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SUMMARY WITH CRITICAL APPRAISAL

Tiered Care for Chronic Non-Malignant Pain: A Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines

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Abbreviations

AGREE	Appraisal of Guidelines, Research and Evaluation
AHRQ	Agency for Healthcare Research and Quality
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
CADTH	Canadian Agency for Drugs and Technologies in Health
CBT	cognitive behavioral therapy
CI	confidence interval
GRADE	Grading of Recommendations Assessment Development and Evaluation
HR	hazard ratio
LBP	low back pain
MA	meta-analysis
MSK	musculoskeletal
MTC	mixed treatment comparison
NICE	National Institute for Health and Care Excellence
NRS	non-randomized studies
PHQ-9	Patient Health Questionnaire-9
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
RCT	randomized controlled trial
RMDQ	Roland Morris Disability Questionnaire
SCS	Stepped Care Strategy
SCM-PM	Stepped Care Model of Pain Management
SIGN	Scottish Intercollegiate Guideline Network
SPPB	Short Physical Performance Battery
SPSI	Social Problem Solving Inventory
SR	systematic review
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index
WSAS	Work and Social Adjustment Scale

Context and Policy Issues

Chronic pain is defined as pain that persists over three months, beyond when an injury should have healed.[1] Chronic or persistent pain is a frequent reason for seeking medical care and is reported by 20% to 50% of primary care patients living in the community.[2,3] The prevalence of chronic pain in Canada varies between 16% and 40%, with the variability in prevalence estimates attributed to differences in the definitions of chronic pain used, sample populations surveyed, and survey methodologies employed.[4,5] A 2007/2008 telephone survey of a representative sample of adults from across Canada found that the prevalence of chronic pain in adults 18 years of age and older was 18.9%, with higher prevalence in older adults.[5] The most commonly affected site of chronic pain was the lower back and arthritis was the most frequently named cause; approximately one-half of respondents reported living with chronic pain for more than 10 years.[5] Chronic pain is a serious health problem in Canada, not only due to its prevalence, but also due to the burden it imparts on physical functioning, disability, quality of life, productivity costs, and use of healthcare resources.[1] One reason identified for the current ineffective prevention and management of chronic pain in Canada is that there are limitations in existing programs and services for treatment and prevention of chronic pain.[1]

Stepped care is a strategy that codifies treatment decision making in a manner that adapts to a patient's needs and behavior.[6] In the context of pain management, tiered or stepped care (also known as stratified care or treatment pathways) matches the level of intensity of care to a patient's needs, in particular to the complexity and severity of their medical condition. Historically, the amount of pain has been the central outcome of pain treatment, with interventions given to immediately reduce the experience of pain.[7] In contrast, stepped-care models provide for an initial proposed intervention, with further treatment to be determined by pre-specified outcome measures that can measure overall functioning.[7] It follows that poor functioning will lead to a higher level of care that may require more multidisciplinary services.[7] Therefore, depending on the complexity, severity, or other factors pertaining to a patient's condition, the most appropriate (and cost-effective) level of care could range from self-directed care (e.g., lifestyle changes, exercise) to brief interventions that can be initiated by general practitioners (e.g., behavioral health assessment, physical therapy, dietary therapy), to complex interventions that require the coordinated, on-going efforts of a multidisciplinary team of healthcare professionals.

A previous CADTH Rapid Response Report and Critical Appraisal on Multidisciplinary Treatment Programs for Patients with Chronic, Non-Malignant Pain that was published in 2017 did not include tiered or stepped care as an intervention.[8] Rather, the prior CADTH report focused on studies of multidisciplinary treatment interventions such as usual care, physical treatment, mindfulness based stress reduction, brief intervention, waitlist, standard rehabilitation, and muscle reconditioning.[8]

More information is needed to determine if tiered or stepped care is clinically-effective and cost-effective when used for the management of patients with chronic, non-malignant pain treated in outpatient settings. There is uncertainty regarding whether or not matching the level of intensity of care to the complexity and severity of a patient's medical condition will result in better outcomes than the usual standard of care or a typical 'one-size fits all' primary care strategy.[9] It is also important to know if there are evidence-based guidelines to inform the use of tiered or stepped care in patients with chronic, non-malignant pain.

The purpose of this report is to synthesize and critically appraise the available evidence on the clinical effectiveness, cost-effectiveness, and guidelines for the use of tiered or stepped care approaches for the treatment of chronic, non-malignant pain in the outpatient setting.

Research Questions

1. What is the clinical effectiveness of tiered or stepped care for patients with chronic, non-malignant pain in outpatient settings?
2. What is the cost-effectiveness of tiered or stepped care for patients with chronic, non-malignant pain in outpatient settings?
3. What are the evidence-based guidelines regarding tiered or stepped models of care for patients with chronic, non-malignant pain in outpatient settings?

Key Findings

Two systematic reviews (one of which included a meta-analysis), one randomized controlled trial, and six non-randomized studies provide limited evidence for the clinical effectiveness of tiered or stepped care for patients with chronic, non-malignant pain. Although evidence was identified to support that tiered or stepped care is clinically effective

based on outcomes such as pain reduction, return to work, mental health parameters, and healthcare or prescription drug utilization, the diversity of outcomes and inconsistent results creates uncertainty in the findings. Therefore, evidence of low quality suggests that tiered or stepped care may be clinically effective for the management of chronic non-malignant pain compared to usual care; however, more research is needed to better inform and guide treatment decisions according to a tiered or stepped care approach.

One economic evaluation of moderate quality was identified that addressed cost-effectiveness of tiered or stepped care. The analysis evaluated the incremental cost-effectiveness of three levels of care for sciatica and found that a stepped approach was most cost-effective relative to direct surgical referral, with positive net benefits if certain ceiling limits were applied. The analysis was from the UK so it is unclear if the results would be the same in a Canadian setting and should be considered when interpreting the results.

Two evidence-based guidelines were included that describe models of tiered or stepped care for the management of chronic, non-malignant pain. One guideline provides specific recommendations for intensity of care based on a model of risk assessment and risk stratification. In considering these recommendations, it should be noted that the supporting evidence was based on a single randomized controlled trial of fair quality.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Ovid Medline, The Cochrane Library, University of York Centre for Reviews and Dissemination databases, 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 January 1, 2014 and January 14, 2019.

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	Tiered or stepped care
Comparator	Q1 & Q2: Standard of care (e.g., general practitioners only, single entity of care) or no comparator Q3: Not applicable
Outcomes	Clinical effectiveness (e.g., improved functional capacity, return to work, mental health outcomes) Cost-effectiveness (e.g., incremental cost effectiveness ratios, quality-adjusted life years) Guidelines

Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies, economic evaluations, guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in **Table 1**, if they were duplicate publications, or if they were published prior to 2014. Additionally, a randomized controlled trial (RCT) or non-randomized study (NRS) was not eligible for our review if it had been included in one of the included systematic reviews (SRs). Guidelines with unclear development methodology were also excluded.

Critical Appraisal of Individual Studies

The included SRs and meta-analysis (MA) were critically appraised by one reviewer using the AMSTAR 2 tool,[10] RCTs and NRS were critically appraised using the Downs and Black Checklist,[11] the economic study was evaluated using the Drummond checklist,[12] and the evidence-based guidelines were assessed using 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 302 citations were identified in the literature search. Following screening of titles and abstracts, 263 citations were excluded and 39 potentially relevant reports from the electronic search were retrieved for full-text review. Five potentially relevant publications were retrieved from the grey literature search for full text review. Of these 44 potentially relevant articles, 32 publications were excluded for various reasons and 12 publications met the selection criteria and were included in this report. These comprised two SRs, one of which was reported in two publications,[14,15] and one of which also included a MA.[16] In addition, one RCT,[17] six NRS,[18-23] one economic evaluation,[24] and two evidence-based guidelines[2,3] were also included in this report. No health technology assessments were identified. Two additional RCTs[25,26] were identified as potentially relevant from the electronic search, but they were not included because they already were included in one of the SRs.[14,15] Appendix 1 presents the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) flowchart[27] of the study selection.

Summary of Study Characteristics

The body of evidence includes one SR,[14,15] one SR/MA,[16] one RCT,[17] and six NRS,[18-23] that address the clinical effectiveness of tiered or stepped care for chronic, non-malignant pain. One economic evaluation[24] was identified that was a cost-effectiveness analysis based on a SR, pair-wise MAs, and a mixed-treatment comparison (MTC). Lastly, two evidence-based guidelines[2,3] are included that provide recommendations to inform the use of tiered or stepped care approaches for the management of chronic, non-malignant pain. Study characteristics are summarized below. Additional details regarding the characteristics of the included publications are available in Appendix 2: Tables 2 to 5.

Study Design

Systematic reviews

For both the SR and SR/MA, comprehensive literature searches in two or more electronic bibliographic databases were performed in accordance with standard search methodology. In addition, existing SRs and reference lists of relevant publications were searched and consultations conducted with content experts. The date ranges covered by the searches were from 1996 to October 2016[14,15] and from 1990 to 2016 inclusive.[16] Both the SR and SR/MA reported findings in accordance with the PRISMA statement.[27] In addition, the SR and SR/MA included criteria for the inclusion of patient populations, interventions, comparators, outcomes, and study types. In addition, risk of bias was assessed in one SR[14,15] by applying Drug Effectiveness Review Project methods[28] to RCTs and the Cochrane Risk of Bias tool[29] to cohort studies, whereas the other SR/MA[16] used the Cochrane Risk of Bias tool[29] for all studies. The quality of the evidence was assessed in the SR[14,15] using the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Comparative Effectiveness Reviews[30] whereas in the other SR/MA,[16] the Grading of Recommendations Assessment, Development, and Evaluation (GRADE)[9] approach was used. The SR[14,15] included nine studies, of which eight were RCTs and one was a retrospective cohort study; however, only one RCT was relevant to this report. The SR/MA[16] included 20 studies, of which 19 were RCTs and one was a cluster RCT. Of these, four RCTs were relevant to this report. There was no overlap of studies between the SR and SR/MA. Further information about the characteristics of the included SR and SR/MA is available in Appendix 2: Table 2

Randomized Controlled Trial

The included RCT[17] was a prospective, open-label, single-centre study conducted at a university-based, late-life depression clinic. Patients with chronic low back pain (LBP) and depression entered into phase I where they received low dose venlafaxine with supportive management for six weeks, following which non-responders were randomized in phase II to the intervention and control groups for 10 weeks.

Non-Randomized Studies

A total of six NRS[18-23] were included. Two NRS[18,19] were retrospective comparative cohort studies. The first NRS[18] compared a 'pain cohort' treated according to a stepped-care model of pain management (SCM-PM) with a 'non-pain' cohort treated in an integrated Veteran's health system over the same 5-year period. The second NRS[19] was based on data from a single-payer military claims database where two cohorts of patients with MSK pain were compared. One NRS[20] was a retrospective chart review of 12 primary health centres that compared electronic health record data for one year prior to the implementation of a SCM-PM for chronic pain with data for one year following implementation. Another NRS[21] was a mixed-methods study that quantitatively followed a cohort of patients referred to a community MSK service that provided three tiers of care and also included qualitative information from focus groups exploring patients and physiotherapy clinicians' views regarding case complexity. The remaining two NRS[22,23] were both prospective observational cohort studies. One NRS[22] followed a single cohort of patients over six months who received stepped care for non-cardiac chest pain. The other NRS[23] compared a cohort of patients who received stepped-care strategy-consistent (SCS-consistent) care for hip or knee pain due to osteoarthritis with a cohort who received SCS-inconsistent care over two years. All studies had follow-up periods of one year unless otherwise stated.

Further information about the characteristics of the included RCT and six NRS is available in Appendix 2: Table 3.

Economic Evaluation

The one cost-effectiveness analysis[24] included in this report examined the relative cost-effectiveness of three levels of treatment for sciatica. The perspective was that of the UK National Health System and the time horizon was 12 months. A decision analytic tree model was constructed based on the results of a SR and pair-wise MAs, the latter which informed a MTC. Cost inputs were derived from expert opinion, the UK National Health System, and the British National Formulary. The main assumption was that patients would be managed through 1 of 3 pathways: primary care, stepped care, or immediate referral to surgery. Additional base-case assumptions were that there was no reduction in utility for previous unsuccessful treatments and that when individual therapies are combined in sequence, effectiveness would be as high as stand-alone treatments. Multiple sensitivity analyses were undertaken to address uncertainty in the modeling assumptions and inputs (e.g., best and worst case scenarios, utility values for symptoms and symptom remission, reductions in effectiveness of intermediate therapies and/or surgery, and utility achieved with symptom resolution only as a results of successive failures).[24] Additional details are available in Appendix 2: Table 8.

Guidelines

The two included evidence-based guidelines were developed by the Scottish Intercollegiate Guideline Network (SIGN)[3] and the National Institute for Health and Care Excellence (NICE)[2] in the UK. Evidence for both guidelines was derived from comprehensive literature searches of four or more electronic bibliographic databases. To assess and rate the quality of the evidence and make recommendations, the Short Life Working Group for Paediatric Pain used accredited SIGN methodology,[5] whereas a NICE multidisciplinary guideline development group used adapted GRADE methodology and standard NICE advice on making recommendations.[9,31] Both guidelines underwent public and peer validation processes. Further information on the characteristics of the included guidelines and levels of evidence considered is available in Appendix 2: Table 5.

Country of Origin and Year of Publication

The SR was from the US and was published in 2018;[14] however, it was also available earlier (2017) as a full report.[15] The SR/MA[16] was from Ireland and was published in 2017. The RCT[17] and two NRS[18,19] were all published in 2018 and were from the US. Two NRS[20,21] were published in 2016 and were from the US and the UK, respectively. The remaining two NRS[22,23] were published in 2015 and 2014, and were from the UK and the Netherlands, respectively. The economic evaluation[24] was published in 2014 and was from the UK. The SIGN guideline[3] was released in 2018 and the NICE guideline[2] in 2016 and were developed for use in Scotland and the UK, respectively.

Patient Population

Systematic Reviews

The patient populations in the SR and SR/MA[14-16] were similar as they both included adult patients with MSK pain treated on an outpatient basis; however, the SR[14,15] required that patients have chronic pain persistent for at least three months, whereas the SR/MA[16] required that the majority (≥ 80%) of patients be in paid employment but have not accrued more than three months of sickness absence from work in the previous year due to MSK

pain. The number of included patients in the SR/MA[16] (N = 16,319) was more than four times larger than in the other SR[14,15] (N = 3,816). The settings were also similar as the SR[14,15] included studies that were integrated within primary care and excluded interventions that occurred entirely within intensive pain rehabilitation, specialty, or tertiary care facilities whereas the SR/MA[16] included a variety of settings including hospital, community, and the workplace. Detailed information regarding the characteristics of the included patient populations in the SR and SR/MAs is available in Appendix 2: Table 2.

Randomized Controlled Trial

The patient population in the one included RCT[17] comprised older (≥ 60 years of age) adult patients with a diagnosis of depression and chronic LBP of at least moderate severity (i.e., score of ≥ 8 on a numerical rating scale of 0 to 20) for three months or more. Patients also had to have failed to maintain a sustained response to any physician-prescribed treatment for chronic LBP (e.g., prescription or over-the-counter analgesics, physical therapy, acupuncture, injection therapy, back surgery) and to be without symptoms of dementia. The inclusion criteria were selected to identify representative older primary care patients living with depression and chronic LBP who were assessed and treated at a single-centre university-based late-life depression research centre. In the randomized phase of the study, patients (N = 139) were required to be non-responders to low-dose venlafaxine (≤ 150 mg/day) and supportive management after an initial six week run-in phase.

