseline month: 3, 6, 12		
Lambeek et al[39] (RCT)	N = 134 Female = 63% Age: 18-65 Pain sites: LBP Pain duration: > 12 wk	A = usual care with advice (following the Dutch physiotherapy guideline) B (MD) = GAP and work ergonomic change (integrated care) + physio	A = general practitioner and occupational physician B = medical specialist, occupational therapist, physiotherapist, and clinical occupational physician[40]	Societal perspective Costs: Direct health care cost Nondirect health care cost Production loss Absenteeism from paid Work Currency: UK Pound sterling (2007) Discounting: Was not applied Outcome measures: EuroQoL, Duration until sustainable return to work Follow-up = baseline month: 12	CEA, CUA, and CBA	B significantly better than A on duration until sustainable return to work and QALYs gained. B more cost-effective than A. ICER based on sustainable return to work was −3, ie, £3 extra investment for 1 day earlier return to work for B than A. ICUR based on QALYs was—£61,000 per QALYs gained
Schweikert et al[40] (RCT)	N = 409 Female = 17% Age: employed adults Pain sites: nonspecific LBP Pain duration: > 6 mo	A (MD) = usual care + CBT B (MD) = usual care (including physiotherapy, massage, seminars, and exercise)	A = clinic physician and psychologist B = clinic physicians and psychologist	Societal perspective Costs: Direct health care cost Nondirect health care cost Indirect cost during rehabilitation and 6 mo follow-up Currency: Euro (2001) Discounting: NA Outcome measures: VAS, EuroQol, Return to work Follow-up = baseline, directly after treatment/at discharge Months: 3, 6	CUA	No significant difference in absence from work ($P = 0.12$) HRQoL improved transforming in QALY ($P = 0.396$). A may be more cost saving than B ICER was €-126,731 per QALYs gained
Smeets et al[41] (RCT)	N = 160 Female = 45% Age: 18-65 y Pain sites: LBP Pain duration: ≥ 3 mo	A = Active Physical training (APT) B (MD) = behavioral therapy (GAP) C (MD) = APT+GAP (Combined training)	A = 2 physiotherapists B = physiotherapist or occupational therapist and psychologist or social worker C = physiotherapist, psychologist and physician	Societal perspective Costs: Direct health care cost Nondirect health care cost Absenteeism from paid work Currency: Euro (2003) Discounting: Was not applied Outcome measures: RMDQ, EuroQol Follow-up = baseline, immediately after 10 wk of active treatment Months: 6, 12	CEA and CUA	No significant difference between A and C ($P > 0.17$) or B and C ($P > 0.14$) for RMDQ or QALY (EuroQol). All treatments improved significantly from baseline ($P \leq 0.002$). C was not more cost-effective than A or B. CE plane indicates most of the CE pairs are on the north west quadrant

(*Continued*)

TABLE 1. (*continued*)

Study Design	Participants	Intervention	Intervention Team	Study Perspective, Cost Domain and Outcome Measures	Type of Economic Evaluation	Results
						indicating C as less expensive but also less reduction in RMDQ and in terms of QALYs gained
Wayne et al[42] (Cohort study)	N = 278 Female = 71% Age: ≥ 21 y Pain sites: Nonspecific LBP Pain duration: ≥ 3 mo for chronic LBP or ≥ 6 mo for intermittent LBP	A (MD) = complementary and medical integrative therapy (OCC). B (MD) = usual care (non-OCC)	A = integrated multidisciplinary team including chiropractors, acupuncturists, and physicians. B = not as a team but individuals providing primary care, specialists and physiotherapy	Societal perspective Costs: Direct health care cost Nondirect health care cost Absenteeism from paid work Currency: US dollars (2012, 2015) Discounting: NA Outcome measures: ICER based on RDQ and BOP, QALYs based on SF-12 Follow-up = baseline, immediately after 10 wk of active treatment Months: 6, 12	CEA and CUA	A is more effective than B at 12 mo (RMDQ, $P = 0.001$) but not 3 or 6 mo ($P \geq 0.13$). A is more effective than B (BOP) at 3,6 and 12 mo ($P \leq 0.02$). A is more costly than B. CE plane shows 76.3% of the CE pairs are on NE quadrant indicating A more effective at a higher cost

