Healthcare Improvement Scotland

Scottish Intercollegiate Guidelines Network

SIGN 173

Management of chronic pain

A national clinical guideline

Published November 2026

NHS SCOTLAND

Key to evidence statements and recommendations

Levels of evidence

1^{++}	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1^{+}	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1^{-}	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2^{++}	High-quality systematic reviews of case-control or cohort studies High-quality case-control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
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, eg case reports, case series
4	Expert opinion
sufficient/ insufficient	Network meta-analyses are given a binary rating (sufficient/insufficient) according to relevance and credibility.

Recommendations

Some recommendations can be made with more certainty than others. The wording used in the recommendations in this guideline denotes the certainty with which the recommendation is made (the 'strength' of the recommendation).

The 'strength' of a recommendation takes into account the quality (level) of the evidence. Although higher-quality evidence is more likely to be associated with strong recommendations than lower-quality evidence, a particular level of quality does not automatically lead to a particular strength of recommendation.

Other factors that are taken into account when forming recommendations include: relevance to the NHS in Scotland; applicability of published evidence to the target population; consistency of the body of evidence; and the balance of benefits and harms of the options.

R For '**strong**' recommendations on interventions that '**should**' be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more good than harm. For '**strong**' recommendations on interventions that '**should not**' be used, the guideline development group is confident that, for the vast **majority** of people, the intervention (or interventions) will do more harm than good.

R For '**conditional**' recommendations on interventions that should be '**considered**', the guideline development group is confident that the intervention will do more good than harm for **most** patients. The choice of intervention is therefore more likely to vary depending on a person's values and preferences, and so the healthcare professional should spend more time discussing the options with the patient.

Good-practice points

✓ Recommended best practice based on the clinical experience of the guideline development group.

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Gyle Square, 1 South Gyle Crescent
Edinburgh EH12 9EB

www.sign.ac.uk

Published November 2026

978-1-917629-26-3

Citation text

Scottish Intercollegiate Guidelines Network (SIGN).
Management of chronic pain 2026. (SIGN publication no. 173). [November 2026].
Available from URL: http://www.sign.ac.uk

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1 Introduction

1.1 The need for a guideline

Chronic pain is pain that persists for more than three months, or beyond normal injury healing time.[1] It is a major clinical and public health challenge: prevalence figures vary, with estimates in 2016 of between 35.0 and 51.3% in the United Kingdom (UK), increasing with age (18–25 years old: 14.3%; 25–64 years: 30–50%; over 75 years old: 62% – age strata did not overlap precisely across the studies).[2] The prevalence of moderate to severely disabling chronic pain is up to 14.3%.

A more recent systematic review of chronic pain in Europe found that, across 16 studies, point prevalence ranged from 12% to 48%. Factors associated with higher risk of having chronic pain included female sex, older age, lower education and unemployment.[3] In Scotland, in 2022, there was an overall prevalence of 38%, with more than 15% of people reporting significant limitations on work or life because of chronic pain. A higher proportion of women compared with men (43% vs 33%) was affected, increasing with age (25–34 years: 23%; 65–74 years: 51%) and deprivation (least deprived: 29%, most deprived: 50%).[4] Chronic pain is projected to increase over the coming years, with a higher rate of increase in more deprived areas, compared with less deprived.

It has a considerable impact on quality of life, resulting in significant suffering and disability.[5-7] Globally, back pain remains the leading cause of years lived with disability.[8] While in many cases it is accepted that a cure is unlikely, the impact on quality of life, mood and function can be significantly reduced by appropriate management. Chronic pain not only has an impact on affected individuals and their families, but also has substantial economic costs, although accurate up-to-date figures for these are hard to obtain. In 2014, in the National Health Service (NHS), musculoskeletal pain accounted for around 40% of sickness absence.[9] A more recent Norwegian study of healthcare and work absence costs estimated that 4% of gross domestic product (GDP) was spent on chronic pain, although up-to-date, accurate figures in the UK are not available.[10]

While a proportion of patients will require access to specialist secondary and tertiary care pain services, the majority of patients will be managed in the community or primary care. In Scotland, 69% of adults with chronic pain receive support from their general practitioner (GP)[4] with 22% of GP consultations focusing on pain management.[11] Only 2–3% of people with chronic pain see a specialist. It is vital that GPs and other healthcare professionals have the best possible resource and support to manage their patients properly and have facilities for accessing appropriate specialist services when required. In Scotland, there is evidence of wide variation in clinical practice, service and resource provision, with a general lack of knowledge about chronic pain and the management options that are available.[12]

The Scottish Government Framework for Chronic Pain Service Delivery[13] includes approaches to help increase knowledge in the non-specialist setting, through a Chronic Pain Knowledge Hub for health and social care professionals. Further actions include scaling up improved pain service planning and delivery, establishing the NHS pain service managers network to improve co-ordination and planning of specialist services and improving local access to advice and care.

1.1.1 Lived-experience perspective

People with lived experience may have different perspectives on healthcare processes and outcomes from those of healthcare professionals. The involvement of people with lived experience in guideline development is therefore important to ensure that guidelines reflect their needs and concerns and address issues that matter to them.

In 2021, the Scottish Government asked the Health and Social Care Alliance Scotland (the ALLIANCE), the national third-sector intermediary for health and social care, to conduct a survey that would be used to inform their ongoing work on chronic pain policy. Based on responses gathered from 462 people, the report describes how chronic pain impacts their day-to-day life, the level of importance placed on public information about chronic pain and how to access support. It highlighted the following points.[14]

- Raising awareness and improving pathways for supported self management in all people affected by chronic pain and ensuring it can be delivered on an ongoing basis to adequately support individuals in the longer term.
- More public information about what chronic pain is, its impact on people in Scotland and how to access support.
- Information about the different types of treatment available for chronic pain and when they are used.
- Information about what services and health and care teams are available locally and how they might help individuals to manage their pain closer to home.
- Access to support to help individuals manage the impact of their pain on their mental health and well-being, and to remain physically active and carry out day-to-day tasks.

The Framework for Chronic Pain Service Delivery aims to better meet the needs of people living with chronic pain in Scotland by improving timely and equitable access to a range of evidence-based treatments through a person-centred approach. The Framework acknowledges current inequity of access.[13] Healthcare Improvement Scotland gathered information from people in Scotland living with chronic pain to support the Framework.[15] The work involved gathering lived experience from people living with chronic pain by asking questions about the care and support they had experienced through health and social care services and local support groups. The report summarises feedback from 92 people with chronic pain and includes recommendations for improved service delivery in the following areas:

- staff understanding and attitudes
- access to support services
- different types of support
- self management
- feedback from people with lived experience.

The plain language version of this guideline will:

- help people understand the latest evidence around diagnosis, treatment and self care
- empower people to actively participate in decisions about managing their condition in discussions with health and social care professionals
- highlight areas of uncertainty for people, making them aware of where more information or research is needed.

1.2 Remit of the guideline

1.2.1 Overall objectives

This guideline aims to synthesise the available evidence on chronic pain management to inform patient-centred choices. It provides recommendations based on current evidence for best practice in managing adults with chronic non-malignant pain in non-specialist settings, defined as any setting where the training and infrastructure is not specifically designed for treating chronic pain. This might include management in the community, primary care or secondary care. The guideline is structured according to interventions used to manage chronic pain.

This guideline includes evidence for comprehensive pain management programmes *(see section 9)*, which are generally delivered in secondary care. Pain management programmes can be delivered in primary care and, therefore, should not be defined as an intervention limited to secondary care only. At present, this model is not delivered widely in Scotland, where most pain management programmes involve input from multidisciplinary teams in secondary care settings.

It does not cover:

- interventions that can only be delivered in secondary or tertiary care.
- treatment of patients with migraine or headache *(see SIGN 155, Pharmacological management of migraine)*.[16]
- pain caused by cancer.
- management of chronic pain in children (see the Scottish Government guideline Management of chronic pain in children and young people[17] and World Health Organization (WHO) guideline on the management of chronic pain in children.[18])
- underlying conditions. Chronic pain is caused by many underlying conditions. The treatment of these conditions is not the focus of this guideline.

1.2.2 How this guideline has been developed

This guideline has been developed in line with SIGN methodology *(see section 24.1)* This methodology involves an iterative systematic literature search, which means that systematic reviews and meta-analyses are identified first due to their ability to minimise risk of bias better than other types of study. If insufficient evidence is identified at this level to support development of recommendations, the searches investigate lower levels of primary study evidence. For this guideline, a very large volume of systematic reviews was identified so evidence has been restricted to this type of study for most questions. Where SIGN has carried out searches for additional evidence, this is explained in the supporting materials (see Methodology supplement). The use of systematic reviews maximises the overall quality of evidence for each question, and allows the certainty of evidence to be stated for each effect, but also means that primary studies involving people with specific pain types, or with specific characteristics (such as men, women, older people, younger people or those with disabilities or with different levels of socioeconomic deprivation) are pooled within the systematic reviews in order to provide estimates of effect synthesised from a broad body of relevant evidence. This means that it has not always been possible to develop separate recommendations for some of these groups based on the evidence reviewed in this guideline. Where relevant, the guideline development group (GDG) has used their clinical experience to provide guidance for specific groups when it may have different implications from the general recommendations.

The use of systematic reviews may limit the estimation of clinical effectiveness to interventions with a more mature body of published evidence, as reviews may not yet exist for new and emerging treatment options.

1.2.3 Comorbidities to consider when managing patients with chronic pain

The prevalence of chronic pain increases with age *(see section 1.1)*. Older adults are at increased risk of multimorbidity, including cardiovascular disease, diabetes, dementia and renal disease, with consequential increased risk of experiencing pain and incapacity. Multimorbidity in the ageing population can also impact on overall medication safety.[19] Chronic pain is experienced with higher prevalence among socially, economically and historically marginalised groups, and multiple factors are involved in the development, maintenance and exacerbation of these inequalities.[20,21] Further information on inequalities associated with chronic pain and the person-centred 7-Steps medication review process, which matches therapeutic objectives to life

priorities for the individual, is included in the Scottish Government Quality Prescribing for Chronic Pain Guide.

Common comorbidities and coexisting health issues that were considered when reviewing the evidence for this guideline are:

- mood disorders (including depression and anxiety)
- cardiovascular disease and stroke
- diabetes
- surgical and medical interventions
- obesity.[22]

1.2.4 Target users of the guideline

This guideline will be of particular interest to all healthcare professionals involved in the management of people with chronic pain, including general practitioners, pharmacists, anaesthetists, psychologists, psychiatrists, physiotherapists, rheumatologists, occupational therapists, and nurses. Importantly, this guideline is also for people with chronic pain, carers and those working in the third sector, including voluntary organisations with an interest in chronic pain.

1.3 Definitions and classification of chronic pain and other terms

1.3.1 Chronic pain

Pain is defined by the International Association for the Study of Pain (IASP) as 'an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage'.[23] The IASP notes that pain is complex and nuanced and has expanded on the definition with the following key points.

- Pain is always a personal experience that is influenced to varying degrees by biological, psychological, and social factors.
- Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurones.
- Through their life experiences, individuals learn the concept of pain.
- A person's report of an experience as pain should be respected.
- Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being.
- Verbal description is only one of several behaviours to express pain; inability to communicate does not negate the possibility that a human or a non-human animal experiences pain.

The Scottish Government recognised chronic pain as a long-term condition in 2009[24] with specific Read codes for diagnosis of chronic pain (1M52) and chronic pain review (66n) introduced in 2014. However, it is only in the most recent International Classification of Diseases (ICD-11) that a comprehensive and systematic classification has been developed for chronic pain.[25,26] The ICD is the main tool used in many countries for coding diagnoses and interventions, but the lack of effective coding for chronic pain to date has led to major deficiencies in epidemiological understanding of chronic pain and its impact. The ICD-11 chronic pain coding is a significant advance, which will help to increase the recognition of chronic pain in primary care as an important condition, supporting service planning, education and research for chronic pain.[27]

In this guideline, chronic pain is defined as pain that has been present for more than three months, consistent with the World Health Organization's definition in ICD-11.[25]

The International Association for the Study of Pain classifies pain mechanisms into three primary categories based on pathophysiology: nociceptive (tissue damage), neuropathic (nerve damage), and nociplastic (altered nervous system function) pain *(see Table 1)*. Many people experience a mix of these mechanisms. People can have a genetic predisposition to a heightened pain response, meaning an injury or illness in one area can trigger heightened sensitivity throughout the entire nervous system.

Table 1: Primary biological pain mechanisms and their characteristics

Pain type / Feature	Neuropathic	Nociceptive	Nociplastic
Origin	nerve damage (peripheral/central)	tissue damage (peripheral)	altered nervous system processing
Pain description	burning, shooting, electric	throbbing, aching, localised	widespread, intense, fuzzy
Mechanism	direct damage to the nerves themselves, either peripherally or centrally	'bottom-up' signalling - peripheral damage sends signals to the central nervous system	central sensitisation – a dysfunction in how the central nervous system processes sensory input (increased amplification)
Example	diabetic neuropathy, postherpetic neuralgia, stroke-related pain	arthritis, fracture, postoperative pain	fibromyalgia, chronic back pain, irritable bowel syndrome

1.3.2 Overdose

An overdose can occur when a medicine is administered in quantities greater than can be physically tolerated or is taken in combination with other substances that increase adverse effects. Overdoses can be accidental or deliberate and involve prescribed, over-the-counter and illicit drugs.[28]

1.3.3 Treatment duration

For recommendations on treatment duration, short term is defined as less than three months, medium term as three to 12 months and long term as over 12 months.

1.4 Reporting in pain trials

Difficulties in reporting make the interpretation of the evidence base challenging. Chronic pain is a complex phenomenon with consequent challenges for its assessment and management both in clinical trials and routine clinical practice. This is further complicated by the fact that even in the same condition the underlying pain mechanisms may differ significantly between individuals. While changes in peripheral pain processing might predominate in one patient, central changes may be much more important in another, with implications for the most effective treatment approaches in each case.[29-31]

These limitations have been recognised internationally, leading to the development of the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT, www.immpact.org) in 2002. In clinical trials, unless there is careful assessment of the chronic pain syndrome in each patient, potentially useful treatments may be discarded as being ineffective when the average response is considered. Even good-quality, adequately powered double-blind randomised controlled trials (RCTs) may not provide the best approach for developing a strong evidence base for pain management.[32-34]

To allow comparison between studies, a standardised approach to outcome measures is recommended by IMMPACT.[32] Four key domains were recommended to adequately assess outcomes:

1. Pain intensity. A numerical rating scale 0–10 is the most practical and sensitive.
2. Physical functioning. Assessment with validated self-report questionnaires such as the Multidimensional Pain Inventory or Brief Pain Inventory interference scales.
3. Emotional functioning. The Beck Depression Inventory and the Profile of Mood States.
4. Patient rating of overall improvement. The Patient Global Impression of Change (PGIC) scale.

Side effects and detailed information about patient recruitment and progress through the trial should also be recorded.[35,36]

In addition to the limitations of assessment and trial design, concerns have been raised about how analysis methods may either obscure clinically important positive outcomes, or overestimate treatment effects. This is further discussed in the SIGN methodology supplement. If the average response is considered, a treatment may appear ineffective, whereas it could have the potential to be effective in a particular subgroup of the patients being studied. It may, therefore, be useful to analyse responders to a particular treatment separately from non-responders.[34]

While there are numerous good-quality systematic reviews and meta-analyses that provide an evidence base for managing patients with chronic pain, the published primary literature has some limitations. This has been taken into consideration by the GDG when appraising the evidence. Where there are areas of potential doubt, recommendations have been downgraded accordingly. Research recommendations have been made where clear gaps and limitations in the evidence were identified *(see section 24.2)*.

1.4.1 What is a clinically important difference?

While the statistical significance of trial results may be established, a more directly applicable question for healthcare professionals is whether or not results are also clinically important. The minimum clinically important difference (MCID) determines and communicates whether there is clinical relevance associated with the observed differences between treatments in a clinical trial. It has been defined as 'the smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate, in the absence of troublesome side effects and excessive cost, a change in the patient's management.'[37] There is no agreement on a single MCID for people living with chronic pain as it is recognised to vary between different patient populations and the various health outcome measures used in clinical trials. Variability may also be seen among studies examining the same patient population because of differences in study design, study location, and treatment administered.

A systematic review, including 66 studies of treatments for chronic pain found a median absolute MCID of 23 mm on a 0–100 mm scale (interquartile range (IQR) 12–39), with very high heterogeneity (I^2=99%) around two-thirds of which was associated with baseline pain.[38] The authors note that MCID for chronic pain relief varied considerably among published studies and was influenced by the operational definition of relevant pain relief and clinical condition of participants in the studies.

1.4.2 Interpreting effect sizes

The Agency for Healthcare Research and Quality (AHRQ), whose evidence reviews are cited in this guideline, has summarised their definitions of magnitude of effects in meta-analyses of chronic pain trials as follows:

- A small effect on pain was defined as a mean between-group difference following treatment of 0.5 to 1.0 points on a 0- to 10-point numeric rating scale or visual analogue scale (VAS) and on function as a standardised mean difference (SMD) of 0.2 to 0.5 or a mean difference (MD) of 5 to 10 points on the 0–100-point Oswestry Disability Index (ODI), 1 to 2 points on the 0 to 24-point Roland-Morris Disability Questionnaire (RMDQ), or equivalent.
- A moderate effect on pain was defined as an MD of 10 to 20 points on a 0- to 100-point VAS and on function as an SMD of 0.5 to 0.8, or an MD of 10 to 20 points on the ODI, 2 to 5 points on the RMDQ, or equivalent.
- Large or substantial effects were defined as greater than moderate.

1.5 Statement of intent

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results.

The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at through a process of shared decision making with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be documented in the patient's medical records at the time the relevant decision is taken.

1.5.1 Influence of financial and other interests

It has been recognised that financial or academic interests may have an influence on the interpretation of evidence from clinical studies.

It is not possible to completely eliminate any possible bias from these sources, nor even to quantify the degree of bias with any certainty. SIGN requires that all those involved in the work of guideline development should declare all financial and academic interests, whether direct or indirect, annually for as long as they are actively working with the organisation. By being explicit about the influences to which contributors are subjected, SIGN acknowledges the risk of bias and makes it possible for guideline users or reviewers to assess for themselves how likely it is that the conclusions and guideline recommendations are based on a biased interpretation of the evidence.

Signed copies of declaration of interests forms are retained by SIGN and a register of interests is available in the supporting material section for this guideline at www.sign.ac.uk

1.5.2 Prescribing of licensed medicines outwith their marketing authorisation

Recommendations within this guideline are based on the best clinical evidence. Some recommendations may be for medicines prescribed outwith the marketing authorisation (MA) also known as product licence. This is known as 'off-label' use.

Medicines may be prescribed 'off label' in the following circumstances:

- for an indication not specified within the MA
- for administration via a different route
- for administration of a different dose
- for a different patient population.

An unlicensed medicine is a medicine which does not have MA for medicinal use in humans.

Generally 'off-label' prescribing of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the MA. Such use should be supported by appropriate evidence and experience.[39]

'Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability'.[39]

The General Medical Council (GMC) recommends that when prescribing a medicine 'off label', doctors should:[40]

- be satisfied that there is no suitably licensed medicine that will meet the patient's need
- be satisfied that there is sufficient evidence or experience of using the medicine to show its safety and efficacy
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine, and any follow-up treatment, or ensure that arrangements are made for another suitable doctor to do so
- make a clear, accurate and legible record of all medicines prescribed and, when not following common practice, the reasons for prescribing an unlicensed medicine.

Non-medical and medical prescribers should ensure that they are familiar with the legislative framework and the Royal College of Pharmacy's Competency Framework for all Prescribers.[41]

Prior to any prescribing, the licensing status of a medication should be checked in the Summary of Product Characteristics (SmPC) (www.medicines.org.uk). The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.[42]

1.5.3 Health technology assessment advice for NHS Scotland

Specialist teams within Healthcare Improvement Scotland issue a range of advice that focuses on the safe and effective use of medicines and technologies in NHS Scotland.

The Scottish Medicines Consortium (SMC) provides advice to NHS boards and their Area Drug and Therapeutics Committees about the status of all newly licensed medicines, new formulations of existing medicines and new indications for established products. NHS Scotland should take account of this advice and ensure that medicines accepted for use are made available to meet clinical need where appropriate.

SMC advice relevant to this guideline is summarised in section 23.4.

2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation.

2.1 Self-help interventions

R **Consider**

- **peer support interventions, and**
- **digital self-management interventions**

as part of the holistic and individualised management for people with chronic musculoskeletal pain.

2.2 Physical therapies (hands-off)

R **Physical activity (including exercise and exercise therapies), regardless of form, is recommended in the management of patients with chronic pain.**

2.3 Psychological interventions

R **Offer CBT (either face-to-face or remotely) to people experiencing chronic pain.**

R **Consider offering face-to-face ACT to manage chronic pain in people who have a preference for an acceptance approach to pain.**

2.4 Pain management programmes

R **Following appropriate assessment, consider comprehensive pain management programmes for people with chronic pain.**

2.5 Topical analgesics

R **Consider topical diclofenac in people with chronic musculoskeletal pain.**

2.6 Opioids

R **Opioids should not be considered routinely for people with chronic non-malignant pain.**

R **If prescribing opioids, undertake early and frequent review to identify any benefits and potential or actual adverse events or drug reactions. If necessary, the dose should be adjusted or treatment stopped.**

R **All people receiving opioid doses of >50 mg MED/day should be reviewed regularly (at least annually and preferably more often) to detect emerging harms and consider ongoing effectiveness.**

3 Key principles in managing chronic pain

3.1 Introduction

Chronic pain is a complex and personal experience, and objective measurements do not show its full impact. The management of chronic pain requires a considered, person-centred approach, drawing from a range of options rather than relying on any one treatment. Realistic goal setting in partnership with people experiencing pain, empowering self management early, and using non-pharmacological methods are central. The use of medication sits alongside these principles, when appropriate. Each management plan should be tailored to what matters to the individual, with a focus on improving function and quality of life, rather than an exclusive focus on pain removal, which is often unattainable.[23]

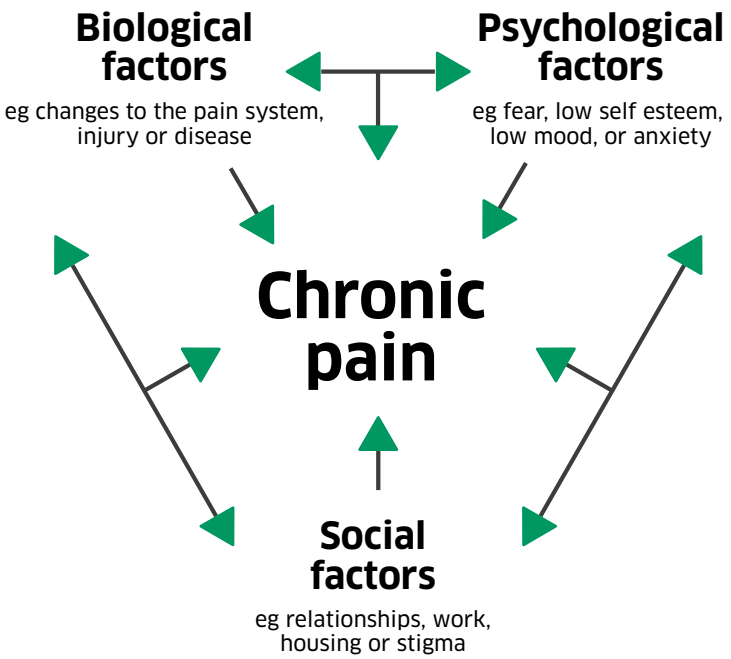
Scottish Government's Realistic Medicine puts people affected by health conditions at the centre of their care and encourages healthcare professionals to find out what matters most to people. The initiative treats those who use services and those working in health and social care as equal partners in decision making, promotes sharing information about treatment options and supports informed choice about what's right for individuals.

3.2 Understanding chronic pain

The International Association for the Study of Pain (IASP) definition of chronic pain *(see section 1.3)* reinforces that pain is more than a physical sensation.[23] While acute pain often accompanies illness or injury and resolves with healing, chronic pain may persist after tissues have healed and its intensity may not appear to correlate with the degree of damage. It can often arise without any obvious injury.

Chronic pain has been recognised as a long-term condition by the Scottish Government[24] and should be considered a complex condition requiring a compassionate, comprehensive and targeted approach that acknowledges the reality of each person's experience of pain, regardless of cause.

Figure 1: The biopsychosocial model of chronic pain



Chronic pain is understood within the biopsychosocial model of health. This considers the complex interaction of biological, psychological, social and cultural factors, advocating for a more holistic approach to management and the use of multidisciplinary treatment programmes that integrate medical, psychological, and social support.[43]

Biological factors may include the mechanism of injury or disease process, ageing, sex, hormonal factors, sleep, and the dynamic nature of the nervous system in processing pain (neuroplasticity). Psychological influences involve thoughts, beliefs emotions and coping patterns, including fear, low mood, catastrophising and confidence in managing symptoms. Social and cultural factors include relationships, work demands, financial pressures, housing, deprivation, race, ethnicity, stigma and support.

Research into the neurophysiology of pain as a complex, multidimensional experience has identified imbalances in nervous system excitation and inhibition, with both peripheral and central changes, and a shift from acute adaptation to chronic sensitisation.[44] This transition involves dynamic changes in a matrix of brain, spinal cord and peripheral systems influencing neuronal excitability. Understanding these mechanisms, involving peripheral nociceptors (high-threshold sensory neurones that function as a possible-threat detector, alerting the central nervous system to potentially damaging stimuli to central pathways) and the contribution of non-neuronal cells (such as glial or immune cells), is believed to be important for developing targeted therapies that address the transition from acute to chronic pain.

Recognising these interacting influences provides the basis for a co-ordinated approach, combining physical rehabilitation and medical treatments, psychological therapies and education, and attention to social, cultural and work-related challenges. This partnership-based model supports autonomy, encourages self management, and aims to reduce the day-to-day impact of pain.

3.3 Limitations of medical treatments

The biopsychosocial approach is not offered as an alternative to medical treatment, but in recognition of the complex and multifactorial nature of chronic pain. Persistent pain rarely responds to a single intervention.

Medications that are usually effective for acute pain (such as opioids and anti-inflammatory drugs) are often of limited value if pain persists beyond a few months. For many, this may be due to tolerance (in the case of opioids) or unacceptable side effects (in the case of anti-inflammatories). Medications designed for long-term use, such as antiepileptic or antidepressant drugs, help a minority of those with specific types of persistent pain. Adverse effects often limit their use. For those with complex multiple conditions, frailty, dementia or approaching the end of their lives, using combinations of drugs recommended for individual conditions may increase the risk of medicine-related harm and may not align with the individual's preferences (see the Scottish Government's Polypharmacy Guidance: appropriate prescribing for pragmatic advice on using combination pharmacological therapies).

A minority of people may benefit from injections or neuromodulation techniques for specific conditions following specialist assessment, but may be limited by potential complications and a short duration of effect. These treatments are not considered in this guideline but several specialist interventions for adults with chronic non-malignant pain that has not been resolved by non-specialist services in the primary care setting have been evaluated by the Scottish Health Technologies Group.

Recognising these limitations can help healthcare professionals set realistic expectations, emphasise non-pharmacological strategies and prioritise medicines where the balance of benefit and harm is clearly favourable.

3.4 Aims and principles of care

The primary aim of pain management is to enhance quality of life, reduce distress, improve function and participation, and support self efficacy, rather than to achieve complete pain elimination, which is often not possible. This is reflected in research where pain studies often use a 30% and 50% reduction in pain scores as a measure of moderate and substantial improvement in pain. These and other descriptions can be conveyed in individual conversations to clarify expectations and support realistic goals from therapies.

It is important that people living with chronic pain and the clinicians guiding their treatment can identify medicines that may be beneficial for the individual patient, and medication that is unlikely to bring benefit. This avoids patients taking ineffective medication and thus avoid unnecessary polypharmacy.

It is also important to be aware of the potential harms from medication, the likelihood of these harms occurring and any scenarios where the risk of harm is increased (for example, use alongside other medicines and individual patient risk factors). This allows for appropriate assessment of the balance of risks and benefits of using a medication in individual patients for chronic pain management. Medication reviews help to support prescribers match therapeutic goals with individuals' life priorities (see the Quality Prescribing for Chronic Pain Guide for description of the 7-steps medication review process).

Key principles of management include:

- diagnosing (and coding) chronic pain, and recognising its status as a long-term condition that requires ongoing, adaptive support
- working in partnership with the person (and their family or carers, where appropriate) to understand what matters to them
- using education to support shared decision making about realistic, meaningful goals
- prioritising interventions with a clear evidence base and a favourable balance of benefit and harm as set out in this guideline.

These principles are consistent with those of Realistic Medicine: reducing unnecessary interventions, minimising avoidable harm and working to reduce unwarranted variation in care, particularly in primary care settings where most chronic pain is managed.

3.5 Person-centred approach with shared decision making

A person-centred approach begins with exploring each person's perspective on their pain: what it feels like, how it affects their daily life, and their priorities for change. Care planning should use collaborative goal-setting methods (for example, specific, measurable, achievable, relevant, and time bound (SMART) goals), focusing on valued activities, roles and participation rather than pain intensity scores alone.

Shared decision making is central. Clinicians should offer clear, balanced information about potential benefits and harms of reasonable options (including deprescribing, appropriate levels of investigation and 'watchful waiting' strategies), explore the person's preferences and context, and arrive at a joint plan. Tools such as BRAN (Benefits, Risks, Alternatives, doing Nothing) questions, pain diaries and accessible written or digital information can facilitate these conversations and help people prepare for reviews. Shared decision plans should take factors such as geography and access to services into account, particularly in remote and rural settings.

None of the recommendations in this guideline should be seen in isolation, but should form a holistic package of measures to support people living with chronic pain. Each section of the guideline can be seen as an evidence-based component of a larger management plan, which may or may not be appropriate for individuals to different degrees, based on the extent and

type of their experience of pain, personal history, preferences and clinical requirements. Some components of treatment can be delivered as supported self management *(see section 3.8)* while other components are delivered in partnership with members of the multidisciplinary teams across primary, secondary and tertiary care that support people with chronic pain.

Scotland has a diverse population with different needs; for example, many frail or older people have fewer active or interventional treatment options. In some people with limited life expectancy, an approach more aligned with palliative care should be considered, as described in the Scottish Palliative Care Guidelines.

People with chronic pain may feel dismissed or disbelieved. Acknowledging this and being transparent about the balance of modest benefits with well-known risks of interventions are important for building trust in the long term.

3.6 Healthy lifestyle changes to mitigate chronic pain and its impact

Chronic pain is influenced by how the body and brain process signals of threat or safety. Body and brain systems that respond to threat tend to become more reactive when someone is physically depleted, stressed, socially isolated or sleeping poorly.

Conversely, good physical health, psychological well-being and strong social connections can support healthier pain processing and reduce the overall burden of symptoms. Although lifestyle changes do not cure chronic pain, they can lessen its impact, improve function and enhance resilience in day-to-day life.

While direct evidence for pain reduction from individual lifestyle changes varies, people should be supported, where possible, to:

- eat a healthy, balanced diet
- engage in regular physical activity
- avoid smoking and limit alcohol use
- adopt comfortable and sustainable postures at work and at home
- prevent and manage stress
- seek timely support for physical or mental health concerns
- maintain good sleep hygiene
- build and sustain social connections.

3.7 Multimodal and multidisciplinary approach

In practice, most physical, psychological and pharmacological interventions are co-ordinated within primary care. This might involve pharmacists, clinical nurse specialists, practice nurses, community link workers, physiotherapists and mental health professionals as well as primary care clinicians all working collaboratively to support people with chronic pain.

Multidisciplinary pain services, typically involving physiotherapy, psychological input, pharmacy and medical review, are a key resource when further support is required. From these services, more intensive multidisciplinary pain management programmes *(see section 9)* and selected specialist interventions can be accessed, where appropriate.[45]

3.8 Supported self management

Supported self management is an important principle that underlies the management of any long-term condition. The aim of supported self management is to empower people to become active participants in their own care, abandoning strategies that are not helping, and adopting approaches that may improve physical and mental well-being in the presence of ongoing

medical issues. Although self-management strategies do not cure chronic pain, they can reduce its impact and salience, as well as supporting a life more closely aligned with the person's values.

Supporting people to manage their own medication is an important part of any supported self-management approach to persistent pain. Since there is no objective measure of pain, there is no objective measure of efficacy of any medication taken for pain control. People taking medication for pain control should therefore be empowered to make informed choices based on their subjective experience of benefits and burdens of the medication they take. Resources such as the Pain Toolkit, Pain Concern leaflets and the NHS Scotland Manage My Meds app can help with this *(see section 22.2)*.