Non-Randomized Studies

The patient populations in the six NRS represent a range of chronic pain conditions. In two NRS, inclusion criteria specified that adult patients (N = 31,286) had documentation of moderate to severe pain (i.e., evidenced by a rating of ≥ 4 on a numerical rating scale of 0 to 10)[18] or adult patients (N = 3,357 pre-implementation and N = 4,385 post-implementation) had chronic pain identified by a validated algorithm using available electronic health record data elements (e.g., diagnostic codes, pain scores, and prescribed medication) of any etiology.[20] In two NRS, adult patients with MSK pain were included, one study in which patients (N = 1,876) were seeking primary care for their MSK pain,[19] and the other in which patients (N = 484) were referred to a community MSK service offering tiered interventions.[21] One NRS included adult patients (N = 77) with non-cardiac chest pain occurring more than once per month referred to a chest pain clinic.[22] The remaining NRS included adult patients (N = 313) with hip or knee complaints due to symptomatic hip or knee osteoarthritis.[23] Two NRS were conducted at single centre specialty clinics[21,22] and four NRS included data from multicentre sites comprising an integrated Veteran's health system,[18] claims data from a single-payer military database,[19] multisite community primary health centres,[20] and from community-based general practitioners practicing within the same region.[23]

Additional details regarding the population characteristics of the patients in the RCT and each of the NRS are available in Appendix 2:Table 3.

Economic Evaluation

The patient population in the cost-effectiveness analysis[24] was based on a SR that included studies of adult patients with sciatica or lumbar nerve root pain diagnosed clinically or confirmed by imaging, with a requirement for leg pain to be worse than back pain (i.e., to distinguish sciatica from nonspecific LBP). To ensure consistency, the same population also formed the basis for the economic model.[24] The base-case analysis incorporated best-available assumptions and data derived from the SR with one-way sensitivity analyses

undertaken to evaluate the impact of changes in important assumptions and input parameter values.[24] No patient subgroup analyses were undertaken. Additional details regarding the population characteristics of the patients in the economic evaluation are available in Appendix 2: Table 4.

Guidelines

Both guidelines[2,3] are intended for use by healthcare providers, clinicians, and patients to guide chronic pain management. The NICE guideline[2] also indicated it can be used to develop standards and to assess clinical practice and assist in the education of healthcare practitioners and to improve communication between patients and healthcare practitioners. The specified target population for the SIGN guideline[3] is children and young people with chronic, non-malignant pain, whereas for the NICE guideline[2] it is patients (≥ 16 years of age) with LBP and sciatica. Additional details regarding the population characteristics of the patients in the economic evaluation are available in Appendix 2: Table 5.

Interventions and Comparators

Systematic Reviews

The intervention in the SR was defined *as "any model with system-based mechanisms aiming to increase the uptake and organization of multimodal care"* [14,15] (page S72)*,* which included stepped-care, among other modalities such as collaborative care, care management, integrated care, telecare, peer-delivered care, informal care-giving, and treatment algorithms. The comparator was any other type of care. In the SR/MA,[16] the intervention had to include two or more elements of the biopsychosocial model delivered as a coordinated or integrated program by a multidisciplinary team or a single healthcare professional or a physical (bio) component and at least one psychosocial element. For definitions of the physical (bio), psychological, and social/occupational elements considered, see Appendix 2: Table 2. Comparators consisted of usual care, wait-list, or active intervention arms.

Randomized Controlled Trial

The intervention in the one RCT[17] was problem solving therapy (i.e., a primary-care, depression-specific, stepwise approach to pain and depression management and behavioral activation) in combination with high-dose venlafaxine (defined as 300 mg per day or highest tolerable dose). The comparator was high-dose venlafaxine in combination with supportive management (i.e., reassurance to take medication despite mild but anxiety-provoking side effects, conveying a sense of hope and optimism, education, advice, and encouragement to express feelings of depression and frustration).

Non-randomized Studies

In two of the NRS,[18,20] the intervention was primary care delivered in accordance with the SCM-PM, which is a 3-step individualized approach for managing pain. The comparator in the first NRS[18] was primary care of all other patients treated over the same time period whereas the second NRS[20] did not have a comparator group. Similarly, another NRS[21] evaluated a community MSK service that provided three levels of care in a single cohort with no comparator group. For details of the SCM-PM and the community-based MSK service and levels of care provided, see Appendix 2: Table 3. In one NRS,[19] the intervention was manual therapy (i.e., hands-on movement of joints and/or soft tissues by a healthcare professional) compared with manual therapy plus opioid therapy. In another NRS,[22] the intervention was a stepped-care, biopsychosocial management program

comprising assessment only (medical therapy), low-intensity cognitive behavioral therapy (CBT) or high-intensity CBT. There was no comparator as this was a single cohort study. The remaining NRS[23] evaluated a cohort of patients who received care consistent with a multidisciplinary SCS comprised of three steps of increasing intensity of services (i.e., SCS-consistent) with a SCS-inconsistent cohort. For details of the SCS, see Appendix 2: Table 3.

Economic Evaluation

In the cost-effectiveness analysis,[24] the interventions and comparators were any treatments used for sciatica. Three levels of treatments were categorized according to the level of complexity (e.g., initial, intermediate, and invasive therapies) and compared in pair-wise MA followed by MTC analysis. For details of the various therapies included in each level, please see Appendix 2: Table 4.

Guidelines

The SIGN guideline[3] considered various aspects of pain management including assessment and planning of care, pharmacological management, physiotherapy, psychological therapies, surgical interventions, dietary therapies, and complementary and alternative therapies. The NICE guideline[2] encompasses risk assessment and risk stratification, imaging, self-management, exercise therapies, postural therapies, orthotics and appliances, manual therapies, acupuncture, electrotherapies, psychological interventions, pharmacological interventions, multidisciplinary biopsychosocial programs, and return to work programs.

Outcomes

Systematic Reviews

In the SR[14,15] the key outcome was clinical effectiveness which was defined as the percentages of patients obtaining reductions in pain intensity and pain-related function from baseline of at least 30% or greater. One RCT[9] included in the SR provided information on risk and complexity-matched treatment pathways. In this RCT[9] adult patients with LBP, who were assessed according to the STarT Back screening tool,[32] were randomized to stratified primary care management or non-stratified current best practice. The key outcome was the effect of the treatment on the Roland Morris Disability Questionnaire (RMDQ) score at 12 months (i.e., RMDQ scale 0 to 24; high scores indicate severe disability).[33] A within-in group change of 2.5 points in the RMDQ or change from baseline of 30% is generally considered to be clinically meaningful.[34,35] While other outcomes were identified a priori in the SR, depression, quality of life, anxiety, and satisfaction with care for the relevant RCT[9] were reported in the SR. In the SR/MA,[16] key outcomes identified a priori were duration of sick leave or time to return to work, of which only data for return to work could be synthesized by MA. In the SR/MA, the outcomes reported for stepped care models were return to work and sickness absence. For details pertaining to all the outcomes identified a priori for the SR and SR/MA, see Appendix 2: Table 2.

Randomized Controlled Trial

The primary outcome in the RCT[17] was the cumulative rate of response (defined as a composite score of ≤ 5 on the Patient Health Questionnaire-9 [PHQ-9] and at least a 30% reduction in pain from baseline measured on a numerical rating scale of 0 to 20) over time using Cox proportional hazard models adjusting for randomization strata (i.e., referral source and diagnosis of fibromyalgia). The analyses were repeated for pain and depression

as individual outcomes. In addition, back-related disability was assessed using the RDMQ and physical performance was evaluated using the Short Physical Performance Battery (SPPB) for which an increase of 0.5 points indicates clinically meaningful improvement.[36] Social problem solving ability to assess patients' ability to cope with stress was measured using the Social Problem Solving Index (SPSI) which yields scale scores for five component processes of problem solving. In the RCT, the total SPSI score and negative and positive-orientation subscales were used; however, no information was provided the magnitude of effect that was considered to be clinically relevant.

Non-Randomized Studies

The six NRS reported on a wide range of outcomes. Four NRS[18,19,22,23] reported on health care utilization (e.g., referrals, visits, services, prescription utilization, order and timing of care). One NRS[20] included outcomes pertaining to provider's knowledge and attitudes regarding pain management, quality of pain care, patient-reported pain scores, opioid prescribing, behavioral health, and pain referrals. Another NRS[21] reported on significant predictors of requiring complex care, as well as the views of patients and providers regarding case complexity. Two NRS[20,22] included patient-reported pain scores and three NRS[18-20] reported on opioid prescribing. One NRS[23] reported on pain and functional outcomes assessed with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) where standardized scores ranging from 0 to 100 were used, and for which higher scores reflect better health status.[37] The same NRS[23] also assessed self-efficacy and active pain coping using the Dutch General Self-Efficacy Scale[38] and Pain Coping Inventory.[8] Higher scores on the Dutch General Self-Efficacy Scale, ranging from 10 to 40, reflect higher self-efficacy.[38] Higher scores on the subscales for active coping, ranging from 12 to 48, indicate greater use of an active coping style.[8]

Economic Evaluation

In the cost-effectiveness analysis,[24] probabilities of success for individual treatments within each of three categories (initial, intermediate, and invasive therapies) were derived from the MTC analysis based on three main outcomes: global effect, reduction in pain intensity, and improvement in function. The mean cost, probability of success, and 12-month utility gains for all possible treatment strategies were reported. In turn, the incremental cost per patient with symptoms successfully resolved was reported for all treatment strategies that were not excluded on the grounds of strict or extended dominance (i.e., where the next regime was both more effective and less costly or whereby a regime had an incremental cost-effectiveness ratio that is higher than the next more effective regime, respectively). In addition, the incremental cost per utility gained over a 12-month period was also reported. The results of a series of sensitivity analyses were also reported where baseline estimates were adjusted to reflect best and worst case scenarios, utility values were adjusted for symptoms and symptom remission, potential for reductions in effectiveness of intermediate therapies and/or surgery in the stepped approach, and utility achieved with symptom resolution only as a result of successive failures).

Summary of Critical Appraisal

Detailed summaries regarding the strengths and limitations of the included SR and SR/MA, RCT, NRS, economic evaluation, and evidence-based guidelines are provided in Appendix 3: Tables 6 to 9.

Systematic Reviews

Both the SR and SR/MA[14-16] were conducted according to standard methodology and reporting requirements (e.g., PRISMA). A research question was stated and comprehensive literature searches of numerous electronic bibliographic databases and hand searches were conducted. Furthermore, the types of studies, selection criteria including population, intervention, comparator, and outcomes were clearly identified. Lists and characteristics of included studies were also provided; however, excluded studies were not identified in either the SR or SR/MA. The SR[14,15] was streamlined to meet a condensed timeframe which precluded a more exhaustive literature search being conducted in addition to undertaking sequential, rather than dual, review processes (e.g., study selection was performed by one reviewer and checked by another reviewer rather than both reviewers independently selecting studies for inclusion). In the case of disagreements; however, resolution was by consensus between the reviewers. No MA was conducted along with this SR.[14,15] In the SR/MA,[16] a number of potentially eligible studies were excluded because the authors were unable to make contact with the study authors to confirm that the trials met the selection criteria. The MA was limited by combining data from a range of MSK conditions; however, the majority of included trials in the SR (13 of 20 studies) were in LBP. Overall, the risk of bias was considered to be low and the quality of included studies to be fair to good (although three studies were considered of poor quality) in the SR.[14,15] Nonetheless, despite strong methodology in this SR, the strength of evidence was considered to be low because each intervention was supported by a single study with imprecise findings. In the SR/MA,[16] the risk of bias assessed according to GRADE[9] was considered to be low, although in some cases there was insufficient information to make a judgment. As with the other SR, despite strong methodology, the quality of the included studies and evidence overall was considered to be very low to moderate as per GRADE.[9] This was primarily due to risk of bias and imprecise results due to small sample sizes (e.g., only one RCT was rated as being of high quality).[16]

Randomized Controlled Trial

There were numerous strengths identified for the included RCT;[17] however, a major limitation was that assessors (i.e., clinicians with backgrounds in social work, psychology, education, and nursing) were not blinded to treatment allocation. The primary outcome was the cumulative proportion of patients responding over time with response defined as a composite score of PHQ-9 score ≤ 5 and at least a 30% reduction in pain numerical rating scale from baseline for depression and pain individually. Other outcomes were back-related disability measured with the RMDQ and social problem-solving assessed with the SPSI. As these instruments are based in large part on subjective elements, it is possible that since the assessors administered the instruments and were not blinded to the treatment, they could have rated patients in the intervention and control groups differently, thus resulting in significant performance and detection biases. Other important considerations are the limited generalizability of findings to other settings as the study was conducted at a single centre specialty clinic as well as the lack of a placebo control group, given the importance of placebo effects in trials of depression and pain interventions. According to the methodology for the RCT, adverse events were monitored, but were not reported nor was compliance with the intervention reported.

Non-Randomized Studies

Although various methodological strengths were identified, all six NRS[18-23] are subject to high risk of bias due to their study designs and lack of randomization which predisposes to

selection bias and the potential for unknown confounders to have influenced the treatment effect. Four NRS[18-21] were retrospective analyses and as such are limited by the quality of the data inputted in the past. Two NRS[21,22] were conducted at single centre specialty clinics which could limit the generalizability of findings to the general population of patients with chronic pain. In addition, two NRS[18,19] were conducted in selected populations (e.g., Veterans and military personnel) which could also limit generalizability to civilian populations if there are differences in access to, and provision of care. For all NRS, patient flow was not described, and both safety outcomes (e.g., adverse events) and compliance with the respective interventions or comparators (if applicable) were not reported.

Economic Evaluation

The included cost-effectiveness analysis[24] had a number of strengths, notably that the effectiveness data were based on a SR conducted according to standard methodology, that clinical- and cost-effectiveness studies were reviewed separately, and that MAs and a MTC were undertaken. Furthermore, a decision analytic model was developed and clearly presented and various sensitivity analyses were conducted to assess uncertainty in the modeling assumptions and inputs. Nonetheless, there were limitations such as the short time horizon (12 months) which precluded consideration of relapse and recurrence within the model, costs were presented only in aggregate form and were not discounted, and the majority of treatment strategies were excluded on the grounds of strict dominance.

Guidelines

The two included guidelines[2,3] were developed by well-recognized international health technology agencies (NICE and SIGN) with peer-reviewed, published methodology for guideline development.[5,31] As assessed using the AGREE II instrument,[13] the limitations identified with the NICE guideline[2] pertained to applicability (e.g., lack of addressing implementation issues and potential resource implications of putting the recommendations into practice). The SIGN guideline[3] also had limitations pertaining to applicability, but was also limited by a lack of detailed information on the strengths and limitations of the body of evidence considered in developing the recommendations. Furthermore, the process for linking evidence with the recommendations in the SIGN guideline and ultimately how the recommendations were formulated was unclear. For both guidelines, the majority of recommendations were based on expert consensus opinion due to evidence limitations.

Summary of Findings

The overall findings of this review are summarized below. Additional details are available in Appendix 4: Tables 10 to 13, in which the main study findings and author's conclusions are provided.

Clinical Effectiveness of Tiered or Stepped Care for Chronic Non-Malignant Pain

Pain Outcomes

The SR[14,15] included one RCT of fair quality that examined the clinical effectiveness of risk stratification coupled with risk-matched treatment pathways for the treatment of chronic MSK pain in primary care that is relevant to this review. A greater clinically significant improvement in pain intensity or pain function (≥ 30% decrease in RMDQ scores) with stepped care was reported when compared with non-stratified current best practice at 12 months..[14,15] The SR also reported that the best evidence of providing clinically relevant improvement in pain intensity and pain-related function was provided by decision support (e.g., algorithm-guided treatment and/or stepped care) coupled with proactive treatment

monitoring. This was based on evidence from five RCTs of fair to good quality (Number Needed to Treat: 4 to 13 over 12 months).[14,15] Overall, the evidence in the SR was judged to be low as each model was only supported by a single RCT with imprecise findings.[14,15] In the SR/MA,[16] although pain was included as an outcome, there was no consistent evidence that any of the intervention categories (including stepped care) had an effect on pain intensity above that of the comparison.