BOP indicates bothersomeness of pain; CBA, cost-benefit analysis; CBT, cognitive-behavioral therapy; CEA, cost effectiveness analysis; CUA, cost-utility analysis; EuroQoL, an instrument to measure quality of life; GAP, graded activity plus problem solving training; HRQoL, health-related quality of life; ICER (ICUR), incremental cost-effectiveness (utility) ratio; LBP, low back pain; MD, multidisciplinary; OCC, Osher Clinical Centre; PSEQ, Pain Self-Efficacy Questionnaire; QALY, quality adjusted life years; QBPDS, Quebec Back Pain Disability Scale; QoL, Quality of Life; RCT, randomized controlled trial; RMDQ, Roland and Morris Disability Questionnaire; SF-12, Short-Form Survey 12 item; SF-36/6D, the 6-dimensional health state short form derived from Short-Form 36 health survey.

costs of health care resources used.[37,41] No included study applied discounting as the follow-up period was either 6[40] or 12 months.[36–39,41,42] None of the included studies were based on decision models extrapolating long-term costs and effects of multidisciplinary programs beyond the time horizon of the intervention.

Cost per QALYs gained was evaluated by an ICER/ICUR in 6 studies.[36,38–42] An ICER based on sick leave was calculated by 1 study.[37]

All 7 studies performed a CEA, 6 studies added a CUA[36,38–42] and 2 studies added a CBA.[37,39] Five studies[36,38,39,41,42] provided a CEAC derived from joint distributions of incremental costs and incremental effects and estimated CEAC using nonparametric bootstrapping. Six studies constructed a cost-effectiveness plane to show the uncertainty regarding the CEA outcomes.[36,38–42] Five studies measured the degree of uncertainty in the ICER (or ICUR) using both a CEAC and cost-effectiveness plane.[36,38,39,41,42] One study conducted an incremental analysis of costs and outcomes but did not include any CEAC or cost-effectiveness plane.[37] Only 1 study did not conduct sensitivity analysis.[42]

Economic Quality Assessment

Results of the economic methodological quality assessment using Drummond and colleagues' checklist are shown in Table 2. The methodological quality of included studies appeared moderate with positive responses to 7/10 questions for 1 study,[38] 6/10 questions for 4 studies,[39–42] and 5/10 questions for 2 studies.[36,37] Four studies failed to establish effectiveness of the multidisciplinary intervention, thus an economic evaluation to assess cost-effectiveness has limited interpretability (Table 2).[36,37,40,41] None of the included studies extrapolated costs and outcomes to predict long-term cost-effectiveness for a time horizon beyond the follow-up period, hence negative responses were noted for all studies in relation to extrapolation. Further, none of the included studies applied discounting although adjustments were made to costs for differential timing. For example, outcome and cost data were extrapolated for only 3 months beyond the follow-up and no discounting was applied in 1 study,[36] the 2009 cost value (last year of study) was used in the Jensen et al[37] study, the cost was adjusted to 2008 consumer price index in the study of Lamb et al,[38] exchange rates were applied to measure cost in 2 studies,[39,40] cost data was collected between 2002 and 2004 with the 2003 cost value used,[41] existing cost data was extrapolated for patients with <12 months cost data.[42] Unit costs were measured but not presented by 2 studies.[37,41]

Risk of Bias

Responses to the risk of bias assessment were similar across all included studies (Table 3). These studies were considered to have a low risk of bias for most criteria. Blinding of assessors was not used in most of the studies as outcomes were self-reported. Participants were not blinded to their intervention for any of the studies which could lead to bias.

TABLE 2. Methodological Assessment of Included Studies Following Drummond and Colleagues' 10-point Checklist

Checklist Item	Goossens et al[36]	Jensen et al[37]	Lamb et al[38]	Lambeek et al[39]	Schweikert et al[40]	Smeets et al[41]	Wayne et al[42]
1. [Economic] question well-defined and answerable?	Y	Y	Y	Y	Y	Y	Y
2. Comprehensive description of alternatives?	Y	Y	Y	Y	Y	Y	Y
3. Effectiveness established?	N	N	Y	Y	N	N	Y
4. All costs and consequences for alternatives identified?	Y	Y	Y	Y	Y	Y	Y
5. Costs and consequences measured appropriately prior to valuation?	N*	N	N	N*	N*	N*	N*
6. Costs and consequences valued credibly?	N*	N*†	N*	N*	N*	N*†	N*
7. Costs and consequences adjusted for differential timing?	N	N	Y	N	Y	Y	N
8. Incremental analysis of costs and consequences of alternatives performed?	Y	Y	Y	Y	Y	Y	Y
9. Allowance made for uncertainty in the estimates of costs and consequences?	Y	Y	Y	Y	Y	Y	Y
10. Presentation and discussion of results include all issues of concern to users?	N	N	N	N	N	N	N

*Did not capture long term health and economic consequences.
†Unit cost measured but not presented.
N indicates no; Y, yes.