3.9 Addressing psychosocial factors

Psychological and social pressures shape how people experience and cope with chronic pain. Low mood, anxiety, sleep difficulties, financial strain, caring responsibilities, loneliness or unstable housing can all make pain more intrusive and harder to manage. These influences do not suggest the pain is psychological in origin but remind us that people live in circumstances that can amplify or ease their symptoms. A history of current or past trauma (including during childhood) can affect people's risk of developing chronic pain as well as the severity and impact of chronic pain, further highlighting the need for trauma-informed care.[46] See the National Trauma Transformation Programme for further information.

In primary care, it is rarely possible to explore every aspect in depth, but small, compassionate steps can have a meaningful impact. Simple questions about sleep, stress, relationships, work, or day-to-day hurdles can help identify where support might be most needed. Compassion and avoiding judgement are important, including explaining that stress, worry and exhaustion are common consequences of long-term pain, and not failings. Practical support might involve utilising third sectors or signposting to psychological therapies, such as cognitive behavioural therapy (CBT) or acceptance and commitment therapy (ACT), when appropriate *(see section 7)*.

3.10 Quality Prescribing for Chronic Pain: A Guide for Improvement 2026–2029

Scottish Government and multidisciplinary teams across primary and secondary care in NHS Scotland, supported by individuals with lived experience and patient organisations, have jointly developed a guide to enable understanding and assessment of chronic pain, improve communication and highlight the benefits and harms of non-pharmacological approaches alongside the appropriate use of medication. The guide provides a practical resource for practitioners who help people living with chronic pain.

In addition to reinforcing key messages from this SIGN guideline on the safe and effective management of chronic pain, the Quality Prescribing Guide provides further information on topics not included in this guideline, such as implementation of medication reviews, health inequalities in chronic pain, a primary care consultation model, information on deprescribing and clinical case studies.

The guide is informed by evidence from this guideline and the experience of clinicians, academics, experts by experience, patient groups and policy makers in Scotland, and is designed to be complementary to this guideline.

The guide is available online on the Scottish Government website, and as an interactive version on the Right Decision Service (RDS) app and website.

4 Self-help interventions

4.1 Introduction

Self management is seen as a cornerstone of chronic pain care.[47] Within the NHS, these skills are often imparted by physiotherapists in outpatient settings and by multidisciplinary pain management programmes in secondary care. These programmes typically involve a multidisciplinary team of pain consultants, specialist nurses, occupational therapists, pharmacists, physiotherapists, and psychologists.

There is no 'gold standard' definition of self management, but it may be broadly interpreted as the day-to-day tasks an individual may undertake to control or reduce the impact of a disease on physical or psychological health status. Self management describes the individual's ability to manage symptoms, treatment, physical and psychological consequences and lifestyle changes associated with a chronic condition.[48]

Barriers exist to people's engagement with secondary care pain management programmes.[49] Logistical challenges, including transportation difficulties, reliance on public transport, the costs associated with private vehicle use and parking, the navigation of hospital grounds, poor mental health or dependence on family or friends may pose hurdles.[50]

The resources in specialised pain management healthcare services within the NHS may pose another challenge. Consequently, waiting times for pain management programmes are often protracted.[51] These limitations suggest a need for innovative solutions to improve the accessibility and effectiveness of pain management support for individuals living with chronic pain.

Evidence was, therefore, sought on a range of interventions that involve no or minimal ongoing healthcare professional input and which are self led, with or without intermittent supportive contact. Evidence was only identified on peer support and digital self-management interventions.

4.2 Peer support interventions

Peer support has been defined as 'the giving of assistance and encouragement by an individual considered 'equal' as part of a created network or intervention by "peers" who are trained to deliver the intervention'.[52]

In the context of chronic pain, the evidence base for peer support is weak, making it challenging to draw definitive conclusions about its benefits and harms. Recommendations are therefore based on the professional and lived experience of the GDG supported by a limited body of effectiveness evidence and considering wider qualitative data.

4.2.1 Evidence of benefit

One systematic review with meta-analysis was identified, which examined the effectiveness of peer support interventions for adults with chronic musculoskeletal pain.[52] Twenty-four RCTs were included, all of which were rated at high or unclear risk of bias leading to all outcomes having low or very low-certainty of evidence.

When compared with usual care (nine RCTs), there was no evidence of benefit from peer support on pain intensity in the short term (up to three months) but, in the medium (four to nine months) and long term (longer than nine months), peer support resulted in small reductions in pain intensity. In the medium term this reduction was in the range of 0.35 to 6.61 points on a

1^{++}

100-point scale. There was no evidence of effect from peer support on pain intensity compared with waiting list control (eight RCTs) or active control (seven RCTs) at any follow-up timepoint.

When compared with usual care (nine RCTs) there was no evidence of benefit from peer support on function in the short or medium term. In the long term, peer support was superior to usual care; SMD -0.10 (95% confidence interval (CI) -0.19 to 0.00; five RCTs, 1,730 participants: very low-certainty evidence). When this measure was converted to the function subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) the degree of benefit (2.06 points) did not reach the minimal clinically important difference of nine points on a 0 to 68 scale. There was no evidence of effect from peer support on function compared with waiting list control (six RCTs) or active control (three to four RCTs) at any follow-up timepoint. 1++

Four studies compared peer support with usual care and found no significant effect on quality of life (QoL) at any time point. Only one study compared peer support with waiting list and, while there were significant improvements in QoL at six weeks, these were not sustained at six months. Two studies compared the effect of peer support on QoL with active control. One reported significant improvement in QoL, while the other found no significant effects.

4.2.2 Evidence of harm

The systematic review did not report outcome data on adverse effects. There is the potential for harm where people who may be managing chronic pain themselves attribute misinformation or provide unhelpful advice. Delivery of peer support interventions may place a burden on individuals, which could represent a harm over time, and there is no standardisation or governance of training for delivery of such interventions. It was suggested that providers should establish support mechanisms to avoid this.

4.2.3 Other factors

Peer support may offer a rewarding experience for both the individuals providing and receiving support, according to qualitative and non-randomised evidence supplied by Pain Concern and Pain Association Scotland and their representatives. Self efficacy (how able you feel you are to manage your condition), depression, anxiety and specific task-related outcomes were felt to be more relevant outcomes to this intervention than pain intensity and function.

Testimony from people with chronic pain on peer support interventions includes:

- *This pain course has helped and given me such hope in such subtle ways. Amazed, such a big improvement in helping me to manage my pain better on a day-to-day basis*. (Person with lived experience after attending a Pain Association Scotland self-management course)
- *Proof you're not alone* (Feedback following sessions led by Pain Concern).

4.2.4 Summary of benefits and harms of peer support interventions for chronic pain

The evidence showed that peer support interventions for people with chronic musculoskeletal pain may provide a small benefit in reducing pain intensity in the medium and long term and on improving function in the long term compared with usual care. No evidence was identified for people with other pain types, such as neuropathic or visceral pain, which may have distinct underlying mechanisms and treatment responses, limiting the generalisability of these findings. There may be benefits from peer support interventions that have not been reported by using outcome measures such as pain scores. For example, both peer supporters and recipients may experience benefits such as increased self efficacy, a sense of agency, reassurance, access to information, and improved self-management skills.

No evidence was identified on adverse effects of these interventions, however, there is a burden of care on peer supporters. Because of the lack of governance or standardised training for delivery, there is a risk that peer supporters, who may themselves be managing the

condition, could inadvertently offer unhelpful advice or misinformation in unsupervised settings while struggling with their own challenges.

4.2.5 Recommendations

R **Consider peer support interventions as part of the holistic and individualised management for people with chronic musculoskeletal pain.**

✓ Services providing peer support pain management interventions should establish mechanisms for monitoring and supporting individuals delivering peer support.

4.3 Digital self-management interventions

While evidence was sought on a wide range of self-management approaches, adequate evidence was only identified on digital self-management tools. These include technologies that support the individual to carry out activities to inform or assist management of their condition, for example smartphone and tablet apps to track symptoms rather than a paper diary, or wearable technology or web-based interventions to monitor activity rather than a written record.

Three systematic reviews were identified.[53-55] Intervention definitions varied across the reviews as did the populations of interest. The three reviews encompassed a total of 48 trials. Two trials were common to all three reviews. There was inconsistency across the reviews in the quality ratings assigned to the trials.

4.3.1 Evidence of benefit

One systematic review examined the effectiveness of a wide range of digital self-care interventions for pain and function in people with spine musculoskeletal disorders (neck pain, back pain or low back pain). Most interventions were smartphone apps or websites, with smaller numbers of email-based tools, virtual reality, telemedicine and video games. In general, the interventions involved physical exercises, education and CBT. The physical exercises were provided in the form of videos, audios or image-based instructions. The certainty of evidence was not reported.[53]

In meta-analysis of ten out of 20 RCTs of people with chronic back pain, there was a small but statistically significant benefit from digital self-care interventions on pain intensity after the treatment; SMD -0.19 (95% CI -0.28 to -0.09; nine RCTs, 1,775 participants) and small-to-moderate benefits on pain intensity in the medium term; SMD -0.21 (95% CI -0.33 to -0.08; five RCTs, 940 participants) and in the long term; SMD -0.24 (95% CI -0.37 to -0.11; four RCTs, 908 participants) compared with usual care. For functional disability there were small benefits from the digital self-care interventions after the treatment SMD -0.18 (95% CI -0.26 to -0.10; nine RCTs, 2,513 participants) and in the medium term; SMD -0.13 (95% CI -0.24 to -0.02; four RCTs, 1,207 participants) and long term SMD -0.14 (95% CI -0.25 to -0.04; four RCTs, 1,452 participants). 1++

Meta-analysis of the three RCTs of neck pain was not undertaken due to high heterogeneity (I^2=89%). Of these, two studies had positive and statistically significant findings for pain and function (clinical significance not stated) and one reported no evidence of benefit to pain.

A second systematic review explored the effectiveness of mobile health (mHealth) interventions for pain, function and QoL in people with a range of chronic pain conditions.[54] mHealth interventions were diverse and apps included combinations of the following components: 1+

- monitoring and tracking of physical activity and healthy lifestyle goals
- symptom monitoring
- treatment delivery (such as physical activity programmes, CBT and pain education).

Meta-analysis was not undertaken because of the heterogeneity across the study interventions and outcome measures. The most frequent pain conditions were osteoarthritis, lower back pain and neck pain. Intervention duration ranged from four to 24 weeks and follow-up from none (measured at end of intervention) to six months.

Ten of the 17 studies assessing pain intensity and functional disability separately reported statistically significant effects for mHealth interventions compared with controls. Two and one of these studies, respectively, were at high risk of bias. The extent and clinical significance of the benefits was not assessed. Six of 15 studies that assessed QoL found benefits from mHealth interventions. One of these was at high risk of bias. 1+

A third systematic review with meta-analysis examined the effect of digital self-management interventions (either using a digital intervention accessible via smartphone, smartwatch, tablet, computer or internet browser, or using a guided or unguided self-management technique) on various aspects of pain (intensity, catastrophising and interference or disability) for people with chronic low back pain.[55]

In meta-analysis of 12 RCTs there was a small improvement in pain intensity after treatment as a result of the digital self-management intervention (SMD 0.24, 95% CI 0.09 to 0.40; 12 RCTs, 1,545 participants: high-certainty evidence). Pain interference (which encompassed pain disability) showed a small-to-moderate improvement as a result of the intervention (SMD 0.43, 95% CI 0.27 to 0.59; 11 RCTs, 930 participants: moderate-certainty evidence). There was no statistically significant benefit to pain catastrophising. When all three pain concepts were combined into one measure there was a small-to-moderate positive effect from the intervention (SMD 0.33, 95% CI 0.17 to 0.49; 12 RCTs, 1,545 participants: high-certainty evidence). Sensitivity analysis identified that this positive effect was lost when only studies at low risk of bias were included (SMD 0.08, 95% CI -0.18 to 0.34; six RCTs, number of participants not stated). 1++

4.3.2 Evidence of harm

The systematic reviews noted that most included trials did not present adverse event data, and one review did not evaluate harms.[55] Where events were reported, they were mainly related to increase in pain associated with increased physical activity.

4.3.3 Other factors

The widespread adoption of digital interventions may exacerbate existing health inequalities. Individuals with limited digital literacy, access to technology, or reliable internet connectivity may be excluded from these services, potentially widening the gap in healthcare access. This should be balanced with potential benefits in addressing certain aspects of health inequality, such as access in rural areas.

Concern was expressed by the GDG about the diversity of commercial interventions; ethical concerns were raised regarding the prioritisation of financial gain over optimal patient outcomes, complicated by factors including motivation, bias, evidence methodology and heterogeneity. The GDG also noted that it was not always clear how digital tools maintained the security of individual's data.

NHS Scotland digital facilitators have an important role in transforming healthcare for those who lack access to technology. Facilitators:

- deliver support to clinical staff and service users to build their confidence and ability to join virtual programmes and interventions.
- work with library service colleagues to support those without devices or connectivity, eg loan schemes.
- work with organisations who deliver digital interventions to help them reach those who lack access to technology.

While evidence on the optimal timing of communication about self-management options was not reviewed, the National Institute for Health and Care Excellence (NICE) guideline NG193 recommends healthcare professionals provide advice and information relevant to the person with chronic primary pain's individual preferences at all stages of care to help them make decisions about managing their condition, including self management.[47] Although this recommendation was based on a single qualitative study, which described beliefs gathered in focus groups that discussions about self management often happen late in the care pathway, or not at all, the NICE guideline committee decided that this was particularly important to highlight as initiating this type of discussion early on and at subsequent consultations can make a difference to how people are able to manage their pain. The primary care consultation model in the Scottish Government Quality Prescribing for Chronic Pain Guide also describes providing introduction to self-management options at the first consultation and reinforcing them in consultation 3.

The feasibility of delivering digital self-management interventions as a prescribed treatment option has not been evaluated. While they may potentially reduce the need for certain healthcare resources, the initial costs of funding access to individuals and supporting their use must be considered.

Given the wide range of digital interventions reviewed, assessing their specific feasibility and economic impact in real-world Scottish settings is complex. Further research is needed to identify practical barriers and facilitators to implementation, as well as to evaluate the cost effectiveness of these interventions.

4.3.4 Summary of benefits and harms of self-management interventions for chronic pain

Digital self-management interventions have a small effect on reducing pain intensity and functional disability with little evidence of harms. As these interventions most commonly involve exercise and physical activity, education and CBT, potential benefits and harms are likely to be associated with the facilitation of these interventions *(see sections 5 and 7)*.

The effectiveness of digital interventions may vary across different chronic pain conditions and by the specific intervention offered. While promising collective results have been observed in people with musculoskeletal pain, further research is needed to evaluate their efficacy in groups with other chronic pain conditions, such as neuropathic pain or fibromyalgia and to clarify optimal delivery pathways.

4.3.5 Recommendations

✓ Provide advice about self-management tools at the earliest opportunity in line with individuals' preferences and circumstances.

R **Consider digital self-management interventions as part of the holistic and individual management for people with chronic musculoskeletal pain.**

✓ As digital self-management tools can, in themselves, be a barrier to practising self care for people who do not have access to, or are not able to use, digital tools, hybrid models of care, whereby they receive support from a digital facilitator or healthcare professional that encourages them to self care, should be available.

Data security measures should be clearly explained to people in an easy-to-understand way, fostering trust and transparency. When recommending digital support interventions for chronic pain management, it is crucial to prioritise safety and trust in people living with chronic pain.

✓ Robust measures must be in place to ensure the confidentiality and security of all patient data.

5 Physical therapies (hands-off)

5.1 Introduction

This section focuses on hands-off physical therapies including physical activity and mobility aids. The WHO defines physical activity as any bodily movement produced by skeletal muscles that results in energy expenditure. Physical activity can consist of a range of categories, such as occupational, sports, household or other activities.

Exercise is a subset of physical activity that is planned, structured and repetitive. It has a goal and objective in mind, for example, building strength or increasing functional capacity.

Physical activity is regularly used to manage a number of health conditions, including chronic pain. Chronic pain can impact physical fitness, activity levels, energy levels and overall function, resulting in a significant impact on quality of life.[56,57]

People in Scotland living with chronic pain may access support from various healthcare professionals, across all sectors of health and social care, where conversations, referral, signposting and direct input to support physical activity is often a core part of their management. However, there remains uncertainty about the relative effectiveness of types of exercise and physical activity across a range of chronic pain conditions.

5.1.1 Definitions of hands-off physical therapies

While some of the following interventions may also be classified as complementary therapies, studies are included in systematic reviews of physical therapies to assess effects on pain and function because they involve active self-directed physical retraining or neuromuscular education with a biomechanical focus.

Aerobic exercise: any rhythmic, repetitive physical activity that uses large muscle groups, increases the heart rate, and forces the body to use oxygen to produce energy, for example, running, cycling, swimming or dancing.

Resistance exercise: any physical activity where muscles work against an external force or weight to build strength, power, and muscle size. It is also known as strength training or weight training.

Flexibility exercise: any physical activity involving movement designed to lengthen muscles and improve the range of motion in the joints, for example dynamic stretching, Pilates, tai chi or yoga.

Kinesiology taping: adhesive acrylic medical tape used to relax or compress muscles, aiming to reduce pressure and inflammation and improve symptom relief.

Pilates: a low-impact mind–body exercise system which focuses on core strength, muscle control, flexibility, posture, and breathing alignment.

Qigong: an ancient Chinese discipline which has both psychological and physical components and involves the regulation of the mind, breath, and body's movement and posture. Dynamic (active) qigong techniques focus on body movements, especially movements of the whole body or arms and legs.

Tai chi: an ancient Chinese discipline consisting of slow, continuous, gentle physical movements, deep breathing, and mental focus to improve balance, flexibility, muscle strength, and overall health. When tai chi is performed for health, it is considered a form of qigong and is one of the hundreds of forms of qigong exercises that was developed in China.

Ai chi: a water-based exercise and relaxation technique that combines slow, fluid physical movements with deep, controlled breathing and is based on tai chi and qigong.

McKenzie therapy: a physical therapy system used to evaluate and treat back, neck, and extremity joint pain by focusing on specific repeated movements and postures.

Yoga: a practice that connects the body, breath, and mind using physical postures, breathing exercises, and meditation to improve overall health. While originally developed as a spiritual practice it is now more commonly used for exercise or to reduce stress.

Hot sand fomentation (HSF): a traditional Ayurvedic practice that involves applying heated sand to specific areas of the body. The treatment aims to reduce pain, inflammation, and stiffness by stimulating nerve endings, relaxing muscles, and increasing blood flow to the affected area.

Alexander Technique: an educational modality that teaches individuals how to recognise and release unnecessary muscular tension and habitual postural patterns that contribute to pain and functional impairment.

5.2 Evidence of benefit

Sixteen systematic reviews were selected that assessed the effectiveness of hands-off physical activity interventions for chronic non-cancer pain in adults aged 18 years or older. Twelve reviews used meta-analysis and four reviews used network meta-analysis (NMA).

Seven systematic reviews focused on chronic lower back pain,[58-64] five on fibromyalgia,[63,65-68] four on chronic neck pain,[63,69-71] one included evidence on osteoarthritis,[63] one focused on chronic pain secondary to temporomandibular joint disorders[72] and one on a range of musculoskeletal pain disorders.[73]

The systematic reviews included a range of hands-off physical therapy interventions. These were aquatic aerobic and strengthening exercise,[66] dance,[68] flexibility,[67] targeted temporomandibular joint exercises and stretching,[72] kinesiology taping,[61] mind–body exercise,[62,70] mixed exercise including two or more types of exercise (aerobic, resistance or flexibility),[65] multiple types of exercise (for example aerobic exercise, high-intensity interval training, Pilates, resistance exercises, stretching, swimming, tai chi and yoga),[59,60,63,69,72] neck and shoulder exercise,[71] water-based exercise,[58,73] and structured exercise programmes.[64] No evidence was identified on the effect of mobility aids on chronic pain.

Nine systematic reviews were rated high quality.[59,62-68,71] Three systematic reviews were rated acceptable quality.[58,61,73] All four NMAs were rated as sufficient quality.[60,69,70,72]

1++
1+
sufficient

5.2.1 Pain intensity

Exercise

Chronic lower back pain

A Cochrane systematic review evaluated the effect of exercise interventions on pain and function in people with chronic lower back pain. Exercise was statistically significantly more effective than no treatment, placebo or usual care at the earliest follow-up point, at short-term follow-up (6–12 weeks), at medium-term follow-up (around 6 months) and at long-term follow-up (greater than 12 months). The authors note that the effect met the definition of a clinically important difference in outcome, which was a difference in pain of 15 points on a 100-point scale, at earliest follow-up (MD -15.22, 95% CI -18.26 to -12.18; 35 RCTs, 2,746 participants: moderate-certainty evidence) and short-term follow-up (MD 16.36, 95% CI -20.32 to 12.40; 26 RCTs, 2,247 participants: no evidence certainty rating).[59]

1++

The same researchers also published an NMA that evaluated the relative effectiveness of different exercise treatments planned or prescribed by a healthcare professional for people with chronic lower back pain. The review found that most exercise types were more effective than minimal treatment for reducing pain outcomes. Within the network of effects measured using 0–100-point VAS, Pilates (MD -18.7, 95% CI -24.4 to 13.1; 17 RCTs, 719 participants: moderate-certainty evidence), McKenzie therapy (MD -14.8, 95% CI -21.4 to -8.2; eight RCTs, 428 participants: moderate-certainty evidence), and functional restoration (14.7, 95% CI -21.3 to -8.1; 9 RCTs, 459 participants: moderate-certainty evidence) were most likely to be compatible with a clinically important effect on pain. The authors note that the confidence in results was limited by the quality of the evidence, and highlighted incomplete reporting of trial and population characteristics, differing opinions about treatment type classifications, and potential misclassification of exercise types and population characteristics as potential concerns. They also note that 'the interventions that appeared to be the most effective were also interventions that are costly to deliver and to "purchase" for patients. It is possible that our results were conflated with other factors related to higher socioeconomic status in these patient groups (eg, physical labour, other healthcare access and health status).'[60] — sufficient

A further meta-analysis evaluated the effects of exercise or yoga on chronic lower back pain. Compared with usual care, an attention control (a group of participants that receives the same amount of time, personal contact, and social support from researchers as the experimental group, without receiving active components of the intervention) or a placebo intervention, exercise yielded a moderate reduction in pain at short-term (MD -1.05 in 0–10-point VAS, 95% CI -1.58 to -0.51; 13 RCTs, 1,131 participants: low-certainty evidence) and long-term follow-up timepoints (MD -1.55, 95% CI 2.76 to 0.34; one RCT, 64 participants: no evidence certainty rating) and a small reduction at intermediate term (MD 0.84, 95% CI -1.49 to 0.22; six RCTs, 712 participants: low-certainty evidence).

Yoga resulted in a small reduction in pain compared with an attention or waiting list control in the short term (pooled difference -0.87 on a 0–10 scale, 95% CI 1.49 to -0.24; seven RCTs, 710 participants: low-certainty evidence) and a moderate reduction in the intermediate term (pooled difference 1.16, 95% CI 2.16 to -0.27; two RCTs, 268 participants: moderate-certainty evidence).[63] — 1++

A systematic review investigating the benefits and harms of structured exercise programmes reported that while the quality and volume of evidence to support individual exercise types was low, based on pooled data, exercise (including aerobic, motor control, Pilates, yoga, core strengthening, and mixed exercise) probably reduces pain in the immediate term (SMD -0.33, 95% CI 0.58 to 0.08; eight RCTs, 619 participants: moderate-certainty evidence). — 1++

Exercise probably makes little or no difference to pain in the short term (MD 0.68 on a 0–10-point scale, 95% CI -1.82 to 0.46; two RCTs, 97 participants: very low-certainty evidence), or long term (between-group MD 8.88 on a 0–100-point scale, 95% CI -0.36 to 18.13; one RCT; 119 participants: very low-certainty evidence).[64]

A systematic review investigated the effects of the mind–body practice tai chi on pain in people with chronic lower back pain. Six RCTs evaluated tai chi alone, three RCTs evaluated tai chi as an add-on therapy in combination with other treatments (such as massage, acupuncture and other conventional physical therapy), and one RCT with ai chi. Pooling evidence from these trials, tai chi had a large effect on pain reduction compared with controls (weighted mean difference (WMD) 1.09, 95% CI 1.26 to 0.92; ten RCTs, 886 participants: medium-certainty evidence).[62] — 1++

One systematic review, which included evidence from randomised and non-randomised studies, compared the effects of water-based exercise training with land-based exercise and non-active controls in people with chronic lower back pain. A very large effect on pain reduction was — 1+

reported with water-based exercise compared with non-active controls (effect size 3.61, 95% CI -4.89 to -2.32; nine studies, 338 participants: very low- to low-certainty evidence) but there was no difference in effect between water-based and land-based exercise groups (effect size -0.14, 95% CI 0.42 to 0.15; five studies, 177 participants: very low- to low-certainty evidence).[58] 1+

Chronic neck pain

An NMA evaluated the relative effectiveness of different physical exercise interventions for people with chronic non-specific neck pain. Studies included interventions with durations and follow-up assessments ranging from three weeks to 12 months, but it was not possible to analyse results within this category because of insufficient data in the network nodes. Compared with no treatment, very low-certainty evidence indicated several types of exercise reduced pain intensity, including proprioceptive exercise (SMD 1.47, 95% CI -2.76 to -0.18), strengthening and motor control exercise (SMD -1.44, 95% CI -2.42 to -0.47), motor control exercise (SMD -1.32, 95% CI -1.99 to -0.65), yoga/Pilates/tai chi/qigong (SMD -1.25, 95% CI -1.85 to -0.65), stretching exercise (SMD -1.23, 95% CI -2.23 to 0.24), strengthening exercise (SMD 1.21, 95% CI -1.63 to -0.78) and prescribed physical activity (SMD 0.84, 95% CI -1.47 to -0.20; all effects based on a network of 38 RCTs, 3,151 participants: very low-certainty evidence).[69] sufficient

A further NMA investigated the relative effectiveness of nine mind–body exercise interventions in people with chronic neck pain. Yoga (MD 26.12, 95% CI 35.87 to -16.36), yoga plus HSF (MD 62.52 on a 0–100-point scale, 95% CI -85.76 to -39.27), Pilates (MD -22.35, 95% CI -32.36 to 12.35) and qigong (MD -12.92, 95% CI -21.96 to -3.89) each resulted in statistically significant reductions in pain compared with usual care (all based on a network of 18 RCTs, 1,442 participants: no evidence certainty rating).[70] sufficient

One systematic review reported that exercise had no significant effect on chronic neck pain compared with no treatment, waiting list or an attention control in the short term (MD -0.70, 95% CI -1.62 to 0.15; three RCTs, 444 participants: low-certainty evidence), intermediate term (MD -0.25, 95% CI -0.81 to 0.31; three RCTs, 353 participants: low-certainty evidence) and long term (MD 0.07, 95% CI -0.51 to 0.88; three RCTs, 349 participants: low-certainty evidence).

There was insufficient evidence available on mind–body practices to draw a conclusion.[63] 1++

One systematic review evaluated the effect of home-based or workplace neck and shoulder exercises on office workers with non-specific chronic neck pain. Neck and shoulder exercises reduced pain intensity compared with no training (pooled effect size 7.31, 95% CI 4.95 to 9.67; four RCTs, 296 participants: very low-certainty evidence).[71] 1++

Fibromyalgia

Five systematic reviews were identified that provided evidence on the effect of exercise on pain in people with fibromyalgia. In general, results suggest exercise, dance and mind–body practices in their different forms, but not flexibility exercise, provide small reductions in pain.

One systematic review evaluated the benefits and harms of mixed exercise training protocols that include two or more types of exercise (for example, aerobic, resistance or flexibility) for adults with fibromyalgia against control (treatment as usual, waiting list control), non-exercise interventions (for example, biofeedback), or other exercise (for example, mixed versus flexibility) interventions. Mixed exercise reduced pain postintervention compared with control, but not in the longer term (MD -7.01 on a 0–100-point scale, 95% CI 10.64 to -3.38; 10 RCTs, 487 participants: moderate-certainty evidence). The authors note that this small effect did not meet the threshold for clinical relevance (a between-group difference of 15 points on a 100-point scale).[65] 1++

A further systematic review evaluated the effect of aquatic training based on aerobic and strengthening exercises compared with no intervention or land-based exercise in women with fibromyalgia. Aquatic combined aerobic and strengthening exercise improved pain postintervention only compared with no intervention or land-based exercise (MD -1.16 on a 0–10-point scale, 95% CI -1.75 to -0.57; four RCTs, 171 participants: very low-certainty evidence). This improvement may be small and clinically unimportant as the authors assumed a minimum clinically important difference of 2 points on a 0–10 scale. The authors also note that several of the included studies had insufficient sample sizes, which could lead to inaccuracies in effect estimates and that several studies were published by the same research group, limiting the generalisability of findings.[66] 1++

Another systematic review investigated the effects of flexibility exercise on pain in adults with fibromyalgia compared with either land-based aerobic training, resistance training or a no treatment control. There was no evidence of any effect of flexibility exercise on pain postintervention compared with aerobic exercise (MD 2.48 on a 0–100-point scale, 95% CI 6.29 to 11.85; four RCTs, 131 participants: very low-certainty evidence), resistance exercise (MD 1.84, 95% CI -4.15 to 7.83; three RCTs, 152 participants: very low-certainty evidence) or no treatment control (MD -18.0, 95% CI -37.63 to 1.63; one RCT, 28 participants: low-certainty evidence).[67] 1++

One systematic review considered the effects of dance on pain associated with fibromyalgia. The review separately evaluated creative dance interventions, which use the five basic elements of dance (body, range of movement, space, time, and energy) to create original movements or ideas, and repetitive dance interventions, which consist of the repetition of movements provided by an instructor instead of inspiring new movements. Both creative dance (SMD -1.43, 95% CI -1.72 to -1.13; five RCTs, 268 participants: moderate-certainty evidence) and repetitive dance interventions (SMD -0.34, 95% CI -0.69 to -0.10; four RCTs, 259 participants: moderate-certainty evidence) reduced pain postintervention compared with controls of any other intervention.[68] 1++

A fifth systematic review evaluated the effect of exercise or mind–body practices (yoga, tai chi or qigong) on pain intensity compared with usual care, an attention control, a placebo intervention or waiting list in people with a range of chronic pain conditions, including fibromyalgia. Compared with control, exercise resulted in a small reduction in pain intensity in the short term (MD -0.84 on a 0–10-point scale, 95% CI -1.24 to -0.30; seven RCTs, 406 participants: moderate-certainty evidence) and intermediate term (MD 0.51, 95% CI -0.92 to 0.06; eight RCTs, 382 participants: moderate-certainty evidence). There was no significant effect of exercise in the long term (MD -0.18, 95% CI -0.77 to 0.42; four RCTs, 241 participants: moderate-certainty evidence). The authors note that a moderate treatment effect (>1 to 2 points on a 10-point scale) roughly corresponds to the reported minimum clinically important difference for the measure, suggesting that these effects may not be clinically relevant.[63] 1++

Osteoarthritis

One systematic review evaluated the effect of exercise or mind–body practices (yoga, tai chi or qigong) compared with usual care, no treatment or an attention control in people with chronic osteoarthritic pain of the hand, knee or hip. For people with knee osteoarthritis, exercise resulted in a small reduction in pain compared with controls in the short term (MD 0.50 on a 0–10-point scale, 95% CI -0.84 to 0.16; nine RCTs, 832 participants: moderate-certainty evidence) and long term (MD -0.26, 95% CI -0.43 to -0.01; six RCTs, 1,538 participants: low-certainty evidence) and a moderate reduction in the intermediate term (MD 1.21, 95% CI 1.96 to 0.44; 12 RCTs, 1,141 participants: low-certainty evidence). For people with hip osteoarthritis, exercise resulted in a small reduction in pain compared with controls in the short term (MD -0.30 on a 0–10-point scale, 95% CI -0.70 to -0.02; three RCTs, 371 participants: low-certainty 1++

evidence) but not in the intermediate term (MD -0.14, 95% CI 0.40 to 0.12; two RCTs, 307 participants: low-certainty evidence) or long term (MD 0.25, 95% CI -0.62 to 0.11; one RCT, 118 participants: insufficient certainty evidence). There was insufficient evidence from one poor-quality RCT of exercise in people with hand osteoarthritis to determine effectiveness.