Three NRS[20,22,23] reported on other pain-related outcomes. A retrospective chart review of multiple primary health centres providing MSK pain care found that implementation of the SCM-PM was statistically significantly associated with improvements in provider's pain knowledge ($P = 0.001$) and pain care documentation ($P \leq 0.025$).[20] Another NRS[22] of patients with non-cardiac chest pain found that a stepped-care biopsychosocial approach was statistically significantly associated with reduced frequency of pain (i.e., 44% at baseline to 13% at three months and 7% at six months; $P < 0.001$). Chest pain interference was also significantly reduced by more than half at six months ($P < 0.001$). In a NRS[23] comparing SCS-consistent and SCS-inconsistent care for patients with pain due to hip or knee osteoarthritis, no statistically significant differences were found between cohorts, even after adjusting for potential confounders, as measured by WOMAC pain scores, self-efficacy scores, or active pain coping scores.

Return to Work and Sickness Absence

The SR/MA[16] that was conducted to determine the clinical effectiveness of early multidisciplinary interventions in promoting return to work and reducing work absence in adults with MSK pain concluded there was substantial uncertainty due to clinical heterogeneity and varying health and social insurance systems across the 20 included RCTs. Nonetheless, based on low quality evidence from four RCTs that are relevant to this review that examined the effects of stepped care at 12 months, it was reported that programs with a stepped-care approach were more effective in promoting return to work than comparators (e.g., treatment as usual and active interventions that did not meet the biopsychosocial criterion for an intervention in the SR). The corresponding hazard ratio (HR) was 1.29 (95% CI, 1.03 to 1.61); $P = 0.03$, $I^2 = 50\%$.[16] The SR also found limited effectiveness to support a difference in sickness absence rates due to very low quality evidence for stepped care approaches, as with the other interventions (e.g., back-to-school programs, case management, increased physical activity, or a psychosocial component), given the high statistical heterogeneity.

Disability and Functional Outcomes

In the SR/MA,[16] although disability was included as a outcome, there was no consistent evidence that any of the intervention categories (including stepped care) had an effect on disability above that of the comparator.

In the RCT[17] there were no statistically significant differences observed between groups (i.e., high-dose venlafaxine plus either problem solving therapy or supportive management) in physical performance scores measured by the SPPB and disability scores measured by the RMDQ at any of the post-randomization visits or after 12 months' follow-up. In one NRS, there were no statistically significant differences over two years between SCS-consistent and SCS-inconsistent care in physical function as measured by the WOMAC index.

Mental Health and Psychosocial Outcomes

The SR[14,15] reported that three included RCTs of fair to good quality demonstrated improvements on depression outcomes. Of these, one RCT[9] of fair quality had provided the sole evidence for the clinical-effectiveness of risk stratification coupled with risk-matched treatment pathways for the treatment of chronic MSK pain in the SR. Of note, while the intervention in the RCT (the STarT Back screening tool) was also associated with improved quality of life, it did not impact anxiety or satisfaction with care.[9]

The one included RCT[17] assessed cumulative rates of response as a composite outcome in older adults with LBP and depression. Response was defined as PHQ-9 score ≤ 5 and ≥ 30% reduction in pain numerical rating scale measured over two weeks). There was no statistically significant difference in response between patients who received high-dose venlafaxine and problem solving therapy compared with patients who received high-dose venlafaxine and supportive management.[17] There were also no significant differences in rate and time to initial response for depression and pain as independent outcomes, or in PHQ-9 scores, NRS pain scores, or RMDQ measures of pain and functional disability after 12 months' follow-up.[17] Patients in the high-dose venlafaxine plus problem solving therapy group did have greater improvement in the SPSI total score and greater decreases on the negative problem-solving subscale of the SPSI than patients who received high-dose venlafaxine plus supportive management.[17]

In one NRS[22] that evaluated a stepped care approach for non-cardiac chest pain, depression scores measured by the PHQ-9 and anxiety scores measured by the Generalized Anxiety Disorder-7 instrument were statistically significantly decreased from baseline at three and six months ($P < 0.05$). In addition, impact on daily life as measured by the WSAS significantly decreased from baseline at three and six months as well ($P < 0.001$).

Healthcare Utilization

The impact of stepped care approaches on healthcare utilization was reported in five NRS.[18-20,22,23] In a retrospective cohort analysis[18] based in an integrated Veteran's health system, the SCM-PM was associated with increased referrals by primary care providers for any consultations (e.g., 43.4% in Year 1 to 51.8% in Year 5; $P < 0.001$). The largest increases were in referrals to physiotherapy (14.8% to 27.4%) and occupational therapy (5.2% to 11.0%); both $P < 0.001$.[18] Similarly, patient visits for any reason increased from 27.9% (Year 1) to 37.3% (Year 5); $P < 0.0001$, with the largest increases being in visits for mental health (28.0% to 30.5%), clinical health psychology (4.7% to 7.2%), physiotherapy (16.2% to 22.9%), occupational therapy (5.6% to 10.0%), and chiropractic services (1.4% to 3.8%) which were all statistically significant.[18] In another NRS,[20] referrals from primary care providers to behavioral health providers increased from 24.3% to 29.1%; $P = 0.009$ and decreased from 19.9% to 15.8% for neurologic orthopedic surgery; $P < 0.001$ following implementation of the SCM-PM. Another NRS[19] that compared manual therapy alone with manual therapy plus opioids, found that mean 1-year costs in the manual therapy only group were statistically significantly lower than in the manual therapy plus opioids group; $P < 0.05$. Furthermore, in the manual therapy plus opioids group, mean 1-year costs were significantly lower in patients who received manual therapy first compared with patients who received opioids first.[19] Early manual therapy was associated with statistically significantly lower 1-year costs for total outpatient medical visits and costs as well as visits and costs specific to spine or shoulder pain.[19] The use of a stepped care approach was significantly associated with reductions from baseline in use of numerous healthcare resources (e.g.,

general practitioner, emergency department, cardiologist, appointments, consultations, etc.) at six months in patients with non-cardiac chest pain; $P < 0.05$.[22] In the NRS[23] comparing SCS-consistent and SCS-inconsistent care for patients with hip or knee osteoarthritis, it was shown that more patients in the SCS-consistent group received significantly more education, lifestyle advice, paracetamol, exercise therapy, dietary therapy, and significantly fewer intra-articular injections, than patients in the SCS-inconsistent group; all $P \leq 0.02$.

Prescription Drug Use

Three NRS[18-20] provided information on the effects of stepped care on prescription drug use, including opioid therapy. In one NRS,[18] long-term opioid therapy (> 90 days) decreased from 4.2% in Year 1 to 3.3% in Year 5 after implementation of the SCM-PM; $P < 0.0001$. On the other hand, non-opioid medication prescriptions increased from 36.7% (Year 1) to 39.8% (Year 5); $P < 0.0001$, which mainly reflected increases in topical analgesics (3.5% to 4.8%); non-steroidal anti-inflammatory drugs (15.7% to 19.3%); antidepressants (5.7% to 5.9%), and anticonvulsants (10.9% to 12.8%); all $P < 0.0058$.[18] In another NRS,[19] patients who received manual therapy first before opioid therapy for spine or shoulder pain had a significantly lower mean days supply of opioids (34.2 versus 70.9) and number of unique opioid prescriptions (3.1 versus 6.5); both $P < 0.001$ compared to patients who received opioids first. In another NRS,[20] there were no changes in opioid prescribing or chronic opioid therapy following implementation of the SCM-PM. In one SR[14,15] that had identified opioid doses as an outcome, no evaluation could be undertaken due to under-reporting of opioid use at baseline in the included studies.

Predictors of Complex Care

One NRS,[21] with both a quantitative and qualitative component (focus groups), evaluated predictors of requiring complex care. This was based on a sample of patients who had received treatment at a community-based adult MSK service delivering three levels of care: Tier 1: standard physiotherapy, Tier 2: complex care beyond the scope of standard physiotherapy, and Tier 3: Referral to Orthopedic Clinics.[21] Statistically significant predictors of requiring complex care were peripheral joint problems, unclear diagnosis (atypical presentation), and symptoms affecting sleep; $P < 0.05$.[21] These results supported some of the main themes that were raised at the focus groups.[21] The authors concluded that further studies are needed to evaluate if the predictive factors may be useful for development of a triage tool for use in MSK care.[21]

Cost-Effectiveness of Tiered or Stepped Care for Chronic, Non-Malignant Pain

One cost-effectiveness analysis[24] from the UK calculated the incremental cost per patient with symptoms successfully resolved and the incremental cost per utility gained for a patient with sciatica managed through one of three treatment pathways (i.e., primary care, stepped approach, or immediate referral to surgery) over a 12-month period. None of the strategies were 100% successful; however the most successful regime in the primary care pathway was non-opioids, whereas in the stepped approach pathway it was non-opioids, followed by biologic agents, epidural/nerve block, and disk surgery.[24] The third pathway of immediate surgery was not cost-effective.[24] Sensitivity analyses using the highest cost estimates resulted in similar results. In terms of positive net benefit, the stepped care approaches would be regarded as cost-effective if the ceiling ratio for an additional unit of utility gain over 12 months was less than £5100 and if the ceiling ratio for each additional success was less than £2500.[24] The authors cautioned that the findings remain tentative and that more research is required to develop more structurally appropriate economic models.[24]

Guidelines

The SIGN guideline[3] describes a pediatric pain treatment pathway with three levels of interventions as follows: Level 1: Family, Education, and Healthcare, Level 2: Secondary care: Gastroenterology, Neurology, Surgery, Pediatrics, Orthopedics, Rheumatology, and Pediatric Psychology, and Level 3: Pediatric Pain Clinic, Child and Mental Health Service, Multidisciplinary Team, and Rehabilitation Model. Specific recommendations are provided for the assessment and planning of care, pharmacologic management, physical therapies, psychological therapies, surgical therapies, dietary therapies, and complementary and alternative therapies as detailed in **Error! Reference source not found.**. These r ecommendations were developed using evidence of varying quality, ranging from very low quality (e.g., expert opinion) to high quality (e.g., well conducted MAs, SRs of RCTs, or RCTs with low risk of bias). The majority of recommendations were based on group consensus rather than on high-level evidence.

The NICE guideline[2] describes a treatment algorithm for chronic pain; however, most relevant to this review are the recommendations pertaining to risk assessment and risk stratification which are as follows: *"(1) Consider using risk stratification (e.g., the STarT Back risk assessment tool) at first point of contact with a healthcare professional for each new episode of LBP with or without sciatica to inform shared decision-making about stratified management. (2) Based on risk stratification, consider either simpler and less intensive support for people with LBP with or without sciatica likely to improve quickly and have a good outcome (for example, reassurance, advice to keep active and guidance on self-management) or more complex and intensive support for people with LBP with or without sciatica at higher risk of a poor outcome (e.g., exercise programs with or without manual therapy or using a psychological approach)."*[26] (page 18) These recommendations were based on evidence of low or very low quality, mainly due to risk of bias and sometimes due to imprecision. Due to the use of the word 'consider' in the recommendation, the guideline development group considered the recommendation to be weak.

Limitations

There are various limitations associated with the body of evidence reviewed for this report.

Although the included SR[14,15] and SR/MA[16] were methodologically strong, they included few primary studies that specifically addressed the clinical effectiveness of tiered or stepped care for chronic, non-malignant pain (i.e., one RCT of fair quality in the SR and four RCTs of low quality in the SR/MA). In addition, only one RCT[17] of low quality due to lack of assessor blinding to treatment allocation was identified for inclusion in this report. As a result, the majority of evidence is derived from NRS that are associated with a high risk of bias due to the non-randomized study design and potential for confounding effects.

There were many diverse outcomes identified for the assessment of clinical effectiveness and for the majority of these outcomes, the results were inconsistent. In addition, it would have been helpful to have more detailed descriptions given as at times the terminology for interventions considered to be tiered or stepped care was unclear, as well as for comparators which were typically identified as usual care, primary care, best care, or the standard of care. Lastly, there was a paucity of information regarding compliance with the intervention or comparator, quality of life, and potential unintended consequences of tiered or stepped care such as adverse effects on patient or provider satisfaction, time burden,

and sustainability. Although one SR[14,15] did include these unintended consequences as an outcome, there was insufficient evidence upon which to assess a treatment effect.

Chronic, non-malignant pain encompasses a wide range of medical conditions; however, the preponderance of evidence in this report was derived from studies of LBP, sciatica, or other MSK pain. In addition, with the exception of the SIGN guideline, all the identified studies pertained to adult patients so there is limited evidence regarding pediatric or adolescent patients. There were no Canadian studies identified for inclusion in this report, thus the evidence is derived from studies conducted mainly in the US or UK. Therefore, it is unclear how generalizable the results of these studies are to patients with pain of different etiology or to the Canadian setting. The latter is especially true with regard to the cost-effectiveness analysis or NRS reporting on healthcare utilization and prescription drug use. Similarly, the included evidence-based guidelines are from Scotland and the UK, and it is unclear how the recommendations would apply to Canadian clinical practice. In addition, the guidelines describe a model of tiered or stepped care or a treatment algorithm, respectively; however, they provide recommendations based on varying quality of evidence for the interventions delivered via the tiered or stepped care model, rather than recommendations on the tiered or stepped process itself. Overall, the quality of the body of evidence in this report is considered to be low; however, research gaps could potentially be addressed by more primary studies, preferably conducted in Canadian settings.

Conclusions and Implications for Decision or Policy Making

The current report summarizes the results of 12 publications, including one SR and one SR/MA,[14-16] one RCT,[17] six NRS,[18-23] one economic evaluation,[24] and two evidence-based guidelines.[2,3]

To address the research question of the clinical effectiveness of tiered or stepped care, evidence from the SR and SR/MA,[14-16] one RCT,[17] and six NRS[18-23] was considered. Limited evidence from one SR[14,15] that included a single RCT[9] of fair quality that was of relevance to the research question reported a greater clinically significant improvement in pain intensity or pain function (≥ 30% decrease in RMDQ scores) with stepped care when compared with non-stratified current best practice. In the SR/MA,[16] although pain was included as an outcome, there was no consistent evidence that stepped care had an effect on pain intensity that differed from the comparator. Of three NRS[20,22,23] that reported on other pain-related outcomes, two studies[20,22] found statistically significant benefits on pain or pain reporting with stepped care approaches, whereas the third study[23] found no differences from the comparator. In the SR/MA[16], based on low quality evidence from four RCTs, it was reported that stepped-care approaches were more effective in promoting return to work than comparators.[16] None of the included studies demonstrated a significant effect of tiered or stepped care on disability or functional outcomes. One SR[14,15] reported that three included RCTs of fair to good quality demonstrated improvements on depression outcomes by tiered or stepped care. A positive effect on mental health outcomes was also supported by a NRS[22] that evaluated a stepped care approach for non-cardiac chest pain as depression scores measured by the PHQ-9, anxiety scores measured by the Generalized Anxiety Disorder-7 instrument, and impact on daily life measured by the WSAS, were all statistically significantly decreased from baseline. In contrast, the one included RCT[17] in this report that assessed cumulative rates of response for depression and pain found that there was no statistically significant difference in response between patients on high-dose venlafaxine who received stepped care (problem solving therapy) as compared with supportive management. The impact of stepped care approaches on

healthcare utilization was reported in five NRS,[18-20,22,23] which taken together, generally support increased referrals from primary care providers to behavioral health providers and reduced referrals to specialty care, lower 1-year costs with manual therapy provided before opioid therapy, reduced use of healthcare resources such as general practitioners, emergency departments and specialist visits, and significantly different patterns of utilization of education, lifestyle, exercise, and dietary resources, etc. for patients treated according to a tiered or stepped care model. Three NRS[18-20] provided information on the effects of stepped care on prescription drug use, of which two studies[18,19] supported reductions in use of opioid therapy with stepped care (although this was compensated by an increase in non-opioid analgesic use) and one study[20] where no changes in opioid prescribing or chronic opioid therapy were observed following implementation of the SCM-PM. Overall, the diversity of outcomes used to quantify clinical effectiveness of tiered or stepped care, which were often inconsistent, creates uncertainty in the findings and so more research is needed to better inform and guide treatment decisions based on a tiered or stepped care approach.