Summary of Results of Economic Evaluation of the Multidisciplinary Intervention

The results of the CEA are described in Table 1 and summarized below.

Cost-effectiveness of a Multidisciplinary Intervention Compared With Nonmultidisciplinary Intervention

One study,[37] conducted in Denmark, compared a multidisciplinary intervention with a brief intervention for CLBP patients who had reduced working hours due to pain or patients who were on full-time sick leave for 4 to 12 weeks. The multidisciplinary intervention included examination and guidance followed by a return-to-work plan. The plan was discussed with a multidisciplinary team consisting of a rehabilitation doctor, a physiotherapist, a social worker and an occupational therapist. The brief intervention, primarily involving the provision of reassuring advice, was provided by a rehabilitation doctor and a physiotherapist. Jensen et al[45] found no significant difference between the multidisciplinary and brief interventions ($P=0.18$). Overall, the multidisciplinary intervention was not cost-effective compared with the brief intervention from a health care provider and a societal perspective (ICER: Kr 2631 [€353] for one additional sick leave week; 2009 prices). However, when the patients with longer sick leave histories were examined, it emerged that the multidisciplinary approach was more cost-effective for those patients with worse sick leave histories. The authors did not calculate net societal benefit (increase in welfare of a society derived from a project) and/or return on investment while conducting a CBA from a societal perspective.

The study of Lamb et al[38] evaluated multidisciplinary intervention (advice plus cognitive-behavioral therapy [CBT]) with advice alone in patients with subacute and CLBP. Advice was provided by a nurse or physiotherapist and CBT, which targeted activity avoidance and beliefs about exercise, was provided by trained physiotherapists, nurses, psychologists, and occupational therapists. This study found evidence that the multidisciplinary intervention was effective ($P\leq0.03$).[38] The probability of the multidisciplinary intervention being cost-effective was >90% at a threshold of £3000 per QALYs gained implying that the multidisciplinary intervention was most likely cost-effective. This study reported additional QALYs gained from the multidisciplinary intervention was 0.099 and the incremental cost per QALY gained was £1786 indicating low cost and improved quality of life.

Lambeek et al,[39] in a Dutch study, compared a multidisciplinary program (integrated care provided by occupational therapists, medical specialists and a general practitioner, and physiotherapy) with usual care provided by an occupational physician and general practitioner following Dutch guidelines for patients with CLBP on sick leave. This study found the multidisciplinary intervention resulted in significantly fewer days until return to work ($P=0.002$). The CBA found that every £1 invested in the multidisciplinary intervention would return an estimated £26. The net societal benefit of the multidisciplinary treatment compared with usual care was £5744. The CEA showed that the probability of the multidisciplinary being cost-effective in terms of return to work was 95% from a societal perspective implying that the multidisciplinary intervention was likely cost-effective. The multidisciplinary intervention was more effective and associated with higher costs than usual care. The QALY gain of 0.09 in the multidisciplinary intervention group compared with the usual care was statistically significant ($P=0.01$). All economic outcomes favored the multidisciplinary intervention.

Cost-effectiveness of a Nonmultidisciplinary Intervention and a Multidisciplinary Intervention Compared With a Combination of These Interventions

A 3-armed study by Smeets et al,[41] also from the Netherlands, compared a nonmultidisciplinary intervention termed active physical training (APT) and a multidisciplinary graded activity (GA) with problem solving skills (GAP) with a combined multidisciplinary treatment (CT, CT = APT+GAP) programs for CLBP in adults. The APT intervention was provided by physiotherapists, GAP was provided by a physiotherapist or occupational therapist +problem solving training provided by psychologists. The