Mind–body practices consisting of tai chi or qigong resulted in a moderate improvement in pain in people with knee osteoarthritis compared with usual care, attention control or placebo (SMD -0.75, 95% CI -1.05 to -0.42; two RCTs, 306 participants: low-certainty evidence). There was insufficient evidence to determine the effect of yoga.[63]

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Chronic pain secondary to temporomandibular disorder

An NMA evaluated all available interventions for the management of chronic temporomandibular disorder (TMD) pain. Network estimates for pain reduction indicated that supervised jaw exercise plus mobilisation (MD 2.86 on a 0–10 point scale, 95% -3.21 to -2.52; modelled risk difference (RD) for achieving the minimally important difference in pain relief of 1 cm on a 10 cm scale 36%, 95% CI 33 to 39: low-certainty evidence), supervised postural exercise (MD 1.56, 95% CI -2.33 to -0.79; RD 26%, 95% CI 14 to 34: medium-certainty evidence), supervised jaw exercise plus stretching (MD 1.55, 95% CI -1.99 to -1.11; RD 26%, 95% CI 20 to 31: high-certainty evidence), supervised jaw exercise plus stretching plus trigger point therapy (MD -1.31, 95% CI -1.99 to -0.62; RD 23%, 95% CI 11 to 31: medium-certainty evidence) each reduce pain significantly more than placebo (all estimates are based on a network of 153 RCTs with 8,713 participants).[72]

sufficient

Chronic musculoskeletal disorders

One systematic review evaluated the effects of aquatic exercise on a range of outcomes in the treatment of people with chronic musculoskeletal disorders. Included studies had treatment durations ranging from three to 32 weeks. Aquatic exercise reduced participants' pain compared with no exercise (SMD -0.64, 95% CI -0.87 to -0.41; 22 RCTs, 1,551 participants: no evidence certainty rating). Subgroup analysis showed that aquatic exercise significantly reduced pain in people with osteoarthritis (SMD 0.36, 95% CI 0.59 to -0.13; 12 RCTs, 995 participants), fibromyalgia (SMD -0.64, 95% CI -0.85 to -0.43; seven RCTs, 367 participants) and low back pain (SMD 1.68, 95% CI -2.29 to -1.07; three RCTs, 189 participants). Aquatic exercise also relieved pain compared with land-based exercise (SMD -0.35, 95% CI -0.67 to -0.03; 11 RCTs, 578 participants).[73]

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Kinesiology taping

Chronic lower back pain

One systematic review evaluated the effects of kinesiology taping on pain in people with chronic lower back pain. Kinesiology taping compared with addition of kinesiology taping to another intervention, no intervention or placebo had no statistically significant effect on pain at any follow-up point.[61]

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5.2.2 Function

Exercise

Chronic lower back pain

A Cochrane systematic review evaluated the effects of exercise interventions in people with chronic lower back pain. Exercise was more effective in reducing functional limitations compared with no treatment, placebo or usual care at the earliest follow-up timepoint (MD -6.81 on a 0–100-point scale, 95% CI -8.32 to -5.31; 38 RCTs, 2,942 participants: moderate-certainty evidence). The authors note that this effect does not meet the prespecified threshold for minimal clinically important difference (a difference in function of ten points).[59]

1++

The same researchers also published an NMA that evaluated the relative effectiveness of different exercise treatments planned or prescribed by a healthcare professional for people with chronic lower back pain.

Within the network of effects measured using 0–100-point scale, McKenzie therapy (MD -11.7, 95% CI -16.7 to -6.7; seven RCTs, 419 participants: high- to moderate-certainty evidence), flexibility exercise (MD -11.0, 95% CI 17.2 to -4.8; four RCTs, 151 participants: high- to moderate-certainty evidence) and Pilates (MD -10.2, 95% CI -13.8 to -6.6; 15 RCTs, 667 participants: high- to moderate-certainty evidence) all had a clinically significant positive effect on function (≥10 points) compared with controls.[60] — sufficient

A further meta-analysis evaluated the effects of exercise or yoga on function in people with chronic lower back pain. Exercise improved function compared with usual care, an attention control or a placebo intervention in the short term (SMD -0.33, 95% CI -0.51 to -0.16; 13 RCTs, 1,126 participants: moderate-certainty evidence) and intermediate term (SMD 0.20, 95% CI -0.41 to -0.03; six RCTs, 712 participants: low-certainty evidence) but not in the long term. — 1++

Yoga had moderate effects on function compared with an attention or waiting list control in the short term (SMD -0.45, 95% CI -0.69 to -0.28; eight RCTs, 982 participants: moderate-certainty evidence) and small effects in the intermediate term (SMD -0.29, 95% CI 0.47 to 0.11; three RCTs, 540 participants: low-certainty evidence).[63]

A systematic review investigating the benefits and harms of structured exercise programmes in people with chronic primary lower back pain reported that exercise improved function compared with no intervention, placebo or sham interventions in the immediate term (around two weeks postintervention) (MD -1.32, 95% CI 1.80 to -0.85; 41 RCTs, 2,068 participants: low-certainty evidence) and short term (around three months postintervention) (MD -0.54, 95% CI -0.88 to -0.20; five RCTs, 347 participants: very low-certainty evidence) but not in the long term (around 12 months postintervention) (MD -0.10, 95% CI -1.32 to 1.12: one RCT, 70 participants: very low-certainty evidence).[64] — 1++

A systematic review investigated the effects of tai chi on pain in people with chronic lower back pain either alone or in combination with other treatments. Tai chi significantly improved disability compared with controls (routine care or other interventions) (SMD -1.75, 95% CI -2.02 to -1.48; four RCTs, 296 participants: low-certainty evidence).[62] — 1++

One systematic review compared the effects of water-based exercise training with land-based exercise and non-active controls in people with chronic lower back pain. A very large effect on disability was reported with water-based exercise compared with non-active controls (effect size 2.15, 95% CI 1.12 to 3.19; nine studies, 395 participants: very low- to low-certainty evidence).[58] — 1+

Chronic neck pain

An NMA evaluated the relative effectiveness of different physical exercise interventions for people with chronic non-specific neck pain. Based on a network of 29 RCTs with 2,336 participants, several types of exercise reduced pain-related disability compared with no treatment, including yoga/Pilates/tai chi/qigong (SMD -1.16, 95% CI -1.75 to -0.57: very low-certainty evidence), strengthening exercise (SMD -0.75, 95% CI -1.28 to 0.22: very low-certainty evidence) and motor control exercise (SMD 0.87, 95% CI -1.45 to -0.29: very low-certainty evidence).[69] — sufficient

A further NMA investigated the relative effectiveness of nine mind–body exercise interventions in people with chronic neck pain. Based on a network of 15 RCTs with 1,165 participants, yoga plus HSF (MD -19.13 on a 0–100-point scale, 95% CI -27.90 to -10.37), tai chi (MD -14.90, 95% CI 22.76 to -7.04), yoga (MD 6.93, 95% CI -11.01 to 2.86) and Pilates (MD -5.61, 95% CI 9.27 to -1.96) each resulted in statistically significant reductions in functional disability compared with usual care.[70] — sufficient

One systematic review in people with chronic neck pain reported that exercise had no significant effect on function compared with no treatment, waiting list or an attention control in the short term (SMD -0.42, 95% CI 1.03 to 0.09; four RCTs, 487 participants: low-certainty evidence) or in the intermediate term (SMD 0.14, 95% CI -0.12 to 0.40; one RCT, 230 participants: low-certainty evidence) but may improve function in the long term (SMD -0.39, 95% CI -0.74 to -0.03; one RCT, 125 participants: low-certainty evidence). 1++

Alexander Technique resulted in a small improvement in function in the short term (difference -5.56 on a 0–100% scale, 95% CI -8.33 to -2.78; one RCT, 344 participants: low-certainty evidence) and intermediate term (difference -3.92, 95% CI -6.87 to -0.97 one RCT, 344 participants: low-certainty evidence) compared with usual care alone.

There was insufficient evidence available to determine the effect of qigong on function in people with chronic neck pain.[63] 1++

One systematic review evaluated the effect of home-based or workplace neck and shoulder exercises on office workers with non-specific chronic neck pain. Neck and shoulder exercises reduced pain-related disability compared with no training (pooled effect size 13.75, 95% CI 2.69 to 24.83; three RCTs, 249 participants: very low-certainty evidence).[71] 1++

Fibromyalgia

One systematic review evaluated the benefits and harms of mixed exercise training protocols for adults with fibromyalgia against control (treatment as usual, waiting list control), non-exercise interventions or other exercise interventions. Mixed exercise improved physical function compared with control (MD -12.77 on a 0–100 scale, 95% CI -17.63 to -7.9; six RCTs, 311 participants: no evidence certainty rating). The authors note that the minimum clinically important difference for this outcome was a relative difference of 15%, therefore the confidence intervals of this estimate include effects which are both clinically important and not important.[65] 1++

A further systematic review considered aquatic training (hydrotherapy) compared with no intervention or land-based exercise in women with fibromyalgia. Combined aquatic, aerobic and strengthening exercise improved physical function compared with no intervention immediately postintervention (MD 14.82 on a 0–100 scale, 95% CI 7.97 to 21.28; three RCTs, 118 participants: low-certainty evidence) and up to 16 weeks postintervention (MD 9.80, 95% CI 2.38 to 17.22; two RCTs, 88 participants: very low-certainty evidence). The authors note that no MCIDs were prespecified for physical function.[66] 1++

One systematic review investigated the effects of flexibility exercise on pain in adults with fibromyalgia. The review identified a single, small RCT that reported no significant difference in physical function between the group receiving flexibility exercise and untreated controls (MD -3.33 on a 0–100-point scale, 95% CI -16.29 to 9.63; one RCT, 28 participants: low-certainty evidence).[67] 1++

In a further systematic review that evaluated the effect of exercise or mind–body practices (yoga, tai chi or qigong) on physical function in people with a range of chronic pain conditions, including fibromyalgia, exercise significantly improved physical function compared with usual care, an attention control or a placebo intervention in the short term (MD -8.39, 95% CI -12.87 to -3.61; nine RCTs, 545 participants: low-certainty evidence) and intermediate term (MD -6.04, 95% CI -9.25 to -3.01; eight RCTs, 461 participants: moderate-certainty evidence) but not in the long term (MD 4.33, 95% CI -10.46 to 1.97; three RCTs, 178 participants: low-certainty evidence). Mind–body practices did not significantly improve function compared with waiting list or attention control (MD -15.44, 95% CI -31.11 to 0.23; two RCTs, 154 participants: low-certainty evidence).[63] 1++

Osteoarthritis

One systematic review evaluated the effect of exercise or mind–body practices (yoga, tai chi or qigong) compared with usual care, no treatment or an attention control in people with chronic osteoarthritic pain of the hand, knee or hip. In people with knee osteoarthritis and in people with hip osteoarthritis, exercise improved function in the short, medium and long term with standardised mean differences ranging from 0.18, which represents a result below the threshold of a small effect, to 0.57, which represents a moderate effect.

Analysis of evidence for mind–body therapies in people with chronic knee osteoarthritis showed a large effect from treatment compared with controls (pooled SMD -0.92, 95% CI -1.74 to -0.15; three RCTs, 398 participants: low-certainty evidence) but heterogeneity was substantial. Excluding the poor-quality outlier RCT substantially reduced the heterogeneity and resulted in a small improvement in function (pooled SMD -0.48, 95% CI 1.03 to -0.18; two RCTs, 304 participants: low-certainty evidence).[63]

1++

Chronic pain secondary to temporomandibular disorder

An NMA evaluated all available interventions for the management of chronic TMD pain. Based on a network of 33 RCTs with 1,910 participants, compared with placebo, supervised jaw exercise with stretching (MD on a 0–100 scale, 16.23, 95% CI 11.58 to 20.88; RD for achieving the minimally important difference of 5 points on the 100 point short form-36 physical component summary score 43%, 95% CI 33 to 51), manipulation (MD 16.30, 95% CI 7.77 to 24.83; RD 43%, 95% CI 25 to 56) and supervised jaw exercise with mobilisation (MD 13.11, 95% CI 5.42 to 20.81; RD 36%, 95% CI 19 to 51) all probably improved physical functioning.[72]

sufficient

Chronic musculoskeletal disorders

One systematic review evaluated the effects of aquatic exercise on a range of outcomes in the treatment of people with chronic musculoskeletal disorders. Aquatic exercise improved participants' physical function compared with no exercise (SMD 0.62, 95% CI 0.32 to 0.91; 14 RCTs, 739 participants: no evidence certainty rating) but there was no evidence of a difference compared with land-based exercise (SMD 0.13, 95% CI -0.20 to 0.46; seven RCTs, 369 participants: no evidence certainty rating).[73]

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Kinesiology taping

Chronic lower back pain

One systematic review evaluated the effects of kinesiology taping on disability in people with chronic lower back pain. Kinesiology taping was not better than placebo for managing disability in the short (SMD -0.14, 95% CI -0.72 to 0.45; four RCTs, 287 participants: low-certainty evidence) or intermediate term (SMD -0.34, 95% CI -1.42 to 0.75; two RCTs, 168 participants: very low-certainty evidence). When combined with physical activity, kinesiology taping did not improve disability more than physical activity alone (SMD 0.14, 95% CI -0.33 to 0.61; four RCTs, 254 participants: very low-certainty evidence).[61]

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5.2.3 Quality of life

Exercise

Chronic lower back pain

No evidence was identified that reported on quality-of-life outcomes for hands-off physical therapy interventions in people with chronic lower back pain.

Chronic neck pain

In the NMA that investigated the relative effectiveness of nine mind–body exercise interventions in people with chronic neck pain, based on a network of eight RCTs with 855

sufficient

participants, yoga plus HSF (MD 16.22 on a 0–100-point scale, 95% CI 0.67 to 31.77) and qigong (MD 6.52, 95% CI 1.40 to 11.64) significantly improved physical component scores of the 36-Item Short Form Health Survey (SF-36).[70] — sufficient

Fibromyalgia

One systematic review of mixed exercise interventions reported that individuals undertaking mixed exercise programmes that involved at least two of the three categories of aerobic/cardiorespiratory exercise, resistance/muscle training exercise or flexibility exercise, had improved health-related quality of life (HRQL) compared with those in control groups (MD -8.38 on a 0–100 scale (high scores indicate worse HRQL), 95% CI 13.00 to 3.75; nine RCTs, 412 participants: moderate-certainty evidence). Statistically significant benefits were reported at short-term (6–12 weeks) and intermediate-term (13–26 weeks) but not longer term (27–52 weeks) follow-up points. The authors note that, for fatigue, physical function, HRQL, and stiffness, a clinically relevant change cannot be ruled in or out, as the confidence intervals include both clinically important and unimportant effects.[65] — 1++

One systematic review reported that flexibility exercise training was not more effective than aerobic exercise (MD 4.41, 95% CI -5.77 to 14.05; two RCTs, 193 participants: very low-certainty evidence) or resistance exercise (MD 5.55, 95% CI -1.8 to 12.9; one RCT, 56 participants: low-certainty evidence) in improving HRQL in adults with fibromyalgia postintervention.[67] — 1++

A systematic review that evaluated the effects of creative or repetitive dance-based interventions in women with fibromyalgia reported that repetitive dance improved HRQL compared with control interventions (SMD 0.43, 95% CI 0.09 to 0.76; two RCTs, 138 participants: moderate-certainty evidence). No studies were identified that reported on the effects of creative dance on HRQL, however, the authors note that these were associated with larger effects on pain and fibromyalgia impact than repetitive dance interventions *(see section 5.2.1)*.[68] — 1++

Chronic musculoskeletal disorders

One systematic review evaluated the effects of aquatic exercise on a range of outcomes in the treatment of people with chronic musculoskeletal disorders. Aquatic exercise improved quality of life for participants compared with no exercise (SMD -0.64, 95% CI -0.94 to -0.34; 18 RCTs, 1,387 participants: no evidence certainty rating) but there was no evidence of effect for the comparison with land-based exercise (SMD -0.18, 95% CI 0.51 to 0.16; six RCTs, 277 participants: no evidence certainty rating).[73] — 1+

5.2.4 Advice

The addition of interventions based on CBT to physiotherapy programmes may be effective for people with whiplash-associated disorder.[74] — 1++

A systematic review of advice for the management of chronic low back pain found strong evidence to suggest that advice as an adjunct to exercise was more effective for improving pain, back specific function and work disability as opposed to advice alone. Advice in this sense was to stay active, along with specific advice regarding exercise and functional activities.[75] — 1++

5.2.5 Exercise delivery

Supervised exercise was found to be more effective for improving weekly training frequency than unsupervised exercise. Supplementing a home exercise programme with group exercise may increase overall physical activity levels.[74] — 1++

Performance accuracy is improved by refresher sessions or by providing audiotapes or videotapes of exercises.[74] — 1++

A systematic review of therapeutic interventions for patients with whiplash-associated disorder, including chronic whiplash of more than 12 weeks duration, indicated that an exercise programme was effective in relieving chronic whiplash-related pain in the short term although these gains were not maintained in the long term. The relative effectiveness of different exercise regimens was not determined.[76] 2+

5.2.6 Exercise adherence

A Cochrane review considering adherence to exercise in patients with chronic musculoskeletal conditions identified moderate-certainty evidence that:[74] 1++

- Individual-specific exercises are more effective than generic group exercise for improving attendance at exercise classes.
- Therapeutic programmes that specifically address adherence are effective in improving the frequency and duration of exercise, and attendance at sessions.
- Graded activity is effective in improving adherence to a home exercise programme.
- Adding CBT-based approaches to physiotherapy programmes is not effective in improving exercise adherence.

5.3 Evidence of harms

Exercise

Chronic back pain

Systematic reviews reported that adverse events from exercise interventions were generally not reported in the included trials and that it was not possible to draw conclusions about the safety or harms associated with exercise in people with chronic back pain. The small number of trials where adverse events were recorded report these to be few and minor in nature, for example, temporary muscle pain.[59,60,62-64] 1++ sufficient

Systematic reviews reported no clear difference between mind–body exercises (tai chi, yoga and qigong) and controls in risk of any adverse event.[62,63] 1++

Chronic neck pain

Three systematic reviews did not report the adverse events from exercise.[69-71] A further systematic review noted that no serious adverse events were reported in the four RCTs that included data on harms.[63] 1++ sufficient

Fibromyalgia

One systematic review described that mixed exercise interventions appeared to be well tolerated in people with fibromyalgia, but there was insufficient data on adverse events to calculate an effect estimate. There was no difference in all-cause study withdrawal between those undertaking exercise interventions and controls (risk ratio or relative risk (RR) 1.02, 95% CI 0.69 to 1.15; 19 RCTs, 1,065 participants: moderate-certainty evidence).[65] 1++

Similarly, a further systematic review reported flexibility exercise training to be well tolerated in people with fibromyalgia, but there was insufficient data on adverse events to calculate an effect estimate. There was no difference in study withdrawal between those undertaking flexibility exercise training compared with aerobic exercise (RR 0.97, 95% CI 0.61 to 1.55; five RCTs, 301 participants: very low-certainty evidence), or with resistance exercise (RR 1.43, 95% CI 0.77 to 2.67; three RCTs, 159 participants: low-certainty evidence) or with untreated controls (RR 1.78, 95% CI 0.37 to 8.44; one RCT, 34 participants: low-certainty evidence).[67] 1++

One systematic review noted that adverse events were poorly reported, and recorded no serious adverse events in any trial of exercise for people with fibromyalgia.[63] 1++

Two systematic reviews did not report on adverse events from exercise in people with fibromyalgia.[66,68] 1++

Osteoarthritis

One systematic review of exercise in people with knee, hip or hand osteoarthritis noted that most trials did not report harms. One of the 18 RCTs that provided data on knee osteoarthritis reported a larger, but temporary, increase in minor pain in people completing exercise interventions compared with sham interventions, however, the authors note the wide confidence interval (RR 14.7, 95% CI 2.0 to 107.7; one RCT, 150 participants: no evidence certainty rating). Four RCTs found no difference between exercise and comparators in worsening of pain symptoms and two RCTs reported no difference between exercise and standard analgesics in any adverse event. For hip osteoarthritis, two RCTs included data on harms and neither reported any adverse events in groups receiving exercise or usual care.[63] 1++

Chronic pain secondary to temporomandibular disorder

An NMA of interventions to manage TMD reported that no intervention was associated with significantly increased adverse events compared with placebo or sham procedures.[72] sufficient

Chronic musculoskeletal disorders

No evidence was identified on adverse effects of interventions for people with chronic musculoskeletal disorders specifically.

Kinesiology taping

Chronic lower back pain

No evidence was identified on adverse effects of kinesiology taping for people with chronic back pain.

5.4 Summary of benefits and harms of hands-off physical therapies for chronic pain

There is evidence of benefit for a wide range of exercise interventions across different pain types.

In people with chronic low back pain various exercise interventions can reduce pain in the short, intermediate and long term and can improve function in the short and intermediate term. In people with chronic neck pain various exercise interventions can reduce pain and improve function, although the effects were more inconsistent and based on low-certainty evidence. In people with fibromyalgia, exercise in different forms can provide small improvements in pain, although these may not be clinically significant. Effects on function were inconsistent and, where positive effects were reported, it was unclear whether these were clinically significant. There is evidence of short-term reduction in pain with mind–body exercises (yoga, tai chi or qigong) in people with osteoarthritis of the knee or hip which was sustained in the intermediate and long term for people with knee osteoarthritis. Similar effects on function were reported, although effect sizes varied from less than small to moderate. In people with TMD exercise combined with a range of structured physical therapies can reduce pain and improve function. No evidence was identified on the effects of exercise alone in people with chronic TMD pain. In people with mixed musculoskeletal pain types, one systematic review reported that aquatic exercise can reduce pain and that this effect may be greater than land-based exercise therapies. Aquatic exercise may also improve physical function compared with no exercise, but there was no evidence for an improvement compared with land-based exercise. Where reported, exercise interventions generally improved health-related quality of life.

Kinesiology taping did not improve pain or function compared with placebo in people with chronic low back pain.

No evidence was identified on the effect of mobility aids on chronic pain.

5.5 Other factors

The GDG acknowledged that while effects of individual physical activity interventions described in systematic reviews were limited to specific pain conditions, this does not always reflect the routine delivery of care to people with chronic pain, where exercise interventions are tailored to the individual's needs and may involve a range of activities.

Clinicians noted that there was restricted access to aquatic therapy or hydrotherapy facilities in NHS Scotland which may limit the implementation of this intervention.

Physical activities and exercise are available both within NHS Scotland and in self-led approaches with information freely available on NHS Inform. Members with lived experience of chronic pain in the GDG reflected on the fears and concerns experienced by the chronic pain community when considering and initiating physical activity. They acknowledged that many people were worried about further exacerbating existing pain. A realistic and achievable approach to initiating and maintaining physical activity based on shared understanding between individuals and professionals is vital. It is the responsibility of healthcare professionals to ensure a shared decision-making approach.

5.6 Recommendations

R **Physical activity (including exercise and exercise therapies), regardless of form, is recommended in the management of patients with chronic pain.**

R **Advice to stay active should be given alongside exercise therapy for patients with chronic low back pain to improve disability in the long term. Advice alone is insufficient.**

R **The following approaches should be used to improve adherence to exercise:**

- **supervised exercise sessions**
- **individualised exercises in group settings**
- **addition of supplementary material**
- **provision of a combined group and home exercise programme.**

✓ Any person-centred exercise and exercise therapies chosen should be based on shared decision making. It is pertinent that any recommendation is based on an individual's needs, capabilities and unique circumstances to help reduce barriers and facilitate a positive and meaningful experience.

6 Physical therapies (hands-on)

6.1 Introduction

Hands-on physical therapies are physical manipulation or manual contact using the hands to treat an injury, disability, condition or musculoskeletal pain. The main components are manual therapies (manipulation and mobilisation) and massage therapy. Manual therapy is a term encompassing mobilisation, or slow passive movements performed by a therapist within the physiological range of movement, while manipulation refers to application of manual thrust to a joint, at or near the end of the physiological range of motion by a physiotherapist, osteopath or chiropractor. Massage therapy is another form of passive treatment encompassing deep tissue massage, myofascial release, reflexology, sports massage and trigger point therapy.

While reflexology is often classified as a complementary therapy, studies are included in systematic reviews of massage techniques to assess effects on pain and function because it involves the direct, mechanical manipulation of soft tissues and physical nerve stimulation to create biological changes in the body.

6.2 Evidence of benefit

Nine systematic reviews, which were rated at high, acceptable or sufficient quality, were included. Seven employed meta-analysis[63,77-82] one used NMA,[83] and one conducted a narrative synthesis because of study heterogeneity.[84] Most reviews focused on chronic pain related to specific conditions (for example, low back pain, multiple sclerosis, myogenous TMD, neck pain, and pelvic pain), with two reviews covering multiple pain conditions. The certainty of evidence varied significantly across the outcomes of interest. While some evidence was rated as high quality, most of the evidence was rated as low to very low quality, affecting the reliability of their findings. Reasons identified for the lower certainty rating included methodological flaws, inconsistent study designs, and limited sample sizes, leading to uncertainty about the conclusions drawn from those studies.

1++
1+
sufficient

6.2.1 Pain intensity

Manual therapy

Chronic lower back pain

Three systematic reviews provide inconsistent evidence that manual therapy (manipulation and mobilisation) may reduce chronic low back pain[63,77,82] when compared with different comparators such as exercise or usual care in the short term, but the effect sizes are generally small, and the clinical significance of these reductions varies and is often unclear.

1++
1+

One systematic review reported that manipulation or mobilisation compared with an active comparator (exercise or physical therapy) resulted in a reduction in chronic lower back pain measured closest to one-month postintervention (4–8 weeks from baseline) (SMD -0.28, 95% CI 0.47 to 0.09; nine RCTs, 1,176 participants: moderate-certainty evidence). Compared with other active comparators, manipulation resulted in reduced pain at three-months follow-up (SMD -0.68, 95% CI -1.14 to 0.23; three RCTs, 370 participants: moderate-certainty evidence) and six-months follow-up (SMD -0.72, 95% CI 0.99 to 0.45; three RCTs, 223 participants: moderate-certainty evidence). Effects of mobilisation at both three- and six-months follow-up did not significantly change from post-treatment.[77]

1+

In contrast, a systematic review of spinal manipulative therapies, including manipulation and mobilisation manual therapies, for chronic low back pain reported no clinically important benefits in pain reduction. Comparators included recommended pharmacological (for example,

1++

non-steroidal anti-inflammatory drugs (NSAIDs) or other analgesics) and non-pharmacological active (for example, exercise) treatments, non-recommended treatments (for example, light tissue massage, waiting list control or no treatment) and sham procedures.[82]

Spinal manipulative therapy was not statistically better than recommended comparators at one month (WMD -3.17, 95% CI -7.85 to 1.51; 17 RCTs, 3,155 participants: moderate-certainty evidence) and 12 months (WMD 1.86, 95% CI -4.79 to 1.07; 10 RCTs, 2,502 participants: moderate-certainty evidence). Although the difference was statistically significant at six months (WMD -3.09, 95% CI -5.42 to -0.77; 11 RCTs, 2,462 participants: moderate-certainty evidence), the size of the effect was reported by the authors as not clinically important.

Spinal manipulative therapy did not reduce pain at one-month follow-up (MD -7.55, 95% CI 19.86 to 4.76; eight RCTs, 831 participants: low-certainty evidence), at six-months follow-up (MD 0.96, 95% CI -6.34 to 8.26; two RCTs, 114 participants: very low-certainty evidence) or at 12-months follow-up (MD 0.20, 95% CI -5.33 to 5.73; one RCT, 63 participants: very low-certainty evidence). 1++

Spinal manipulative therapy employed as an adjuvant therapy resulted in a small, statistically significant, but not clinically important reduction in pain at one month (MD -6.93, 95% CI -10.36 to -3.49; six RCTs, 1,046 participants: moderate-certainty evidence) and 12 months (MD -3.31, 95% CI -6.60 to 0.02; two RCTs, 1,000 participants: moderate-certainty evidence). There was no statistical difference at six months (MD -6.77, 95% CI -14.07 to 0.53; two RCTs, 143 participants: low-certainty evidence).

The systematic review reported no significant difference in pain reduction between studies using manipulation and mobilisation techniques at one-month follow-up (MD 0.32, 95% CI -3.05 to 3.69; four RCTs, 509 participants: moderate-certainty evidence).[82]

A third systematic review reported no difference in the short term between spinal manipulation therapy and sham manipulation, usual care, an attention control-, or a placebo intervention for people with chronic lower back pain (MD -0.32 on a 0–10 VAS, 95% CI -0.55 to 0.10; four RCTs, 683 participants: low-certainty evidence). There was a small improvement in pain in those receiving spinal manipulation therapy at intermediate-term follow-up (MD 0.64, 95% CI 0.93 to -0.35; three RCTs, 978 participants: low-certainty evidence). 1++

Comparing manipulation with exercise, there were no differences in short-term (MD 0.31, 95% CI -0.42 to 1.06; three RCTs, 636 participants: low-certainty evidence) or intermediate-term pain outcomes (MD 0.23, 95% CI -0.14 to 0.59; four RCTs, 1,093 participants: low-certainty evidence).[63]

Chronic neck pain

Spinal manipulation was associated with a large improvement in pain (difference -3.05 on a 0–10 scale, 95% CI -3.30 to -2.80; one RCT, 42 participants: low-certainty evidence) over the short term compared with sham manipulation in people with chronic neck pain, but when compared with exercise therapy, there were no differences between groups (data not reported).[63] 1++

Another systematic review evaluated the effect of manipulation and mobilisation manual therapy techniques on chronic non-specific neck pain. Manipulation combined with an exercise programme did not result in a statistically significant reduction in postintervention pain compared with exercise alone measured closest to one-month postintervention (4–8 weeks from baseline) (SMD -0.37, 95% CI -0.77 to 0.03; five RCTs, 535 participants: moderate- to low-certainty evidence), closest to three-months follow-up (SMD -0.27, 95% CI -0.60 to 0.06; five RCTs, 481 participants: moderate to low-certainty evidence) or closest to six-months follow-up (SMD -0.20, 95% CI -0.54 to 0.14; four RCTs, 473 participants: moderate- to low-certainty evidence).[78] 1+

Fibromyalgia pain

Spinal manipulation did not reduce fibromyalgia pain compared with sham at short-term follow-up (adjusted difference (AD) on the 0–10 VAS -0.56, 95% CI -2.21 to 1.08; one RCT, 101 participants: low-certainty evidence) or at intermediate-term follow-up (AD -0.50, 95% CI -2.48 to 1.47; one RCT, 101 participants; low-certainty evidence).[63] 1++

Chronic pain associated with osteoarthritis of the hip

One systematic review identified two RCTs that evaluated manual therapy compared with usual care or exercise therapy. The only study reporting a pain outcome showed that manual therapy provided a small improvement in the short term in pain at rest and during walking compared with exercise (AD on the 0–10 VAS -0.72, 95% CI -1.38 to -0.05, and -1.21, 95% CI -2.29 to -0.25, respectively; one RCT, 53 participants: low-certainty evidence). In the intermediate term, effects on pain were inconsistent compared with exercise. A moderate effect on pain during walking was reported following manual therapy compared with exercise (AD -1.27, 95% CI -2.40 to -0.19), but there was no difference for pain at rest (AD -0.70, 95% CI -2.03 to 0.59).[63] 1++

Myogenous temporomandibular disorders

TMDs are common benign musculoskeletal disorders affecting up to 1 in 15 of the UK population.[85] Myogenous TMDs involve pain or dysfunction in the muscles used for chewing. One NMA evaluated the effects of manual therapy interventions on pain intensity in people with chronic myogenous TMDs. Manual therapy reduced pain intensity postintervention compared with placebo (SMD -1.10, 95% CI -1.69 to -0.51; based on network of 42 RCTs, 1,989 participants: low-certainty evidence).[83] sufficient

A further NMA evaluated the comparative effects of a wide range of interventions for TMDs, including manual therapies, on pain. Trigger point therapy (MD -2.08, 95% CI -2.31 to -1.84; based on a network of 153 RCTs, 8,713 participants: moderate-certainty evidence), jaw exercise plus stretching plus trigger point therapy (MD -1.31 on a 0–10-point scale, 95% CI -1.99 to -0.62: moderate-certainty evidence) and jaw exercise plus mobilisation (MD -2.86, 95% CI -3.21 to -2.52: low-certainty evidence) all reduced pain compared with placebo.[72] sufficient

Massage

Chronic lower back pain

One systematic review evaluated the effects of massage compared with attention control, sham or usual care on pain. A small short-term improvement in pain was reported in people receiving massage (MD -0.58 on a 0–10 scale, 95% CI -0.93 to -0.29; six RCTs, 703 participants: moderate-certainty evidence). There was no difference between massage and controls in intermediate-term pain (MD -0.02, 95% CI -0.56 to 0.44; three RCTs, 680 participants: moderate-certainty evidence).[63] 1++

Chronic neck pain

A systematic review evaluating myofascial release for chronic mechanical neck pain reported no significant difference in pain between myofascial release and a wide range of conventional interventions (for example, manual therapy, muscle energy technique, static stretching, suboccipital muscle inhibition technique, manual suboccipital inhibition technique, dry needling, postisometric relaxation, ultrasound therapy, combined interferential therapy, transcutaneous electric nerve stimulation (TENS) and massage) (SMD 0.35, 95% CI -0.80 to 0.09; 12 RCTs, 539 participants: low-certainty evidence).[81] 1+

A further systematic review identified two RCTs that evaluated the effects of massage (Swedish and Tuina) on pain compared with attention control (self-care education), exercise or waiting list. The review did not pool results for these RCTs as each used different comparators. 1++

In one small RCT, Tuina massage was associated with moderate improvement in pain intensity experienced during the previous seven days compared with waiting list controls (difference -1.8 on a 0–10 scale, 95% CI -2.7 to -0.9; one RCT; 64 participants: evidence certainty not reported). Another RCT reported no difference in intermediate-term pain comparing classical massage with neck co-ordination exercises (difference 0.2 on a 0–10 scale, 95% CI -0.82 to 1.22) or muscle performance exercises (no data given, p>0.05; one RCT, 108 participants: low-certainty evidence).[63] 1++

Fibromyalgia pain

One systematic review identified two RCTs (64 and 94 participants, rated at poor to fair quality) that evaluated myofascial release therapy compared with sham (for example, electrotherapy or disconnected magnotherapy). The authors note that there was insufficient evidence to determine the effects of myofascial release therapy on short-term pain or intermediate-term pain compared with sham.[63] 1++

Chronic pain associated with osteoarthritis of the knee

A systematic review included two RCTs that compared the effects of massage with usual care on pain. In the first RCT (125 participants) no significant effects were seen on the WOMAC subscale or VAS at four months after massage treatment versus usual care. The other RCT was of poor quality and reported a small short-term improvement in pain according to WOMAC pain score (difference -1.65 on a 0 to 20 scale, 95% CI -2.93 to -0.37; one RCT, 60 participants: insufficient certainty evidence).[63] 1++

Multiple sclerosis pain

A Cochrane systematic review identified two RCTs evaluating reflexology for chronic pain associated with multiple sclerosis. A meta-analysis was not possible because of methodological, clinical and statistically heterogeneity of included studies. Both RCTs compared reflexology (ten 45-minute weekly sessions provided by an accredited reflexology specialist) with sham. The review authors reported that in one RCT with 71 participants, compared with baseline, there was a similar clinically and statistically significant decrease in median pain measured using the VAS score in both the reflexology (50% decrease at week 10) and sham (50% decrease at week 10) groups which was maintained up to 22 weeks, but no significant differences between groups.