One economic evaluation[24] from the UK was identified to address the research question pertaining to the cost-effectiveness of tiered or stepped care. The cost-effectiveness analysis was of moderate quality and calculated the incremental cost per patient with symptoms successfully resolved and the incremental cost per utility gained for a patient with sciatica managed through one of three treatment pathways. The analysis found that stepped care approaches based on initial treatment with non-opioids represent the most cost-effective regime relative to direct referral to disk surgery, with positive net benefit if the acceptable ceiling ratio for an additional unit of utility gain over 12 months was less than £5100 and if the ceiling ratio for each additional success was less than £2500.[24] Nonetheless, the findings remain tentative as the authors cautioned that more research is needed to develop more structurally appropriate economic models.[24]

Two evidence-based guidelines[2,3] were identified that were developed by well-recognized international health technology agencies. The SIGN guideline[3] describes a pediatric pain treatment pathway with three levels of interventions with specific recommendations based on evidence of very low to high quality for the assessment and planning of care, pharmacologic management, physical therapies, psychological therapies, surgical therapies, dietary therapies, and complementary and alternative therapies. The majority of recommendations were based on group consensus rather than on high-level evidence. The NICE guideline[2] describes a treatment algorithm for chronic pain and most relevant to this review are two specific recommendations pertaining to risk assessment and risk stratification and subsequent intensity of care. It should be noted that these recommendations were based on a single RCT[9] of fair quality and were considered to be weak by the guideline development group.

The findings of this report are in general agreement with those of a previous CADTH Rapid Response Report and Critical Appraisal on Multidisciplinary Treatment Programs for Patients with Chronic, Non-Malignant Pain.[8] The prior CADTH report concluded that while multidisciplinary management of chronic, non-malignant pain appears to be promising, the effect was modest and that statistically significant differences between multidisciplinary treatment and control treatment was not always observed for the various outcome measures that were evaluated.[8] Furthermore, the body of evidence was limited by the different types and varied definitions of multidisciplinary treatments and comparators used in the included studies which made comparisons difficult.[8] While no economic evaluations were identified in the previous CADTH report, this report includes one economic

evaluation[24] of moderate quality that suggests stepped care approaches are a cost-effective strategy compared with direct referral to surgery for management of sciatica.

Further research is required to validate and confirm the clinical effectiveness and cost-effectiveness of tiered or stepped care approaches for the management of patients with chronic, non-malignant pain, and particularly for patients with non-MSK or back pain. More primary studies are needed that specifically evaluate clearly described tiered or stepped care interventions and comparators, preferably conducted in a Canadian setting, to better inform treatment decisions and development of evidence-based guidelines pertaining to tiered or stepped care.

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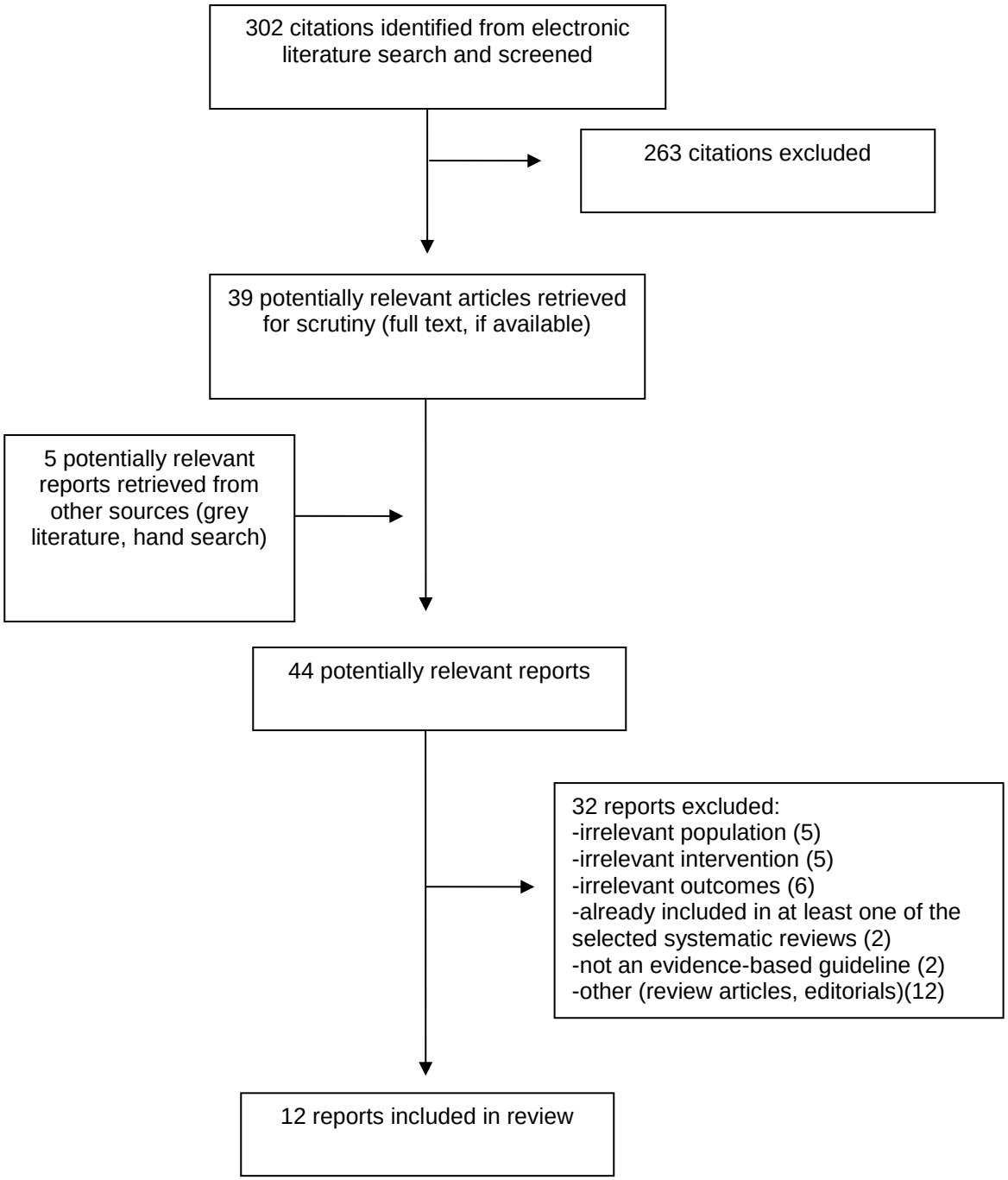
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Peterson, 2018[14,15] United States	Design: SRs, RCTs, or concurrently-controlled cohort studies. Included: 9 studies: 8 RCTs and 1 retrospective cohort study MEDLINE (Ovid) and CINAHL were searched from 1996 to October 2016 as well as various other sources (e.g., Cochrane Database of Systematic Reviews, AHRQ, Google Scholar, hand-searching reference lists and consultation with content experts).	Total patients: 3,816 adults with chronic MSK pain (persistent for ≥ 3 months) 1 RCT (N = 851) was relevant to this review Setting: Integrated within primary care; not to include interventions occurring entirely within intensive pain rehabilitation, specialty, or tertiary care	Intervention: Any model with system-based mechanisms aiming to increase the uptake and organization of multimodal care (e.g., collaborative care, care management, integrated care, telecare, peer-delivered care, informal care-giving, stepped care models, and algorithms Comparator: Any	Outcomes: -Effectiveness (percentages of patients obtaining reductions in pain intensity and pain-related function from BL of ≥ 30 or 50%, QoL, depression, anxiety, sleep, and opioid doses -Unintended consequences (adverse effects on patient satisfaction, provider satisfaction, time burden, sustainability) Follow-up: -Duration was 12 months in the majority of studies (range: 6 to 18 months)
Cochrane, 2017[16] Ireland	Design: RCTs, cluster randomized trials and quasi-RCTs. Included: 20 studies: 19 RCTs and 1 cluster RCT CENTRAL, MEDLINE, CINAHL, EMBASE, SCOPUS, PEDro, and OT seeker were searched between 1990 and 2016 inclusive as well as screening of existing SRs and reference lists of relevant articles. SR was conducted in accordance with the PRISMA statement.[39]	Total patients: 16,319 adults with MSK pain (e.g. back pain, shoulder/neck/forearm pain and knee pain) who met following criteria: -≥ 80% of the sample were in paid employment at time of recruitment -≤ 3 months of sickness absence from work, related to MSK pain, during the previous year -if the sample involved participants with longer periods of sick leave, the study was included if < 20% of the sample had ≥ 3 months' sick leave -Trials focused on patients with inflammatory conditions (e.g., RA, AS, etc.)	Intervention: - 2 or more different components from the biopsychosocial model delivered as an integrated program by a multidisciplinary team or a single HCP; OR a physical (bio-) component and ≥ 1 psychosocial element: -*Physical/bio* (participant was assessed by a HCP for causes of pain and received exercise/PT if indicated -*Psychological* (education, self-management training, coping with pain and unhelpful beliefs, counseling, and CBT -*Social/occupational* (workplace assessment and adaptations or	Outcomes: -Duration of sick leave -Time to return to work -Pain -Disability -Psychological functioning -QoL -Fatigue -Adverse effects Follow-up: -Short term (3 to 6 months) -Long-term (≥ 12 months)

First Author, Publication Year, Country	Study Designs and Numbers of Primary Studies Included	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
		were excluded -if mixed population and inflammatory conditions comprised < 10% of overall sample, the trial was included. 4 RCTs (N = 13,421) were relevant to this review Setting: Variety of settings including hospital, community and the workplace	barriers to work, development of communication and problem-solving skills) Comparator: -Usual treatment -Wait-list -Alternative active intervention arms	

AHRQ = Agency for Healthcare Research and Quality; AS = ankylosing spondylitis; BL = baseline; CBT = Cognitive Behavioral Therapy; HCP = health care professional; MA = meta-analysis; MSK = musculoskeletal; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses; PT = physiotherapy; QoL = quality of life; RA = rheumatoid arthritis; RCT = randomized controlled trial; SR = systematic review

Table 3: Characteristics of Included Primary Clinical Studies

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Randomized Controlled Trial				
Karp, 2018[17] United States	Prospective open-label RCT conducted at a single university-based late-life depression research centre Patients (N = 227) discontinued current pharmacotherapy and entered into Phase 1 where patients received venlafaxine (≤ 150 mg/day) with supportive management. After 6 weeks, responders were required to have 2 weeks of PHQ-9 score ≤ 5 and NRS for pain improvement of ≥ 30% from BL. Non-responders (N=139) progressed to Phase 2 and were randomized to intervention and	Inclusion criteria: Adults (≥ 60 years of age) with diagnosis of depression and chronic LBP more days than not of at least moderate severity (i.e., score of ≥ 8 on a NRS of 0 to 20) for ≥ 3 months and failure to maintain sustained response to any physician-prescribed treatment for chronic LBP, MMSE score ≥ 80, PHQ-9 score ≥ 10 Exclusion criteria: Medically emergent condition (e.g., vertebral fracture, infection, cancer), substance abuse, psychotic or bipolar spectrum disorders,	Intervention: Venlafaxine 300 mg/day or highest tolerable dose plus problem-solving therapy (i.e., stepwise approach to pain and depression management and behavioral activation) x 10 weeks (N = 68) Comparator: Venlafaxine 300 mg/day or highest tolerable dose plus supportive management x 10 weeks (N = 71)	Outcomes: -Cumulative rate of response -Back-related disability assessed with the RMDQ (MCID is improvement of 30%) -Physical performance assessed with the SPPB (MCID is an increase of 0.5 points) -Social problem-solving assessed with the SPSI (MCID not reported) -Adverse events Follow-up: 12 months

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	comparator treatment. Randomization was stratified by referral source (primary or other) and diagnosis of fibromyalgia (yes or no)	medical instability, wheelchair-bound, or involved in legal action related to chronic LBP		
Non-Randomized Clinical Trials				
Edmond, 2018[18] United States	Retrospective comparative cohort analysis based on EHR data conducted within an integrated Veterans health system comprising tertiary, inpatient, and outpatient facilities as well as community-based outpatient clinics Veterans in a 'pain cohort' with moderate to severe pain (i.e. pain intensity rating of ≥ 4 on a NRS of 0 to 10) were compared with all other veterans in a 'non-pain cohort' (i.e., no pain or intensity ratings of 1 to 3) that received primary care treatment over a 5-year period	Inclusion criteria: Veteran patients receiving primary care through an integrated Veterans health system who had ≥ 1 visit with a documented pain intensity rating of ≥ 4 (moderate to severe pain) over a 5-year period (July 2008 to June 2013) Exclusion criteria: None	Intervention: Primary care as per SCM-PM (3-step approach as follows) (N = 31,286): -*Step 1* (primary care provider identifies and discusses patient's pain concerns and develops a treatment plan based on self-management and primary care interventions) -*Step 2* (additional resources and collaboration such as behavioral health assessment, medication, consultation with specialists) -*Step 3* (Increased care and involvement from pain management team) Comparator: Primary care of 'non-pain cohort' (N = 157,561)	Outcomes: -Prescription data -Health care utilization (e.g., primary care visits, referrals, specialty pain care services) Follow-up: 5 years
Rhon, 2018[19] United States	Retrospective observational cohort based on claims data from a single-payer healthcare database for the US military	Inclusion criteria: Adult patients (18 to 65 years of age) seeking initial care for MSK spine or shoulder pain who received ≥ 1 visit for manual therapy. Exclusion criteria: NR	Intervention: Manual therapy only (i.e., hands-on movement of joints and/or soft tissues by HCP) (N = 714) Comparator: Manual therapy plus opioid therapy (N = 1,162)	Outcomes: -Healthcare utilization (e.g., medical costs and visits) -Order and timing of care in patients who received both manual therapy and opioids Follow-up: 1 year

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Anderson, 2016[20] United States	Retrospective chart review conducted across 12 primary health centres	Inclusion criteria: All primary care providers who were present during the 3-year implementation of the SCM-PM (March 2011 to February 2014) and adult patients with chronic pain under the care of the providers with ≥ 1 medical visit in the previous year Exclusion criteria: NR	Intervention: SCM-PM (3-step individualized approach to managing pain as described for Edmond, 2018[18]) (N = 25 primary care providers and N = 3,357 pre-intervention and N = 4,385 post-intervention patients) Comparator: NA	Outcomes: -Provider's knowledge and attitudes regarding pain management -Quality of pain care -Patient-reported pain scores -Opioid prescribing information -Behavioral health -Pain referrals Follow-up: 1 year prior to and after implementation
Comer, 2016[21] United Kingdom	Mixed methods study with quantitative analysis and qualitative focus groups based on a community MSK service 2 separate focus groups included N = 6 patients and N = 5 PT clinicians	Inclusion criteria: Patients who received a new MSK referral to tier 1 or tier 2 care over a 1-year period (April 2013 to March 2014) Exclusion criteria: Patients with referrals to allied services (e.g., domiciliary PT, podiatry service, spinal triage, community falls service) or who had not completed treatment or assessment in the MSK service	Intervention: Community MSK service providing 3 levels of care: -*Tier 1* (standard MSK PT) -*Tier 2* (more complex assessment and PT care with an extended role or MSK physicians) -*Tier 3* (secondary care orthopedic clinics) (N = 484 patients) Comparator: NA	Outcomes: -Significant predictors of requiring complex care after quantitative data analysis -Views of patients and physiotherapy clinicians regarding case complexity Follow-up: 1 year
Chambers, 2015[22] United Kingdom	Pilot prospective observational cohort study conducted at a single centre chest pain clinic	Inclusion criteria: Adult patients (18 to 80 years of age) with non-cardiac chest pain occurring more than once per month referred for care to clinic Exclusion criteria: NR	Intervention: Stepped care, biopsychosocial management program comprising: -Assessment only (medical therapy) -Low intensity CBT (guided self-help) -High intensity CBT (clinical psychologist) (N = 77) Comparator: NA	Outcomes: -Change in frequency and severity of chest pain -Negative beliefs about chest pain -Psychosocial scores -Healthcare resource utilization Follow-up: 6 months