TABLE 3. Risk of Bias Assessment of the Included Studies

Bias Type	Criteria	Goossens et al[36]	Jensen et al[37]	Lamb et al[38]	Lambeek et al[39]	Schweikert et al[40]	Smeets et al[41]	Wayne et al[42]
Selection	Random sequence generation	Y	Y	Y	Y	Y	Y	NA
	Allocation concealment	N	N	N	N	N	N	NA
	Participants analyzed within originally assigned groups	Y	Y	Y	Y	Y	Y	NA
	Inclusion/exclusion criteria uniformly applied to groups	Y	Y	Y	Y	Y	Y	Y
	Recruitment strategy same across study groups	Y	Y	Y	Y	Y	Y	Y
	Design or analysis controls for confounding /modifying variables	Y	Y	Y	Y	N	Y	Y
Performance	Rule out any impact from concurrent intervention/ unintended exposure	Y	N	Y	Y	N	N	ND
	Maintain fidelity to the intervention protocol	Y	Y	Y	Y	Y	Y	NA
Attrition	Missing data handled appropriately	Y	Y	Y	Y	Y	Y	ND
Detection	Length of follow-up same between the groups	Y	Y	Y	Y	Y	N	NA
	Outcome assessors blinded to intervention or exposure status of participants?	N*	N*	Y	N*	N*	Y	N*
	Interventions/exposures assessed/defined using valid and reliable measures, implemented consistently across all study participants	Y	Y	Y	Y	Y	Y	Y
	Confounding variables assessed using valid and reliable measures, implemented consistently across all study participants	NA	NA	NA	NA	NA	NA	Y
Reporting	Potential outcomes prespecified? All reported?	Y	Y	Y	Y	Y	Y	Y
Summary	Number of positive (Y) responses	11/13	10/13	12/13	11/13	9/13	10/13	5/9

*Self-reported questionnaire.
N indicates no; NA, not applicable; ND, not described; Y, yes.

combined multidisciplinary treatment was provided by therapists who were informed about the integrative aspect of CT. Analysis indicated that the CT was not significantly different to the APT or GAP groups ($P > 0.05$). Relative to CT, the ICER showed that APT cost €371 more and GAP cost €3759 less to achieve improvement of one point on the RMDQ. Relative to CT, the ICUR showed that APT cost €35,060 more and GAP cost €108,857 less to obtain improvement of one QALY. The CE plane indicated most of the CE pairs were in the northwest (NW) quadrant (CT: APT, 37% NW versus 31% southeast (SE)—meaning that CT was inferior but less expensive with having less reduction in the RMDQ score (CT:GAP, 83% NW vs. 1% SE) and in terms of QALYs gained, the results indicated that CT was a less effective intervention in terms of reduction in RMDQ (CT:GAP, 89% NW vs. 1% SE). As such, CT was not cost-effective compared with APT or GAP. Although GAP was the most cost-effective intervention, there was no significant difference in treatment effect between APT and GAP ($P > 0.05$).

Cost-effectiveness of a Multidisciplinary Intervention Compared With an Alternative Multidisciplinary Intervention

One Dutch study[36] evaluated the use of a CBT-based pain-related fear reduction approach called "exposure in vivo treatment" (EXP) conducted by a multidisciplinary team with another multidisciplinary CBT approach aimed at improved functional ability by reinforcing healthy behaviors and activities using a GA approach in patients with CLBP. The EXP intervention was led by a rehabilitation physician and a multidisciplinary team (comprising a psychologist and a physiotherapist or occupational therapist) and GA was provided by a multidisciplinary team without the physician (comprising a psychologist and physiotherapist or occupational therapist). Although improvement in QALYs, quality of life and reduced disability were in favor of the EXP program, the differences between EXP and GA were not statistically significant ($P > 0.30$). At WTP €16,000, the probability of EXP being CE was 81%. And at a WTP of €80,000, the probability of EXP being CE was 76%. The cost-effectiveness plane indicated 56% of bootstrapped CE pairs were in the SE quadrant, meaning that in 56% of cases the EXP intervention was more effective and at a lower cost than GA. The overall finding was that the EXP group may be more cost-effective than the GA group. However, it should be noted that both elements are usually integrated with most CBT-based multidisciplinary pain management programs as this is likely to be more feasible (service delivery and economic benefit), than conducting separate programs for typically heterogeneous groups of patients.[9]

An economic evaluation study by Schweikert et al[40] estimated cost-effectiveness results using QALYs as the only health outcome. This German study assessed the efficacy and cost-effectiveness of adding CBT to the usual multidisciplinary 3-week inpatient medical rehabilitation program (multidisciplinary vs. multidisciplinary+CBT) for patients with CLBP. Both multidisciplinary and multidisciplinary plus CBT interventions involved a psychologist, physiotherapists, and pain physicians. There was no evidence of a difference in treatment effect between the 2 interventions ($P > 0.05$). The multidisciplinary+CBT intervention (ICER: € –126,731 per QALYs gained, 2001 prices) was associated with lower indirect cost resulting in fewer workdays lost and hence was cost-saving. The cost-effectiveness plane showed that in 61% of cases, multidisciplinary +CBT intervention was more effective and cost saving compared with multidisciplinary intervention alone implying that multidisciplinary+CBT may be more cost effect than the usual multidisciplinary intervention alone.