In the second RCT, 75 participants were randomised equally to either reflexology, relaxation or control groups. There were statistically and clinically significant differences in pain scores in the reflexology group (MD 2.56, confidence intervals not reported, p<0.001) and relaxation group (size of effect not reported p=0.01) immediately post-treatment, whilst no significant changes were reported in the control group (MD -0.28, confidence intervals not reported, p=0.34: very low-certainty evidence). The authors reported a significantly higher reduction in pain intensity scores in the reflexology group after the intervention, compared with the two other groups, but no significant differences between relaxation and control groups. This reduction in pain intensity was not sustained when measured two months after treatment.[84] 1++

Chronic pelvic pain

A systematic review evaluated myofascial manual therapies for chronic pelvic pain syndrome compared with active interventions (for example, general exercise, classic global massage, and anaesthetic injection) or usual care (for example, oral medications and counselling). Myofascial manual therapies did not significantly reduce pain compared with control (SMD -0.54, 95% CI -1.16 to 0.08; four RCTs, 198 participants: very low-certainty evidence).[79] 1+

Multiple pain conditions

One systematic review evaluated the effect of trigger point manual therapy (TPMT) in people experiencing chronic pain at a range of sites (for example, elbow, facial, foot, neck, pelvic, shoulder and wrist pain). The authors note that trigger points are described as nodules in muscle, located within taut bands, that are painful to palpation, reproduce the patient's symptoms, and cause referred pain. Trigger point manual therapy is believed to reduce symptoms through ischaemic compression by digital pressure and positioning of the affected muscle to ablate the trigger points. The review reported that TPMT did not reduce pain postintervention (SMD -0.53, 95% CI -1.08 to 0.02; 11 RCTs, 535 participants: low-certainty evidence).[80] 1+

6.2.2 Function

Manual therapy

Chronic lower back pain

Three systematic reviews reported on the effects of manual therapies on functional ability in people with chronic lower back pain.[63,77,82]

The first systematic review compared manipulation and mobilisation interventions with an active comparator (exercise or physical activity). Pooled data from people receiving manual therapy showed a statistically significant reduction in disability (SMD -0.33, 95% CI -0.63 to -0.03; seven RCTs, 923 participants: moderate-certainty evidence). Subgroup analysis showed a statistically significant larger effect with manipulation (compared with other active comparators SMD -0.86, 95% CI -1.27 to -0.45; three RCTs, 225 participants: moderate-certainty evidence). Mobilisation interventions did not show a statistically significantly larger reduction in disability after treatment compared with other active comparators (SMD -0.10, 95% CI -0.28 to 0.07; five RCTs, 698 participants: moderate-certainty evidence). Data were available for six-months follow-up comparing manipulation with other active comparators. The pooled estimate was an SMD of -0.71 (95% CI -0.98 to -0.44; three RCTs, 223 patients: moderate-certainty evidence). Mobilisation intervention effects at three and six-months follow-up did not significantly change from post-treatment.[77] 1+

Another systematic review evaluated spinal manipulative therapies including manipulation (thrust) and mobilisation (non-thrust) therapy techniques for chronic low back pain compared with recommended therapies, non-recommended therapies or sham spinal manipulation *(see section 6.2.1)*.

Spinal manipulative therapies resulted in a small improvement in function at one month compared with recommended therapies (SMD -0.25, 95% CI -0.41 to -0.09; 16 RCTs, 3,090 participants: moderate-certainty evidence). There was no statistically significant improvement at six months (SMD -0.09, 95% CI -0.21 to 0.03; 12 RCTs, 2,762 participants: moderate-certainty evidence) or at 12 months (SMD -0.09, 95% CI -0.23 to 0.04; 11 RCTs, 2,635 participants: moderate-certainty evidence).

Spinal manipulative therapies resulted in a small improvement in function at one month compared with non-recommended therapies (SMD -0.41, 95% CI -0.67 to -0.15; seven RCTs, 835 participants: high-certainty evidence), at six months (SMD -0.29, 95% CI -0.50 to -0.09; four RCTs, 373 participants: moderate-certainty evidence) and at 12 months (SMD -0.42, 95% CI -0.72 to -0.11; one RCT, 169 participants: low-certainty evidence). 1++

Spinal manipulative therapies resulted in a small improvement in function at one month compared with sham spinal manipulative therapy (SMD -0.73, 95% CI -1.35 to -0.11; six RCTs, 748 participants: low-certainty evidence) but this was not maintained at six months (SMD -0.12, 95% CI -0.50 to 0.25; two RCTs, 114 participants: very low-certainty evidence) or at 12 months (SMD -0.19, 95% CI -0.69 to 0.31; one RCT, 63 participants: very low-certainty evidence).

Where spinal manipulative therapy was used as adjuvant therapy, there were improvements in function at one month (SMD -0.29, 95% CI -0.55 to -0.03; four RCTs, 955 participants: moderate-certainty evidence) and 12 months (SMD -0.21, 95% CI -0.34 to -0.09; one RCT, 994 participants: low-certainty evidence) but not at six months (SMD -0.30, 95% CI -0.64 to 0.03; two RCTs, 142 participants: low-certainty evidence).

No significant differences were reported in function between groups receiving manipulation or mobilisation at one month (SMD 0.16, 95% CI -0.42 to 0.74; four RCTs, 520 participants: low-certainty evidence) or six months (SMD 0.16, 95% CI -0.16 to 0.46; one RCT, 175 participants: low-certainty evidence).[82] 1++

In the third systematic review, a small improvement in function was identified for manual therapies at short-term follow-up (SMD -0.24, 95% CI -0.61 to -0.09; four RCTs, 859 participants: low-certainty evidence) and intermediate-term follow-up (SMD -0.40, 95% CI -0.85 to -0.05; three RCTs, 1,000 participants: low-certainty evidence).[63] 1++

Chronic neck pain

Two systematic reviews provided evidence on the effects of manual therapies on function in people with chronic neck pain.

The first systematic review provided separate analyses for studies involving unimodal and multimodal therapies. For unimodal studies, the review compared the effect of thrust interventions that included an exercise regimen to exercise alone on function at timepoints closest to one, three, and six-months follow-up. There was no significant difference in function between thrust interventions plus exercise and exercise only groups at any time point.

Given the heterogeneity and varying combinations of interventions being used for each programme, the authors did not conduct a meta-analysis of multimodal studies (which included combination therapies, such as chiropractic care, manual and physical therapy combined with commonly-prescribed exercises, massage, ultrasound, education, or advice in which the effect of the thrust or non-thrust could not be distinguished from that of the programme). Of the eight multimodal RCTs measuring functional disability as an outcome, seven reported improved function using a multimodal approach although the size of effect and clinical significance was not stated.[78] 1+

A further systematic review identified a single RCT which evaluated spinal manipulation compared with sham manipulation or exercise. Spinal manipulation resulted in a moderate improvement in function (difference -18.67 on the 0–100-point Neck Disability Index, 95% CI -26.04 to -11.30; one RCT, 42 participants: low-certainty evidence) over the short term compared with sham manipulation, but when compared with exercise therapy, there were no differences between groups (effects not reported).[63] 1++

Fibromyalgia pain

A systematic review identified one RCT that evaluated the effect of spinal manipulation compared with sham on function. There were no differences between groups in function measured by the Fibromyalgia Impact Questionnaire (0–100, higher score represents greater impact on fibromyalgia) in the short term (AD 1.2, 95% CI -4.9 to 7.3; one RCT, 101 participants: low-certainty evidence) and intermediate term (AD -1.1, 95% CI -7.9 to 5.6; one RCT, 101 participants: low-certainty evidence).[63]

Chronic pain associated with osteoarthritis of the hip

A systematic review identified two RCTs that evaluated the effects of manual therapy compared with usual care (continued routine care from a general practitioner and other providers) and combination exercise programmes on function. One RCT reported that manual therapy resulted in an improvement in function in the intermediate term using the total WOMAC score (0 to 240) 1++

in the manual therapy group (mean change from baseline -22.9, 95% CI -43.3 to -2.6), but there was no significant change from baseline in the usual care group (mean change -7.9, 95% CI -30.9 to 15.3) or exercise group (mean change -12.4, 95% CI -27.1 to 2.3; one RCT, 69 participants: low-certainty evidence). The authors noted that a lack of data prevented calculation of effect size, and further results were not presented. Compared with exercise, one RCT showed that manual therapy resulted in a small improvement in short-term function (adjusted difference on the 0–100-point Harris Hip Score of 11.1, 95% CI 4.0 to 18.6; one RCT, 109 participants: low-certainty evidence) and intermediate-term function (adjusted difference 9.7, 95% CI 1.5 to 17.9; one RCT, 109 participants: low-certainty evidence) compared with exercise.[63] 1++

Chronic pain associated with osteoarthritis of the knee

A systematic review identified a single RCT that evaluated the effect of joint manipulation on function compared with usual care. The manipulation group showed a statistically significant improvement from baseline in function as measured by the WOMAC score (mean change -31.5 on a 0-240 scale, 95% CI -52.7 to -10.3), whereas the usual care group showed no significant improvement (mean change 1.6, 95% CI -10.5 to 13.7; one RCT, 58 participants: insufficient certainty evidence). The authors note that insufficient data was provided to calculate an effect estimate.[63] 1++

Chronic pelvic pain syndrome

A systematic review evaluated studies comparing myofascial manual therapies with various control procedures in people with chronic pelvic pain syndrome. Four RCTs of myofascial manual therapies, which used osteopathic manipulative treatment or global therapeutic massage as comparators, were combined in meta-analysis. Myofascial manual therapies did not significantly improve function compared with other procedures (effect size -0.37, 95% CI -0.87 to 0.13; four RCTs, 187 participants: very low-certainty evidence).[79] 1++

Massage

Chronic lower back pain

A systematic review evaluated the effect of a range of massage techniques (such as acupressure, myofascial release, reflexology and Swedish massage) on function compared with sham or usual care in people with chronic lower back pain. A small improvement in short-term function was reported for people receiving massage compared with control (SMD -0.40, 95% CI -0.62 to -0.24; seven RCTs, 753 participants: moderate-certainty evidence). This improvement was not maintained in the intermediate term (SMD -0.09, 95% CI -0.26 to 0.12; three RCTs, 676 participants: low-certainty evidence).[63] 1++

Chronic neck pain

A systematic review evaluated the effect of massage (Swedish and Tuina) on function compared with attention control (self-care education), exercise or waiting list. There was no significant difference between Swedish massage and attention control (≥5 point improvement on the Neck Disability Index) in the short term (39% versus 17%, RR 2.7, 95% CI 0.99 to 7.5) or intermediate term (57% versus 31%, RR 1.8, 95% CI 0.97 to 3.5; one RCT, 64 participants: low-certainty evidence). People receiving massage experienced a small improvement in function in the short term compared with attention or waiting list control (pooled difference -3.66 on a 0-50 Neck Disability Index scale, 95% CI -6.58 to -0.56; two RCTs, 148 participants: low-certainty evidence).[63] 1++

A further systematic review evaluated the effect of myofascial release therapy on function compared with various interventions including electrotherapy, physical therapy and traction in people with chronic mechanical neck pain. No improvement in function was reported for myofascial release therapy measured using the Neck Disability Index (SMD -0.21, 95% CI -0.58 to 0.16; eight RCTs, 379 participants: moderate-certainty evidence).[81] 1+

Fibromyalgia pain

A systematic review included two RCTs that evaluated myofascial release therapy compared with a sham intervention in people with chronic fibromyalgia pain. Myofascial release therapy resulted in a small improvement in intermediate-term function compared with sham as measured by the Fibromyalgia Impact Questionnaire (FIQ 0–100, higher score represents greater impact of fibromyalgia) (mean score 58.6, standard deviation, (SD) 6.3 versus mean score 64.1, SD 18.1, p=0.048) for the group in one fair-quality trial. The effect did not persist in the long term (mean score 62.8 (SD) 20.1 versus mean score 65.0 (SD) 19.8, p=0.329 at 12 months. (one RCT, 94 participants: low-certainty evidence).[63] 1++

Chronic pain associated with osteoarthritis of the knee

A systematic review evaluated the effect of massage on function compared with usual care in people with chronic pain associated with osteoarthritis of the knee. Two RCTs were identified in which function was measured using the WOMAC total and physical function subscale scores. In one RCT, no significant effects were seen four months after massage treatment compared with usual care (effect sizes not reported; one RCT, 125 participants: insufficient certainty evidence). In the other, poor-quality, RCT there was no difference between groups in short-term function according to the WOMAC physical function scale (difference -1.63 on a 0 to 68 scale, 95% CI -6.72 to 3.46; one RCT, 60 participants: insufficient certainty evidence).[63] 1++

Multiple sclerosis pain

A Cochrane systematic review identified one RCT evaluating the effect of reflexology on function in people with chronic pain associated with multiple sclerosis. The RCT compared reflexology (ten 45-minute weekly sessions provided by an accredited reflexology specialist) with sham. Both intervention and sham groups showed significant decrease in disability at 10 weeks post-intervention on the RMDQ (effect size not reported; one RCT; 71 participants: very low-certainty evidence).[84] 1++

Multiple pain conditions

One systematic review evaluated the effect of TPMT on function in people experiencing chronic pain at a range of sites (for example, elbow, facial, foot, neck, pelvic, shoulder and wrist pain). Trigger point manual therapy improved function compared with control (for example, dry needling, manual therapy and placebo) (SMD -0.81, 95% CI, -1.49 to -0.14; 15 RCTs, 802 participants: low-certainty evidence).[80] 1+

6.2.3 Quality of life

Manual therapy

Chronic neck pain

One systematic review compared the effect of manipulation plus exercise with exercise alone on quality of life in people with chronic neck pain. No statistically significant effects were reported at one-month (SMD 0.19, 95% CI, -0.28 to 0.66; three RCTs, 405 participants), three-months (SMD 0.25, 95% CI, -0.30 to 0.80; three RCTs, 405 participants) and six-months follow-up (SMD 0.07, 95% CI, -0.46 to 0.59; three RCTs, 405 participants). The quality of the evidence was rated as moderate to low overall by the authors.[78] 1+

Massage

Two systematic reviews reported no statistically significant effect from massage interventions on quality of life in people with chronic pain (including musculoskeletal, pelvic and facial pain).[79,80] 1+

In the systematic review of reflexology for chronic pain associated with multiple sclerosis, the authors reported that one RCT found significant improvements on the Multiple Sclerosis Impact Scale-29 psychological subscale in both intervention and sham groups by week 10. The intervention group demonstrated a greater improvement.[84] 1++

6.2.4 Adherence to intervention

No evidence was identified on this outcome.

6.2.5 Healthcare use or attendance

Three systematic reviews were identified that investigated healthcare utilisation associated with manual therapies in people with chronic pain.[63,80,84] The review authors were unable to identify any data. 1++ 1+

6.3 Evidence of harms

Seven out of the nine systematic reviews of hands-on physical therapies for chronic pain reported on adverse events or reactions.[63,77-82] In general, few adverse events were reported and were not associated with significant effects.

6.3.1 Manual therapy

Four systematic reviews provided data on adverse events or reactions associated with manual therapies.[63,77,78,82] Information provided by the included RCTs was limited. The most common adverse event was an increase in pain following manual therapy. In one systematic review, one serious adverse event was judged by the Data Safety Monitoring Board of one RCT as possibly being related to spinal manipulative therapy.[82] 1+ 1++

6.3.2 Massage

Four systematic reviews provided data on adverse events or reactions associated with massage.[63,79-81] Information provided by the included RCTs was limited. The most common adverse event was increase in pain following massage. However, this was mild in severity and temporary in nature. One systematic review investigating TPMT found that most studies reported no adverse events. In the three RCTs that reported any adverse events, these included increased pain, infection, gastrointestinal disturbance and constitutional symptoms. Overall there was no significantly increased risk of adverse events in the treatment group (OR 2.04, 95% CI 0.88 to 4.73; three RCTs, 200 participants: low-certainty evidence).[80] 1+ 1++

6.4 Summary of benefits and harms of hands-on physical therapies for chronic pain

Systematic reviews are largely consistent in suggesting that manual therapy (manipulation and mobilisation) offers modest pain reductions for certain conditions, for example, low back pain, but the effect sizes are generally small, and the clinical significance of these reductions is unclear in some cases. There is also variability in how people with different pain conditions respond to manual therapy, with conditions such as lower back pain responding better than chronic neck pain, where effects were inconsistent, and fibromyalgia, where no beneficial effects of manipulation were reported. For all conditions, the certainty of evidence is often rated as moderate to low, which reduces confidence in these findings.

The evidence for massage therapy as a means of pain reduction is inconsistent. While some interventions show positive effects, in small, short-term studies, the overall certainty of the evidence is low or very low. This suggests that while there may be some potential benefits from reflexology, myofascial release, and massage therapies for chronic pain, these interventions are not consistently effective across all types of chronic pain, and more high-quality research is needed to provide reliable conclusions.

The evidence for the effects of manual therapies or massage on function is also inconsistent. While systematic reviews report modest short-term improvements in function for people with chronic back pain and in those with chronic hip osteoarthritis, manual therapy did not enhance function for people with chronic pelvic pain, fibromyalgia, or chronic neck pain. While certain manual therapies, such as reflexology, trigger point therapy and massage may provide small short-term improvements in function for specific chronic pain conditions, the evidence certainty is often low, and the effects may not be sustained in the long term.

No evidence of the effect of manual therapies on quality of life, adherence to therapies, healthcare use or attendance was identified.

The GDG considered the large volume of low-certainty evidence, which described inconsistent effects on pain and function across different populations of people with chronic pain conditions. As no intervention appeared to be universally beneficial in all groups, the group decided that recommendations supporting manual therapies should not be applied universally to all people experiencing chronic pain and have made more specific recommendations in line with the strongest evidence of benefit.

6.5 Other factors

The study populations are representative of the chronic pain population in Scotland. The current picture across Scotland is that most local clinical pathways for the management of these conditions have a strong focus on supported self-management approaches and active treatments. Realistic medicine has also become an integral approach to care. Therefore, whilst passive treatments such as manual therapy are considered an option in the management of certain chronic pain conditions along with other interventions such as exercise, there is uncertainty with regards to the availability and feasibility of delivering these treatments to patients with chronic pain within Scotland.

The GDG acknowledges that pain scores are not a standard outcome measure used by pain services across Scotland, with the focus being on function and quality of life measures, and has taken this into account in forming the recommendation.

6.6 Recommendations

R **Manual therapy may be considered for short-term improvement in function in people with chronic low back pain or hip osteoarthritis.**

7 Psychological interventions

7.1 Introduction

Psychological factors, alongside biological and social factors, are known to affect the experience of pain. People's beliefs, understanding and responses to living with pain may contribute to their experiences of distress and disability.[86,87] Hence, psychological treatment should always be considered as part of a holistic approach to pain management.

Psychological therapies or interventions may be useful in addressing the complexity of the pain experience. The Psychological Therapies standards published by Public Health Scotland defines psychological interventions as 'a range of evidence-based therapies and interventions, based on psychological concepts and theory, which are designed to help people understand and make changes to their thinking, behaviour, and relationships in order to relieve distress and to improve functioning'.[88]

Following this definition, this section focuses on psychological interventions categorised by the NHS Education for Scotland Matrix – a guide to delivering evidence based psychological therapies and interventions in Scotland as enhanced or specialist psychological practice. The benefits of psychological therapies are described in language and concepts that are considered active in terms of response and control, in contrast to passive and catastrophising behaviours and responses. Psychological therapies reflect Engel's biopsychosocial model, which is the gold standard model to understand chronic pain and which challenges the concept of mind–body dualism (which has the potential for stigmatisation of secondary pain experiences).[89,90]

However, mind–body dualistic thinking remains prevalent and people who live with pain may have to wait a long time to access pain services, which may lead to poor confidence in or mistrust of healthcare provision.[91] It is important that the benefits of psychological therapies are presented clearly with a strong person-centred focus.

Evidence-based national guidelines on management of chronic pain have recommended acceptance and commitment therapy (ACT) and/or CBT alongside pain management programmes (PMP), self-management programmes and mindfulness-based interventions.[47] While there is a large variety of psychological therapies available to manage chronic pain (including music therapy, pain reprocessing therapy, and emotional awareness and expression therapy), the inclusion of therapies is guided by, and overlaps greatly with, the psychological treatments covered by the Matrix. Further information is available in the Matrix – a guide to delivering evidence based psychological therapies and interventions in Scotland.

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7.2 Definitions

Cognitive behavioural therapy is an approach to engaging with how people think and behave in response to pain. CBT is founded on core principles related to addressing unhelpful thoughts and behaviours that result from living with pain.

Acceptance and commitment therapy, a third-wave cognitive therapy, is a form of psychotherapy that encourages people to accept their thoughts and feelings related to living with pain, to identify what they cannot control and put their energy into positive actions that enrich their lives. The focus is on an increase in acceptance and in engagement with valued activities, rather than disability or distress.

Mindfulness-based stress reduction (MBSR) is a group intervention that seeks to reframe a person's relationship to pain through detached self observation. It relies on training in mindfulness meditation to cope with stress, illness and pain.[92]

Biofeedback is a form of operant conditioning where people learn how to modify some of their behavioural responses to improve their health.

Relaxation therapy is a treatment that uses relaxation techniques to promote feelings of well-being and calmness.

7.3 Evidence of benefit

7.3.1 Cognitive behavioural therapy

A Cochrane systematic review with meta-analysis investigated the effectiveness of CBT and ACT delivered face to face for people with chronic pain.[93] The most frequently included pain conditions were fibromyalgia (19 studies), chronic lower back pain (16 studies), mixed chronic pain conditions (15 studies), rheumatoid arthritis (nine studies), osteoarthritis (five studies) and TMD (four studies). CBT was compared with either treatment as usual (TAU) which included participants being placed on a waiting list or an active control. Active comparators included exercise programmes, medical procedures, education or support group.

When compared with treatment as usual, CBT resulted in a small reduction in pain intensity (SMD -0.22, 95% CI -0.33 to -0.10; 29 RCTs, 2,572 participants: moderate-certainty evidence), disability (SMD -0.32, 95% CI -0.45 to -0.19; 28 RCTs, 2,524 participants: low-certainty evidence) and distress (SMD -0.34, 95% CI -0.44 to -0.24; 27 RCTs, 2,559 participants: moderate-certainty evidence) at the end of treatment.[93]

When compared with an active comparator, CBT resulted in a very small reduction in pain (SMD -0.09, 95% CI -0.17 to -0.01; 23 RCTs, 3,235 participants: moderate-certainty evidence), disability (SMD -0.12, 95% CI -0.20 to -0.04; 19 RCTs, 2,543 participants: moderate-certainty evidence) and distress (SMD -0.09, 95% CI -0.18 to -0.00; 24 RCTs, 3,297 participants: moderate-certainty evidence) at the end of treatment for people with chronic pain. Benefits were statistically significant but owing to the range of measurement scales used it was not possible to assess clinical significance. Reductions in pain and disability at the end of treatment did not persist when outcomes were considered at follow-up of six months or more. There was evidence of a small reduction in distress at follow-up (SMD -0.13, 95% CI -0.25 to -0.01; 16 RCTs, 1,757 participants: moderate-certainty evidence).[93] 1++

A further Cochrane systematic review with meta-analysis examined the effectiveness of remote psychological therapies for people with chronic pain.[94] The majority of studies were in people with chronic back pain, fibromyalgia or mixed chronic pain populations. Interventions were scalable to a large group of people with chronic pain, delivered primarily through technology (such as web-based and smartphone apps and virtual reality) and involved less than 30% contact time with a clinician.

Remote CBT resulted in small reductions in pain intensity (SMD -0.28, 95% CI -0.39 to -0.16; 20 RCTs, 3,206 participants, moderate-certainty evidence) and functional disability (SMD -0.38, 95% CI -0.53 to -0.22; 14 RCTs, 2,672 participants, low-certainty evidence) compared with TAU at the end of treatment. There was very low-certainty evidence of no benefit on QoL. The reduction in pain intensity did not persist at follow-up of three to 12 months. There were no statistically significant benefits to functional disability or QoL at follow-up.[94]

Remote CBT resulted in a small reduction in pain intensity (SMD -0.28, 95% CI -0.52 to -0.04; three RCTs, 261 participants, moderate-certainty evidence) compared with active control. There was no evidence of benefit to functional disability or QoL. Based on very low-certainty evidence there was no difference between interventions at follow-up.[94]

7.3.2 Acceptance and commitment therapy

When compared with treatment as usual, ACT resulted in a large reduction in pain intensity at the end of treatment (SMD -0.83, 95% CI -1.57 to -0.09; two RCTs, 162 participants: very low-certainty evidence). No evidence was reported regarding the outcomes of disability or distress. One small study (104 participants) assessed as being very low certainty reported that ACT provided a large reduction in pain intensity at six-months follow-up, (MD -1.10, 95% CI -1.51 to -0.69).[93]

When compared with active comparators, at the end of treatment there was no evidence of benefit to pain intensity (SMD -0.25, 95% CI -0.63 to 0.12; five RCTs, 385 participants: very low-certainty evidence) or distress (SMD -0.30, 95% CI -0.70 to 0.10; five RCTs, 385 participants: very low-certainty evidence). At follow-up, the finding was similar for pain intensity and for distress but for disability there was very low-certainty evidence of a large benefit from ACT (SMD -1.22, 95% CI -2.28 to -0.17; two RCTs, 156 participants).[93]

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For remote ACT (remote delivery with no more than 30% contact time with a clinician) compared with TAU there was no evidence of benefit to outcomes of pain intensity (four RCTs) or functional disability (two RCTs). In both cases evidence was assessed as very low certainty. Findings were similar for follow-up at three to 12 months.[94]

For remote ACT compared with active comparator therapies only one study was identified providing very low-certainty evidence of no likely benefit to pain intensity at the end of treatment. Based on two RCTs there was very low-certainty evidence of no likely benefit to QoL at end of treatment. Only one small trial (50 participants) was identified which provided low-certainty evidence of no benefit to QoL at follow-up.[94]

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7.3.3 Mindfulness-based stress reduction

A network meta-analysis compared CBT with MBSR for the outcomes of pain intensity, physical functioning and depression in adults with chronic pain. The review identified 21 studies, which mostly involved participants with fibromyalgia and chronic low back pain.[95] Nine RCTs were rated as poor quality. The certainty of the evidence was not reported.

Only one study in the network directly compared CBT with MBSR for improving pain intensity. Thirteen studies compared CBT with control and five studies compared MBSR with control. When the direct and indirect evidence (1,364 participants) was combined there was no evidence of a difference between the therapies (SMD 0.02, 95% Credible Interval (CrI) -0.43 to 0.48).

Only one study in the network directly compared CBT with MBSR for improving function. Eleven studies compared CBT with control and five studies compared MBSR with control. When the direct and indirect evidence (1,320 participants) was combined there was no evidence of a difference between the therapies (SMD -0.02, 95% CrI -0.49 to 0.42).

Only one study in the network directly compared CBT with MBSR for improving depressive symptoms. Nine studies compared CBT with control and six studies compared MBSR with control. When the direct and indirect evidence (1,306 participants) was combined there was no evidence of a difference between the therapies (SMD -0.06, 95% CrI -1.08 to 0.47).

sufficient

In one large systematic review and meta-analysis of non-pharmacological treatments for chronic pain, there was no evidence of benefit to pain from MBSR in the short term compared with usual care or attention control (where the control group completes some activities but they are not the same in intensity, time and/or contacts as the intervention activities; activities may or may not be similar to usual care) (MD -0.88 on a 0 to 10-point scale, 95% CI -1.82 to 0.08; five studies, 630 participants: moderate-certainty evidence).[63] When two poor-quality trials were excluded from the analysis there was a small statistically significant improvement

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in short-term pain (MD -0.68, 95% CI -1.29 to -0.28; three studies, 546 participants: moderate-certainty evidence). One study provided evidence of improvement in pain in the intermediate term (MD -0.75, 95% CI -1.16 to -0.34; 229 participants: low-certainty evidence).

For short-term function there was low-certainty evidence that MBSR had no clear effect (SMD -0.14, 95% CI -0.51 to 0.02; four RCTs, 581 participants) when compared with usual care or attention control. Individual trials found no evidence of benefit from MBSR to intermediate or long-term function. 1++

7.3.4 Biofeedback

The systematic review of non-pharmacological treatments for chronic pain identified insufficient and inconsistent evidence for biofeedback in people with fibromyalgia. Four small, poor-quality trials were identified.[63] Because of the wide range of function scales used, no meta-analysis could be conducted. Three of these studies reported no difference in function between people receiving biofeedback or attention control. The fourth trial (40 participants) compared biofeedback with escitalopram and reported improved mean FIQ scores at 4–5 months follow-up and a statistically significant improvement in pain score of -2.7 on a VAS. 1++

7.3.5 Relaxation

The systematic review of non-pharmacological treatments for chronic pain identified one poor-quality study on progressive relaxation therapy compared with usual care, which showed no evidence of benefit to pain or function in people with chronic lower back pain. A further fair-quality trial found no difference in pain or function in the short or intermediate term between relaxation training and no intervention or exercise for people with chronic neck pain.[63] 1++

7.4 Evidence of harms

7.4.1 Cognitive behavioural therapy

Cochrane reviews report that adverse event data for psychological therapies in chronic pain were only recorded in a few studies and were not collected in a consistent manner. Minor events such as temporary pain exacerbation were noted. In one study of remote CBT there was an increase in adverse events, including increased pain, in the intervention group (RR 6.00, 95% CI 2.2 to 16.40; 140 participants, very low-certainty evidence).[93,94] 1++

7.4.2 Acceptance and commitment therapy

Two studies reported that there were no adverse effects linked to ACT compared with active controls.[93] 1++

7.4.3 Mindfulness-based stress reduction

In the systematic review comparing MBSR with usual care or attention control one trial reported temporarily increased pain in 29% of people undergoing MBSR, and three trials reported no harms.[63] 1++

7.4.4 Biofeedback

No evidence of harm was reported.

7.4.5 Relaxation

No evidence of harm was reported.