First Author, Publication Year, Country	Study Design	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Smink, 2014[23] The Netherlands	Prospective observational cohort multicentre study Note: Care was considered "SCS-consistent" if all modalities of the previous steps of the SCS were offered to the patient before the advanced modalities of subsequent steps. If care was inconsistent with SCS, then it was considered "SCS-inconsistent".	Inclusion criteria: Adult patients (≥ 18 years of age) who visited their general practitioner for a new episode of hip or knee complaints due to symptomatic hip or knee osteoarthritis Exclusion criteria: Joint replacement of the hip or knee, being on the wait-list for a joint replacement, language barrier, or terminal illness	Intervention: SCS-consistent care as follows (N = 117): -*Step 1* (education, lifestyle advice, paracetamol, and glucosamine sulphate) -*Step 2* (physical therapy, dietary therapy if overweight, NSAIDs, and tramadol) -*Step 3* (multidisciplinary care, intra-articular injections, TENS) Comparator: SCS-inconsistent care (N = 163)	Outcomes: -Pain and physical function assessed by the WOMAC -Self-efficacy and active pain coping assessed with the Dutch General Self-Efficacy Scale and Pain Coping Inventory -Healthcare resource utilization Follow-up: 2 years

BL = baseline; LBP = low back pain; CBT = cognitive behavioral therapy; EHR = electronic health record; LBP = low back pain; MCID = minimal clinically important difference; MSK = musculoskeletal; MMSE = Mini Mental State Exam; NA = not applicable; NR = not reported; NRS = numerical rating scale; NSAIDs = non-steroidal anti-inflammatory drugs; PHQ-9 = Patient Health Questionnaire-9; PT = physiotherapy; RCT = randomized controlled trial; RMDQ = Roland Morris Disability Questionnaire; SCM-PM = Stepped Model of Pain Management; SCS = Stepped Care Strategy; SPPB = Short Physical Performance Battery; SPSI = Social Problem Solving Inventory; TENS = transcutaneous electrical nerve stimulation; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index

Table 4: Characteristics of Included Economic Evaluation

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
Fitzsimmons, 2014[24] United Kingdom	Type: Cost-effectiveness analysis Time Horizon: 12 months Perspective: UK NHS	To estimate the relative cost-effectiveness of treatment regimens for managing patients with sciatica	Adults with sciatica or lumbar nerve root pain diagnosed clinically or confirmed by imaging. A requirement was that leg pain was worse than back pain.	Any intervention or comparator used to treat sciatica. The following treatments were categorized and compared in pair-wise MAs followed by MTC analysis: -*Initial treatments:* Inactive control, usual care, education/ advice, activity restriction, alternative or	Decision analytic model 3 main outcomes: -*Global effect* (including absence of pain) -*Reduction in pain intensity* (via a continuous scale) -*Improved function*	Clinical effect estimates derived from a SR of clinical-effectiveness and cost-effectiveness Costs of managing patients based on expert opinion and published UK cost sources (2008-2009	Patients presenting with sciatica would be managed through 1 of 3 pathways: primary care, stepped approach, or immediate referral to surgery. Base-case assumptions were that there was no reduction in utility for

First Author, Publication Year, Country	Type of Analysis, Time Horizon, Perspective	Decision Problem	Population Characteristics	Intervention and Comparator(s)	Approach	Clinical and Cost Data Used in Analysis	Main Assumptions
				non-traditional (acupuncture), non-opioids, and opioids *-Intermediate treatments:* Manipulation, traction, passive PT, active PT, biological agents *-Invasive therapies:* Epidural/nerve block, disk surgery	(based on a composite condition-specific outcome measure as continuous data using WMD and standardized MD, respectively	prices). Drug costs were from BNF list prices. Non-traditional/ alternative therapies were based on published NHS reference costs	previous unsuccessful treatments and when individual therapies are combined in sequence, effectiveness will be as high as stand-alone treatments.

BNF = British National Formulary; MA = meta-analysis; MD = mean difference; MTC = mixed treatment comparison; NHS = National Health Service; PT = physiotherapy; SR = systematic review; UK = United Kingdom; WMD = weighted mean difference

Table 5: Characteristics of Included Guidelines

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
2018 SIGN Guideline: Management of Chronic Pain in Children and Young People[3]						
This guideline and pediatric pain pathway are intended for healthcare clinicians and patients to guide pain management. The target population is children and young people with chronic non-malignant pain.	Assessment and management of pain in children and young people Interventions include assessment and planning of care, pharmacological management, PT, psychological therapies, surgical interventions, dietary	Outcomes were not considered apriori, but were reported as part of the process of evaluating the evidence. Outcomes identified within these guidelines comprise a wide range of functionality, disability, pain intensity and	Key questions were developed using the PICO principle. Pre-defined SIGN search strategies[5] were used. A search of MEDLINE, EMBASE, CINAHL, PsycINFO, and the Cochrane database of	The quality of the evidence was assessed and graded according to accredited SIGN methodology.[5] <u>Levels of evidence</u>: 1++ (high quality MAs, SRs of RCTs, or RCTs with very low risk of bias	The Short Life Working Group for Paediatric Pain reviewed the evidence and made recommendations in keeping with SIGN methodology. The majority of recommendations were based on group consensus rather than high-grade evidence.	Consultation for the guideline was launched at the 2017 Scottish Pain Research Community 7th Annual Scientific Meeting and was sent to various organizations for comment. It was also freely available for comment through

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
	therapies, and complementary and alternative therapies.	other pain scores, psychological symptoms (e.g., depression, anxiety), cognitive, school, and social functioning, as well as AEs outcomes.	SRs was conducted for SRs (to July 14, 2015) and primary literature (to January 18, 2016).	1+ (well conducted MAs, SRs of RCTs, or RCTs with low risk of bias) 1- (MAs, SRs of RCTs, or RCTs with a high risk of bias) 2++ (high quality SRs of case control or cohort studies, high quality case control or cohort studies with very low risk of confounding or bias and a high probability the relationship is causal 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) 2- (case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal 3 (non-analytic studies e.g., case reports,		www.sign.ac.uk

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
				case series) 4 (expert opinion)		
2016 NICE Guideline: Low Back Pain and Sciatica in Over 16s: Assessment and Management[2]						
This guideline and algorithm are intended for use by HCP involved in the treatment and care of patients with LBP and sciatica. It can be used to develop standards to assess clinical practice of HCPs, in the education of HCPs, to help patients make informed decisions, and to improve communication between patient and HCP.	Assessment and management of LBP and sciatica in patients ≥ 16 years of age. Interventions include risk assessment and stratification, imaging, self-management, exercise therapies, postural therapies, orthotics and appliances, manual therapies, acupuncture, electrotherapies, psychological interventions, pharmacological interventions, multidisciplinary biopsychosocial programs, and return to work programs.	Numerous outcomes were identified for each of the review questions comprising HRQL, morbidity, pain severity, function, disability, prognostic risk, psychologic distress, healthcare utilization, adverse effects, and many others detailed within the guideline.	Key questions were developed using the PICO principle and the guideline was developed in accordance with NICE guideline methodology.[31] Systematic clinical literature searches of MEDLINE, EMBASE, the Cochrane Library, CINAHL, PsycINFO, and AMED were conducted up to December 15, 2015 Systematic economic literature searches of MEDLINE (Ovid), EMBASE (Ovid), NHS EED, HTA and HEED were conducted up to December 15, 2015.	Evidence was evaluated and presented using an adaptation of the GRADE toolbox[9] that included risk of bias, indirectness, inconsistency, imprecision, publication bias, and other issues. Overall quality was graded as: -High (further research is very unlikely to change confidence in the estimate of effect) -Moderate (further research is likely to have an important impact on confidence in the estimate of effect and may change the estimate) -Low (further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to	A multidisciplinary guideline development group made consensus-based recommendations following review of evidence tables, summaries of clinical and economic evidence and quality, forest plots, and methods of the CEA undertaken for the guideline. The group considered the 'strength' of each recommendation and factors for wording of recommendations based on actions HCPs need to take, information readers want to know, strength of the recommendation, involvement of patients in decisions on treatment and care and consistency with NICE's standard advice on recommendations.[31]	The guideline was subject to a 6-week public consultation and feedback as part of the quality assurance and peer review of the guideline.

Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
				change the estimate) -Very low (any estimate of effect is uncertain)		

AE = adverse events; EED = Economic Evaluations Database; GRADE = Grading of Recommendations Assessment Development and Evaluation; HEED = Health Economic Evaluation Database; HTA = health technology assessment; NICE = National Institute for Health and Care Excellence; NHS = National Health Service; PT= physiotherapy; SIGN = Scottish Intercollegiate Guideline Network

Appendix 3: Critical Appraisal of Included Publications

Table 6: Strengths and Limitations of Systematic Reviews and Meta-Analyses using the AMSTAR 2 Checklist[10]

Strengths	Limitations
Peterson, 2018[14,15]	
-Research questions and inclusion criteria included PICO components -A comprehensive literature search was conducted. MEDLINE (Ovid) and CINAHL were searched from 1996 to October 2016 as well as numerous other sources (e.g., Cochrane Database of Systematic Reviews, AHRQ, CADTH, Google Scholar, hand-searching reference lists and consultation with content experts) -The review was conducted in accordance with the PRISMA statement -The review was guided by AHRQ systematic review methods but was streamlined to meet a condensed timeframe -Study selection was performed by one reviewer and checked by another reviewer -Data abstraction and internal validity ratings were completed by one reviewer and checked by another reviewer -Disagreements between reviewers were resolved by consensus -An explanation for the selection of study design was provided -Pre-defined criteria were used to rate the internal validity of all studies: the Drug Effectiveness Review Project methods was used for RCTs and the Cochrane Risk of Bias tool was used for cohort studies -A list of the included studies was provided (i.e., 8 RCTs and 1 retrospective cohort study were included) -Most studies were of fair or good quality; however, 3 studies were considered of poor quality -Characteristics of the included study were provided -The overall risk of bias was generally considered to be low -The strength of the evidence was graded based on the AHRQ Methods Guide for Comparative Effectiveness Reviews which incorporates 5 domains: risk of bias, consistency, directness, precision of the evidence, and reporting biases -Strength of evidence ratings were completed by one reviewer and checked by another reviewer -Despite strong methodology, the strength of the evidence was generally considered to be low because each intervention was supported by a single study with imprecise findings -Conflict of interest declaration was included -Source of funding for the systematic review was disclosed	-Although an extensive literature search was conducted, it is possible that some eligible trials were not identified (i.e., the search was limited to publications since 1996) -Limitations among fair quality included studies were > 20% attrition and baseline differences in potential prognostic factors whereas poor quality studies had high levels of exclusions (34% to 47%) from analyses. -Generalizability of the findings of the review may be limited due to most included studies consisting of samples from single centres and under-reporting of key patient characteristics such as pain duration, opioid use at baseline, and prevalence of common medical and mental health comorbidities -The assessment of intervention fidelity was generally limited in most studies -The potential confounding effects of co-interventions was largely unknown due to limited data available -The comparator group was typically 'usual care' but in most studies was minimally described as regular access to primary and specialty care -Although statistically significant differences were reported for pain and QoL outcomes, there was uncertainty regarding the clinical relevance of the reported benefits and lack of reporting on other important outcomes (e.g., depression, anxiety, sleep) -To meet shortened timelines, the review methods were impacted by precluding a more exhaustive literature search be conducted, the use of sequential (rather than dual independent) review processes, and the scope (focus on primary care) as this limits the applicability of the findings to a broader range of specialty settings -No meta-analyses of the data were conducted -A list of excluded studies was not provided
Cochrane, 2017[16]	
-Research questions and inclusion criteria included PICO components -A comprehensive literature search was conducted. CENTRAL, MEDLINE, CINAHL, EMBASE, SCOPUS, PEDro, and OT seeker were searched between 1990 and 2016 inclusive as well as screening of existing SRs and reference lists of relevant	-Although an extensive literature search was conducted, it is possible that some eligible trials were not identified (i.e., the search was limited to publications since 1990) -A number of potentially eligible studies were omitted from the review as the authors were unable to make contact with the authors of the studies to confirm that the trials met the inclusion

Strengths	Limitations
articles. -The review was conducted in accordance with the PRISMA statement -Study selection, risk of bias assessment, quality assessment, and data extraction was performed independently by two reviewers -Disagreements between reviewers were resolved by consensus -Risk of bias assessment was done in accordance with Cochrane guidelines: the six main domains of the risk of bias tool and the following other potential sources of bias were assessed: (1) baseline comparability of groups; (2) compliance with intervention; and (3) use of co-interventions. Each item was judged separately as being at high, low, or unclear risk of bias.17 Studies were assigned a low quality (low risk of bias on four or less items); moderate quality (low risk of bias on 5–7 items) or high quality rating (low risk of bias on eight or more items). -Quality of the evidence was assessed using GRADE criteria for each of the following parameters: risk of bias, inconsistency, imprecision, indirectness, and publication bias. A rating of high quality was down-graded by one level for serious concerns and by two levels for very serious concerns -A list of the included studies was provided (i.e., 19 RCTs and 1 cluster RCT were included) -The included studies were judged to be at low risk of bias although in some cases there was insufficient information to make a judgment -Characteristics of the included studies were provided -According to GRADE, the evidence was of very low to moderate quality primarily due to risk of bias and imprecise results due to small sample size; only 1 RCT was rated as being of high quality -Meta-analysis was conducted where the homogeneity was sufficient in terms of the main components of the intervention, outcome domains, and follow-up time point -Conflict of interest declaration was included -Source of funding for the systematic review was disclosed	criteria -Lack of detail and consistency in reporting protocols and procedures and lack of agreement on defining terms such as return to work and a core set of outcomes -Few studies provided adequate information relating to how treatment fidelity, compliance with the intervention, and use of additional healthcare resources or co-interventions were monitored. -Limited information on the methodology used to conduct the meta-analysis was provided -The definition of 'biopsychosocial' interventions was relatively broad which resulted in considerable variation in the active components included in the trials and led the authors to decide which studies could be pooled in the meta-analysis based determination of sufficient clinical homogeneity which is subjective -The meta-analysis is also limited by combining data from a range of musculoskeletal conditions although 13 RCTs were of low back pain -Planned subgroup analyses could not be conducted due to lack of baseline information and the small number of trials within each intervention category -A list of excluded studies was not provided

AHRQ = Agency for Healthcare Research and Quality; CADTH = Canadian Agency for Drugs and Technologies in Health; GRADE = Grading of Recommendations Assessment Development and Evaluation; PICO = Population, Intervention, Comparators, Outcome; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-analyses; QoL = quality of life; RCT = randomized controlled trial; SR = systematic review

Table 7: Strengths and Limitations of Clinical Studies using the Downs and Black Checklist[40]