Finally, a study from the United States by Wayne et al[42] compared CLBP care provided at an Osher Clinical Centre (OCC), comprising complementary and integrative medical therapies with usual care (non-OCC) provided within the same hospital but outside the center. The OCC intervention was provided by an integrated multidisciplinary team of clinicians including physiotherapists, acupuncturists, chiropractors, massage therapists, nutritionists, registered dietitians, nurses while the non-OCC intervention was delivered by clinicians including general practitioners, specialists, and physiotherapists not operating as a team.[47] The OCC group was found to provide significant benefit compared with the non-OCC group ($P \leq 0.003$). The OCC group was associated with higher costs compared with the non-OCC group. The authors reported that the non-QALY based results were in favor of the OCC group in terms of cost per unit change in disability (ICER of US$2,073), and cost per unit change in bothersomeness of pain (ICER of US $4,203). The study showed that in 76.3% cases OCC care was more effective but at a higher cost. There was no statistically significant difference in QALYs between the 2 interventions ($P = 0.36$).

In summary, 2/3 studies that compared a multidisciplinary intervention to a nonmultidisciplinary intervention found that the multidisciplinary pain interventions were cost-effective[38,39] while the other study found that the multidisciplinary intervention of interest was neither effective nor cost-effective.[37] Smeets et al[41] also concluded that the combined multidisciplinary intervention of interest was neither effective nor cost-effective. Two of the 3 multidisciplinary intervention versus alternative multidisciplinary intervention studies[36,40] may have been cost-effective, but there was a lack of a significant difference between study arms which precluded firm conclusions, and the third study[42] found that the intervention by the multidisciplinary team was not cost-effective.

DISCUSSION

Failure to manage pain among chronic pain patients has been shown to lead to higher health care costs. It has been suggested that multidisciplinary interventions lead to better outcomes for patients. Economic evaluation is an important part of assessing interventions so that the potential benefits to patients are not outweighed by the cost of such interventions. This study is the first in 20 years to systematically review complete economic evaluation studies of multidisciplinary pain management programs aimed at rehabilitation of adults with chronic pain compared with nonmultidisciplinary (or unidisciplinary/unimodal) interventions or other multidisciplinary pain management programs/interventions provided by a multidisciplinary team.

While a PubMed search of the terms “multidisciplinary” and “chronic pain” and “intervention” identified almost 2800 publications to date, suggesting that multidisciplinary advice and treatment is well-established, only 7 studies included an economic evaluation and met the inclusion criteria for this review. This indicates the ongoing need for additional economic evaluations of multidisciplinary chronic pain interventions.

Despite the limited number of economic evaluations, this review has several strengths. First of all, the review has shown that economic evaluations appear to be improving in quality and utilize more appropriate methods for evaluating costs, partially addressing the criticism Thomsen et al[14] had of the lack of enough complete economic evaluation studies. In this review, studies were included if they applied an incremental approach (ICER) to analyze costs and consequences to make a meaningful comparison between interventions within a study. In addition, extraction of the uncertainty surrounding the estimates of cost-effectiveness (through a CEAC or a CE plane or both) was undertaken. The CE plane helps decision makers to identify the health and economic value of interventions while a CEAC measuring the probability of cost-effectiveness is useful to decide whether to adopt an intervention since it measures uncertainty surrounding the choice. This review identified studies of multidisciplinary interventions that included return to work as an outcome measure which may generate benefits beyond improved health outcomes such as less dependence on welfare payments, tax paid after return to work and less dependence on other family members for financial support.

This systematic literature review also has a number of limitations. Hand searching for gray literature was not performed and non-English language studies were not included. This could mean that some studies on this topic may have been missed. This review used Drummond and colleagues’ 10-point checklist to assess methodological quality. However, as noted earlier, this checklist is not a standardized rating scale[48] and there are no cut-points that help to determine if the methodological quality of the economic evaluation of a given study is acceptable. Further, interest in this study was in economic evaluations of interventions for any pain site; however, only studies of patients with LBP were found. This limits the generalizability of this study and suggests the need for economic evaluations of interventions for adults with other pain sites, or multiple pain sites.