7.5 Summary of benefits and harms of psychological interventions for chronic pain

CBT, delivered either in person or remotely, can yield small improvements in pain intensity in the short term which are not sustained over time. Face-to-face CBT can also improve functional disability in the short term. ACT delivered in person may reduce pain compared with usual care but is no more effective than active comparators.

MSBR may have similar short-term effects on pain and function to CBT. There is no evidence of benefit of biofeedback or relaxation interventions.

Few harms from psychological therapies were reported, and most interventions appear to be low risk, although there is a lack of clarity on what constitutes an adverse event for psychological therapies, which may persist long term. Many people with chronic pain are affected by mood disorder comorbidities and, although not the target of treatment, psychological interventions may also support individuals' mental health.

7.6 Other factors

Studies included in the systematic reviews used a wide range of controls or TAU conditions, such as waiting lists, standard care, active treatments and attention controls, which makes drawing conclusions difficult. The recommendations are mostly based on evidence for short-term outcomes, that is, effects that are measured immediately after treatment, as the evidence for long-term outcomes is lacking or of low certainty when available. The volume of evidence was limited and evidence for other outcomes, such as acceptance, self efficacy or psychological flexibility was not sought.

Management of chronic pain involves multidisciplinary healthcare teams that can include psychology, nursing, physiotherapy, occupational therapy, pharmacy, medical and administrative staff.[45] For the face-to-face interventions, all studies reported delivery of the intervention by a psychologist or trainee psychologist under supervision of a psychologist. Ideally, psychologists who are trained to a doctoral level in behavioural change techniques (for example, health psychologists or clinical psychologists) deliver psychological treatment for chronic pain, however this is often not feasible in practice due to a lack of psychologists in the workforce. In NHS Scotland, healthcare professionals from other disciplines may deliver some psychological interventions in line with the competency-based approach described in the Matrix. The workforce competencies and skills framework categorises CBT and ACT within the specialist and enhanced types of psychological practices. Depending on local arrangements, further appropriate training may be required before delivering the interventions under supervision and within the structure of psychology-led local clinical governance.[88]

Given the difficulties accessing face-to-face psychological therapy (for example due to waiting times, rural living circumstances or reliance on patient transport), remote delivery should be considered and might be suitable for some circumstances and patients. The free online CBT platform Silvercloud is designed by clinical experts and supported by NHS Scotland and Scottish Government. It provides secure and supportive access to online programmes to help mental well-being and is flexible, allowing users to work at their own pace. Importantly, remote delivery would still involve contact with a trained health professional (typically around 30% contact time), to ensure person-centred delivered treatments rather than reflecting an online manualised intervention.

7.7 Recommendations

R **Offer CBT (either face-to-face or remotely) to people experiencing chronic pain.**

R **Consider offering face-to-face ACT to manage chronic pain in people who have a preference for an acceptance approach to pain.**

✓ CBT and ACT should be delivered by healthcare staff with appropriate training or a trainee under supervision of a trained health professional.

R **Consider offering MBSR (regardless of delivery mode) to manage chronic pain in people where there is a preference for mindfulness approaches to pain.**

8 Occupation-based interventions

8.1 Introduction

What constitutes a meaningful activity will vary from person to person, and might include hobbies, exercise, social activities or employment (paid and voluntary). Chronic pain can hinder people engaging in meaningful activities, affecting their self care, productivity or leisure occupations. Occupation-based interventions in the context of chronic pain support individuals to engage in meaningful activities even in the presence of pain. Occupation is defined by the World Federation of Occupational Therapists as 'the everyday activities that people do as individuals, in families and with communities to occupy time and bring meaning and purpose to life', meaning that the term occupation relates to all activities a person participates in and not restricted to only work and employment-based activities.

Reducing pain intensity is not an intended outcome of occupation-based interventions, although some may report changes in their pain experience. These interventions help individuals identify valued activities and align well with the ACT model of psychological flexibility. Engagement in meaningful activities can support improvements in areas such as mood, motivation, independence, routine and sense of purpose. Activity management interventions, informed by pain science, can improve a person's ability to do more over time despite ongoing pain.

Occupational-based interventions are often part of wider programmes of self management (in a secondary care pain service, and/or a tertiary level PMP) and it can be difficult to measure their impact as stand-alone interventions. They tend to be person-centred and vary in delivery, making objective comparison challenging.

8.2 Evidence of benefit

Three systematic reviews on the effectiveness of occupation-based interventions for chronic non-malignant pain were identified. These focused on pacing,[96] return to work (RTW)[97] and sleep hygiene.[98] After review of the evidence on sleep hygiene, the GDG noted that it aligns more closely with non-pharmacological sleep interventions for people with chronic pain which falls outside of the remit of this guideline.

After excluding sleep hygiene, the evidence base consisted of 18 RCTs across two intervention areas (RTW and pacing). The evidence was inconclusive due to variations in study design, RTW and pacing definitions, and intervention delivery formats, making it difficult to support any specific RTW or pacing approach for people with chronic pain. In addition, occupational performance and participation in meaningful activities were not an outcome focus for these trials.

A systematic review of 13 RCTs examined the effectiveness of RTW interventions for people with chronic pain on sick leave.[97] The primary outcome was RTW, which was measured in a range of ways including, number of days per month without receipt of sickness benefit, self-reported return to occupation, early retirement rates and cessation of wage loss. Most of the studies involved multiple components and there was a wide range of control conditions. Duration of intervention and follow-up also varied and heterogeneity across the studies meant that meta-analysis was not possible. 1+

Five of the 13 studies showed statistically significant improvements in RTW rates, however, three of these five studies were assessed at being at high risk of bias.

Pacing is a strategy for balancing physical, mental, and emotional activity with rest to avoid exacerbating pain and fatigue and improve function, and can involve activity planning as well as adjustment. A narrative systematic review of five RCTs examined the effectiveness of pacing 1+

as a learned strategy for people with chronic pain.[96] Meta-analysis was not possible due to heterogeneity in interventions and outcome measures. Based on three studies that reported pain outcomes, the review concluded that pacing as a learned strategy does not significantly reduce pain in people with chronic pain due to osteoarthritis or fibromyalgia. This finding is in line with expectations, as the aim of this intervention is improved function rather than pain reduction and none of the interventions used an occupation-based approach in which pacing was implemented practically within an occupation under the guidance of a therapist. 1+

Occupational therapists support people with chronic pain to regulate their activity, which aims to improve function by addressing an integrated range of approaches including, but not limited to, pacing alone.

No further RCTs were identified on other occupation-based interventions, including energy conservation strategies, postural and positional strategies, sensory integration strategies, therapeutic education and disease self-management training, advocacy skills development, community reintegration strategies, environmental adaptations and equipment provision, and engagement in meaningful daily activity or meaningful occupation.

8.3 Evidence of harms

There are limited reports of adverse events. One RTW trial focusing on CBT resulted in delayed RTW versus usual care. Findings highlight the need to consider RTW intervention effectiveness and the potential hinderance or delay to RTW.[97] 1+

Since occupation-based interventions encourage people to engage in self-identified movement and activities in a way that is within their capacity, it would not be anticipated for harm to be directly related to these interventions.

8.4 Summary of benefits and harms of occupation-based interventions for chronic pain

The low volume of evidence with inconsistent findings is insufficient to support recommendations. Variations in study designs, heterogeneity across studies, and differences in RTW and pacing definitions impact on generalisation to the wider chronic pain population. Even in the context of low volume evidence, expert clinicians acknowledge that work and activity dysregulation issues are common amongst the chronic pain population and to not address these issues would mean disregarding needs identified by people with lived experience.[45]

The evidence base shows little to no evidence of harm related to occupation-based interventions. Expert clinicians highlight areas for consideration for measuring RTW interventions and for the delivery of pacing (activity management) interventions.[45]

8.5 Other factors

The GDG discussed issues relating to the design and implementation of studies on RTW and pacing interventions. Focusing RTW interventions purely on the primary outcome of return to work is reductive and risks excluding other important benefits. They considered that returning to the same work, doing the same hours may not necessarily be a 'good' outcome for an individual, and that acceptance, considering values and QoL or returning to meaningful activities (such as caring for grandchildren or helping at a community club) can lead to people enacting changes in their work and personal lives. Linking people with employability services can aid career changes and training needs. Confidence and satisfaction in work roles can be more accurate indicators of occupational outcomes.

A UK government website acknowledges the link between employment and health and states 'there is clear evidence that good work improves health and well-being across people's lives, not only from an economic standpoint but also in terms of quality of life'. It defines good

work as 'having not only a work environment that is safe, but also having a sense of security, autonomy, good line management and communication within an organisation.' Conversely, a difficult work environment and unsupportive management can lead to increased stress and pressure and be unhelpful to an individual's pain management.

Pacing interventions delivered from a symptom reduction compensatory approach can lead to functional decline and increased activity avoidance. When pacing interventions are delivered in such a way, and interpreted as being limited to taking breaks, slowing down activities and spacing out tasks, this alone does not encompass the many facets involved in activity management occupation-based interventions. This may lead to clinicians unintentionally supporting activity restrictions and limitations that may then reduce function rather than improve function. There is value in occupation-based interventions being delivered by clinicians with experience in facilitating conversations around planning, grading, chunking, alternating and monitoring activity underpinned by acceptance, awareness and psychologically-informed methods.

The research reflects the diverse nature of occupation-based interventions, as well as the need for an individualised treatment approach. However, considering the current variability in access to these interventions across Scotland, best practice is informed by availability of resources in the first instance.

8.6 Recommendations

✓ Clinicians should be aware that activity management (pacing) interventions focused on symptom reduction may inadvertently lead to greater activity avoidance. However, activity management interventions that are underpinned by a values-based approach, pain science education, and delivered by psychologically informed clinicians may encourage greater activity engagement, improving both occupational performance and satisfaction.

✓ The term 'pacing' is too narrow to fully capture the scope of activity management interventions. Clinicians are encouraged to move away from exclusively using the label 'pacing' and instead adopt terms like 'activity management' or 'activity regulation'. These terms better encompass the many facets involved in the intervention.

✓ Clinicians and people living with chronic pain should understand that occupation-based interventions are not intended to reduce pain. Instead, these interventions aim to increase occupational performance and satisfaction, participation in life roles, participation in social functioning, and engagement in personally meaningful occupations within the domains of self care, productivity and leisure.

✓ Clinicians delivering work-related occupational interventions to individuals with chronic pain should adopt a holistic approach, considering both performance and satisfaction in relation to employment and wider life roles. The intervention may include, but not be limited to addressing:

- quality of life
- satisfaction with work-life balance
- confidence and ability to communicate needs in the workplace
- support in negotiating reasonable adjustments
- the ability to regulate during and outside working hours
- confidence to manage flare ups and work absences, and
- balancing life roles alongside work and chronic pain management.

9 Pain management programmes

9.1 Introduction

Pain management programmes (PMPs) are a fundamental resource provided by secondary care pain services within NHS Scotland. For selected people, they are an intervention of choice when there is significant impact on physical, psychological or social function associated with chronic pain.[47]

Pain management programmes involve multidisciplinary working between various professionals including psychologists, physiotherapists, occupational therapists, clinical nurse specialists, pharmacists and specialist doctors. Typically, these exist within secondary care settings and are deemed comprehensive pain management programmes (CPMPs). Integrated pain management programmes (IPMPs) may also exist when the service is provided within primary care.[99] These programmes do not represent a single model of care but provide a range services at different intensities to meet individual needs. This person-centred and graded approach acknowledges psychological and functional impairment alongside medical and pharmacological complexities while taking into account individuals' experience of previous interventions and characteristics of their pain.

There are examples of IPMPs in Scotland, but this is one form of service delivery that offers a qualitatively different (and more restricted) range of interventions compared with those offered in CPMPs. Many IPMPs do not meet the definition of a pain management programme described in section 9.2.

Pain management programmes consist of methods that promote long-term behavioural change, pain education and insight, including methods based on CBT, acceptance-based methods, mindfulness, skills training, physical exercise and education. This is highly person-centred and tailored to each participant's ability and social context and based on behavioural change theories. These skills are then taken home and integrated into individuals' daily routine. Normally, PMPs are provided in a group format.[99]

Training to support people to make changes to their behaviour that can have a positive impact on their physical and mental health and well-being is available to healthcare and third-sector staff from the Health Behaviour Change Learning Programme.

Currently in Scotland, the demand for pain management programmes is high.[51] They require significant resources because of the number of healthcare professionals involved, and the time taken per patient.[100] It is therefore important to assess their effectiveness and ensure adequate value for users of services within NHS Scotland.

In pain medicine literature, PMPs are often treated as simple, one-off interventions, and the outcome measures used are comparable to those used to evaluate the effect of pharmacological treatments. In practice, PMPs are designed to improve QoL, understanding and self efficacy in the presence of persistent pain.[99] Benefits that patients report, or alternative outcomes following completion of a PMP, are not always reflected in changes in the outcome measures used in published research.

9.2 Definitions

While there is no universal definition of a pain management programme, for the purposes of a consistency, this guideline aligned with existing definitions developed by other groups. A range of definitions of PMPs has been considered.

The British Pain Society defines the aims, methods and delivery of pain management programmes within the UK. They consider a PMP to be a 'group treatment which uses education and practice sessions to help people with chronic pain to manage their pain and everyday activities better… usually will have a psychologist and a physiotherapist providing most of the sessions and other staff such as occupational therapists, nurses and doctors are often involved'.[101] They note that PMPs aim to improve the life experience, emotional well-being, activity levels, coping and self efficacy of those living with pain.

The IASP, while not using the term PMP, defines interdisciplinary treatment as 'Multimodal treatment provided by a multidisciplinary team collaborating in assessment and treatment using a shared biopsychosocial model and goals. For example: the prescription of an antidepressant by a physician alongside exercise treatment from a physiotherapist, and cognitive behavioural treatment by a psychologist, all working closely together with regular team meetings (face to face or online), agreement on diagnosis, therapeutic aims and plans for treatment and review'.[102]

NICE guideline NG193 on chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain defined a PMP as 'any intervention that has two or more components including a physical and a psychological component delivered by trained people, with some interaction/co-ordination between the 2'.[47]

Published research evidence uses a range of definitions for PMPs, for example a Cochrane systematic review of multidisciplinary biopsychosocial rehabilitation for chronic low back pain included multidisciplinary rehabilitation interventions if they 'involved a physical component and one or both of a psychological component or a social/work targeted component. Furthermore, the different components had to be delivered by clinicians with different professional backgrounds, but no specific professional backgrounds were required'.[100]

After reviewing the existing definitions and considering the most important requirements for PMPs in the Scottish context, the GDG agreed on the following definition of a PMP.

A pain management programme involves interventions that are:

- psychologically enhanced (eg, has components such as CBT, pain neuroscience education (PNE) and offer the ability for patients to reflect on their experiences, understand their pain better and develop insight into other factors that are involved in the distress and disability caused by pain. *See sections 7.1 and 7.6* for further discussion on specialisation of psychological interventions).
- comprised of multiple interventions delivered concurrently (eg exercise or physical activity, CBT, PNE, medication review).
- delivered in a group setting, either face to face or remotely (eg online).
- typically run over several sessions or weeks.
- led by healthcare professionals from more than one professional group (eg psychologist, allied health professional, doctor).

9.3 Evidence of benefit

One high-quality systematic review with meta-analysis was selected on the effectiveness of PMPs.[103] This review included 57 RCTs (of low to moderate quality) that compared PMPs with a variety of alternatives (usual care, waiting list or attention control, physical therapy, psychological therapy and combinations of these). Eight studies examined IPMPs (based in primary care) and 49 studies examined CPMPs (not based in primary care). Concerns about bias were low. 1++

Some of the included RCTs investigated IPMPs delivered both in group and individual settings. There was limited evidence on different programme factors and their impact on outcomes. Many IPMPs do not meet the definition of a PMP *(see section 9.2)* and since services providing IPMPs do not exist widely in Scotland at this time, it was decided to limit the analysis to CPMPs (delivered in secondary care) only.

While evidence for a wide variety of musculoskeletal pain conditions was available (chronic low back pain, chronic neck pain, osteoarthritis of the knee, hip, or hand and fibromyalgia), and musculoskeletal pain is one of the most common pain symptoms, other pain conditions are not represented within this evidence base.

9.3.1 Comprehensive pain management programmes compared with usual care

Overall, taking part in CPMPs resulted in a small improvement in pain after the intervention (MD -0.53 on a 0 to 10 scale, 95% CI -0.80 to -0.25; 11 RCTs, 764 participants; moderate-certainty evidence). At short- (1 to <6 months), intermediate- (≥6 to <12 months) and long-term (≥12 months) follow-up, the difference was below the threshold for small effects *(see section 1.4.2)*, was not statistically significant, or both.[103]

CPMPs resulted in moderate improvements in function compared with usual care or waiting list at follow-up after the intervention (SMD -0.52, 95% CI -0.88 to -0.16; 13 RCTs, 981 participants: low-certainty evidence) and short-term follow-up (SMD -0.62, 95% CI -1.02 to -0.24; seven RCTs, 1,097 participants: low-certainty evidence). Heterogeneity was high with I^2 values over 80%. There was no evidence of a difference at intermediate and long-term follow-up timepoints. 1++

CPMPs had a small effect on depression compared with usual care at short-term follow-up (SMD -0.48, 95% CI -0.89 to -0.08; five RCTs, 543 participants: no evidence certainty rating). A statistically significant effect was not reported after the intervention, nor sustained at intermediate- or long-term follow-up.

Based on two trials, there was no evidence that CPMPs affected health-related QoL as assessed by SF-36 physical component summary (PCS) or mental component summary (MCS) scores.

9.3.2 Comprehensive pain management programmes compared with physical activity

There was no significant difference in reported pain intensity at any time point between participants undertaking CPMPs and those undertaking physical activity.[103]

A small improvement in short-term function was identified in those participants taking part in a CPMP (SMD -0.37 95% CI -0.61 to -0.16; three RCTs, 459 participants: moderate-certainty evidence). There was no evidence of benefit after the intervention or at intermediate- or long-term follow-up.

There were no statistically significant differences in the severity of depression between participants undertaking CPMPs and those undertaking physical activity after the intervention, at intermediate- or long-term follow-up timepoints. 1++

There were no statistically significant differences in health status between participants undertaking CPMPs and those undertaking physical activity measured by the 12-item or 36-item Short Form Survey (SF-12 or SF-36, respectively) PCS and MCS after the intervention and at long-term follow-up timepoints.

9.3.3 Comprehensive pain management programmes compared with pharmacological therapies

There was moderate improvement in pain scores in participants undertaking CPMPs compared with those on pharmacological therapy after the intervention (pooled MD -1.28, 95% CI -2.14 to -0.63; two RCTs, 204 participants: low-certainty evidence), and a small improvement at intermediate-term follow-up (pooled MD -0.84, 95% CI -1.64 to -0.15; two RCTs, 265 participants: low-certainty evidence). There was no difference seen at short- and long-term follow-up.[103] 1++

While there was no effect from CPMPs on function after the intervention compared with pharmacological therapy, small improvements were reported at short- (SMD -0.37, 95% CI -0.67 to -0.08; two RCTs, 342 participants: low-certainty evidence), intermediate- (SMD -0.44, 95% CI -0.67 to -0.22; three RCTs, 453 participants: moderate-certainty evidence) and long-term (SMD -0.46, 95% CI -0.76 to -0.16; two RCTs, 301 participants: low-certainty evidence) timepoints. 1++

Evidence on the impact of CPMPs on health status and measures of psychological well-being compared with pharmacological therapy alone are limited. Studies using different assessment measures report conflicting findings.

9.3.4 Comprehensive pain management programmes compared with psychological therapies

There were no statistically significant differences between CPMPs and psychological therapies for the outcomes of pain, function, health-related QoL or depression at any timepoint.[103] 1++

9.3.5 Comprehensive pain management programmes compared with combined pharmacological and physical therapies

There was conflicting evidence from two RCTs about the effect of CPMPs on pain compared with combined pharmacological and physical therapies. In one fair-quality RCT involving 63 people with fibromyalgia, participating in a CPMP was associated with moderate improvements in Multidimensional Pain Inventory (MPI) pain intensity (differences -1.2 to -2.1 on a 0 to 6 scale) and MPI pain interference (differences -1.9 to -2.5 on 0 to 6 scale) at postintervention, intermediate-, and long-term timepoints. Only antidepressants were prescribed in this trial. In contrast, a poor-quality trial in 55 people with low back pain reported no difference in pain between groups after the intervention (difference 0.93 on a 0 to 10 scale, 95% CI -0.19 to 2.1). Medications in this trial included diclofenac, paracetamol, and omeprazole.[103] 1++

There were no statistically significant differences in function between CPMPs and combined pharmacological and physical therapies reported in either of two RCTs.[103]

There was conflicting evidence about the effect on depression from the same two RCTs on CPMPs compared with combined pharmacological and physical therapies. Small improvements in MPI affective distress (0 to 6 scale) were seen in those undertaking CPMP after the intervention, and in the intermediate and long term (differences -1.9 to -2.3) in one trial. In contrast, no difference in emotional distress based on the Profile of Mood States Short Version (POMS-SV) was seen in the other trial after the intervention.[103]

9.4 Evidence of harms

There were limited reports of adverse events from CPMPs (three RCTs reported increased pain as a result of the intervention, and one RCT reported an adverse event as a result of the intervention without further details). Reporting adverse events is inconsistent and lacks detail across the evidence.[103] 1++

Since CPMPs encourage participants to carry out any movements or activities within a range that is safe and sustainable for them, harms directly related to participation would not be anticipated.

9.5 Summary of benefits and harms of pain management programmes for chronic pain

While the clinical significance in many of the reported outcomes is uncertain, the results demonstrated that CPMPs were either more effective or as effective as individual comparators and low levels of harms were reported. The reported benefits were small and mostly limited to people with musculoskeletal pain conditions, which limits generalisability and lowers

confidence in the strength of recommendation. Published evidence from the systematic review may not capture all key benefits of PMPs because of the emphasis on measures of pain and function, rather than self efficacy and agency.

Outcomes concerning acceptability or how suitable CPMPs are for most people with chronic pain in Scotland were not covered in this guideline and evidence of cost effectiveness was not reviewed.

9.6 Other factors

Scotland's population is geographically dispersed, with 17% living in rural areas, which makes providing PMPs challenging.[104]

Evidence on qualitative outcomes was not sought and there was limited perspective from people with lived experience available.

The guideline development group noted evidence of benefit for CPMPs, despite the limitations of the outcome measures for chronic pain interventions (such as pain scores), and the lack of evidence of harms and acknowledged the wider benefits of CPMPs to secondary care pain services, such as learning as part of the multidisciplinary team and innovation and research through interdisciplinary relationships. On this basis the GDG concluded that a conditional recommendation was justified.

9.7 Recommendations

R **Following appropriate assessment, consider comprehensive pain management programmes for people with chronic pain.**

10 Dietary interventions

10.1 Introduction

Healthcare professionals should support all people with chronic pain to self manage their pain in ways which best meet their needs. Non-pharmacological approaches to pain management involve a wide range of lifestyle factors including activity, mental health, stress, sleep, social connection and nutrition *(see section 3 and the Quality Prescribing for Chronic Pain Guide)*. Beyond general healthy eating principles, evidence was sought on the role of specific dietary interventions in the management of chronic pain.

There are many reasons diet could impact on chronic pain including pro- and anti-inflammatory effects, oxidative stress, health of the gut microbiome and impact on musculoskeletal health.[105] Overall energy intake is also important as the prevalence of chronic musculoskeletal pain increases as body mass index rises.[106]

10.2 Evidence of benefit

Eleven systematic reviews or NMAs were identified that provided evidence for a range of dietary interventions in people with a range of chronic pain types *(see Table 2)*.

10.2.1 Pain and function

Anti-inflammatory diet

No systematic review evidence was identified.

Chondroitin sulphate

Chondroitin sulphate is a natural glycosaminoglycan found in all connective tissues, especially in the extracellular matrix of articular cartilage, where it plays a role in its resistance to compression.

One NMA reported that taking chondroitin sulphate had no significant effect on long-term (≥12 months) pain (SMD -0.06, 95% CI -0.17 to 0.05; 42 RCTs, participants not reported: no evidence certainty rating) or function (SMD -0.03, 95% CI -0.20 to 0.14; 13 RCTs, participants not reported: no evidence certainty rating) in people with chronic pain as a result of knee osteoarthritis.[107] — sufficient

Glucosamines

Glucosamine is a naturally occurring amino monosaccharide and is a precursor for a major component of joint cartilage and synovial fluid. It is available in over 50 preparations, most commonly as a hydrochloride or sulphate compound.

Glucosamine hydrochloride is the only preparation licensed for medical use in the UK and the license is restricted to the symptomatic relief of mild to moderate knee osteoarthritis. There is more evidence available for glucosamine sulphate, which does not have a product license but is sold over the counter as a supplement. Neither product is approved by SMC *(see section 23.4)*.

One NMA, which included trials of long-term follow-up (at least 12 months), reported that glucosamine sulphate reduced pain (SMD -0.29, 95% CrI -0.49 to -0.09; two RCTs, 207 participants: no evidence certainty rating) and improved function (SMD -0.32, 95% CrI -0.52 to -0.12; two RCTs, 207 participants: no evidence certainty rating) in people with knee osteoarthritis compared with placebo.[107] — sufficient

The review also reported that other glucosamines (including glucosamine hydrochloride and other complexes involving any glucosamine other than glucosamine sulphate) had no significant effect on pain (SMD -0.11, 95% CI -0.26 to 0.04; three RCTs, 325 participants: no evidence certainty rating) or function (SMD -0.04, 95% CI -0.20 to 0.12; three RCTs, 325 participants: no evidence certainty rating) in people with knee osteoarthritis compared with placebo. — sufficient

A systematic review evaluated the use of any glucosamine in people with chronic back pain and signs of spinal osteoarthritis. Out of three RCTs, compared with placebo, two found no evidence of a difference and one (with high risk of bias) measured a reduction in pain intensity. There was no evidence of any effect on function. The trial that reported a statistically significant effect was open-label design, did not use an intention to treat protocol, recruited older participants than the other studies and had unclear compliance.[108] — 1+

A further systematic review examined the effectiveness of a wide range of dietary supplements and ingredients for pain and pain-related outcomes in adults with chronic musculoskeletal pain. The review incorporated both RCTs and systematic reviews. The authors discussed the complexity of the evidence base for the commonly combined supplements glucosamine and chondroitin and outlined potential reasons for inconsistency in findings depending on patient groups, comparators and the various preparations used in trials. They reported that glucosamine supplements vary substantially from the prescription formulation in their molecular formulation and dose regimens and that pooled results from studies of glucosamine supplements have failed to show an effect on pain, while high-quality studies have demonstrated efficacy of prescribed glucosamine sulphate with moderate effect size for people with osteoarthritis symptoms compared with placebo.[109] — 1++

Table 2: Systematic review evidence for dietary interventions in people with chronic pain

Intervention	**Pain type**				
	Mixed pain types	Crohn's disease and inflammatory bowel disease	Ulcerative colitis	Chronic musculoskeletal pain	Chronic neuropathic pain
Anti-inflammatory diet					
Chondroitin				Gregori et al, 2018 (sufficient)	
FODMAP diet		Sinopoulou et al, 2021a (1++)	Sinopoulou et al, 2021b (1++)	Elma et al, 2020 (1+)	
Glucosamines				Crawford et al, 2019 (1++) Gregori et al, 2018 (sufficient) Sodha et al, 2013 (1+)	
High-fibre diet					
Magnesium					Frediani et al, 2024 (1+)
Mediterranean diet				Field et al, 2021 (1+)	
Polyunsaturated fatty acids (PUFA)	Crawford et al, (1++)				
Turmeric				Crawford et al, 2019 (1++)	

Intervention	Pain type				
	Mixed pain types	Crohn's disease and inflammatory bowel disease	Ulcerative colitis	Chronic musculoskeletal pain	Chronic neuropathic pain
Vitamin D	Straube et al, 2015 (1++)	Chong et al, 2022 (1+)		Gregori et al, 2018 (sufficient) Lee, 2024 (1++)	

High-fibre diet

No systematic review evidence was identified.

Low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) diet

The FODMAP diet is a temporary elimination diet used to help manage symptoms associated with diagnosed irritable bowel syndrome. It involves an elimination phase, a systematic reintroduction of foods to identify triggers then a personalised long-term diet to limit problematic foods while ensuring adequate nutrition.

One systematic review reported that a low FODMAP diet reduced pain intensity in people with chronic inflammatory bowel disease compared with sham diet (MD -8.46 on a 1–100 mm VAS scale, 95% CI -15.76 to -1.16, two RCTs, 82 participants; very low-certainty evidence). There was no evidence of effect in people with Crohn's disease (MD 0.2 on a 1–100 mm VAS scale, 95% CI -8.67 to 9.07, one RCT, 52 participants; very low-certainty evidence). Effects on function were not assessed in this review. Despite the statistically significant effect, the authors note that no conclusions on efficacy of FODMAP diet could be reached because of the low numbers of studies and participants in each comparison and clinical heterogeneity amongst the studies.[110] **1++**

Another systematic review reported no evidence of effect of low FODMAP diet on pain intensity in people with ulcerative colitis compared with sham diet (MD -9.00 on a 1–100 mm VAS scale, 95% CI -20.07 to 2.07, one RCT, 26 participants; very low-certainty evidence).[111] **1++**

A further systematic review included one uncontrolled clinical trial that reported VAS pain scores significantly decreased after an eight-week low FODMAP diet in 38 female participants living with fibromyalgia (week 0: 6.6, week 4: 4.9, week 8: 5.4; p<0.01 difference from baseline at four weeks, scale not described). The authors note that a FODMAP diet might alleviate pain severity in patients with fibromyalgia, but that more rigorous and high-quality clinical trials are needed on this topic.[112] **1+**

Magnesium

A systematic review with qualitative synthesis on the role of diet and non-pharmacological supplements for the management of chronic neuropathic pain included one small RCT on magnesium supplementation. The review reported that magnesium supplementation was not effective for pain reduction compared with placebo (no effect reported; one RCT, 45 participants: low-certainty evidence).[113] **1+**

Mediterranean diet

A systematic review with meta-analysis on dietary interventions for chronic pain included two studies (one RCT, at medium risk of bias, involving 56 participants and one case-control study involving 130 participants) evaluating Mediterranean diet in people living with rheumatoid arthritis.[114] The effect of Mediterranean diet was found to be statistically significant when reported in this trial, however, when standardised within the meta-analysis, the confidence interval touches zero (SMD -0.56, 95% CI -1.12 to 0.0; one RCT, 56 participants: no evidence certainty rating). **1+**

Polyunsaturated fatty acids (PUFA)

One systematic review of dietary supplements and ingredients in adults with chronic musculoskeletal pain,109 used an older, published systematic review[115] as their main evidence base on PUFA, and reported that PUFA supplementation reduced pain across a range of chronic pain conditions (SMD -0.40, 95% CI -0.58 to -0.22, 46 RCTs, 2,783 participants). The majority of trials used omega-3 as the source of PUFA. This small to moderate effect remained when limited, in subgroup analysis, to participants with rheumatoid arthritis (SMD -0.36 95% CI -0.62 to -0.10; 29 RCTs, number of participants not stated) and eight other pain conditions (SMD -0.61, 95% CI -1.03 to -0.20; eight RCTs, number of participants not stated). The cited systematic review did not report evidence quality ratings, however authors of the systematic review have interpreted the evidence certainty as moderate.

1++

Turmeric

One systematic review reported that, at two-months follow-up, turmeric significantly reduced pain intensity in people with chronic musculoskeletal pain (osteoarthritis or rheumatoid arthritis) compared with placebo (SMD -1.05, 95% CI -1.68 to -0.42; three RCTs, 133 participants: low-certainty evidence). Translated into a 0–100-point scale, such as a VAS or WOMAC, pain intensity reduction was 26.25 points higher in the turmeric arm than in the placebo arm (95% CI -42.0 to -0.5).[109]

Based on the same three RCTs, turmeric also significantly improved global function compared with placebo (higher scores represent worse function) (SMD -0.87, 95% CI -1.54 to -0.19; three RCTs 133 participants: very low-certainty evidence).

1++

All studies reported on turmeric delivered in capsule form, as dietary supplements, dosages ranged from 700–2,000 mg/day over durations from 42 days to 12 weeks. However, the main report from this group made a conditional recommendation in favour of turmeric to support pain reduction only as a dietary ingredient, rather than as a supplement, for reasons that are unclear.