Strengths	Limitations
Karp, 2018[17]	
-Objectives of the study were clearly described -Inclusion and exclusion criteria were reported -Baseline demographic and clinical patient characteristics were clearly presented -The intervention, comparator, and main outcomes of the study were clearly described in the methods section	-Certified assessors (clinicians with backgrounds in social work, psychology, education and nursing) were not blinded to treatment allocation and no attempt was made to blind those measuring the main outcomes so an important limitation is the potential for confounders -Single centre RCT so the results may not be generalizable to

Strengths	Limitations
-MCID estimates for key outcomes were provided -Study patients in the intervention and comparator groups were recruited from the same population, using the same inclusion criteria, over the same time period -Study patients were randomized to treatment in phase 2 of the study -Patient flow was described -Appropriate measures of random variability were reported -Main findings were clearly described -Appropriate statistical tests were used to assess the study outcomes -Actual probability values were reported -AEs were monitored	other settings -The study setting (university-based late-life depression centre) was a specialty clinic so it is uncertain if this is representative of the treatment that the majority of patients would receive -Small sample size (N = 139) -A placebo control was not included in the study, which is a limitation given the importance of placebo effects in trials of depression and pain interventions -Characteristics of patients lost to follow-up were not described -Compliance with the intervention was not reported -Although AEs were monitored they were not reported in the study
Edmond, 2018[18]	
-Objectives of the study were clearly described -The intervention, comparator, and main outcomes of the study were clearly described in the methods section -Study patients in the intervention and comparator groups were extracted from the same population over the same time period -Large sample size (N = 31,286 in pain cohort) -Baseline demographic and clinical patient characteristics were clearly presented -Appropriate measures of random variability were reported -Main findings were clearly described -Appropriate statistical tests were used to assess the study outcomes -Actual probability values were reported -The study setting was appropriate (i.e., integrated system of care including various outpatient facilities and community-based outpatient clinics)	- Retrospective comparative cohort analysis -Inclusion and exclusion criteria were not specified a priori -Study patients were not randomized to treatment so an important limitation is the potential for confounders -Study personnel were not blinded to treatment allocation -Patient flow was not described -Compliance with the intervention was not reported -AEs were not reported -The definition of the 'pain cohort' (i.e., veterans reporting moderate to severe pain during at least one outpatient primary care visit) did not distinguish between acute versus chronic pain, did not include veterans with pain of mild intensity, and did not provide information on pain-related diagnoses
Rhon, 2018[19]	
-Objectives of the study were clearly described -Inclusion and exclusion criteria were reported -The intervention, comparator, and main outcomes of the study were clearly described in the methods section -Study patients in the intervention and comparator groups were extracted from the same population over the same time period -Large sample size (N = 1,876) -Baseline demographic and clinical patient characteristics were clearly presented -Adjustments were made for baseline demographic variables and comorbidites that were different between groups by including them as covariates in the generalized linear models used to compare data -Appropriate measures of random variability were reported -Main findings were clearly described -Appropriate statistical tests were used to assess the study outcomes -Actual probability values were reported -The study setting was appropriate (i.e., healthcare claims database for all beneficiaries in the closed, single-payer US Military Health System)	- Retrospective observational cohort study -Study patients were not randomized to treatment so an important limitation is the potential for confounders -Study personnel were not blinded to treatment allocation -Patient flow was not described -Compliance with the intervention was not reported -AEs were not reported -Costs of care and care patterns within the military system may differ from those in civilian facilities, although the study did include the actual reimbursed cost of care for all procedures conducted in civilian hospitals by the military personnel included in the study sample—nonetheless, the results may not be generalizable to other settings -Results rely heavily on the interpretation of the researchers and there may have been other confounding variables that could not be accounted for in the statistical models -Utilization or timing of other interventions were not assessed in the study and could have influenced the differences seen -Reporting on the duration of symptoms and chronicity of the problem would have assisted with interpretation of the results but these data were not available given the nature of the data -Quality of the data in the database is limited by the quality by

Strengths	Limitations
	which it was entered in by clinicians -Compliance with treatment was not reported -AEs were not reported
Anderson, 2016[20]	
-Objectives of the study were clearly described -Inclusion criteria were reported (i.e., a validated identification algorithm was used to identify patients with chronic pain rather than relying on specific diagnoses) -The intervention, comparator, and main outcomes of the study were clearly described in the methods section -Study patients in the intervention and comparator groups were extracted from the same population over the same time period -Large patient sample size (N = 3,357 pre-intervention and N = 4,385 post-intervention) -Baseline demographic patient characteristics were clearly presented -Appropriate measures of random variability were reported -Main findings were clearly described -Appropriate statistical tests were used to assess the study outcomes -Actual probability values were reported -The study setting was appropriate (i.e., 12 primary care health centres)	-Retrospective chart review -Study patients were not randomized to treatment so an important limitation is the potential for confounders -Selected population of patients as were cared for by 25 primary care providers within the primary health centres so the results may not be generalizable to other settings -Study personnel were not blinded to treatment allocation -Small sample size of primary care providers (N = 25) which was limited by provider turnover over the 3-year period which ranged from 11% to 20% -Patient flow was not described -Compliance with the intervention was not reported -AEs were not reported -Outcomes were focused on process measures and did not include other measures of patient outcomes other than pain scores -Interventions were introduced in phases over the 3-year period which limited the ability to evaluate the impact of any one element of the intervention
Comer, 2016[21]	
-Objectives of the study were clearly described -The authors' definition of complex care was clearly described in the methods section -Baseline demographic and clinical patient characteristics were clearly presented -Appropriate measures of random variability were reported -Main findings were clearly described -Appropriate statistical tests were used to assess the study outcomes -Actual probability values were reported -Quantitative findings were largely supported by qualitative evidence from focus groups -The study setting was appropriate (i.e., a community MSK service that receives approximately 30,000 adult patient referrals per year and delivers tier 1 and tier 2 services and acts as a triage centre for tier 3 referrals	-No prior hypothesis was stated and a large number of potential predictors were evaluated therefore results can only be considered to be exploratory -Retrospective analysis (mixed-methods study) -Single centre study so the findings may not be generalizable to other settings -Study personnel were not blinded to treatment allocation so an important limitation is the potential for confounders -No inclusion or exclusion criteria were stated, rather data was extracted from a random sample of patients who had received treatment for MSK conditions -Main study outcomes were not clearly described in the methods section -Study patients were not randomized to treatment -No specific intervention or comparator was included as the aim of the study was to identify factors that are predictors of complex care that may be relevant when designing a triage tool and so were not identified a priori -Factors such as psychosocial issues, beliefs and expectations, access to care, integration of care may be important predictors of requiring complex care but the associations were limited by the statistical power of the study and lack of data availability -Compliance was not reported -Potential selection bias associated with focus group participants -AEs were not reported -Sensitivity of the multivariable models was low

Strengths	Limitations
Chambers, 2015[22]	
-Objectives of the study were clearly described -Prospectively designed study -Inclusion and exclusion criteria were reported -Baseline demographic and clinical patient characteristics were clearly presented -The intervention and main outcomes of the study were clearly described in the methods section -Study patients in the cohort groups were recruited from the same population, using the same inclusion criteria, over the same time period -Appropriate measures of random variability were reported -Main findings were clearly described -Appropriate statistical tests were used to assess the study outcomes -AEs were monitored	-Pilot observational cohort study -Study patients were not randomized to treatment so an important limitation is the potential for confounders -Single centre study so findings may not be generalizable to other settings -Study personnel were not blinded to treatment allocation so an important limitation is the potential for confounders -Small sample size (N = 77) -Selected population based on referrals to a specialty clinic so may not be representative of care available to the patient population -Patient flow was not reported -Length of treatment was not standardized so patients could have received treatment over different lengths of time (e.g., 3 months versus 6 months) -Actual probabilities were not reported (i.e., only as $P < 0.05$ or $P < 0.001$) -Compliance with treatment was not reported -AEs were not reported
Smink, 2014[23]	
-Objectives of the study were clearly described -Prospectively designed study -Inclusion and exclusion criteria were reported in the methods section -The intervention, comparator, and main outcomes of the study were clearly described in the methods section -Study patients in the intervention and comparator groups were extracted from the same population over the same time period -Baseline demographic and clinical patient characteristics were clearly presented -Appropriate measures of random variability were reported -Main findings were clearly described -Appropriate statistical tests were used to assess the study outcomes -Actual probability values were reported -The study setting was appropriate (i.e., multicentre primary care general practices)	-Observational cohort study -Study patients were not randomized to treatment so an important limitation is the potential for confounders -Study personnel were not blinded to treatment allocation -Statistically significant baseline imbalances were detected between the cohorts (but were adjusted for in the analyses) -Only Dutch-speakers were enrolled in the study; therefore, cultural factors could have affected the study results and the findings may not be generalizable to other cultures -Reasons for SCS-inconsistent care were not explored (e.g., an exercise program may not be feasible for patients with cardiovascular disease, insufficient health insurance may have precluded access to some recommended services) -Time-frame (2 years) may have been too short to detect differences in study outcomes (e.g., change in physical function in patient with osteoarthritis) -Patient flow was not reported -Compliance with treatment was not reported -AEs were not reported

AE= adverse event; MCID = minimal clinically important difference; MSK = musculoskeletal

Table 8: Strengths and Limitations of Economic Studies using the Drummond Checklist[12]

Strengths	Limitations
Fitzsimmons, 2014[24]	
-Research question and objective of the cost-effectiveness analysis were clearly stated and justified -The perspective or viewpoint (UK NHS) was clearly stated -The time horizon (12-months) was clearly stated -The source of the effectiveness data was clearly stated and	-The majority of treatment strategies were excluded on the grounds of strict dominance (where the next regime was both more effective and less costly) and by extended dominance (where a regime has an ICER that is higher than the next more effective regime)

Strengths	Limitations
was based on a systematic review undertaken according to the methodology reported in the Centre for Reviews and Dissemination report and the Cochrane Handbook for Systemic Reviews of Interventions -Clinical-effectiveness and cost-effectiveness studies were reviewed separately -Alternatives being compared were clearly described and pair-wise meta-analyses were initially conducted followed by a MTC analysis to enable the simultaneous comparison of all treatment modalities -A decision-analytic model was developed and clearly described and details about the model were provided -Multiple sensitivity analyses were undertaken to address uncertainty in the modeling assumptions and inputs (e.g., best and worst case scenarios, utility values for symptoms and symptom remission, reductions in effectiveness of intermediate therapies and/or surgery, and utility achieved with symptom resolution only as a results of successive failures) -The answer to the study question was provided and conclusions based on the data reported were clearly stated	-The modeled time horizon was limited to 12 months with no evidence to inform the inclusion of relapse and recurrence within the model -The perspective of the UK NHS does not allow consideration of issues relating to work and productivity and preferences of patients for symptom resolution and treatment duration -Lack of personal social services perspective -Currency and costs were reported in British pounds sterling (£) -Costs associated with disk surgery were not included -In the MTC there were a small number of relevant studies for some comparisons, statistical heterogeneity and potential inconsistency for some interventions (e.g., biological agents) -Quantities of the resources used were not reported separately from their unit costs -Costs were presented only in aggregated form (i.e., overall cost of treatment) and not in disaggregated form -Costs were not discounted and no explanation was provided -Currency (£) was not adjusted for inflation

MTC = mixed treatment comparison; UK NHS = United Kingdom National Health System

Table 9: Strengths and Limitations of Guidelines using AGREE II[13]

Item	Guideline	
	SIGN Chronic Pain in Children and Young People, 2018[3]	NICE Low Back Pain and Sciatica, 2016[2]
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	✓	✓
2. The health question(s) covered by the guideline is (are) specifically described.	✓	✓
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	✓	✓
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	✓	✓
5. The views and preferences of the target population (patients, public, etc.) have been sought.	✓	✓
6. The target users of the guideline are clearly defined.	✓	✓
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	✓	✓
8. The criteria for selecting the evidence are clearly described.	✓	✓
9. The strengths and limitations of the body of evidence	X	✓

Item	Guideline	
	SIGN Chronic Pain in Children and Young People, 2018[3]	NICE Low Back Pain and Sciatica, 2016[2]
are clearly described.		
10. The methods for formulating the recommendations are clearly described.	X	✓
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	X	✓
12. There is an explicit link between the recommendations and the supporting evidence.	X	✓
13. The guideline has been externally reviewed by experts prior to its publication.	✓	✓
14. A procedure for updating the guideline is provided.	X	✓
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	✓	✓
16. The different options for management of the condition or health issue are clearly presented.	✓	✓
17. Key recommendations are easily identifiable.	✓	✓
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	X	X
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	X	X
20. The potential resource implications of applying the recommendations have been considered.	X	✓
21. The guideline presents monitoring and/or auditing criteria.	X	X
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	✓	✓
23. Competing interests of guideline development group members have been recorded and addressed.	X	✓

AGREE = Appraisal of Guidelines for Research and Evaluation II; NICE = National Institute for Health and Care Excellence; SIGN = Scottish Intercollegiate Guideline Network

Appendix 4: Main Study Findings and Authors' Conclusions

Table 10: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Peterson, 2018[14,15]	
Included 9 models of multimodal chronic pain care (mainly back pain) from 8 RCTs and 1 retrospective cohort study (N = 3,816), primarily from the USA, of fair or good quality -Most interventions were compared to usual care (i.e., regular access to primary and specialty care) -Risk stratification coupled with risk-matched treatment pathways using the STarT Back screening tool for back pain in 1 RCT[9] (N = 851) demonstrated greater clinically significant improvement in pain intensity or pain-related function (≥ 30% decrease in RMDQ scores) as well as depression and QoL at 12 months than non-stratified current best practice, but did not impact anxiety or satisfaction with care - 5 models (ESCAPE,[25] SEACAP,[41,42] STarT Back,[9] SCAMP,[43] and SCOPE[26]) that included algorithm-guided treatment, stepped- care analgesic optimization, or decision support based on risk stratification from prognostic screening and matched treatment pathways with pro-active ongoing treatment monitoring provided the best evidence of improvement in pain intensity and pain-related function (NNT range: 4 to 13) over 12 months and variable improvements in QoL, depression, anxiety, and sleep -strength of evidence was generally low as each model was only supported by a single RCT with imprecise findings	The authors concluded that *"Five models primarily coupling a decision-support component—most commonly algorithm-guided treatment and/or stepped care—with proactive ongoing treatment monitoring have the best evidence from good-quality RCTs of providing clinically relevant improvement in pain intensity and pain-related function over 9 to 12 months, as well as variable improvement in other important core outcomes. National health care systems may be encouraged to consider wider implementation of any of those models with a clear plan for further evidence development to addresses shortcomings of previous research."*[14] (page S80)
Cochrane, 2017[16]	
Included 19 RCTs and 1 cluster RCT (N = 16,319), primarily from Europe, with interventions pooled according to main components for meta-analysis -according to GRADE assessment, the evidence was of very low to moderate quality owing to risk of bias and imprecise results due to small sample size - low quality evidence based on 4 RCTs and 12 months' follow-up suggests that programs with a stepped care approach were more effective in promoting return to work than comparators (treatment as usual and active interventions that did not meet the biopsychosocial criterion for an intervention) (HR: 1.29 [95% CI: 1.03; 1.61]; *P* = 0.03) -analyses suggested limited effectiveness in reducing sickness absences, pain reduction, or functional improvement across the intervention categories	The authors concluded that *"There is uncertainty as to the effectiveness of early multicomponent interventions owing to the clinical heterogeneity and varying health and social insurance systems across the trials."*[16] (page 1466)

CI: confidence interval; GRADE = Grading of Recommendations Assessment Development and Evaluation; HR = hazard ratio; NNT = number needed to treat; QoL = quality of life; RCT= randomized controlled trial; RMDQ = Rolland Morris Disability Questionnaire