From an individual study perspective, 3 studies[37–39] reported on multidisciplinary compared with nonmultidisciplinary interventions for chronic pain and a fourth study had a multidisciplinary versus nondisciplinary intervention as one of the comparisons in a 3-arm trial.[41] Two[38,39] of the 4 studies concluded favorable effectiveness cost-effectiveness results for the multidisciplinary intervention but Lambeek et al[39] had a smaller sample size limiting confidence in the overall conclusions. One of the studies[38] evaluated the clinical significance of multidisciplinary approaches based on treatment estimates, effect sizes and context, concluding the multidisciplinary approach as a clinically meaningful cost-effective intervention. The other study[39] analyzed duration until sustainable return to work and QALYs and did not report any other clinical outcome measures. Jensen et al[37] reported the health outcomes in terms of their clinical differences but only in related papers.[45,46] Two[37,39] of the 4 studies incorporated return to work as a primary outcome measure but Jensen et al[37] did not report the uncertainty of cost-effectiveness results using a CE plane and/or CEAC. The studies that did not find cost-effectiveness of the multidisciplinary interventions of interest also did not find that they were effective.[37,41]

Two studies[36,40] compared multidisciplinary interventions with an alternative multidisciplinary intervention for chronic pain management. Neither effectiveness nor cost-effectiveness of the multidisciplinary intervention of interest was established in these studies with 1 study having a very small sample size.[36] One study indicated the intervention by the multidisciplinary team was more effective but at a higher cost.[42] In this study, the inclusion of modalities such as chiropractic, massage, acupuncture may have been aimed primarily at pain relief rather than rehabilitation, which makes it somewhat different to the other studies reviewed.

While generalizability is important, only the Lambeek et al study[39] indicated that generalizability of the analysis from a different perspective and context would be possible. Drummond and colleagues suggested that cost-effectiveness results may vary among subgroups and advocated subgroup analysis; only 1 study reviewed included subgroup analysis.[37] None of the studies applied discounting to the costs, health effects or both, as the follow-up period was 12 months or less. A longer follow-up period for primary outcomes would enable richer information to be captured regarding the long-term effectiveness of the multidisciplinary interventions for chronic musculoskeletal pain including if there were any productivity gains and ongoing improvements in quality of life.[49] Further, Drummond and colleagues suggested that for the majority of economic evaluations the relevant time horizon is the patient's lifetime. Future economic evaluation studies should utilize decision analytic models, extrapolating costs and health effects of multidisciplinary programs beyond the trial time period, reflecting all meaningful evidence as described in Drummond et al.[34]

In conclusion, there are few economic evaluations on multidisciplinary chronic pain interventions in the literature that actually report the incremental cost-effectiveness of interventions, and of the studies found, there were significant methodological limitations which make it difficult to draw firm conclusions. This review encourages the publication of additional rigorous CEAs in this important field.

GLOSSARY

Cost-effectiveness analysis (CEA): A type of study design in which outcome of different interventions may vary but can be measured in identical natural units; relative inputs are then costed in monetary units. Interventions can then be compared in terms of cost per unit of outcome.

Cost-utility analysis (CUA): A type of economic study design in which interventions that produce different outcomes in terms of both quantity and quality of life are expressed as utilities. These are measures which comprise both length of life and subjective levels of well-being (eg, quality adjusted life years, QALYs). Costs are measured in monetary units. In this type of analysis, competing interventions are compared in terms of cost per QALYs.

Cost-benefit analysis (CBA): A type of economic study design in which the costs and outcomes of competing interventions are expressed in monetary units. This design allows their direct comparison across programs, including outside health care.

Quality-adjusted life-years (QALYs): QALYs range from 0 to 1 where 0 represents death and a year of life lived in perfect health is equal to 1 QALY.

Incremental cost-effectiveness ratio (ICER): The incremental cost of one intervention over another compared with the incremental health effect or utilities generated in economic evaluation studies is known as the incremental cost-effectiveness ratio (ICER) or incremental cost-utility ratio (ICUR).

Cost-effectiveness acceptability curve (CEAC): Used to summarize and interpret the uncertainty in ICER estimates by graphically showing the probability of an intervention being cost-effective compared with the alternative treatment option over a range of willingness to pay (WTP) thresholds. This is generally expressed as the societal WTP for an additional life year or QALY gained.

Cost-effectiveness plane: Visually presents all combinations of possible outcomes together with the degree of uncertainty of the ICER. The plane is divided into 4 quadrants where incremental cost is shown on the *y*-axis and benefit on the *x*-axis. For example, the further right along the *x*-axis, the more effective the intervention and further up along the *y*-axis, the more costly the intervention.