Vitamin D

An NMA of RCTs in people with knee osteoarthritis reported that vitamin D supplementation did not reduce pain (SMD 0.12, 95% CI -0.29 to 0.05; two RCTs, 310 participants: no evidence certainty rating) or improve function (SMD -0.16, 95% CI -0.33 to 0.02; two RCTs, 310 participants: no evidence certainty rating).[107]

sufficient

A systematic review with meta-analysis in people with chronic low back pain reported that vitamin D supplementation did not reduce pain compared with control (SMD -0.13, 95% CI -0.26 to 0.00; ten RCTs, 1,008 participants: no evidence certainty rating). In a subgroup analysis for the effectiveness of vitamin D in individuals with and without vitamin D deficiency the authors reported no evidence of an effect on pain in either the vitamin D deficient group (SMD -0.28, 95% CI -0.54 to -0.02)[sic] or the non-deficient group (SMD -0.08, 95% CI -0.23 to 0.07) compared with placebo. A further subgroup analysis revealed that neither short-term (SMD -0.19, 95% CI -0.40 to 0.01) nor long-term use of vitamin D (SMD -0.10, 95% CI 0.29 to -0.10) significantly reduced chronic low back pain. Long-term supplementation did not show a significant benefit over short-term supplementation to pain relief or functional improvement in people with chronic low back pain.

Neither supplementation with active forms of vitamin D (such as calcitriol or alfacalcidol; SMD -0.32, 95% CI -0.67 to 0.03) nor non-active forms of vitamin D (SMD -0.10, 95% CI -0.24 to 0.04) significantly reduced pain scores in people with chronic low back pain compared with controls. This was consistent across various baseline levels of vitamin D among participants.[116]

1++

A systematic review of RCTs of vitamin D for treating pain, which included people with a range of painful conditions, noted that the majority of included trials did not report the proportion of participants experiencing ≥50% pain relief nor the effect of the intervention on pain improvement. There was high heterogeneity between the trials in terms of included participants, interventions (amount and schedule of administration of vitamin D, co-interventions), duration, and outcomes reported. Only two studies recruited individuals with vitamin D deficiency, and the authors question the degree to which the trials had the sensitivity to be able to detect any effect of vitamin D on pain. Based on methodological limitations, and lack of consistent effects, the authors concluded there was no convincing evidence of effect of vitamin D on chronic pain.[117] 1++

10.2.2 Quality of life

Only one systematic review was identified that reported effects of dietary interventions on quality of life. The review measured QoL using the Irritable Bowel Syndrome Quality of Life Instrument (IBS-QoL), which has 34 items consisting of dysphoria, body image, health-oriented worries, sexual-related worries, social behaviour, interference with everyday activity, and personal relationship domains. Results were converted to a 0–100-point scale. The review reported that people with irritable bowel syndrome who received vitamin D supplements did not experience a significant improvement in their IBS-QoL scores compared with placebo (SMD 0.54, 95% CI -0.34 to 1.41; four RCTs, 448 participants: no evidence certainty rating).[118] 1++

10.3 Evidence of harms

No evidence was identified reporting adverse effects of anti-inflammatory diet, chondroitin, high-fibre diet, Mediterranean diet, magnesium supplementation or PUFA in people with chronic pain.

One systematic review noted that, in one of the three RCTs included, approximately 30% of participants experienced adverse events irrespective of whether they received glucosamine or placebo. Adverse events included gastrointestinal and dermatological symptoms. There were no adverse events reported in the other two trials.[108] 1+

In two systematic reviews, there was no evidence of a difference in withdrawal from studies because of adverse events between people with inflammatory bowel disease or ulcerative colitis receiving low FODMAP diet and sham diet (a single result was extracted from the same RCT and reported in both systematic reviews) (RR 1.85, 95% CI 95% CI 0.18 to 19.19; one RCT, 52 participants: very low-certainty evidence).[110,111] 1++

A systematic review of six RCTs evaluating the effects of turmeric when used alone reported on adverse events. One study reported that none occurred, and the others cited a variety of adverse events that mainly consisted of minor gastrointestinal complaints. A small number of studies that investigated turmeric in combination with another ingredient noted that adverse events were more common in participants using the combination.[109] 1++

In the systematic review of vitamin D in people with a wide range of painful conditions, adverse events were infrequent, with no consistent difference between those receiving vitamin D and placebo.[117] 1++

10.4 Summary of benefits and harms of dietary interventions for chronic pain

No systematic review evidence was identified on the effects of anti-inflammatory diets or high-fibre diets on pain outcomes in people with chronic pain.

There was mixed evidence of benefit of glucosamines with most studies showing no evidence of effect on pain.

One NMA reported that glucosamine sulphate, which is not licensed for pain reduction in the UK and not approved by SMC, may have a small effect on pain in people with knee osteoarthritis.

Evidence on low FODMAP diet was of very low certainty and based on systematic reviews containing one to two studies. Effects on pain were mixed, with one review suggesting a small reduction in pain for people with inflammatory bowel disease but no effect in people with Crohn's disease, while another review reported no effects in people with ulcerative colitis. It was not possible to reach a conclusion because of the quality and volume of evidence.

One systematic review reported that magnesium supplementation was not effective for pain reduction in people with neuropathic pain.

A systematic review, which included one RCT and one case-control study, reported no evidence of effect of Mediterranean diet on pain in people with rheumatoid arthritis.

Evidence from one systematic review suggests that PUFA supplementation (mostly attributed to omega-3) may have a small effect on pain reduction in people with a range of chronic pain conditions.

Based on low- to very low-certainty evidence, turmeric supplementation may have a large effect on pain reduction and improving function.

Several systematic reviews reported consistently that vitamin D supplementation did not result in pain reduction in people with chronic pain, irrespective of their vitamin D sufficiency.

Adverse events for all dietary interventions were poorly reported and, where identified, were minor and infrequent.

10.5 Other factors

Dietary management is increasingly valued by people with chronic pain as a non-pharmacological option, especially in the context of deprescribing. The GDG acknowledges that some people with chronic pain report benefits from reducing processed foods and sugars.

Scottish Government's Quality Prescribing for Chronic Pain Guide highlights a number of ways in which pain and nutrition are connected, including:

- for people living with pain, nutrient-rich foods can support overall health and may also play a role in managing pain levels
- limited or reduced mobility and functional strength can affect a person's ability to shop, cook and prepare meals
- comfort eating or lack of meaning around mealtimes can lead to low-quality diet
- lack of sleep can result in irregular eating habits.

The low FODMAP diet is an elimination therapy which requires specialist support from dietitians. It is labour intensive and requires commitment from those following it to maintain compliance. While not specifically measured in the evidence base, any diet that alters gastrointestinal microbiota, particularly among people who could have abnormal intestinal bacteria, may result in unintended harm. Furthermore, there is some evidence that people with gastrointestinal disorders who undergo dietary change may be at increased risk for disordered eating behaviours.[119]

Use of dietary supplements is not regulated to the same standards as licensed medications and may involve access to products that vary in intensity, formulation and effect.

The Eatwell Guide is a visual tool to help people achieve a healthy balanced diet and shows the recommended proportions of different food groups most people should be eating. It applies to people over the age of five regardless of weight, dietary restrictions, preferences or ethnic

origin, although registered dietitians can help anyone with special dietary requirements or medical needs to adapt the Eatwell Guide to meet their individual needs. The Eatwell Guide also provides information on hydration, calorie guidelines and nutrition labelling.

Discuss healthy eating with people with chronic pain in line with The Eatwell Guide and provide advice to:

- maintain healthy weight as recommended to the general population by following a healthy balanced diet
- base meals on wholegrain carbohydrate foods
- incorporate fruit and vegetables (fresh, dried, tinned or frozen)
- include omega-3 fatty acids, including two portions of fish every week, one of which should be oily, and/or plant-based sources like walnuts, chia seeds or flax seeds
- include beans and pulses (along with fruit, vegetables and wholegrain foods) to increase fibre intake. Fibre supports gut health and helps to prevent constipation which is a common side effect of medicines commonly prescribed for pain
- choose unsaturated oils and spreads (for example, olive oil, rapeseed oil)
- have foods and drinks that are high in fat, salt or sugar less often and in small amounts
- maintain adequate fluid consumption to prevent constipation.

10.6 Recommendations

✓ Healthcare professionals should provide nutrition advice within their scope of competence and offer referral to a registered dietitian where more complex dietary needs or health conditions are present.

✓ Advise that turmeric consumption may have a role in pain relief with very little evidence of harms, however it is not possible to specify target amounts.

11 Electrotherapy

11.1 Introduction

Electrotherapy is the therapeutic use of different forms of low- or medium-frequency electric currents to achieve physiological responses for clinical benefit. Therapeutic ultrasound is also considered an electrotherapy modality and uses high-frequency sound waves to achieve similar physiological responses to other electrotherapy techniques. Electrotherapy is considered a non-invasive, non-pharmacological treatment and is usually administered as part of physiotherapy management.

There is a broad range of contemporary electrotherapy modalities and, for many, the mechanism of action is currently unclear. Mechanisms of action are thought to include pain modulation via activation of pain gate mechanisms, delivery of mechanical forces to alter the physical properties of tissues and influence tissue healing, and repair by stimulation of cellular activity and reduction of inflammation.[47]

11.2 Evidence of benefit

Six systematic reviews of electrotherapy in people with chronic pain were included, five of which employed meta-analysis[63,120-123] and one narratively reported the results, as pooling data for meta-analysis was not possible because of methodological, clinical and statistical heterogeneity of the included studies.[84]

Two systematic reviews focused on chronic prostatitis/chronic pelvic pain syndrome,[120,123] one on burning mouth syndrome,[122] one on multiple sclerosis,[84] one on pain irrespective of diagnosis, but analysed and reported chronic pain results separately,[121] and one on more than one chronic pain condition (for example, chronic low back pain, chronic neck pain, fibromyalgia and osteoarthritis).[63] These represent conditions that are seen by specialist and non-specialist health services in NHS Scotland. The majority of participants in trials included in the systematic reviews were female, which is consistent with the context in Scotland, where there is a higher incidence of females reporting chronic pain.[124]

Whilst the methodological quality of the systematic reviews was acceptable or high quality, the evidence from the RCTs included in the review conclusions was frequently low to very low certainty. This means confidence in the effect sizes reported across the reviews is reduced.

Relevant interventions included in the reviews were:

- extracorporeal shockwave therapy treatment (ESWT) including low-intensity shockwave therapy (LiST),
- high-level laser therapy (HLLT),
- interferential therapy (IT),
- low-level laser therapy (LLLT),
- shortwave diathermy (SDi),
- therapeutic ultrasound (TU) and
- transcutaneous electrical nerve stimulation (TENS).

11.2.1 Pain

Extracorporeal shockwave therapy treatment including low-intensity shockwave therapy

One systematic review evaluated evidence for a range of interventions in men with chronic prostatitis/chronic pelvic pain syndrome. While the primary outcome was reduction in

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prostatitis symptoms measured using the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI) score (0 to 43), the review also reported NIH-CPSI pain subscore (0 to 21). Compared with sham procedure, ESWT reduced pain in the short term (defined as up to 12 months) (MD -4.74 on a 0 to 21 scale), 95% CI -5.54 to -3.94; one RCT, 37 participants: no evidence certainty rating) but there was no evidence of effect in the long term (MD -0.01 on a 0 to 21 scale, 95% CI -1.26 to 1.24; one RCT, 37 participants: no evidence certainty rating). Compared with no treatment, ESWT reduced pain in the short term (MD -3.83 on a 0 to 21 scale, 95% CI -6.03 to -1.63; one RCT, 60 participants: no evidence certainty rating) and in the long term (over 12 months) (MD -4.27 on a 0 to 21 scale, 95% CI -6.15 to -2.39; one RCT, 60 participants: no evidence certainty rating). The authors note that caution must be taken when interpreting these findings, as the NIH-CPSI subscore has not been validated as a robust independent measure of pain in this population and a MCID has not been developed for the subscores.[120] 1++

A further systematic review explored LiST for the management of chronic prostatitis/chronic pelvic pain syndrome. Compared with sham intervention, LiST reduced pain measured by both NIH-CPSI pain subscore and Numerical Pain Rating Scale (NPRS) immediately postintervention and at one and three-months follow-up after treatment, but not at six months *(see Table 3)*. Certainty of evidence was low for all analyses. The authors note that the absolute improvement in the NIH-CPSI pain domain score, compared with baseline, was within 4–6, points which represents a clinically important difference.[123] 1+

Table 3: Effects of LiST on pain from baseline measured by NIH-CPSI and NPRS compared with sham intervention

Pain measure and timing	Effect (95% CI)	Number of RCTs (participants)
NPRS (0–10) (after the intervention)	WMD 1.43 (0.85 to 2.01)	2 (91)
NPRS (0–10) (one-month follow-up)	WMD 2.59 (1.92 to 3.27)	2 (105)
NPRS (0–10) (three-months follow-up)	WMD 2.64 (2.13 to 3.16)	3 (136)
NIH-CPSI pain domain score (0 to 21) (after the intervention)	WMD 3.2 (0.88 to 5.52)	3 (151)
NIH-CPSI pain domain score (0 to 21) (one-month follow-up)	WMD 4.4 (2.84 to 5.95)	2 (125)
NIH-CPSI pain domain score (0 to 21) (three-months follow-up)	WMD 3.61 (1.49 to 5.74	4 (196)
NIH-CPSI pain domain score (0 to 21) (six-months follow-up)	WMD 0.86 (-2.18 to 3.9)	2 (85)

NIH-CPSI: National Institute of Health Chronic Prostatitis Symptom Index
NPRS: numerical pain rating scale, WMD: weighted mean difference

Transcutaneous electrical nerve stimulation

A systematic review evaluated the efficacy and safety of TENS for acute and chronic pain in adults. Based on pooled analysis of results from studies with any type of chronic pain, TENS reduced pain intensity after the intervention compared with a placebo intervention (SMD -0.87, 95% CI -1.19 to -0.55; 31 RCTs, 1,417 participants: no evidence certainty rating).[121] Pain was also reduced in people with chronic neuropathic pain who received TENS (SMD -1.68, 95% CI -2.58 to -0.78; seven RCTs, 169 participants: no evidence certainty rating) but there was no evidence of an effect in those with chronic secondary musculoskeletal pain (SMD -0.27, 95% CI -0.81 to 0.26; three RCTs, 164 participants: no evidence certainty rating) or chronic 1++

secondary visceral pain (SMD -1.31, 95% CI -2.79 to 0.17; four RCTs, 114 participants: no evidence certainty rating). The authors note that subgroup analyses on pain characteristics found no evidence that the effects of TENS were moderated by pain diagnosis or characteristics and concluded that TENS may alleviate the intensity of pain, irrespective of pain diagnosis. Treatment effects of TENS were not modified when pain was categorised by diagnoses according to the RCT author. Substantial heterogeneity between results from the trials within each subgroup undermined confidence in the magnitude of treatment effect estimates. The authors also note that the primary outcome effect estimate (SMD -0.87) exceeds the prespecified threshold for clinical importance (SMD >0.5 or <-0.5). 1++

One systematic review of non-pharmacological interventions for men with chronic prostatitis identified two small, poor-quality RCTs of TENS that could not be combined in meta-analysis because of differences in study design and small sample sizes.[120] One RCT reported that TENS reduced pain measured on the NIH-CPSI pain domain subscore in the short term compared with sham procedure (MD -15.25 on a 0 to 21 scale, 95% CI -17.71 to -12.79; one RCT, 40 participants: no evidence certainty rating). The second RCT reported TENS reduced pain in the short term compared with no intervention (although the baseline pain scores were not equal between treatment and control groups and categorises the RCT at high risk of bias) (MD -6.88 on a 0 to 21 scale, 95% CI -8.13 to -5.63; one RCT, 16 participants: no evidence certainty rating). 1++

A systematic review carried out by AHRQ evaluated a wide range of non-pharmacological treatments for people with chronic pain. In people with chronic back pain, there was no evidence of an effect of burst TENS (MD -0.80 on a 0–10 scale, 95% CI -2.24 to 0.64; one RCT, 73 participants: low-certainty evidence) or conventional TENS (MD -1.30, on a 0–10 scale, 95% CI -2.74 to 0.14; one RCT, 73 participants: low-certainty evidence) on pain compared with sham procedure in the short term. 1++

In people with knee osteoarthritis, there was no evidence of an effect of TENS compared with placebo (MD 0.90, 95% CI -11.7 to 13.4; one RCT, 70 participants: low-certainty evidence) or compared with sham procedure (MD 0.09, 95% CI -0.41 to 0.59; one RCT, 220 participants: low-certainty evidence) in the intermediate term.[63]

A systematic review of people with chronic low back pain as a result of multiple sclerosis found no evidence of a clinically or statistically significant effect of TENS compared with sham on pain intensity (effect size not reported; one RCT, 90 participants: very low-certainty evidence).[84] 1++

Low-level laser therapy

One systematic review evaluated the effect of LLLT on outcomes in people with burning mouth syndrome, a condition associated with chronic oral pain without an obvious cause, but which may have a neuropathic underpinning. In the short term, LLLT reduced pain compared with sham or placebo (SMD -0.92, 95% CI -1.38 to -0.46; seven RCTs, 321 participants: very low-certainty evidence) but there was no evidence of a difference in effect on pain compared with clonazepam (SMD -0.47, 95% CI -1.17 to 0.23; one RCT, 33 participants: very low-certainty evidence).[122] 1++

The review carried out by AHRQ evaluated, separately, the effect of LLLT in people with chronic low back pain, chronic neck pain, chronic pain associated with hand osteoarthritis and chronic pain associated with knee osteoarthritis.[63]

In people with chronic low back pain, one fair-quality RCT reported that LLLT reduced pain in the short term compared with sham laser (MD -16.0 on a 0–100 scale, 95% CI -28.3 to -3.7; one RCT, 59 participants: low-certainty evidence). 1++

A second RCT, which was assessed to be poor quality, reported a large improvement in pain in those using LLLT (MD -4.40 on a 0–10 scale, 95% CI -5.31 to -3.49; one RCT, 34 participants: low-certainty evidence) compared with sham laser in the short term.

A further poor-quality RCT reported an increased likelihood of having no pain at intermediate-term follow-up in those receiving LLLT compared with sham laser, (44.7% vs 15%, p<0.01; one RCT, 71 participants: low-certainty evidence) but the analysis was restricted to patients who reported that LLLT was effective at the end of a two-week course of treatment.

In people with chronic low back pain, one fair-quality trial reported no clear differences in pain between people who received laser therapy compared with those receiving exercise plus sham laser (mean difference in change from baseline -0.9 on a 0–10 scale, 95% CI -2.5 to 0.7; one RCT, 53 participants: low-certainty evidence) at short-term follow-up.[63]

In people with chronic neck pain, LLLT reduced pain compared with sham laser (MD -1.89 on a 0–10 scale, 95% CI -3.34 to -0.06; three RCTs, 192 participants: moderate-certainty evidence) at short-term follow-up.[63] 1++

There was no evidence of a short-term effect of LLLT on pain compared with sham laser in people with chronic pain associated with hand osteoarthritis (MD 0.1 on a 0–10 scale, 95% CI -0.3 to 0.5; one RCT, 88 participants: low-certainty evidence) or in people with chronic pain associated with knee osteoarthritis (MD -1.50 on a 0–10 scale, 95% CI -3.18 to 0.16; three RCTs, 160 participants: low-certainty evidence). There was also no evidence of an effect of LLLT on pain in the intermediate term (MD -1.24 on a 0–10 scale, 95% CI -2.22 to 0.12; three RCTs, 193 participants: low-certainty evidence).[63]

Therapeutic ultrasound

A systematic review evaluated evidence for the effect of TU on pain in men with chronic prostatitis/chronic pelvic pain syndrome. One small, poor-quality RCT was identified that assessed the effects of TU alone or in combination with westernised Chinese medical therapy or with westernised Chinese medical therapy alone. There was no evidence of an effect of TU on prostatitis symptoms when delivered alone compared with westernised Chinese medical therapy (MD 0.37 on a 0–21 scale, 95% CI -0.18 to 0.92; one RCT, 70 participants: no evidence certainty rating). When added to westernised Chinese medical therapy, the combination therapy reduced pain more than westernised Chinese medical therapy alone (MD -1.87 on a 0–21 scale, 95% CI -2.59 to -1.15; one RCT, 70 participants: no evidence certainty rating).[120] 1++

The AHRQ systematic review identified two RCTs of TU in people with chronic low back pain, which were not combined in meta-analysis. These showed no evidence of an effect on pain in the short term compared with sham ultrasound (two RCTs, 505 participants: low-certainty evidence).[63]

In people with chronic pain associated with knee osteoarthritis, there was no evidence of an effect on pain using pooled evidence from trials that compared continuous and pulsed TU with sham ultrasound (MD -1.07 on a 0–10 scale, 95% CI -2.81 to 0.67; four RCTs, 324 participants: low-certainty evidence).[63] 1++

Interferential therapy

The AHRQ systematic review identified two RCTs on IT, in people with chronic low back pain and chronic pain associated with knee osteoarthritis, respectively. In those with chronic back pain, IT was associated with a small reduction in pain compared with placebo. The review was unable to report an effect size, because of reporting errors in the original study, although the review authors reported that the mean difference between treatment and control groups was below the threshold for a small effect.

In people with chronic pain associated with knee osteoarthritis there was no evidence of an effect of IT on pain at rest compared with sham procedure in the short term (MD -0.87 on a 0–10 scale, 95% CI -2.01 to 0.26; one RCT, 84 participants: low-certainty evidence) or intermediate term (MD -0.32 on a 0–10 scale, 95% CI -1.34 to 0.70 one RCT, 84 participants:

low-certainty evidence). There was also no evidence of an effect of IT on pain during activity in the short term (MD -0.42, 95% CI -1.65 to 0.80) or intermediate term (MD 0.49, 95% CI -1.63 to 0.64; one RCT, 84 participants: low-certainty evidence).[63]

Shortwave diathermy

The AHRQ systematic review identified one RCT evaluating SDi in people with chronic back pain (68 participants) and three RCTs evaluating SDi in people with chronic pain associated with knee osteoarthritis (264 participants). The review authors reported that the evidence was insufficient to determine the effects of SDi over any time period.[63] 1++

11.2.2 Function

Extracorporeal shockwave therapy treatment including low-intensity shockwave therapy

No evidence was identified on the effects of ESWT or LiST on function in people with chronic pain.

Transcutaneous electrical nerve stimulation

The effects from TENS on function in people with chronic pain were generally not reported in systematic reviews. A systematic review of non-pharmacological interventions for chronic pain in people with low back pain as a result of multiple sclerosis identified a single RCT that reported no significant changes in disability between treatment and placebo groups and within groups (no effects reported; one RCT, 90 participants: very low-certainty evidence).[84] 1++

The AHRQ systematic review reported no evidence of an effect on function for either burst TENS (MD -2.90 on a 0–50 scale, 95% CI -7.97 to 2.17; one RCT, 73 participants: low-certainty evidence) or conventional TENS (MD -2.30 on a 0–50 scale, 95% CI -7.77 to 3.17; one RCT, 73 participants: low-certainty evidence) compared with sham in people with chronic low back pain.[63]

In people with chronic pain associated with knee osteoarthritis, there was no evidence of an effect of TENS on function compared with placebo in the intermediate term (MD -1.9 on a 0–100 scale, 95% CI -9.7 to 5.9; one RCT, 70 participants: low-certainty evidence) and no evidence of an effect of TENS on function compared with sham in the short term (MD 0.08 on a 0–63 scale, 95% CI -0.28 to 0.43; one RCT, 220 participants: low-certainty evidence).[63] 1++

Low-level laser therapy

The AHRQ systematic review identified RCTs that reported on the effects from LLLT on function in people with chronic low back pain, chronic neck pain or chronic pain associated with knee or hand osteoarthritis.

In people with chronic low back pain, LLLT improved function in the short term compared with sham laser (MD -8.2 on a 0–100 scale, 95% CI -13.6 to -2.8; one RCT, 56 participants: low-certainty evidence). Based on a further small, poor-quality trial, LLLT improved function compared with sham (MD -5.70 on a 0–24 scale, 95% CI -8.47 to -2.93; one RCT: 34 participants: low-certainty evidence). One trial found no evidence of a difference between LLLT and exercise therapy in intermediate-term function (difference in change from baseline -4.4 on a 0–100 scale, 95% CI -11.4 to 2.5; one RCT, 53 participants: low-certainty evidence).[63] 1++

In people with chronic neck pain, LLLT resulted in a moderately greater effect on short-term function compared with sham (pooled difference -13.60 on a 0–100 scale, 95% CI -26.30 to -6.30; two RCTs, 144 participants: moderate-certainty evidence).[63]

There was no evidence of an effect of LLLT on short-term function compared with sham laser therapy in people with chronic pain associated with hand osteoarthritis (MD 0.2 on a 0–100 scale, 95% CI -0.2 to 0.6; one RCT 88 participants: low-certainty evidence). There was no

evidence of an effect of LLLT on function compared with sham laser therapy in people with chronic pain associated with knee osteoarthritis in the short term (SMD -0.39, 95% CI -0.80 to 0.00, two RCTs, 133 participants: low-certainty evidence) or intermediate term (SMD -0.54, 95% -1.19 to 0.05; three RCTs, 193 participants: low-certainty evidence).[63] 1++

Therapeutic ultrasound

The AHRQ systematic review reported inconsistent effects of TU on function in people with chronic low back pain. One good-quality RCT (455 participants) found no difference between TU and sham ultrasound in RMDQ score (median 3 vs 3). In a further smaller trial (50 participants), TU was associated with better short-term function than sham ultrasound (MD 7.7 on a 0–40 scale, confidence intervals not reported).[63]

There was no evidence of an effect of TU on function compared with sham ultrasound in the short term in people with chronic pain associated with knee osteoarthritis when measured by either Lequesne Index (MD -2.50 on a 0–24 scale, 95% CI -6.37 to 1.22; three RCTs, 249 participants: low-certainty evidence) or WOMAC physical function scale (MD -2.50 on a 0–68 scale, 95% CI -8.11 to 3.12; one RCT, 75 participants: low-certainty evidence).[63] 1++

Interferential therapy

The AHRQ systematic review reported no evidence of any effect of IT on function in people with chronic low back pain or chronic pain associated with knee osteoarthritis. The authors included one trial in people with low back pain which reported that IT was associated with an effect on short-term function that was below the threshold for a small effect (statistical significance uncertain) when compared with a placebo therapy.

In people with chronic pain associated with knee osteoarthritis, there was no evidence of an effect of IT compared with sham procedure in the short term (MD 0.55 on a 0–96 scale, 95% CI -24.31 to 7.05) or intermediate term (MD 1.42 on a 0–96 scale, 95% CI -6.73 to 9.58; one RCT, 84 participants: low-certainty evidence).[63] 1++

Shortwave diathermy

The AHRQ systematic review identified one RCT evaluating SDi in people with chronic back pain (68 participants) and three RCTs evaluating SDi in people with chronic pain associated with knee osteoarthritis (264 participants). The review authors reported that the evidence was insufficient to determine the effects of SDi on function over any time period.[63] 1++

11.2.3 Quality of life

Extracorporeal shockwave therapy treatment including low-intensity shockwave therapy

A systematic review of non-pharmacological interventions for treating chronic prostatitis/chronic pelvic pain syndrome identified two small RCTs that reported on the effect of ESWT on QoL. Each study measured QoL in terms of prostatitis symptoms using the NIH-CPSI quality-of-life subscore (0–12). One RCT found ESWT had a significant effect on QoL compared with sham procedure in the short term (MD -1.73 on a 0–12 scale, 95% CI -2.35 to -1.11; one RCT, 37 participants: no evidence certainty rating) but not in the intermediate term (MD -0.16 on a 0–12 scale, 95% CI -0.98 to 0.66; one RCT, 37 participants: no evidence certainty rating). A further RCT found ESWT had a significant effect on QoL compared with no intervention in the short term (MD -2.46 on a 0–12 scale, 95% CI -3.94 to -0.98; one RCT, 60 participants: no evidence certainty rating) and intermediate term (MD -2.03 on a 0–12 scale, 95% CI -3.62 to -0.44; one RCT, 60 participants: no evidence certainty rating).[120] 1++

A further systematic review evaluated the effects of LiST in men with prostatitis/chronic pelvic pain syndrome. The authors report LiST improved QoL compared with sham immediately postintervention (WMD 2.52 on a 0–12 scale, 95% CI 1.23 to 3.81; three RCTs, 151 participants), 1+

at one-month follow-up (WMD 3.93 on a 0–12 scale, 95% CI 1.40 to 6.47; two RCTs, 125 participants), at three-months' follow-up (WMD 2.81 on a 0–12 scale, 95% CI 0.83 to 4.80; four RCTs, 196 participants) but not at six months (WMD 1.43 on a 0–12 scale, 95% CI -1.22 to 4.07; two RCTs, 85 participants) (no evidence certainty rating for any analysis).[123] 1+

Transcutaneous electrical nerve stimulation

Effects of TENS on QoL in people with chronic pain were generally not reported in systematic reviews.

One systematic review of people with chronic low back pain as a result of multiple sclerosis found no evidence of an effect of TENS compared with sham on QoL (no effects reported; one RCT, 90 participants: very low-certainty evidence).[84] 1++

Low-level laser therapy

A systematic review evaluated the effects of LLLT on pain and QoL in people with chronic burning mouth syndrome. Oral health-related QoL was assessed by the Oral Health Impact Profile-14. There was no evidence of an effect of LLLT on QoL in the short term (SMD 0.03, 95% CI -0.63 to 0.70: seven RCTs, 346 participants: very low-certainty evidence).[122] 1++

Therapeutic ultrasound

A systematic review evaluated the effect of TU on pain in men with chronic prostatitis/chronic pelvic pain syndrome. One small, poor-quality RCT was identified that assessed the effects of TU alone or in combination with westernised Chinese medical therapy or with westernised Chinese medical therapy alone. There was no evidence of an effect of TU on the prostatitis symptoms QoL subscore when delivered alone compared with westernised Chinese medical therapy (MD -0.41 on a 0–12 scale, 95% CI -1.35 to 0.53; one RCT, 70 participants: no evidence certainty rating). When added to westernised Chinese medical therapy, the combination therapy improved QoL more than westernised Chinese medical therapy alone (MD -2.63 on a 0–12 scale, 95% CI -3.60 to -1.66; one RCT, 70 participants: no evidence certainty rating).[120] 1++

Interferential therapy

No evidence was identified on the effects from IT on QoL in people with chronic pain.

Shortwave diathermy

No evidence was identified on the effects from SDi on QoL in people with chronic pain.

11.3 Evidence of harms

Adverse events were not consistently reported across interventions and pain conditions. Where reported, they appear infrequent and, most commonly, there was no evidence of an effect compared with controls.

Extracorporeal shockwave therapy treatment including low-intensity shockwave therapy

One systematic review in men with chronic prostatitis/chronic pelvic pain syndrome identified three RCTs that included information on adverse events from ESWT. In two RCTs, no adverse events were reported. In the third, there was no evidence of a difference in adverse events between people receiving ESWT and those who did not receive ESWT (RR 1.22, 95% CI 0.59 to 2.51; one RCT, 60 participants: low-certainty evidence).[120] 1++

A further systematic review in men with chronic prostatitis/chronic pelvic pain syndrome evaluated the benefits and harms of LiST. Five of the six included RCTs reported that LiST was well tolerated and no adverse events were reported. The remaining RCT reported four cases (out of 16) of transient haematuria and haematospermia in the treatment group.[123] 1+

Transcutaneous electrical nerve stimulation

Where reported, adverse events from TENS were noted to be mild in severity, infrequent in occurrence and included skin irritation, tenderness and TENS discomfort.[63,121] 1++

Low-level laser therapy

One systematic review reported no serious adverse events associated with LLLT in people with burning mouth syndrome.[122] 1++

The AHRQ review reported no adverse events from three RCTs of LLLT in people with chronic low back pain. In people with chronic neck pain, adverse effects were reported with similar frequency in treatment and control groups. In people with chronic pain associated with hand osteoarthritis, no serious adverse events were reported in people receiving LLLT.[63] 1++

Therapeutic ultrasound

A systematic review identified one RCT that evaluated TU alone compared with TU in combination with westernised Chinese medical therapy. The review authors found that the study reported five cases of vertigo, six cases of gastrointestinal discomfort and three cases of sleepiness but indicated the RCT did not specify which group experienced them.[120] 1++

The AHRQ review reported no evidence of an effect of TU compared with sham on any adverse events (RR 1.03, 95% CI 0.49 to 2.13; one RCT, 455 participants: low-certainty evidence) or of serious adverse events (RR 0.48, 95% CI 0.12 to 1.88; one RCT, 455 participants: low-certainty evidence) in people with chronic low back pain.

In people with chronic pain associated with knee osteoarthritis, four RCTs reported no adverse events in people receiving TU and one RCT reported two study withdrawals in the sham group only.