Table 11: Summary of Findings of Included Primary Clinical Studies

Main Study Findings	Authors' Conclusion
Karp, 2018[17]	
Baseline characteristics (N=139): Mean age (SD) : 70.34 (8.32); Mean duration of pain (SD): 24.02 (18.05) years; Female: 62%; White: 84%; Minor depression or dysthymia: 10.95%; Major depressive disorder: 89.05% Depression and pain outcomes: -Cumulative rates of response (at any time during phase) were 41.2% (VEN + PST) and 39.4% (VEN + SM) -36.5% (95% CI: 26.1; 49.4) of VEN + PST and 37.4% (95% CI: 27.2; 49.9) of VEN + SM were responders at Week 13 -Cumulative proportion of response was not statistically significant between groups (HR: 1.07 [95% CI: 0.63; 1.80]; *P* = 0.81) -No statistically significant differences in rate and time to initial response for depression and pain as independent outcomes Functional outcomes: -SPPB scores did not change significantly at post-randomization visits (*P* = 0.26) -Change over time in SPPB scores also did not differ between groups (*P* = 0.88) - Differences in decline of RMDQ scores did not differ between groups (*P* = 0.49) 12 month follow-up: -PHQ-9 scores did not differ significantly between groups (*P* = 0.44) -NRS for pain and RMDQ measures of pain and functional disability did not differ between groups (*P* = 0.74 and *P* = 0.21, respectively) Change in problem-solving orientation: -Patients receiving VEN + PST experienced greater improvement in the SPSI total score than those receiving VEN + SM (β = 5.20; SE: 2.63; 95% CI: 0.04; 0.36; z = 1.97). -Patients who received VEN + PST did not have greater improvements on the positive problem-solving orientation subscale (β = 2.38; SE: 2.88; 95% CI: −3.26; 8.02; z = 0.83) but did have greater decreases on the negative problem-solving subscale (β = −4.87; SE: 2.29; 95% CI: −9.37; −0.39; z = −2.13)	The authors concluded that: "*The combination of antidepressant pharmacotherapy and PST was not superior to antidepressant pharmacotherapy and supportive management. Clinically, the rates of response and stability of response over 1 year observed in both groups suggest that these approaches may have clinical utility in these chronically suffering patients."*[17] (page 765)
Edmond, 2018[18]	
Baseline characteristics (pain cohort) (N = 31,286): Mean age: 61.7 to 62.6 years, Female: 6.8 to 7.7%; Mean maximum pain score: 6.4 to 6.8 (on a scale of 0 to 10) Analgesic use (pain cohort): -Long-term opioid therapy (> 90 days) decreased from 4.2% in Year 1 to 3.3% in Year 5; *P* < 0.0001 -Non-opioid medication prescriptions increased from 36.7% in Year 1 to 39.8% in Year 5; *P* < 0.0001 -Specific medication increases (from Year 1 to Year 5) were	The authors concluded that *"Through a multifaceted comprehensive implementation approach, primary care providers demonstrated increases in guideline-concordant pain care practices. Findings suggest that engagement of interdisciplinary teams and partnerships to promote organizational improvements is a useful strategy to increase the use of integrated, multimodal pain care for veterans, consistent with VHA's SCM-PM."* (page S30)

Main Study Findings	Authors' Conclusion
topical analgesics (3.5% to 4.8%); NSAIDs (15.7% to 19.3%); antidepressants (5.7% to 5.9%), and anticonvulsants (10.9% to 12.8%); all *P* < 0.0058 -Sedatives/hypnotics decreased from 17.4% in Year 1 to 15.1% in Year 3 and increased again in Year 5 to 17.2%; *P* < 0.0001 Healthcare utilization (pain cohort): -Referrals by primary care providers for any consultations increased from 43.4% in Year 1 to 51.8% in Year 5; *P* < 0.0001 -Increases for referrals were found for PT from 14.8% to 27.4%; P<0.0001, occupational therapy from 5.2% to 11.0%; *P* < 0.0001, pain medicine from 3.2% to 3.8%; P<0.0001, and neurology from 10.3% to 10.7%' *P* = 0.002 -Change in referrals for mental health (from 6.0% to 5.0%) and chiropractic (from 1.4% to 3.2%) consultations were not statistically significant; *P* = 0.56 and *P* = 0.43, respectively -Visits (≥ 1) by patients for any reason increased from 27.9% in Year 1 to 37.3% in Year 5; *P* < 0.0001 -Increases for visits for mental health (28.0% to 30.5%), clinical health psychology (4.7% to 7.2%), PT (16.2% to 22.9%), occupational therapy (5.6% to 10.0%), chiropractic (1.4% to 3.8%), neurology (10.0% to 13.3%), pain medicine (2.9% to 3.2%), and multimodal care (from 24.5% to 29.0%) were observed from Year 1 to Year 5; all *P* < 0.0019	
Rhon, 2018[19]	
Baseline characteristics (N = 1,876): Mean (SD) age: 36.9 (10.9) years; Female: 41.5%; Prescribed opioids: 61.9% (45.6% had opioids within first 30 days of consultation and 54.4% had opioids after 30 days); 42.8% had first MT within 30 days of consultation and 57.2% had MT after 30 days Healthcare utilization costs: -Mean 1-year costs in the MT-only group ($5,410 [95% CI: 5,109;5,730]) were statistically significantly lower than in the MT + opioid group ($10,498 [95% CI: 10,043; 10,973]); *P* < 0.05 -In patients with both MT + opioid therapy, mean 1-year costs in patients who received MT first ($10,782 [95% CI: 10,050; 11,567]) were significantly lower than in patients who received opioids first ($11,938 [95% CI: 11,272; 12,643); *P* = 0.030 -Patients who received MT first also had a significantly lower mean days' supply of opioids (34.2 versus 70.9; P<0.001) and mean number of unique opioid prescriptions (3.1 versus 6.5; *P* < 0.001) -Early MT (≤ 30 days from index) was associated with statistically significant lower 1-year costs for total outpatient medical visits, total outpatient medical costs, total visits for all spine or shoulder conditions, total costs for spine and shoulder care, total visits for any spine condition, total costs for all spine care, total visits for any shoulder condition, total costs for all shoulder care, and individuals with opioid prescription fills compared to delayed MT delivery (> 30 days from index); all *P* < 0.001 -Early opioid use (≤ 30 days from index) was associated with statistically significant lower 1-year costs for total visits for any	The authors concluded that *"Following recommended first-line treatments for spine or shoulder pain resulted in significantly less downstream health care utilization and lower costs. MT alone was better than MT plus opioid utilization. Both the order of treatment (MT before opioid prescriptions) and the timing of treatment (MT < 30 days) resulted in a significant reduction of resources (costs, visits, and opioid utilization) in the year after initial consultation. Clinicians should consider the implications of first-choice decisions and the timing of care for treatment choices utilized for patients with spine and shoulder disorders."*[19] (page 9)

Main Study Findings	Authors' Conclusion
spine condition; *P* = 0.048; total costs for all spine care; *P* < 0.001, mean unique opioid prescription fills; P<0.001, and mean days' supply of opioids for all prescription fills; *P* < 0.001 compared to delayed use of opioids (> 30 days after index)	
Anderson, 2016[20]	
Baseline characteristics: Patients: Baseline (N = 3,357); Age (%): 40 to 49 years (31%), 50 to 59 years (26%); Female: 63%; White: 42%, Medicaid insurance: 66% and Post-Intervention (N = 4,385); Age (%) 40 to 49 years (25%); 50 to 59 years (31%); Female: 64%; Caucasian: 42%; Medicaid insurance: 64%. Primary care providers (N = 25); Female: 56%; Caucasian: 76%; Professional degree: 68% MD/DO and 32% APRN -Providers pain knowledge scores increased by approximately 11% from baseline; P = 0.001 -Self-rated confidence in ability to manage pain increased from 2.71 at baseline to 4.67 after implementation (on a scale of 1 to 6 where 1=strongly disagree and 6=strongly agree) -Use of opioid treatment agreements and urine drug screens increased by 27.3% and 22.6%, respectively; *P* < 0.05 -Statistically significant improvements were observed in various pain care documentation data elements (e.g., documentation of pain, source or cause of pain, functional assessment, review of diagnostic tests, treatment plan, pain medication ordered, pain consult ordered, and assessment of treatment effectiveness); all *P* ≤ 0.025 -Referrals by the 25 primary care providers to behavioral health providers increased from 24.3% to 29.1%; P=0.009, for chiropractic consult from 0.1% to 1.1%; P=0.008, and decreased from 19.9% to 15.8% for neurologic or orthopedic surgery; *P* < 0.001 -There were no significant changes in opioid prescribing or chronic opioid therapy	The authors concluded that *" Implementation of the SCM-PM resulted in clinically significant improvements in several quality of pain care outcomes. These findings, if sustained, may translate into improved patient outcomes."*[20] (page 1021)
Comer, 2016[21]	
Baseline characteristics: Patients: (N = 484); Age (%): 31 to 45 years (28.1%), 46 to 60 years (30.6%); Female: 58.1%; White: 45.7%, Working as normal: 44.6%; Incapacity/sick: 11.0%, and Retired: 23.1% -A total of 38.0% (95% CI: 33.8; 42.4) patients required tier 2 complex care -Final logistic regression model for predictors of requiring complex care included age group, sex, anatomic site of problem indicated by PT assessment, unclear MSK diagnosis indicated in PT assessment, and symptoms affecting sleep -Peripheral joint problems, unclear diagnosis (atypical presentation), and symptoms affecting sleep were significant independent predictors of requiring complex care; *P* < 0.05 -Requirement for complex care, communication difficulties, spinal problems, level of pain (score of ≤ 7, 8, 9, or 10) were significant predictors of referral to a service other than a general practitioner; *P* < 0.05	The authors concluded that *"A substantial proportion of patients receive complex care, and the combination of quantitative and qualitative data in our study has highlighted the importance of several significant predictors of case complexity and has also underlined the need for a more effective triage process to ensure efficient access to the appropriate level of care. Further studies are needed to evaluate the value of these predictive factors for the development of a triage tool."*[21] (page 910)

Main Study Findings	Authors' Conclusion
Chambers, 2015[22]	
Baseline characteristics: (N = 77); Mean (SD) age: 50 (10.9) years; Female: 54%; Caucasian: 47%; Chest pain present > 6 months: 79%; Atypical chest pain: 84%; Other cardiac problems: 8%, Any psychiatric disorder: 55%; Diagnosis of other physical illness (e.g., gastric, glaucoma, allergy, etc.): 70% -Proportion of patients with daily or more often chest pain decreased from 44% at baseline to 13% at 3 months and 7% at 6 months; (*P* < 0.001) -Chest pain interference reduced from 5.9 [SD 2.2] at baseline to 3.2 [SD 2.6] at 3 months and 2.6 [SD 2.1] at 6 months; P<0.001 -Depression scores measured by the PHQ-9 were 8.8 [SD 7.2] at baseline and 5.4 [SD 5.8] at 3 months and 4.4 [SD 5.0] at 6 months; *P* < 0.05 -Anxiety scores measured by the GAD7 decreased from 6.9 [SD6.0] at baseline to 4.6 [SD 5,0] at 3 months and 3.6 [SD:4.7] at 6 months; *P* < 0.05 -Impact on daily life as measured by the WSAS score decreased from 10.4 [SD 10.4] at baseline to 3.9 [SD 7.5] at 3 months and 2.5 [SD 5.7] at 6 months; *P* < 0.001 -Reductions in use of healthcare resources (e.g., general practitioner, emergency department, cardiologist, other hospital physician, mean number of healthcare appointments, and mean number of consultations for chest pain) were all statistically significantly reduced at 6 months compared with baseline; *P* < 0.05	The authors concluded that *"A stepped-care biopsychosocial approach to non-cardiac chest pain reduced chest pain frequency, interference and severity, avoidance of activity and psychological distress and led to improvements in work and social adjustment and more appropriate use of healthcare resources. The programme can be delivered by a cardiac nurse, a clinical psychologist, and a cardiologist. It could therefore be integrated into any chest pain clinic."*[22] (page 927)
Smink, 2014[23]	
Baseline characteristics: (N = 163 SCS-inconsistent/N = 117 SCS-consistent); Mean (SD) age: 65 (10)/62 (10) years; Female: 62%/63%; Location of OA: Hip: 49%/54% or Knee: 80%/74% Note: Imbalances were found for number of baseline characteristics (SCS-inconsistent/SCS-consistent): Age: 65/62 (*P* = 0.05), Number of co-morbidities 1.2/1.0 (*P* = 0.04), Health insurance with additional coverage: 88%/95% (*P* = 0.05), Number of painful joints: 1.3/1.1 (*P* = 0.02) -Over the 2-year period there were statistically significant differences between SCS-inconsistent/SCS-consistent cumulative healthcare use for the following modalities: -Step 1: Education (69%/100%); *P* < 0.01, Lifestyle advice (52%/100%); P<0.01 and Paracetamol (78%/87%); P=0.05 -Step 2: Exercise therapy (56%/70%); *P* = 0.02 and Dietary Therapy (6%/15%); *P* = 0.02 -Step 3: Intra-articular injections (28%/13%); *P* < 0.01 -There were no statistically significant differences (even after adjusting for potential confounders) between patients who received SCS-consistent or SCS-inconsistent care as follows: -WOMAC pain score (Adjusted difference: -4.3 [95% CI: -10.3; 1.7]; *P* = 0.16) -WOMAC physical function score (Adjusted difference: -1.9 [95% CI: -7.0; 3.1]; *P* = 0.45)	The authors concluded that *"The results raised several important issues that need to be considered regarding the value of the SCS, such as the reasons that GPs provide SCS-inconsistent care, the long-term effects of the SCS, and the effects on costs and side effects."*[23] (page e538)

Main Study Findings	Authors' Conclusion
-Self-efficacy (Adjusted difference: 0.6 [95% CI: -8.3; 2.0]; *P* = 0.41) -Active pain coping (Adjusted difference: 1.7 [95% CI: -1.5; 4.9); *P* = 0.30	

APRN = Advanced Practice Nurse Practitioner; CI = confidence interval; DO = Doctor of Osteopathic Medicine; GAD7 = Generalized Anxiety Disorder 7-item Scale; GP = General Practitioner; HR = hazard ratio; MD = Medical Doctor; MSK = musculoskeletal; MT = manual therapy; NSAIDs = non-steroidal anti-inflammatory drugs; OA = osteoarthritis; PHQ-9 = Patient Health Questionnaire-9; PST = problem-solving therapy; PT = physiotherapy; ; RMDQ = Roland Morris Disability Questionnaire; SCM-PM = Stepped Model of Pain Management; SCS = Stepped Care Strategy; SD = standard deviation; SE = standard error; SM = supportive management; SPPB = Short Physical Performance Battery; SPSI = Social Problem Solving Inventory; VEN = venlafaxine; VHA = Veterans Health Administration; WOMAC = Western Ontario and McMaster Universities Osteoarthritis Index; WSAS = Work and Social Adjustment Scale