REFERENCES

1. Global Burden of Disease 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*. 2018;392:1789–1858.
2. Fayaz A, Croft P, Langford RM, et al. Prevalence of chronic pain in the UK: a systematic review and meta-analysis of population studies. *BMJ Open*. 2016;6:e010364.
3. Nahin RL. Estimates of pain prevalence and severity in adults: United States, 2012. *J Pain*. 2015;16:769–780.
4. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain*. 2012;13:715–724.
5. Schofield DJ, Shrestha RN, Percival R, et al. The personal and national costs of early retirement because of spinal disorders: impacts on income, taxes, and government support payments. *Spine J*. 2012;12:1111–1118.
6. Schofield DJ, Shrestha RN, Percival R, et al. Early retirement and the financial assets of individuals with back problems. *Eur Spine J*. 2011;20:731–736.
7. Deloitte Access Economics. The cost of pain in Australia. 2019. Available at: https://www.painaustralia.org.au/static/uploads/files/the-cost-of-pain-in-australia-final-report-12mar-wfxbrfyboams.pdf. Accessed August 21, 2019.
8. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic therapies for low back pain: a systematic review for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med*. 2017;166:493–505.
9. Kamper SJ, Apeldoorn AT, Chiarotto A, et al. Multidisciplinary biopsychosocial rehabilitation for chronic low back pain: Cochrane systematic review and meta-analysis. *BMJ*. 2015;350:h444.
10. Banerjee S, Argáez C. Multidisciplinary treatment programs for patients with chronic non-malignant pain: a review of clinical effectiveness, cost-effectiveness, and guidelines. 2017. Available at: https://www.ncbi.nlm.nih.gov/books/NBK525038/. Accessed August 22, 2019.
11. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. *JAMA*. 2016;315:1624–1645.
12. Turk DC, Wilson HD, Cahana A. Treatment of chronic non-cancer pain. *Lancet*. 2011;377:2226–2235.
13. Karjalainen K, Malmivaara A, van Tulder M, et al. Multidisciplinary biopsychosocial rehabilitation for neck and shoulder pain among working age adults: a systematic review within the framework of the Cochrane Collaboration Back Review Group. *Spine (Phila Pa 1976)*. 2001;26:174–181.
14. Thomsen AB, Sorensen J, Sjogren P, et al. Economic evaluation of multidisciplinary pain management in chronic pain patients: a qualitative systematic review. *J Pain Symptom Manage*. 2001;22:688–698.
15. Nicholas MK, Asghari A, Corbett M, et al. Is adherence to pain self-management strategies associated with improved pain,