Interferential therapy

The AHRQ review reported no evidence of an effect of IT on adverse events compared with placebo in people with chronic low back pain (RR 1.0, 95% CI 0.14 to 6.8; one RCT, 150 participants: no evidence certainty rating).

In people with chronic pain associated with knee osteoarthritis, one RCT reported no difference in withdrawal as a result of any adverse event between those receiving IT compared with controls.[63] 1++

Shortwave diathermy

The AHRQ review reported insufficient evidence available to determine the effects from SDi on adverse events in people with chronic pain.[63]

11.4 Summary of benefits and harms of electrotherapy for chronic pain

There is inconsistent evidence to support any electrotherapy modality in people with chronic pain.

Shockwave therapy (ESWT or LiST) reduced pain and improved QoL in men with chronic prostatitis/chronic pelvic pain syndrome in the short term but the effects on function are not known.

There is inconsistent evidence that TENS may reduce pain in people with a range of pain conditions, although different systematic reviews include results that suggest clinically significant benefit or no evidence of any effect depending on the pain conditions included, and the volume and certainty of evidence. There was no evidence of any effect of TENS on function or QoL.

There is evidence that LLLT may reduce short-term pain in people with burning mouth syndrome to a greater degree than placebo, but not more than those receiving benzodiazepine treatment. There was moderate-certainty evidence of short-term improvements in chronic neck pain and function with LLLT. Low-certainty evidence from small, poor- to fair-quality single studies suggests LLLT may reduce chronic low back pain in the short and intermediate term and may improve function in the short term compared with sham, but this effect may not be sustained when combined with exercise therapy. There was no evidence of any effect on pain or function in people with osteoarthritis and no evidence of any effect on QoL for any condition.

Generally, there was no evidence of an effect of TU on pain or QoL (except when combined with westernised Chinese medical therapy in one small, poor-quality study) and inconsistent evidence of an effect on function in people with chronic low back pain.

There was no clear evidence that IT reduced chronic pain in any group, except in one small study of people with low back pain, where the result was below the threshold for a small effect. There was no evidence of an effect on function or QoL.

Evidence on SDi was insufficient to determine potential effects.

Few harms were reported for any intervention and where noted, there was no evidence of a significant difference from groups receiving control procedures.

11.5 Other factors

While some electrotherapy modalities may be available within some physiotherapy departments across Scotland, their accessibility varies by locality and service. TENS devices, where available, are typically self administered. Access to loan or prescription of TENS is inconsistent.

Given the low risk of harms from TENS and its accessibility, individuals could be signposted to access in the community setting.

12 Complementary therapies

12.1 Introduction

Chronic pain can be difficult to manage with available conventional medical therapies. Many people who experience chronic pain will try complementary therapies in an attempt to reduce their pain. A national survey of people with chronic pain in Scotland reported that 27% of respondents had used an osteopath, chiropractor or acupuncturist to help manage their pain, while 20.8% had used a homeopath or complementary medicine professional.[14] These therapies are often not provided by NHS Scotland.

Evidence was sought on the effectiveness of complementary interventions (acupuncture, aromatherapy, homeopathy, herbal products, hypnotherapy, music therapy and reiki) on pain scores, functional ability, quality of life and adverse events.

12.2 Evidence of benefit

12.2.1 Pain intensity

Acupuncture and dry needling

Several systematic reviews report evidence that acupuncture produces small short-term improvements in both pain and function but only some may be clinically important.

Chronic low back pain

In one systematic review, acupuncture reduced pain compared with control (sham, usual care, attention control or placebo) (MD -0.61 on a 0–10 scale, 95% CI -0.99 to -0.27; six RCTs, 2,207 participants: moderate-certainty evidence). However, the improvement is less than one point on a 0–10 pain scale and therefore appears to be clinically insignificant.[63] 1++

In a further review, acupuncture reduced pain to a level where the difference did not meet predefined clinically relevant change when compared with sham (MD -9.22 points on 100-point VAS, 95% CI -13.82 to -4.61; seven RCTs, 1,403 participants: low-certainty evidence) and with usual care (MD -10.26, 95% CI -17.11 to -3.40; five RCTs, 1,054 participants: low-certainty evidence). Acupuncture reduced pain compared with no intervention (MD -20.32, 95% CI -24.50 to -16.14; four RCTs, 366 participants: moderate-certainty evidence).[125] 1++

Chronic neck pain

A systematic review evaluated the effectiveness of acupuncture on functional disability against a range of comparators in people with chronic neck pain. When compared with sham acupuncture, there was no effect on pain intensity at three months (MD -0.12 cm on a 0–10 cm scale, 95% CI -0.06 to 0.36; one RCT, 178 participants: no evidence certainty rating), six months (MD: 0.01 on a 0–10 cm scale, 95% CI -1.16 to 1.18; one RCT, 60 participants: no evidence certainty rating) or 12 months (MD -0.42 on a 0–10 cm scale, 95% CI -1.55 to 0.71; one RCT, 58 participants: no evidence certainty rating).[126] When compared with active controls (such as traction treatment, stretching or massage), there were no significant differences in pain intensity between groups receiving acupuncture and controls in the short term (up to three months) (SMD -0.17, 95% CI -0.46 to 0.12; three RCTs, 188 participants: no evidence certainty rating) or six months (MD -1.27 on a 0–100-point scale, 95% CI -17.41 to 14.87; two RCTs, 70 participants: no evidence certainty rating). The systematic review also included comparison of acupuncture with active control against active control alone. The combined intervention was more effective than active control in the short term (up to three months) (SMD -0.79, 95% CI -1.13 to -0.46; three RCTs, 150 participants: no evidence certainty rating) and intermediate term (up to six months) (MD -18.13 on a 0–100-point scale, 95% CI -30.18 to -6.07; three RCTs, 239 participants: no evidence certainty rating).[126] 1+

In one systematic review, acupuncture did not improve pain compared with placebo or sham in the short term (pooled difference -0.27 on a 0–10 scale, 95% CI -0.59 to 0.05; four RCTs, 490 participants: low-certainty evidence), intermediate term (pooled difference 0.40, 95% CI -0.45 to 1.44; three RCTs, 354 participants: low-certainty evidence), or long term (difference -0.35, 95% CI -1.34 to 0.64, one RCT, 107 participants: low-certainty evidence).[63] 1++

A further review reported that dry needling was effective in reducing chronic neck pain postintervention (MD -0.45, 95% CI -0.90 to -0.01; 12 RCTs, 1,009 participants: no evidence certainty rating).[127] 1++

Chronic pelvic pain in women

In one review, there was no evidence of a difference between groups receiving acupuncture compared with conventional treatment for chronic pelvic pain measured using the total effectiveness rate (an outcome measure used in China) (RR 1.00, 95% CI 0.66 to 1.53; two RCTs, 277 participants: no evidence certainty rating). There was a small difference in total effectiveness rate when acupuncture plus conventional treatment was compared to conventional treatment alone (RR 1.29, 95% CI 1.13 to 1.47; two RCTs, 197 participants: no evidence certainty rating).[128] 1+

A further systematic review of non-pharmacological therapies for chronic pelvic pain in women also reported no significant effect of acupuncture. There was no significant difference in pain intensity between groups receiving acupuncture and control (an inert or non-conservative intervention) immediately postintervention (SMD 1.08, 95% CI -1.38 to 3.54; five RCTs, 221 participants: insufficient certainty evidence).[129] 1++

Chronic prostatitis/chronic pelvic pain syndrome

One review of men with chronic prostatitis or chronic pelvic pain syndrome reported that acupuncture reduced pain compared with sham acupuncture (MD -0.93 in 100-point NIH-CPSI, 95% CI -1.18 to -0.70; six RCTs, 769 participants: moderate-certainty evidence) and reduced pain compared with medication (MD -1.04, 95% CI -1.29 to -0.79; five RCTs, 282 participants: low-certainty evidence).[130] These small effects may not be clinically significant. 1++

Fibromyalgia

In one review of people with chronic fibromyalgia, acupuncture did not reduce chronic pain compared with control (sham, attention control or no intervention) (MD -1.04 on a 0–10 scale, 95% CI -2.27 to 0.16; six RCTs, 466 participants: low-certainty evidence).[63] 1++

There was insufficient evidence to draw conclusions for acupuncture compared with exercise.[63]

Osteoarthritis of the knee

One review found that acupuncture did not improve pain in the short term (SMD -0.25 on a 0–10 scale, 95% CI -0.58 to 0.07; seven RCTs, 1,148 participants: low-certainty evidence) or intermediate term (SMD -0.16, 95% CI -0.32 to -0.01 [sic]; four RCTs, 767 participants: moderate-certainty evidence) compared with control (usual care, no intervention, waiting list or sham). There was insufficient evidence to draw conclusions for acupuncture compared with exercise.[63] 1++

Temporomandibular disorder

One NMA reported that acupuncture did not significantly reduce pain (MD -2.04 on a 0–10 cm scale, 95% CI -2.38 to 1.71 cm; 148 RCTs, 7,867 participants: low-certainty evidence).[72] sufficient

A further NMA reported that dry needling reduced overall pain compared with placebo postintervention (SMD -0.70, 95% CI -1.27 to -0.14; 42 RCTs, 1,989 participants: very low-certainty evidence). This improvement was maintained in the short term (equal to or less than five months) (SMD -0.87, 95% CI -1.48 to -0.27; 42 RCTs, 1,525 participants: low-certainty evidence). It is worth noting that in the short term, dry needling was ranked lower than other therapies, ie manual therapy, ozone, counselling and appliances.[83] sufficient

Herbal products

Chronic low back pain

One systematic review evaluated the effects of several herbal products on pain intensity in people with chronic low back pain.[131] Meta-analysis of results was not possible because of insufficient data and clinical heterogeneity. Based on a single small study, individuals who received Brazilian arnica experienced reduced perception of pain compared with the baseline values recorded for the intervention group (effect size not reported; one RCT, 20 participants: very low-certainty evidence). The review authors reported it was unclear if the RCT included individuals with acute or chronic low back pain.

Two RCTs were identified that evaluated the effects of *Harpagophytum procumbens* (devil's claw) at two different doses (standardised to 50 mg and 100 mg of the active natural ingredient harpagoside) in people with chronic non-specific low back pain. In both trials, a significant increase in the number of pain-free patients was reported in the group receiving 50 mg *H. procumbens* (9% to 17%) compared with those receiving placebo (2% to 5%). The Arhus score, which is a composite measure of pain and disability, improved equally in both intervention and control groups (pooled effect not reported; two RCTs, 315 participants: very low-certainty evidence). One trial also evaluated effects of 100 mg dose of *H. procumbens* compared with 50 mg or placebo. The review authors report that the number of patients who were pain-free for at least five days in the fourth week of treatment (with 100 mg *H. procumbens*) was significantly higher (n=10) than in either the placebo (n=3) or lower dose (50 mg) groups (n=6). There was no significant difference in Arhus score between any group (one RCT, 197 participants: very low-certainty evidence). 1+

Two RCTs were identified that evaluated the effects of *Salix alba* (white willow bark) at two different doses (standardised to 120 mg and 240 mg of the active ingredient salicin) in people with chronic low back pain compared with placebo. The authors report that the number of patients who were pain-free for at least five days in the fourth week of treatment increased from baseline in the placebo (n=4), 120 mg salicin group (n=15) and the 240 mg salicin group (n=27), with the trend for dose being significant. There was no change in Arhus scores in the placebo group, but improvement in those receiving 120 mg and 240 mg salicin with the trend for dose being significant (two RCTs, 261 participants: moderate-certainty evidence).

One RCT compared the effects of Spiroflor SRL homeopathic gel (the main ingredients of which include *Symphytum officinale, Rhus toxicodendron and Ledum palustre* – SRL) with Cremor Capsici Compositus (CCC) (a rubefacient gel containing Capsici Oleoresin and other active ingredients) in a mixed group of patients with new acute low back pain or acute episodes of chronic low back pain. The authors report that both groups showed a significant reduction in pain on the (0–100-point) VAS scale, with a decrease of 38.2 mm in the SRL group and 36.6 mm in the CCC group (one RCT, 161 participants: very low-certainty evidence).

Neuropathic pain

One systematic review identified two RCTs that evaluated benefits and harms of herbal products in people with neuropathic pain. The first trial included topical application of a compound containing mace oil 2%, nutmeg oil 14%, methyl salicylate 6%, menthol 6%, coconut oil and alcohol. The second trial involved St John's wort taken in capsule form at a dose of 2,700 mg/day for five weeks. Neither study reported substantial pain relief of 50% or greater. One study reported no significant participant-reported pain relief of 30% or above over baseline in response to the nutmeg compound compared with placebo (RR 1.12, 95% CI 0.69 to 1.85; one RCT, 74 participants: very low-certainty evidence). The authors note that there was no observable reduction in the total pain score in response to either nutmeg or St John's wort.[132] 1+

Hypnotherapy

Musculoskeletal and neuropathic pain

One systematic review reported that hypnosis reduced pain intensity postintervention (SMD 0.42, 95% CI 0.78 to 0.07; nine RCTs, 530 participants: moderate-certainty evidence) and pain interference (SMD 0.39, 95% CI 0.73 to 0.06; six RCTs, 239 participants: low-certainty evidence) compared with control (no intervention, usual care or other interventions).[133] — 1++

Chronic pelvic pain in women

A systematic review of women with chronic pelvic pain reported no statistically significant effect of hypnotherapy on pain (SMD -0.80, 95% CI -2.12 to 0.52; three RCTs, 100 participants: no evidence certainty rating) compared with control (physical rest, NSAIDs or usual care).[134] — 1+

Temporomandibular disorder

One NMA evaluated the relative effectiveness of a range of interventions on pain intensity in people with TMD. The authors concluded that hypnosis did not reduce overall pain postintervention (SMD -0.67, 95% CI -1.59 to 0.24; based on a network of 42 RCTs with 1,989 participants: very low-certainty evidence) or at less than five-months follow-up (SMD -0.62, 95% CI -2.06 to 0.81; based on a network of 42 RCTs with 1,525 participants: very low-certainty evidence) compared with placebo.[83] — sufficient

Multiple pain types

A systematic review that investigated effects of hypnosis adjunctive to other primary interventions (medical therapies, psychological therapies or educational interventions) reported that hypnosis adjunctive to usual care had a small effect on postintervention pain, which may not be clinically significant, in people with chronic pain (MD -8.2 on a 0–100-point scale, 95% CI -11.8 to -4.6; 15 RCTs, 929 participants: very low-certainty evidence). The effect was maintained in the short term (up to 3 months) (MD -8.5 on a 0–100-point scale, 95% CI -15.7 to -1.30; four RCTs, number of participants not reported) but not over the long term (at 12 months) (MD -6.4 on a 0–100-point scale, 95% CI -18.5 to 5.7; three RCTs, number of participants not reported).[135] — 1+

12.2.2 Function

Acupuncture and dry needling

Chronic low back pain

In one systematic review, acupuncture improved function in the short term (SMD -0.27 95% CI -0.42 to -0.08; five RCTs, 2,164 participants: low-certainty evidence).[63] — 1++

Acupuncture did not improve back-specific function compared with sham (MD 3.33 points on a 100-point Hanover Functional Ability Questionnaire scale, 95% CI -1.25 to 7.90; five RCTs, 1,481 participants: very low-certainty evidence) and improved function to a level where the difference did not meet predefined clinically relevant change when compared with no intervention (MD 11.50, 95% CI 7.38 to 15.84; five RCTs, 2,960 participants: moderate-certainty evidence) and when compared with usual care (MD 9.78, 95% CI 3.54 to 16.02; five RCTs, 1,381 participants: low-certainty evidence).[125] — 1++

Chronic neck pain

A systematic review reported that acupuncture was associated with small improvements in short-term function (pooled SMD -0.40, 95% CI -0.67 to -0.14; five RCTs, 919 participants: low-certainty evidence) but not intermediate-term function (pooled SMD -0.19, 95% CI -0.37 to 0.05, three RCTs, 563 participants: low-certainty evidence) compared with sham acupuncture, a placebo (sham laser), or usual care. A single RCT cited in this review reported no difference — 1++

in function in the long term (SMD -0.23, 95% CI -0.61 to 0.16; 107 participants: low-certainty evidence).[63] 1++

A systematic review evaluated the effectiveness of acupuncture on functional disability against a range of comparators in people with chronic neck pain. When compared with a sham procedure, acupuncture was associated with different effects depending on the measurement instrument used. Studies using the Neck Disability Index (NDI) reported no difference in the reduction in disability scores from baseline between people receiving dry needling or sham at six months (MD 2.40 on a 0–100-point scale, 95% CI -5.46 to 10.26; one RCT, 60 participants: no evidence certainty reported) or 12 months (MD -0.11, 95% CI -7.69 to 7.47; one RCT, 58 participants: no evidence certainty rating) following treatment. Studies using the Northwick Park Neck Pain Questionnaire (NPQ), which is a 0–36-point scale that can be converted to percentage, reported a statistically significant improvement in function at three months following treatment (MD -6.06, 95% CI -8.20 to -3.92; two RCTs, 704 participants: no evidence certainty rating). The authors note that this effect did not meet the MCID of 25% reduction from baseline.[126] 1+

When compared with active control, individual studies using NDI reported no difference in disability scores at three months (MD -0.29, 95% CI -2.37 to 1.80; three RCTs, 175 participants: no evidence certainty rating) but a statistically and clinically significant effect at six months (MD -9.00, 95% CI -14.06 to -3.94; one RCT, 30 participants: no evidence certainty rating). Statistically and clinically significant effects were measured at all follow-up points in studies that used NPQ: at three months (MD -6.67, 95% CI -9.42 to -3.92; two RCTs, 335 participants: no evidence certainty rating), six months (MD -6.33, 95% CI -9.22 to -3.44; one RCT, 304 participants: no evidence certainty rating) and 12 months (MD -4.75, 95% CI -7.86 to -1.64; one RCT, 294 participants: no evidence certainty rating).[126] 1+

Acupuncture combined with active control interventions compared with active control alone did not significantly improve function at three months (MD -3.83, 95% CI -9.22 to 1.57; two RCTs, 190 participants: no evidence certainty rating) or six months after treatment (MD -9.00, 95% CI -19.22 to 1.22; four RCTs, 346 participants: no evidence certainty rating).[126]

A further review reported no effect of dry needling on functional capacity in people with chronic neck pain postintervention (MD -0.20, 95% CI -0.61 to 0.22; nine RCTs, 651 participants: no evidence certainty rating).[127]

Chronic pelvic pain in women

No evidence was identified on the effectiveness of acupuncture on function in women with chronic pelvic pain.

Chronic prostatitis/chronic pelvic pain syndrome

No evidence was identified on the effectiveness of acupuncture on function in men with chronic prostatitis.

Fibromyalgia

In one review of people with chronic fibromyalgia, acupuncture improved function in the short term when compared with sham or no intervention (MD -8.60 on a 0–100-point scale, 95% CI -12.00 to -5.42; four RCTs, 350 participants: moderate-certainty evidence). Acupuncture also improved function in the short term compared with sham acupuncture alone (MD -9.21, 95% CI -13.65 to -5.78; three RCTs, 283 participants: moderate-certainty evidence). There was insufficient evidence to draw conclusions for acupuncture compared with exercise.[63] 1++

Osteoarthritis of the knee

One systematic review found that acupuncture did not improve function in people with chronic pain because of osteoarthritis of the knee in the short term (SMD -0.11, 95% CI -0.27 to 0.22; four RCTs, 954 participants: low-certainty evidence) and intermediate term (SMD -0.15, 95% CI -0.31 to 0.02; four RCTs, 767 participants: low-certainty evidence). There was insufficient evidence to draw conclusions for acupuncture compared with exercise.[63] 1++

Temporomandibular disorder

One NMA reported that acupuncture improved physical function compared with placebo or sham procedures (MD 16.04 mm on a 1–100 mm scale, 95% CI 11.60 to 20.48 mm; 36 RCTs, 2,009 participants: moderate-certainty evidence).[72] sufficient

Herbal products

No evidence was identified on the effects of herbal products on function in people with chronic pain.

Hypnotherapy

No evidence was identified on the effects of hypnotherapy on function in people with chronic pain.

12.2.3 Quality of Life

Acupuncture and dry needling

Chronic low back pain

In one systematic review evaluating acupuncture in people with chronic low back pain, acupuncture improved quality of life to a level where the difference did not meet predefined clinically relevant change compared with sham (MD 2.33 on a 100-point SF-12 scale, 95% CI 0.29 to 4.37; three RCTs, 1,068 participants: low-certainty evidence).[125] 1++

Chronic low back pain

One systematic review, which evaluated the effects of acupuncture in people with chronic neck pain, included a single study that reported on quality-of-life outcomes. There was no statistically significant difference between groups receiving acupuncture and sham acupuncture in either MCS scores (MD 5.36, 95% CI -1.53 to 12.25) or PCS scores (MD 1.02, 95% CI -6.20 to 8.24; one RCT, 190 participants: no evidence certainty rating).[126] 1+

Herbal products

No evidence was identified on the effects of herbal products on quality of life in people with chronic pain.

Hypnotherapy

Chronic pelvic pain

A systematic review that evaluated the effects of hypnotherapy in women with chronic pelvic pain reported no difference in quality of life in groups receiving hypnotherapy compared with controls (physical rest, NSAIDs or usual care) (SMD -0.11, 95% CI -0.56 to 0.35; two RCTs, 75 participants: no evidence certainty rating).[134] 1+

12.3 Evidence of harms

There are relatively few harms reported with any of the interventions, and in most cases these were described as mild and did not happen significantly more often than in groups receiving sham interventions or usual care.[63,127,128,131] Where harms were identified, most were reported in association with acupuncture or dry needling, which can cause local bruising, worsening of pain and local swelling.[63,126]

Herbal products are not licensed for the treatment of chronic pain and are not regulated to the same degree as medicines. A systematic review reported no significant difference in adverse events between nutmeg compound or St John's wort and placebo (RR 1.00, 95% CI 0.55 to 1.81; two RCTs, 128 participants: very low-certainty evidence).[132] 1++

However, the GDG acknowledges that herbal products may cause adverse effects when taken in combination with prescribed medications or make these less effective.

It is unclear if hypnotherapy may be associated with adverse events as systematic reviews on hypnotherapy in people with chronic pain did not report on this outcome.[83,133,134] sufficient 1+ 1++

12.4 Summary of benefits and harms of complementary therapies for chronic pain

There is a lack of evidence of long-term benefit of complementary therapies to pain or function.

Acupuncture is associated with small, short-term improvements in pain in people with chronic low back pain and prostatitis, which may not be clinically significant. Dry needling produced a small, short-term reduction in neck pain and pain associated with temporomandibular joint dysfunction in one systematic review for each condition, while further reviews reported no evidence of effect. Effects were not sustained beyond the short term. Combining acupuncture with another active treatment (such as traction therapy, stretching or massage) offered greater benefits than these treatments given alone in people with chronic neck pain.

Evidence of a small benefit of acupuncture on function in the short term was reported in people with chronic low back pain, chronic neck pain, fibromyalgia and temporomandibular joint dysfunction.

There was insufficient evidence to draw a conclusion about the use of herbal products for chronic pain.

There was inconsistent evidence for the effectiveness of hypnotherapy, with systematic reviews reporting a small benefit in people with musculoskeletal and neuropathic pain and when used as an adjunctive therapy in people with a range of pain types, but no effect in people with chronic pelvic pain or TMD.

Available evidence is insufficient to recommend the use of herbal products or hypnotherapy for chronic pain.

No evidence was identified on the effectiveness of aromatherapy, music therapy or reiki in people with chronic pain.

12.5 Other factors

There is widespread use of complementary therapies by people in Scotland for many conditions, including long-term pain, with some individuals reporting benefit. Those using complementary therapies perceive a low risk of harm. The biopsychosocial approach to pain reflects that pain is a complex subjective experience influenced by biological, psychological and social factors and it is acknowledged that it is difficult to design studies which objectively measure the effects of complementary therapies as experienced by individuals.

Many complementary therapies are not provided by the NHS.

There is some evidence for short-term improvement in pain and function in certain conditions with acupuncture, with a low risk of harm but effect sizes were small, and not clearly clinically significant. There was insufficient evidence available to determine the most appropriate setting to deliver acupuncture, ie as a privately operated service, in the community, in primary care or as an NHS specialist service.

Over recent years, pain services in some areas of Scotland have withdrawn the provision of acupuncture. The GDG acknowledges that delivery of acupuncture requires resources, including administration, staffing, equipment and facilities. The cost effectiveness of providing acupuncture was not investigated in this guideline.

Experience from many healthcare professionals working in pain services is that interventions (not just acupuncture) performed in isolation, with the hope of producing short-term pain reduction, can foster a reliance on healthcare. It is the view of the GDG that interventions, if thought appropriate for an individual based on shared decision making, should be part of a long-term self-management plan *(see sections 3.5 and 3.8)*.

12.6 Recommendations

✓ Support individuals with chronic low back pain, chronic neck pain, chronic pelvic pain or temporomandibular disorder who wish to manage their pain with acupuncture for short-term benefit, and discuss how they might access the intervention.

13 Simple analgesics

13.1 Introduction

Chronic pain is a common condition that can be difficult to manage with medicines. Many patients use multiple medications, both prescribed and over the counter, to try to manage their condition, often with little evidence of benefit to support their use, particularly in the long term. The use of these medicines may also present a risk of harm to the patient, particularly when they are used alongside other medicines (which is often the case) or in patients with multiple comorbidities (such as cardiovascular conditions, renal impairment and gastrointestinal conditions). It is important to identify new evidence (or lack thereof) that could impact practice. Increasing concerns regarding the safety and long-term effectiveness of opioids means it is important to fully understand the benefits and harms of using simple analgesics in managing chronic pain.

Simple analgesics include paracetamol, NSAIDs and nefopam. For the purposes of this guideline nefopam is classed as a non-opioid, centrally-acting analgesic. Its mechanism of action is not well understood.

Non-steroidal anti-inflammatories have both an analgesic and an anti-inflammatory effect which makes them particularly useful for the treatment of chronic pain associated with inflammation. These medications act by inhibiting enzymes, called cyclo-oxygenases (COX). There are two main types of NSAIDs, non-selective and selective, which refer to different NSAIDs' ability to inhibit specific types of COX enzymes. Non-selective NSAIDs (such as diclofenac, ibuprofen or naproxen) inhibit both COX-1 and COX-2 enzymes to a significant degree. Medications which target COX-2 enzymes only (such as celecoxib or etoricoxib) are selective NSAIDs.

In Scotland, paracetamol and NSAIDs are frequently used for the management of various conditions that cause chronic pain. They are often used long term. Which NSAIDs are prescribed has some variation between health boards and is largely determined by the local prescribing formulary. Nefopam is not used as widely, but there is variation across Scotland. Many health boards have guidance against prescribing nefopam in place.

13.2 Evidence of benefit

13.2.1 Pain

Oral NSAID vs placebo

Osteoarthritis

A well conducted systematic review and meta-analysis of RCTs carried out by AHRQ explored the effectiveness and harms of non-opioid pharmacological treatments for chronic pain. In the short term (three to less than six months), NSAIDs resulted in a small reduction in pain compared with placebo (MD -0.73 on a 10-point scale, 95% CI -0.84 to -0.62; 27 RCTs, 13,478 participants: moderate-certainty evidence). Most trials were in patients with knee or hip osteoarthritis and the main drugs were celecoxib and naproxen. The proportion of study participants reporting a pain response to NSAIDs was significantly greater than placebo (56% vs 46%, RR 1.23, 95% CI 1.18 to 1.31; 15 RCTs, 8,253 participants: high-certainty evidence).[136] 1++

In the intermediate term (six to <12 months), pain reduction was sustained, based on a single study in patients with knee osteoarthritis taking celecoxib compared with placebo (MD -0.63, 95% CI -1.10 to -0.16; one RCT, 345 participants: no evidence certainty rating). The relative risk of reporting a pain response was not statistically significant (RR 1.13, 95% CI 0.94 to 1.35; one RCT, unclear participants: no evidence certainty rating).

An NMA explored the long-term outcomes (≥12 months) of medications for people with knee osteoarthritis. When expressed in terms of mean difference compared with placebo on a 0–100 scale there was no NSAID that offered a long-term benefit over placebo (based on a network of 42 RCTs, 22,037 participants).[107] — sufficient

Inflammatory arthritis

The AHRQ systematic review reported that NSAIDs reduced pain severity compared with placebo at short-term follow-up (MD -0.97, 95% CI -1.33 to -0.74; nine RCTs, 4,543 participants: moderate-certainty evidence). The proportion of patients who recorded a short-term pain response was significantly higher with NSAIDs than with placebo (45% vs 32%, RR 1.58, 95% CI 1.34 to 2.06; seven RCTs, 3,434 participants: moderate-certainty evidence). Statistically significant responses were also reported at intermediate and long-term follow-up, but based on single studies in each case.[136] — 1++

Lower back pain

The same systematic review identified two short-term RCTs (654 participants) comparing the effects of naproxen with placebo in people with chronic lower back pain. The authors noted that results were inconsistent, it was not possible to determine a pooled effect and that the certainty of the evidence was insufficient.[136] — 1++

Oral NSAID vs oral NSAID

Osteoarthritis

There was only low-certainty evidence from trials in which different NSAIDs were compared with each other. Most comparisons had only one or two trials contributing and there were no differences between drugs in pain or function outcomes for patients with osteoarthritis in the short, intermediate, or long term with the exception of the comparison between diclofenac and celecoxib, which showed a moderate effect in favour of diclofenac for pain (MD -12.2 on a 0–100 point WOMAC scale, lower numbers indicate greater relative effect; 95% CI -22.1 to -2.2; one RCT, participants not reported: low-certainty evidence).[136] — 1++

Inflammatory arthritis

In short-term follow-up there was no evidence of a difference in pain reduction between any two NSAIDs studied (low- to moderate-certainty evidence). For intermediate-term pain outcomes there was low-certainty evidence for no difference in outcomes between meloxicam and naproxen and nabumetone and naproxen in single studies.[136] — 1++

Paracetamol

Osteoarthritis

The AHRQ systematic review evaluated the effects of paracetamol (acetaminophen) on outcomes for people with chronic osteoarthritis pain. Paracetamol did not have an impact on osteoarthritis pain in the short term (MD -0.34, 95% CI -0.66 to 0.03; three RCTs, 1,082 participants: low-certainty evidence) or intermediate term (MD -0.30, 95% CI -0.77 to 0.17; one RCT, 212 participants: low-certainty evidence).[136] — 1++

An NMA found no evidence of the long-term effect of paracetamol on pain reduction in people with knee osteoarthritis compared with placebo (MD 7.00, 95% CrI -10.86 to 23.95; one RCT, 27 participants: no evidence certainty rating).[107] — sufficient

Cross class comparisons

The AHRQ systematic review identified one small short-term RCT (85 participants) that compared diclofenac (150 mg daily) with paracetamol (4,000 mg daily) and found diclofenac to be superior for improvement in pain (-53.9 vs -23.8 difference from baseline on WOMAC pain subscale; p=0.003).[136] — 1++

13.2.2 Function

Oral NSAID vs placebo

Osteoarthritis

The AHRQ systematic review reported that NSAIDs resulted in a small improvement in function in people with osteoarthritis compared with placebo in the short term (3 to <6 months) (SMD -0.32, 95% CI -0.37 to 0.28; 28 RCTs, 13,473 participants: high-certainty evidence) and intermediate term (SMD -0.25, 95% CI -0.47 to -0.04; one RCT, 345 participants: no evidence certainty rating).[136] — 1++

An NMA reported on long-term effects of NSAIDs on physical function in people with knee osteoarthritis. Data was only reported for celecoxib which did not significantly improve physical function compared with placebo (SMD -0.13, 95% CrI -0.32 to 0.07; two RCTs, 232 participants: no evidence certainty rating).[107] — sufficient

Inflammatory arthritis

The AHRQ systematic review reported that NSAIDs improved function in people with chronic pain as a result of inflammatory arthritis compared with placebo at short-term follow-up (SMD -0.34, 95% CI -0.51 to -0.20; seven RCTs, 4,284 participants: moderate-certainty evidence).[136]

There were only single trials reporting on function at intermediate- and long-term follow-up. One trial reported a small improvement in function compared with placebo in the intermediate term. In the other trial (365 participants) the review reported that meloxicam did not improve function in the long term compared with placebo, although there was a very small statistically significant effect. For each trial the certainty of evidence was assessed as low.[136] — 1++

Oral NSAID vs oral NSAID

The same systematic review reported no evidence of a difference in effect on function between any NSAID, except the comparison between diclofenac and celecoxib, where a single RCT found that diclofenac had a moderate improvement in function over celecoxib (RR 2.06, 95% CI 1.37 to 3.08; low-certainty evidence).[136] — 1++

Paracetamol

Osteoarthritis

The AHRQ systematic review reported that paracetamol did not have an impact on osteoarthritis function in the short term compared with placebo (SMD -0.14, 95% CI -0.29 to 0.04; three RCTs, 1,082 participants). A very small, clinically insignificant improvement in function was reported in the intermediate term compared with placebo (MD -3.7 on a 1–100-point WOMAC function subscale, 95% CI -6.9 to -0.5; one RCT, 212 participants: low-certainty evidence).[136] — 1++

Cross class comparisons

The same systematic review identified one small short-term RCT (85 participants) that compared diclofenac (150 mg daily) with paracetamol (4,000 mg daily) and found a significant improvement in function in those taking diclofenac (mean difference from baseline on WOMAC function subscale -163.0 (24.4% improvement), p<0.001) but not in those taking paracetamol (-41.8, p=0.28: insufficient evidence certainty).[136] — 1++

13.2.3 Quality of life

Oral NSAID vs placebo

Osteoarthritis

Based on short-term trials in the AHRQ systematic review, there was no evidence of an effect on QoL from oral NSAIDs as measured by the SF-36 (MCS). There was an improvement in the PCS which did not reach the three-point minimal clinically important difference stipulated by the review authors (MD 2.95 on a standardised 0–100-point scale, 95% CI 1.79 to 4.18; three RCTs, 1,027 participants: moderate-certainty evidence).[136] 1++

Inflammatory arthritis

The same systematic review identified two RCTs that reported QoL data associated with NSAIDs in people with inflammatory arthritis. One small trial (55 participants) reported moderate improvement in QoL in people with ankylosing spondylitis who received naproxen. A larger trial (1,148 participants) found some improvements in QoL with naproxen and celecoxib. The authors note that for most doses these improvements were statistically significant, but not clinically significant.[136] 1++

Oral NSAID vs oral NSAID

No evidence was identified that reported on QoL in head-to-head comparisons of NSAIDs.