Table 12: Summary of Findings of Included Economic Evaluation

Main Study Findings	Authors' Conclusion
Fitzsimmons, 2014[24]	
Base case analysis: -Costs for the base case were inactive control (0), usual care (£73.74), education/advice (£81), activity restriction (£70), alternative/non-traditional therapies (£70), non-opiods (£122.23), opioids (£130.26), biological agents (£1646.74), manipulation, traction, passive PT, active PT (all £349), epidural (£602.76) and disk surgery (£1433.66) Results were expressed as incremental cost per patient with symptoms successfully resolved and incremental cost per utility gained over a 12-month period. One-way sensitivity analyses were used to address uncertainty. -The model demonstrated that none of the strategies resulted in 100% success -The most successful regime in the 1st treatment pathway was non-opioids with a probability of success of 0.613 (i.e., 39 patients would be unsuccessful for every 100 treated) -The most successful strategy in the 2nd treatment pathway was non-opioids, followed by biological agents, followed by epidural/nerve block and disk surgery, with a probability of success of 0.996 (i.e., 3 patients would be unsuccessful for every 1000 treated) -The 3rd treatment pathway of immediate surgery was not cost-effective -Compared to inactive control, the following ICERs were associated with the followed stepped approaches: treatment with non-opiods and alternative/non-traditional treatments (£999), non-opiods, alternative/non-traditional treatments, and epidural (£1992), non-opioids, alternative/non-traditional treatments, epidural, and disk surgery (£5023), and non-opioids, biological therapies, epidural and disk surgery (£388,478) -In terms of net benefit, the stepped care approaches would be regarded as cost-effective if the ceiling ratio for an additional unit of utility gain over 12 months was < £5100 and if the ceiling ratio for each additional success was < £2500 -Sensitivity analyses identified that use of the highest cost estimates results in similar findings	The authors concluded that *"The stepped approaches to managing sciatica based on an initial treatment with non-opioids represent the most cost-effective regimens relative to direct referral to disk surgery, with positive net benefits emerging if the acceptable ceiling ratio for an additional unit of success was < £2500 with base-case costs and < £6000 if higher costs were applied to the model. The strategy of referring patients who fail initial treatments directly to disk surgery is unlikely to be cost-effective, with highly improbable reductions in cost and/or rates of success being required to elevate these regimens to the efficiency frontier. However, these findings remain tentative, and more research is required to develop the evidence base to inform more structurally appropriate economic models to inform decision-making and to determine patient preferences regarding treatment durations and extent of invasive treatments that would be acceptable."*[24] (page 1327)

Main Study Findings	Authors' Conclusion
-For immediate referral for surgery to be considered cost-effective, the costs associated with treatment following non-opioids would have to decrease by 49% or the likelihood of success would have to increase by 10 percentage points to 0.95	

ICER = incremental cost-effectiveness ratio

Table 13: Summary of Recommendations in Included Guidelines

Recommendations	Strength of Evidence and Recommendations
2018 SIGN Guideline: Management of Chronic Pain in Children and Young People[3]	
A Pediatric Pain Pathway with 3 levels of intervention for the management of chronic pain in children and young people is included in the guideline: -Level 1 (Family, Education, Healthcare with type of intervention pain education, sleep, exercise) -Level 2 (Secondary Care: Gastroenterology, Neurology, Surgery, Pediatrics, Orthopedics, Rheumatology, Pediatric Psychology with type of intervention physiotherapy and pediatric psychology -Level 3 (Pediatric Pain Clinic, Child and Mental Health Service, Multidisciplinary team, Rehabilitation model with type of intervention mental health, multidiscplinary rehabilitation model, pain clinic) -Patients are fast-tracked in cases of complex regional pain syndrome, neuropathic pain, child protection concerns, life-limiting diagnosis, pain arising from medical treatment, mood disturbance, or if school attendance is affected. Recommendations pertaining to specific treatment modalities are as follows: *"2.1 Assessment and Planning of Care* *- Use of a screening tool to identify children and young people at risk of adverse outcomes due to chronic pain should be considered to aid in planning intensity and type of intervention.* *- Early biopsychosocial assessment and psychological intervention should be considered, particularly where the risk of disability and distress is high.* *- The potential effects (both positive and negative) of children's interactions with family, clinicians, educators and peers on assessment and management of chronic pain should be considered. Regarding the nature of interactions with healthcare providers and clinical interventions, remote or online delivery may be considered as an alternative to face to face.* *2.2 Pharmacological Management* *-Pharmacological treatment should only be started after careful assessment. If being used, it should be part of a wider approach utilising supported self-management strategies within the context of a multidisciplinary approach.* *-If pharmacological therapy is being used, then there should be regular review with planned reassessment of ongoing efficacy*	Due to limitations in the evidence base, unless otherwise stated, the majority of recommendations are based on expert consensus opinion. The level of evidence was only provided for some of the evidence considered for each recommendation. The level of evidence and quantity are summarized below for each category of recommendations: Levels of Evidence*: 2.1 Assessment and Planning of Care: 1+, 2++, 2++, 4, 4 2.2 Pharmacological Management: 1+, 1-, 1-, 3, 3, 1-, 3, 3, 1+, 2+, 2+, 2+, 2-, 2-, 1+, 1+, 3, 1-, 3, 2.3 Physical Therapies: 1+, 1++, 1-, 2-, 4, 1+, 4 2.4 Psychological Therapies: 1+, 1+, 2++ 2.5 Surgical Therapies: 1- 2.6 Dietary Therapies: 1+, 1+ 2.7 Complementary and Alternative Therapies: 1-, 1-, 1+ *Definitions of levels of evidence: 1++ (high quality MAs, SRs of RCTs, or RCTs with very low risk of bias 1+ (well conducted MAs, SRs of RCTs, or RCTs with low risk of bias) 1- (MAs, SRs of RCTs, or RCTs with a high risk of bias) 2++ (high quality SRs of case control or cohort studies, high quality case control or cohort studies with very low risk of confounding or bias and a high probability the relationship is

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and side effects. Treatment should only be continued if benefits outweigh risks, and limited to the shortest possible duration. Review should be a minimum of once per year, to assess continued benefit in terms of pain relief and improvement in function and/or quality of life. *-Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) should be considered in the treatment of chronic non-malignant pain in children and young people. Use should be limited to the shortest possible duration, such as during acute on chronic pain episodes.* *-Topical NSAIDs should be considered for treatment of children and young people with localised, non CRPS and non-neuropathic pain.* *- 5% lidocaine patches should be considered in the management of children and young people with localised neuropathic pain, particularly when aiming to improve compliance with physiotherapy regimes. They are well accepted, with a low incidence of side effects, restricted to occasional hypersensitivity reactions.* *-Antiepileptic drugs should be considered as part of a multi-modal approach in the management of children and young people with neuropathic pain:* *- Gabapentin should be considered as first line anti-convulsant (specialist use only). It should be used in the lowest effective dose, with ongoing monitoring for efficacy and adverse effects.* *- Pregabalin should be considered as a second line anticonvulsant drug if gabapentin is not tolerated or is ineffective (specialist use only).* *- Low dose amitriptyline should be considered in the treatment of children and young people with functional gastrointestinal disorders.* *- Low dose amitriptyline should be considered in the treatment of children and young people with chronic daily headache, chronic widespread pain and mixed nociceptive/neuropathic back pain.* *-If amitriptyline is effective but particularly sedative in an individual, nortriptyline should be considered as a less sedating alternative.* *- Bisphosphonates should be considered in the management of children and young people with osteogenesis imperfecta who have bone pain.* *-Intrathecal baclofen should be considered for reducing spasticity-related pain in children and young people with cerebral palsy.* *-In children and young people with recurrent abdominal pain pizotifen should be considered for abdominal migraine; famotidine for dyspepsia; and peppermint oil for irritable bowel syndrome.* *-Opioids and compound analgesics containing opioids are rarely indicated for chronic pain because of their adverse effect profile. Be aware of MHRA advice on codeine. Strong opioids should be used with caution and only with specialist advice or assessment.* *-Use of opioids should be for as short a time as possible with regular review and monitoring of efficacy and side effects.* *-The use of codeine is not recommended in children under the age of 12 (MHRA), as it can be associated with a risk of opioid*	causal 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) 2- (case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal 3 (non-analytic studies e.g., case reports, case series) 4 (expert opinion)

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toxicity and respiratory side effects. In general it should also be avoided in adolescents, particularly if they have respiratory problems and individuals known to be CYP2D6 rapid metabolisers should also avoid codeine. Caution is also needed with tramadol use due to genetic variability in metabolism, and production of active metabolites. *2.3 Physical Therapies* *- Exercise should be considered as a key component of chronic pain management in children and young people.* *-There should be consideration of early interventions to increase movement, physical activity and restore function.* *-Exercise should be used with the aim of producing functional improvement in children and young people with CRPS. Mirror therapy should be considered.* *-Exercise therapy should be considered for children and young people with Patellofemoral Pain Syndrome (PFPS) to enhance long term recovery and reduce pain.* *-Relaxation and TENS are low risk interventions that should be considered for the treatment of children and young people with chronic pain.* *2.4 Psychological Therapies* *-Psychological interventions should be part of a multi-disciplinary approach to managing chronic pain in children and young people.* *-Face-to-face psychological interventions should be delivered by suitably trained and supervised practitioners.* *-Online or computerised delivery of Cognitive Behavioural Therapy (CBT) interventions should be considered if face-to-face therapy is not suitable or not available.* *2.5 Surgical Interventions* *-Local anaesthetic blockade or other interventions should be considered on an individual patient basis in specialist centres.* *2.6 Dietary Therapies* *-The use of probiotics (LGG and VSL#3) should be considered in children and young people with functional gastro-intestinal disorders.* *2.7 Complementary and Alternative Therapies* *-Acupuncture may be considered for managing chronic pain in children and young people, for back pain and headache. If used, efficacy should be formally assessed.* *-While evidence is very limited, music therapy may be considered for children and young people with chronic migraine."*[3] (pages 12-14)	
2016 NICE Guideline: Low Back Pain and Sciatica in Over 16s: Assessment and Management[2]	
An algorithm for the management of LBP and sciatica in people 16 years of age and older is included in the guideline. *"The term 'low back pain' is used to include any non-specific low back pain which is not due to cancer, fracture, infection or an*	The guideline development group considered the following factor when agreeing on the wording of the recommendations: -The strength of the recommendation (for example the word 'offer' was used for strong recommendations and 'consider' for

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inflammatory disease process. *1. Consider using risk stratification (for example, the STarT Back risk assessment tool) at first point of contact with a healthcare professional for each new episode of low back pain with or without sciatica to inform shared decision-making about stratified management.* *2. Based on risk stratification, consider:* *-simpler and less intensive support for people with low back pain with or without sciatica likely to improve quickly and have a good outcome (for example, reassurance, advice to keep active and guidance on self-management)* *-more complex and intensive support for people with low back pain with or without sciatica at higher risk of a poor outcome (for example, exercise programmes with or without manual therapy or using a psychological approach).* *3. Do not routinely offer imaging in a non-specialist setting for people with low back pain with or without sciatica.* *4. Explain to people with low back pain with or without sciatica that if they are being referred for specialist opinion, they may not need imaging.* *5. Consider imaging in specialist settings of care (for example, a musculoskeletal interface clinic or hospital) for people with low back pain with or without sciatica only if the result is likely to change management.* *6. Think about alternative diagnoses when examining or reviewing people with low back pain, particularly if they develop new or changed symptoms. Exclude specific causes of low back pain, for example, cancer, infection, trauma or inflammatory disease such as spondyloarthritis. If serious underlying pathology is suspected, refer to relevant NICE guidance on:* *- Metastatic spinal cord compression in adults* *-Spinal injury* *-Spondyloarthritis* *-Suspected cancer* *7. Provide people with advice and information, tailored to their needs and capabilities, to help them self-manage their low back pain with or without sciatica, at all steps of the treatment pathway. Include:* *- information on the nature of low back pain and sciatica* *- encouragement to continue with normal activities.* *8. Consider a group exercise programme (biomechanical, aerobic, mind–body or a combination of approaches) within the NHS for people with a specific episode or flare-up of low back pain with or without sciatica. Take people's specific needs, preferences and capabilities into account when choosing the type of exercise.*	weaker recommendations. -For the first and second recommendations, which are most relevant to this review, the quality of evidence for risk assessment and risk stratification was rated as low or very low quality, mainly due to risk of bias and sometimes due to imprecision.

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9. Do not offer belts or corsets for managing low back pain with or without sciatica. *10. Do not offer foot orthotics for managing low back pain with or without sciatica.* *11. Do not offer rocker sole shoes for managing low back pain with or without sciatica.* *12. Do not offer traction for managing low back pain with or without sciatica.* *13. Consider manual therapy (spinal manipulation, mobilisation or soft tissue techniques such as massage) for managing low back pain with or without sciatica, but only as part of a treatment package including exercise, with or without psychological therapy.* *14. Do not offer acupuncture for managing low back pain with or without sciatica.* *15. Do not offer ultrasound for managing low back pain with or without sciatica.* *16. Do not offer percutaneous electrical nerve simulation (PENS) for managing low back pain with or without sciatica.* *17. Do not offer transcutaneous electrical nerve simulation (TENS) for managing low back pain with or without sciatica.* *18. Do not offer interferential therapy for managing low back pain with or without sciatica.* *19. Consider psychological therapies using a cognitive behavioural approach for managing low back pain with or without sciatica but only as part of a treatment package including exercise, with or without manual therapy (spinal manipulation, mobilisation or soft tissue techniques such as massage).* *20. For recommendations on pharmacological management of sciatica, see NICE's guideline on neuropathic pain in adults.* *21. Consider oral non-steroidal anti-inflammatory drugs (NSAIDs) for managing low back pain, taking into account potential differences in gastrointestinal, liver and cardio-renal toxicity, and the person's risk factors, including age.* *22. When prescribing oral NSAIDs for low back pain, think about appropriate clinical assessment, ongoing monitoring of risk factors, and the use of gastroprotective treatment.* *23. Prescribe oral NSAIDs for low back pain at the lowest effective dose for the shortest possible period of time.*	

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24. Consider weak opioids (with or without paracetamol) for managing acute low back pain only if an NSAID is contraindicated, not tolerated or has been ineffective. *25. Do not offer paracetamol alone for managing low back pain.* *26. Do not routinely offer opioids for managing acute low back pain (see recommendation 24).* *27. Do not offer opioids for managing chronic low back pain.* *28. Do not offer selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors or tricyclic antidepressants for managing low back pain.* *29. Do not offer anticonvulsants for managing low back pain.* *30. Consider a combined physical and psychological programme, incorporating a cognitive behavioural approach (preferably in a group context that takes into account a person's specific needs and capabilities), for people with persistent low back pain or sciatica:* *- when they have significant psychosocial obstacles to recovery (for example, avoiding normal activities based on inappropriate beliefs about their condition) or* *-when previous treatments have not been effective.* *31. Promote and facilitate return to work or normal activities of daily living for people with low back pain with or without sciatica.* *32. Do not offer spinal injections for managing low back pain.* *33. Consider referral for assessment for radiofrequency denervation for people with chronic low back pain when:* *-non-surgical treatment has not worked for them and* *-the main source of pain is thought to come from structures supplied by the medial branch nerve and* *-they have moderate or severe levels of localised back pain (rated as 5 or more on a visual analogue scale, or equivalent) at the time of referral.* *34. Only perform radiofrequency denervation in people with chronic low back pain after a positive response to a diagnostic medial branch block.* *35. Do not offer imaging for people with low back pain with specific facet join pain as a prerequisite for radiofrequency denervation.* *36. Consider epidural injections of local anaesthetic and steroid in people with acute and severe sciatica.* *37. Do not use epidural injections for neurogenic claudication in people who have central spinal canal stenosis.*	

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38. Do not allow a person's BMI, smoking status or psychological distress to influence the decision to refer them for a surgical opinion for sciatica. *39. Do not offer disc replacement in people with low back pain.* *40. Do not offer spinal fusion for people with low back pain unless as part of a randomised controlled trial.* *41. Consider spinal decompression for people with sciatica when non-surgical treatment has not improved pain or function and their radiological findings are consistent with sciatic symptoms."[2] (pages 18-20)*	

CBT = Cognitive Behavioral Therapy; CRPS = complex regional pain syndrome; MA = meta-analysis; MHRA = Medicines and Healthcare Products Regulatory Agency; NICE = National Institute for Health and Care Excellence; NSAID = non-steroidal anti-inflammatory drug; RCT = randomized controlled trials; SR = systematic review; TENS = transcutaneous electrical nerve stimulation