depression and disability in those with disabling chronic pain? *Eur J Pain*. 2012;16:93–104.
16. Clark VP, Parasuraman R. Neuroenhancement: enhancing brain and mind in health and in disease. *NeuroImage*. 2014;85:889–894.
17. International Association for the Study of Pain (IASP). Pain treatment services. Available at: https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1381. Accessed August 21, 2019.
18. Grant SJ, Frawley J, Bensoussan A. Process of care in outpatient integrative healthcare facilities: a systematic review of clinical trials. *BMC Health Serv Res*. 2015;15:322.
19. Xie F, Tanvejsilp P, Campbell K, et al. Cost-effectiveness of pharmaceutical management for osteoarthritis pain: a systematic review of the literature and recommendations for future economic evaluation. *Drugs Aging*. 2013;30:277–284.
20. Salathe CR, Melloh M, Crawford R, et al. Treatment efficacy, clinical utility, and cost-effectiveness of multidisciplinary biopsychosocial rehabilitation treatments for persistent low back pain: a systematic review. *Global Spine J*. 2018;8:872–886.
21. Freyd M. The graphic rating scale. *J Educ Psychol*. 1923;14: 83–102.
22. Heller GZ, Manuguerra M, Chow R. How to analyze the Visual Analogue Scale: myths, truths and clinical relevance. *Scand J Pain*. 2016;13:67–75.
23. Dunn KM, Croft PR. Classification of low back pain in primary care: using "bothersomeness" to identify the most severe cases. *Spine (Phila Pa 1976)*. 2005;30:1887–1892.
24. Cherkin DC, Sherman KJ, Balderson BH, et al. Effect of mindfulness-based stress reduction vs cognitive behavioral therapy or usual care on back pain and functional limitations in adults with chronic low back pain: a randomized clinical trial. *JAMA*. 2016;315:1240–1249.
25. Ware J Jr, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34:220–233.
26. McCaffrey N, Kaambwa B, Currow DC, et al. Health-related quality of life measured using the EQ-5D-5L: South Australian population norms. *Health Qual Life Outcomes*. 2016;14:133.
27. Waddell G, Newton M, Henderson I, et al. A Fear-Avoidance Beliefs Questionnaire (FABQ) and the role of fear-avoidance beliefs in chronic low back pain and disability. *Pain*. 1993;52: 157–168.
28. Nicholas MK. The Pain Self-Efficacy Questionnaire: taking pain into account. *Eur J Pain*. 2007;11:153–163.
29. Roland M, Morris R. A study of the natural history of back pain. Part I: development of a reliable and sensitive measure of disability in low-back pain. *Spine (Phila Pa 1976)*. 1983;8: 141–144.
30. Kopec JA, Esdaile JM, Abrahamowicz M, et al. The Quebec Back Pain Disability Scale. Measurement properties. *Spine (Phila Pa 1976)*. 1995;20:341–352.
31. Kopec JA, Esdaile JM, Abrahamowicz M, et al. The Quebec Back Pain Disability Scale: conceptualization and development. *J Clin Epidemiol*. 1996;49:151–161.
32. Nymark L, Vassall A. A comprehensive framework for considering additional unintended consequences in economic evaluation. *Cost Eff Resour Alloc*. 2020;18:27.
33. Kim N, Yang B, Lee T, et al. An economic analysis of usual care and acupuncture collaborative treatment on chronic low back pain: a Markov model decision analysis. *BMC Complement Altern Med*. 2010;10:74.
34. Drummond M, Sculpher MJ, Claxton K, et al. *Methods for the Economic Evaluation of Health Care Programmes*. Oxford, UK: Oxford University Press; 2015.
35. Viswanathan M, Ansari MT, Berkman ND, et al. Assessing the risk of bias of individual studies in systematic reviews of health care interventions. 2012. Available at: https://effectivehealthcare.ahrq.gov/products/methods-guidance-bias-individual-studies/methods. Accessed August 22, 2019.
36. Goossens ME, de Kinderen RJ, Leeuw M, et al. Is exposure in vivo cost-effective for chronic low back pain? A trial-based economic evaluation. *BMC Health Serv Res*. 2015;15:549.
37. Jensen C, Nielsen CV, Jensen OK, et al. 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 (Phila Pa 1976)*. 2013;38:1059–1067.
38. Lamb SE, Lall R, Hansen Z, et al. A multicentred randomised controlled trial of a primary care-based cognitive behavioural programme for low back pain. The Back Skills Training (BeST) trial. *Health Technol Assess*. 2010;14:1–253; iii–iv.
39. Lambeek LC, Bosmans JE, Van Royen BJ, et al. Effect of integrated care for sick listed patients with chronic low back pain: economic evaluation alongside a randomised controlled trial. *BMJ*. 2010;341:c6414.
40. Schweikert B, Jacobi E, Seitz R, et al. Effectiveness and cost-effectiveness of adding a cognitive behavioral treatment to the rehabilitation of chronic low back pain. *J Rheumatol*. 2006;33:2519–2526.
41. Smeets RJ, Severens JL, Beelen S, et al. More is not always better: cost-effectiveness analysis of combined, single behavioral and single physical rehabilitation programs for chronic low back pain. *Eur J Pain*. 2009;13:71–81.
42. Wayne PM, Buring JE, Eisenberg DM, et al. Cost-effectiveness of a team-based integrative medicine approach to the treatment of back pain. *J Altern Complement Med*. 2019;25:S138–S146.
43. Leeuw M, Goossens ME, van Breukelen GJ, et al. Exposure in vivo versus operant graded activity in chronic low back pain patients: results of a randomized controlled trial. *Pain*. 2008; 138:192–207.
44. Lambeek LC, Anema JR, Van Royen BJ, et al. Multidisciplinary outpatient care program for patients with chronic low back pain: design of a randomized controlled trial and cost-effectiveness study [ISRCTN28478651]. *BMC Public Health*. 2007;7:254.
45. Jensen IB, Busch H, Bodin L, et al. Cost effectiveness of two rehabilitation programmes for neck and back pain patients: a seven year follow-up. *Pain*. 2009;142:202–208.
46. Jensen C, Jensen OK, Christiansen DH, et al. One-year follow-up in employees sick-listed because of low back pain: randomized clinical trial comparing multidisciplinary and brief intervention. *Spine (Phila Pa 1976)*. 2011;36:1180–1189.
47. Wayne PM, Eisenberg DM, Osypiuk K, et al. A multidisciplinary integrative medicine team in the treatment of chronic low-back pain: an observational comparative effectiveness study. *J Altern Complement Med*. 2018;24:781–791.
48. Edmunds K, Ling R, Shakeshaft A, et al. Systematic review of economic evaluations of interventions for high risk young people. *BMC Health Serv Res*. 2018;18:660.
49. Chuang LH, Soares MO, Tilbrook H, et al. A pragmatic multicentered randomized controlled trial of yoga for chronic low back pain: economic evaluation. *Spine (Phila Pa 1976)*. 2012;37:1593–1601.