Cross class comparisons

No evidence was identified that reported on QoL in cross-class comparisons.

13.3 Evidence of harms

13.3.1 NSAIDs

The AHRQ systematic review reported estimates of harmful effects of non-opioid pharmacological therapies for chronic pain based on their own meta-analyses of individual RCTs and on narrative review of published systematic reviews. In the following sections, where identified, systematic reviews cited within the AHRQ review are reported but have not been reanalysed or critically appraised.[136]

Serious adverse events

A meta-analysis of short-term RCTs concluded there was no increased risk of serious adverse events (SAEs) with NSAIDs compared with control (RR 0.96, 95% CI 0.73 to 1.27; 25 RCTs, 13,736 participants: low-certainty evidence).[136]

In the intermediate term, a single RCT (563 participants) did not find an increased risk of SAEs with naproxen (RR 0.51, 95% CI 0.05 to 5.58), but this evidence was insufficient to draw conclusions. The authors of the AHRQ review cite a further Cochrane review, which evaluated celecoxib 200 mg daily versus any non-selective NSAID or placebo in people with osteoarthritis.[138] It found no significant differences in the incidence of SAEs with celecoxib compared with non-selective NSAIDs (nine RCTs) or placebo (32 RCTs, participants varied according to comparison: very low-certainty evidence). The AHRQ review found no significant increase in SAEs with topical diclofenac compared with placebo (RR 1.03, 95% CI 0.29 to 27.01; two RCTs, 912 participants: very low-certainty evidence).[136] 1++

Withdrawals due to adverse events

In the AHRQ systematic review, which pooled data for harms across all chronic pain types, withdrawals due to adverse events (WAE) were increased with NSAIDs overall in the short term (RR 1.30, 95% CI 1.14 to 1.49; 38 RCTs, 20,060 participants: moderate-certainty evidence).[136] 1++

Subgroup analysis showed that the size and direction of effect varied by individual drug. The review reported a moderate increase in WAE in the short term with diclofenac (RR 1.71, 95% CI 1.22 to 2.65; six RCTs), ibuprofen (RR 1.96, 95% CI 1.42 to 2.69; five RCTs), and naproxen (RR 1.50, 95% CI 1.23 to 1.84; 15 RCTs), while celecoxib (RR 1.05, 95% CI 0.86 to 1.24; 16 RCTs) and meloxicam (RR 1.16, 95% CI 0.51 to 2.32; three RCTs) showed no statistically significant increased risk (number of participants for subgroup analyses was not reported).

Three RCTs found that NSAIDs did not significantly increase risk of WAE in the intermediate or long term, based on low certainty and insufficient evidence. There was not a significant increase in WAEs with topical diclofenac compared with placebo (RR 1.03, 95% CI 0.29 to 27.01; four RCTs, 1,549 participants: low-certainty evidence). The authors of this review report a further Cochrane review of celecoxib 200 mg daily versus any non-selective NSAID or placebo in patients with osteoarthritis.[136] It reported no significant differences in the incidence of WAEs in groups using celecoxib compared with non-selective NSAIDs (nine RCTs) or placebo (32 RCTs). 1++

Cardiovascular events

The AHRQ systematic review notes a large number of RCTs of cardiovascular risks of NSAIDs.[136] The authors of this review cite a further systematic review of 639 RCTs that evaluated cardiovascular harms using individual patient data and standard meta-analysis.[138] While not limited to people with chronic pain, the authors note that the indication for an NSAID in around four fifths of the participants was rheumatoid arthritis or osteoarthritis. The analyses combined data on four selective COX-2 inhibitor drugs; celecoxib, rofecoxib, etoricoxib, and lumiracoxib ("coxibs"). This review found an increased risk in major vascular events with a coxib (adjusted RR (aRR) 1.37, 95% CI 1.14 to 1.66; 190 RCTs, 88,605 participants: evidence certainty not reported) and with diclofenac (aRR 1.41, 95% CI 1.12 to 1.78; estimate based on indirect comparison, total number of participants not reported) compared with placebo. Major coronary events were increased with coxibs, diclofenac, and ibuprofen, and increased risk of hospitalisation for heart failure was found with all NSAIDs *(see Table 4)*. This review reported that there may be increased risk of major vascular events in the first six months of treatment with diclofenac (but no evidence of increased risk over longer treatment periods for any NSAID or coxib studied), and that, for all drugs analysed, higher doses were associated with greater risk. 1++

Table 4: Individual patient data meta-analysis of NSAID cardiovascular risks compared with placebo

Event	**Diclofenac Adjusted RR** (95% CI)	**Ibuprofen Adjusted RR** (95% CI)	**Naproxen Adjusted RR** (95% CI)	**Coxibs Adjusted RR** (95% CI)
Major vascular events[a]	**1.41 (1.12 to 1.78)**	1.44 (0.89 to 2.33)	0.93 (0.69 to 1.27)	**1.37 (1.14 to 1.66)** Celecoxib 1.36 (1.00 to 1.84)
Vascular mortality	1.65 (0.95 to 2.85)	1.90 (0.56 to 6.41)	1.08 (0.48 to 2.47)	1.58 (1.00 to 2.49)[c]
Major coronary events[b]	**1.70 (1.19 to 2.41)**	**2.22 (1.10 to 4.48)**	0.84 (0.52 to 1.35)	**1.76 (1.31 to 2.37)**
Heart failure (hospitalisation)	**1.85 (1.17 to 2.94)**	**2.59 (1.19 to 5.20)**	**1.87 (1.10 to 3.16)**	**2.28 (1.62 to 3.20)**

CI confidence interval; NSAID nonsteroidal anti-inflammatory drug; RR risk ratio

a Non-fatal myocardial infarction, coronary death, myocardial infarction or chronic heart failure death, non-fatal stroke, stroke death, any stroke, other vascular death

b Non-fatal myocardial infarction, coronary death, myocardial infarction or coronary heart disease death

c 99% CI calculated because of multiple comparisons

bold values: 95% certainty that the true RR is not 1.0 and we conclude that the observed RR is statistically significantly different from 1.0 at the 0.05 level.

Reproduced with permission from McDonagh MS, Selph SS, Buckley DI, Holmes RS, Mauer K, Ramirez S, et al. Nonopioid Pharmacologic Treatments for Chronic Pain. Rockville (MD): Agency for Healthcare Research and Quality; 2020 Apr. Report No. 20-EHC010

Authors of the AHRQ systematic review report that, in the intermediate term, three RCTs compared the risk of cardiovascular events with celecoxib and non-selective NSAIDs, with none finding a significant difference.[136]

In the long term, one large good-quality RCT (7,297 participants) randomised patients with osteoarthritis or rheumatoid arthritis who were under the age of 60 years, had no known cardiovascular disease, and who were currently taking a non-selective NSAID, to celecoxib or to continue their non-selective NSAID. At follow-up (median three years), there was no significant difference in the incidence of hospitalisation for non-fatal myocardial infarction or other biomarker positive acute coronary syndrome, non-fatal stroke, or cardiovascular death (hazard ratio (HR) 1.12, 95% CI 0.81 to 1.55). The results demonstrate non-inferiority between celecoxib and non-selective NSAIDs for these outcomes.[136] 1++

Serious upper gastrointestinal events

In the short term, the AHRQ systematic review found increased risk of serious gastrointestinal (GI) events with NSAIDs (largely bleeding), with the size of risk varying by specific drug. The systematic review cited in the AHRQ review, which analysed data on risks associated with coxibs and traditional NSAIDs using individual patient data meta-analysis, found moderate increased risk of serious upper GI harms from coxibs compared with placebo (RR 1.81, 95% CI 1.17 to 2.81: no evidence certainty rating), and from diclofenac compared with placebo (RR 1.89, 95% CI 1.16 to 3.09). A large increase in risk of serious GI harms was reported for ibuprofen (RR 3.97, 95% CI 2.22 to 7.10) and for naproxen (RR 4.22, 95% CI 2.71 to 6.56). The evidence certainty was not reported for these analyses. The authors reported no evidence of a difference in effect related to the specific coxib used. Most of the harms were GI bleeds and the findings were not affected by lower or higher baseline risk of GI events. The risk was greater in the first six months of coxib (RR 2.55, 99% CI 1.49 to 4.35), diclofenac (RR 3.93, 99% CI 2.16 to 7.13), ibuprofen (RR 5.73, 99% CI 3.24 to 10.14), and naproxen use (RR 6.31, 99% CI 3.81 to 10.44).[136]

The systematic review noted mixed evidence for the harms associated with coxibs compared with non-selective NSAIDs. The authors cite a Cochrane review that directly compared GI harms in people with osteoarthritis who used celecoxib with those using any non-selective NSAID. Their analysis found no difference between celecoxib and non-selective NSAIDs or placebo (odds ratio (OR) 0.61, 95% CI 0.15 to 2.43; four RCTs, 1,755 participants: very low-certainty evidence). The AHRQ meta-analysis reported no significant difference in the risk of serious short-term GI events between celecoxib and placebo (7.5% vs 6.7%, RR 1.04, 95% CI 0.67 to 1.54; four RCTs, 4,399 participants: low-certainty evidence). In contrast, a pooled analysis of diclofenac, ibuprofen, naproxen, and meloxicam found a large increased risk of serious GI events compared with placebo (13% vs 3%, RR 4.29, 95% CI 2.75 to 6.93; nine RCTs, 4,448 participants: low-certainty evidence). The authors noted that the evidence was inconsistent and imprecise and insufficient to draw conclusions. 1++

In the intermediate term, based on a single study comparing celecoxib with any non-selective NSAID in people with osteoarthritis over six months, non-selective NSAIDs had a moderately

greater risk of clinically important GI events than celecoxib (OR 1.82, 95% CI 1.31 to 2.55; one RCT, 8,067 participants: low-certainty evidence).[136] 1++

Hepatic events

The AHRQ review cited one fair-quality systematic review that evaluated the hepatic harms of NSAIDs (specifically diclofenac, naproxen, ibuprofen, meloxicam, celecoxib, rofecoxib, and valdecoxib) in people with osteoarthritis or rheumatoid arthritis.[136] This systematic review included 64 RCTs, most of which were six months or longer in duration.[139] Diclofenac was found to be associated with a large increased incidence of elevated liver enzymes (aminotransferases more than three times the upper limit of normal) than placebo (3.55%, 95% CI 3.12 to 4.03 vs 0.29%, 95% CI 0.17 to 0.51: low-certainty evidence). Diclofenac use also resulted in a larger increase in liver-related discontinuations from treatment (2.17%, 95% CI 1.78 to 2.64) than placebo (0.08%, 95% CI 0.02 to 0.29: low-certainty evidence). Liver enzyme elevations and liver-related discontinuations with diclofenac were higher with greater dose (>100 mg daily) and duration of treatment (>13 weeks). Liver-related serious adverse events were infrequent, but naproxen use resulted in the highest incidence (0.06%, 95% CI 0.02 to 0.15) compared with placebo (0.00%, 95% CI 0.00 to 0.08: low-certainty evidence). One liver-related hospitalisation and one liver-related death occurred, both from naproxen. 1++

The AHRQ review also cited a further systematic review that investigated liver injury associated with NSAIDs, although with no limit to population or study duration. The authors note that this reached similar conclusions.[140]

Renal events

No evidence was identified that reported on renal dysfunction or renal failure events in people with chronic pain. Authors of the AHRQ systematic review cite adverse event findings from other sources to address missing evidence.

They identified two systematic reviews on NSAIDs and acute kidney injury (published in 2015–2017) from wider populations not directly related to NSAIDs use in the management of chronic pain. Those studies showed a moderate to large increased risk of renal harm associated with NSAID use which was higher in older patients and in those with chronic kidney disease (CKD) (evidence from observational studies, includes short-term use) and no difference between NSAIDs.[136] 1++

13.3.2 Paracetamol

In people with chronic pain as a result of osteoarthritis, the AHRQ review included two short-term and one intermediate-term RCT that reported on adverse events from paracetamol compared with placebo.[136] 1++

Serious adverse events

At short-term follow-up, meta-analysis found no statistically significant difference in SAEs between people receiving paracetamol compared with those receiving placebo (2.4% vs 0.9%, RR 2.57, 95% CI 0.60 to 10.8; two RCTs, 1,023 participants: low-certainty evidence). A single study found no meaningful difference in SAEs between people who received 1,950 mg daily versus 3,900 mg daily of paracetamol (1.9% vs 1.9%, RR 1.01, 95% CI 0.21 to 4.94; one RCT, 318 participants: low-certainty evidence). There was also no meaningful difference in SAEs between paracetamol and placebo at intermediate-term follow-up (4.6% vs 4.8%, RR 0.96, 95% CI 0.29 to 3.23; one RCT, 212 participants: low-certainty evidence).[136] 1++

Withdrawals due to adverse events

Paracetamol use did not result in an increase in WAEs compared with placebo in the short or intermediate term. At short-term follow-up, meta-analysis found no meaningful difference in 1++

WAEs between those taking paracetamol and placebo (7.4% vs 7.1%, RR 1.14, 95% CI 0.67 to 1.95; two RCTs, 1,023 participants: low-certainty evidence)). A single study found no meaningful difference in WAEs between people who received 1,950 mg and 3,900 mg daily of paracetamol (6.3% vs 5.0%, RR 1.27, 95% CI 0.51 to 3.12; one RCT, 318 participants: low-certainty evidence). At intermediate-term follow-up there was no statistically significant difference in WAEs between people who received paracetamol compared with placebo (11.1% vs 8.7%, RR 1.28, 95% CI 0.56 to 2.92; one RCT, 212 participants: low-certainty evidence).[136] **1++**

13.4 Summary of benefits and harms of simple analgesics for chronic pain

Evidence shows that oral NSAIDs slightly reduce pain and improve function in people with osteoarthritis in the short term, with these effects maintained in the intermediate term with celecoxib (based on a single RCT). There is no evidence of benefit over placebo in the long term (>12 months) from NSAIDs or paracetamol in people with knee osteoarthritis.

Oral NSAIDs result in small improvements in pain severity and function, and moderate improvement in pain response compared with placebo for people with inflammatory arthritis.

There were no significant differences in effect between different doses of oral NSAIDs.

Evidence on QoL is inconsistent, with studies finding different effects, although none were clearly clinically significant.

Evidence suggests that NSAIDs do not significantly increase the risk of SAEs but lead to a small increase in WAEs, with ibuprofen, diclofenac, and naproxen each having moderately-increased risk in the short term.

There was no increased risk of any cardiovascular adverse event with NSAIDs as a class compared with placebo, although there was a small increase in risk with diclofenac. There was a moderate increased risk of major coronary events with both diclofenac and celecoxib, and a large increased risk with ibuprofen. In the intermediate and long term there was no difference in cardiovascular events between non-selective NSAIDs and celecoxib.

Non-selective NSAIDs led to a moderate to large increase in GI events (largely bleeding) in the short term, particularly in the first six months of treatment. Evidence on non-selective NSAIDs versus celecoxib was mixed and inconclusive in the short term, while in the intermediate term non-selective NSAIDs had a moderately increased risk of serious GI events.

Evidence showed hepatic harms (for example, liver enzyme elevations) with both diclofenac and naproxen in the intermediate term.

Based on the wider population using these drugs, studies show a moderate to large increased risk of renal harms with NSAID use, particularly in older people and patients with CKD. There was no difference in the risk between different NSAIDs.

In contrast paracetamol did not significantly improve pain or function in the short, intermediate or long term, across all doses. The use of paracetamol (in the short or intermediate term) had no statistically significant difference in adverse events compared with placebo.

13.5 Other factors

When choosing and prescribing medication for chronic pain management it is good practice to follow the 5As of analgesic prescribing:

- analgesia (improvement in pain)
- activities of daily living (function and QoL)
- adverse effects

- affect
- aberrant drug behaviours.

The recommendations in this guideline should be used in conjunction with the Quality Prescribing for Chronic Pain Guide *(see section 9 of that document)*. This provides practical advice to clinicians regarding applying SIGN guideline recommendations to individual patients.

Oral medication is easily obtainable and straightforward from a patient or carer perspective, therefore an acceptable intervention. Medication options for chronic pain are limited, and so patients are willing to accept risk of harm, with risk of benefit. Potential adverse events caused by the medication ceases if the patient stops medication, thus not long term.

The BRAN approach can be used to aid discussion regarding treatment options and reach shared decision making with patients:

- Benefits
- Risks
- Alternatives
- do Nothing.

Patients with chronic pain commonly purchase over-the-counter medicines and remedies to manage their condition. It is prudent to check what (if any) medication patients are purchasing over the counter before making any prescribing decisions.

Paracetamol has a high tablet burden if being taken regularly at full dose. While there is evidence that paracetamol does not reduce chronic osteoarthritis pain, individuals are comfortable using this drug based on its availability over the counter and its familiarity in treating acute pain, for which it remains effective. On this basis, while paracetamol is not routinely recommended, in people who cannot tolerate other analgesics, it may be worth trialling use of paracetamol in line with advice in the Quality Prescribing for Chronic Pain Guide.

Nefopam is included in the items of limited clinical value listed in Achieving Value and Sustainability in Prescribing (2024) which makes the following recommendation:

- prescribe only if the item is for an exception named in this guidance or no other item or intervention is clinically appropriate or available
- consider deprescribing where safe and appropriate in individuals currently prescribed this item. Continued prescribing of these medicines should be subject to regular review.
- Exceptions: nefopam may be considered for specific individuals, when choice of alternative analgesia is limited due to other comorbidities, eg patients with renal failure.
- particular caution should be used in adults who would be at elevated risk of anticholinergic side effects, eg older adults or in those with cognitive impairment.

The Specialist Pharmacy Service website includes warnings about the harms associated with use of nefopam. Nefopam overdose is characterised by neurological symptoms (seizures, hallucination and agitation) and cardiovascular symptoms (coma and tachycardia). Serotonin toxicity can also occur in overdose, particularly if taken with other serotonergic drugs such as selective serotonin reuptake inhibitors (SSRIs).

An NMA, which explored the long-term outcomes (≥12 months) of medications for people with knee osteoarthritis and included 47 RCTs in total, reported that diclofenac was the most frequently studied NSAID (five RCTs), followed by naproxen and celecoxib (four RCTs), rofecoxib and etoricoxib (two RCTs) and remaining NSAIDs in one RCT each.[107] Rofecoxib is not available for prescribing in Scotland and has been withdrawn from the worldwide market after a study showing that long-term use significantly increased risk of heart attack compared with patients receiving placebo. The European Medicines Agency has completed a review of

the safety and effectiveness of systemic medicines containing nimesulide and concluded that the benefits of nimesulide, when used systemically, continue to outweigh its risks but that its use should be restricted to the treatment of acute pain and primary dysmenorrhoea. It has issued a recommendation that nimesulide should no longer be used for the treatment of painful osteoarthritis. Nimesulide is not available in the UK.

13.6 Recommendations

R **Consider NSAIDs (non-selective and selective) for short-term (less than six months) or intermittent use in patients with osteoarthritis or inflammatory arthritis.**

✓ The use of NSAIDs (non-selective and selective) increases the risk of GI bleeding and may increase the risk of cardiovascular issues (diclofenac and celecoxib) and this should be considered carefully before initiation. Patients often have comorbidities or other medication that would increase their individual risk of harm (eg older age, CKD, cardiac conditions, previous gastric ulcer or bleed, other nephrotoxic medication or medication increasing the risk of adverse GI effects such as SSRIs - this list is not exhaustive). Safety measures to reduce risk of harms include coprescribing GI protection, renal function monitoring and sick day rules counselling.

✓ NSAIDs should be used at the lowest effective dose for the individual patient to minimise the risk of harms.

✓ In people unable to tolerate other analgesics, consider a two- to four-week-trial of paracetamol taken three to four times daily (maximum dose 4 g per 24 hours) to assess efficacy.

14 Antidepressants

14.1 Introduction

Depression and chronic pain are often interconnected, with pain symptoms worsening depression and depression causing pain and many symptoms overlapping within these clinical diagnoses (for example, fatigue and loss of motivation or pleasure in activities).[141]

Antidepressants, including tricyclic antidepressants (TCAs), serotonin-noradrenaline reuptake inhibitors (SNRIs) and SSRIs are indicated for the treatment of depression and other mood disorders but some antidepressants also have limited indications for the treatment of neuropathic pain *(see Table 5)*.

Table 5: Licensed indications of commonly used antidepressants

Drug (class)	Main indication for mood disorders	Additional indication for pain
amitriptyline (TCA)	major depressive disorder	neuropathic pain
clomipramime (TCA)	depressive illness	none
imipramine (TCA)	depressive illness	none
nortriptyline (TCA)	depressive illness	none*
trimipramime (TCA)	depressive illness	none
duloxetine (SNRI)	major depressive disorder	diabetic neuropathy
venlafaxine (SNRI)	major depression	none
escitalopram (SSRI)	depressive illness	none
fluoxetine (SSRI)	major depression	none
paroxetine (SSRI)	major depression	none
sertraline (SSRI)	depressive illness	none

Source: British National Formulary (BNF)[142]

*while nortriptyline is listed in the BNF with an indication and dose for use in neuropathic pain, it is not licensed for this indication

NICE has published guidance on the safe prescribing and withdrawal of medicines associated with dependence or withdrawal symptoms.[143]

14.2 Evidence of benefit

A large Cochrane NMA assessed the effectiveness and safety of antidepressants compared with placebo or any active comparator for pain management and included 176 RCTs involving 28,644 adult participants (mean age 50.6 years, 68.3% were female) with fibromyalgia, neuropathic pain, musculoskeletal or other types of chronic pain. Study duration ranged from two weeks to nine months, with an average duration of 10 weeks. Only six of the 176 trials included long-term follow-up data and the authors were unable to draw any conclusions on the long-term efficacy or safety of antidepressants. The NMA includes some studies of medications that are not available in the UK.[144]

sufficient

The NMA considered the proportion of participants reporting substantial (at least 50%) reduction in pain, pain intensity, and mood as primary outcomes. Secondary outcomes were the proportion of participants reporting moderate (at least 30%) reduction in pain, physical function, sleep, QoL, PGIC score, serious adverse events, and withdrawal.

While study populations were similar to the target populations in Scotland, the authors note that most studies did not include people with anxiety or depression. All results and rankings were based on comparison of each antidepressant with placebo.

Duloxetine was consistently the highest-ranked antidepressant for pain relief, pain intensity, physical function and QoL outcomes (although not significantly different from placebo in terms of quality of life). Both standard and high-dose duloxetine were equally effective for most outcomes. Milnacipran was often ranked second among the antidepressants, although the certainty of evidence was lower than for duloxetine. There was insufficient evidence to draw conclusions about the effectiveness or safety of any other antidepressant.

Compared with placebo, standard-dose (60 mg) duloxetine showed a small-to-moderate effect on substantial pain relief (OR 1.91, 95% CI 1.69 to 2.17; 16 RCTs, 4,490 participants, moderate-certainty evidence) and pain intensity (SMD -0.31, 95% CI -0.39 to -0.24; 18 RCTs, 4,959 participants, moderate-certainty evidence). High-dose (>100 mg) milnacipran had a small effect on substantial pain relief (OR 1.72, 95% CI 1.13 to 2.62; one RCT, 384 participants, low-certainty evidence). Standard-dose (100 mg) milnacipran had a small effect on pain intensity (SMD -0.22, 95% CI -0.39 to -0.06; four RCTs, 1,866 participants, moderate-certainty evidence). — sufficient

Duloxetine (OR 1.79, 95% CI 1.67 to 1.91; 24 RCTs, 7,833 participants, moderate-certainty evidence) and milnacipran (OR 1.70, 95% CI 1.48 to 1.92; seven RCTs, 3,056 participants, moderate-certainty evidence) had a small effect on moderate pain relief. Standard-dose duloxetine (SMD -0.24, 95% CI -0.32 to -0.18; 15 RCTs, 3,887 participants, high-certainty evidence), high-dose (>60 mg) duloxetine (SMD -0.23, 95% CI -0.30 to -0.16; 13 RCTs, 3,503 participants, moderate-certainty evidence) and standard-dose milnacipran (SMD -0.18, 95% CI -0.30 to -0.07; three RCTs, 1,840 participants, moderate-certainty evidence) had small effects on physical function. No antidepressant showed a significant effect on QoL (low- or very low-certainty evidence).

Due to small sample sizes and network sparseness the authors were unable to analyse results across different pain conditions but note that there is no high-quality or high-certainty evidence for the efficacy of amitriptyline, desipramine, desvenlafaxine, imipramine, mirtazapine, nortriptyline, or venlafaxine for any of the included outcomes. They note that this aligns with previous systematic reviews in participants with neuropathic pain, which showed no high-quality evidence for the efficacy of amitriptyline, desipramine, imipramine, milnacipran, nortriptyline, or venlafaxine[145-150] but moderate-quality evidence that duloxetine is effective for people with diabetic peripheral neuropathy.[151] For people with fibromyalgia, systematic reviews have reported no unbiased evidence that amitriptyline, desvenlafaxine, venlafaxine, or SSRIs were better than placebo,[152,153] and low-certainty evidence that duloxetine, milnacipran, and mirtazapine may yield moderate pain relief.[153] The authors suggest that the previous literature is mixed on the efficacy of antidepressants for musculoskeletal pain.[144]

A further systematic review and meta-analysis examined the efficacy and safety of antidepressants for pain in older (over 65 years) adults. Data from 15 studies were included and all trials reported on chronic pain. Compared with placebo, 12–16 weeks of duloxetine treatment reduced pain (MD -9.07 on a 0 to 100 scale, 95% CI -11.77 to -6.38; three RCTs: 721 participants, high-certainty evidence) for older people with knee osteoarthritis. The authors note that this was considered a very small effect.[154] — 1++

Included trials on TCAs were not consistent in the dose, study duration or comparator medications and it was not possible to conduct pooled analyses. The effectiveness of amitriptyline for pain reduction in older people varied across six trials depending on the condition and comparator. In people with diabetic neuropathy, amitriptyline reduced pain from baseline but was less effective than gabapentin. For mixed pain conditions, it did not

demonstrate a significant advantage over distigmine. However, in people with postherpetic neuralgia, amitriptyline consistently showed greater pain relief compared with placebo and lorazepam, and was comparable to other antidepressants such as desipramine and fluoxetine. 1++

14.3 Evidence of harms

14.3.1 Adverse events

Adverse events were recorded as a primary outcome of harm, while secondary outcomes included serious adverse events, and withdrawal.

The NMA was unable to draw any conclusions about the safety of antidepressants for treating chronic pain because adverse event data were sparse and studies were underpowered to detect them. All safety evidence had very low certainty. Adverse event rates for the highest-ranked antidepressants (those which had highest probability of being associated with few adverse events) – desvenlafaxine and mirtazapine – were not significantly different from placebo but were based on results from only two studies each. Standard- and high-dose duloxetine and standard-dose milnacipran were equally ranked.[144]

Low-dose (<60 mg) duloxetine, high-dose milnacipran, standard-dose (25–75 mg) amitriptyline, and standard-dose (4–8 mg) esreboxetine were the lowest-ranked antidepressants, and people taking each of these drugs had more than double the odds of reporting an adverse effect compared with people receiving placebo. sufficient

No antidepressants showed any significant difference for the outcome of serious adverse events when compared with placebo, and the confidence intervals were very wide.

Nortriptyline, mirtazapine, amitriptyline, desvenlafaxine, and venlafaxine all showed no significant difference compared with placebo for withdrawal. Duloxetine, milnacipran, esreboxetine, desipramine, and paroxetine all showed significant effects, ranging from small to moderate. The authors note that conclusions on the ranking of the individual drugs for this outcome were unreliable due to all antidepressants having wide and overlapping credible intervals.

Physiological or psychological drug dependency were not assessed in the NMA.

14.3.2 Adverse events in older people

In the systematic review of antidepressants for pain in older people, the authors noted that safety data were poorly reported across all antidepressants, but they reported an increased risk of discontinuation of treatment or withdrawal from trials associated with the use of SNRIs or TCAs.[154] The authors also note that previous studies have reported higher rates of harms in older people using antidepressants, including a significantly increased risk of falls. 1++

See section 21 for further information on benefits and harms of combination pharmacological therapies in people with chronic pain.

14.3.3 Harms from polypharmacy

There is the potential for harm when individuals are prescribed multiple medications with anticholinergic properties. The Polypharmacy Guidance: Appropriate Prescribing - Making medicines safe, effective and sustainable 2025-2028 provides advice on measurement of anticholinergic burden (using the modified Anticholinergic Risk Scale (mARS)) and recommends caution when prescribing medicines with anticholinergic properties, prescribing only the minimum needed, especially for older adults, people with frailty, or people with complex multimorbidities. The guidance notes that TCAs are highly anticholinergic (mARS 2 and 3) while SSRIs have some anticholinergic properties (mARS 1). 4

The Quality Prescribing Guide for Antidepressants (2024–2027) supports healthcare professionals to facilitate the appropriate use of antidepressants and highlights potentially harmful scenarios that could be prevented by proactive medication review. These include:

- individuals receiving the same antidepressant continuously, long term (≥2 years)
- older adults (≥65 years) or frail adults receiving a SSRI plus antiplatelet, non-steroidal anti-inflammatory drug, direct oral anticoagulant or warfarin without gastroprotection
- individuals receiving >1 defined daily dose per day of citalopram (>20 mg per day) or escitalopram (>10 mg per day)
- individuals receiving TCAs and other anticholinergics.

The guide also highlights combination pharmacological therapies that may be associated with particular harms, including:

- antidepressants plus long-term benzodiazepines (≥8 weeks) and/or z-drugs
- combination antidepressant treatments
- combinations which may increase the risk of QTc prolongation (citalopram or escitalopram or TCAs plus: methadone, antipsychotics, quinine, some antinausea medicines, etc).

4

14.4 Summary of benefits and harms of antidepressants for chronic pain

The NMA results and rankings are limited to comparisons of each antidepressant with placebo. There are no head-to-head comparisons of antidepressants reported. This is probably because of the size and complexity of the network. In some analyses in the NMA, pharmacological interventions were split into dose categories (low, standard and high) to address between-study heterogeneity.

The only antidepressant that the review authors had confidence in for the treatment of chronic pain was duloxetine. Duloxetine probably has a moderate effect on reducing pain and improving physical function in the short term, with no evidence of longer-term effects. Higher doses of duloxetine probably provide no more benefits than standard doses. Milnacipran may reduce pain but had a smaller effect and was supported by less evidence. It is not possible to draw conclusions about the effectiveness of any other antidepressant. There was very low-certainty evidence for all safety outcomes for all antidepressants and it is not possible to draw conclusions about the safety of any antidepressant prescribed for the management of chronic pain.

The SmPC notes that duloxetine has been associated with an increase in blood pressure and clinically significant hypertension in some patients.

Therefore, in patients with known hypertension or other cardiac disease, blood pressure monitoring is recommended, especially during the first month of treatment. Duloxetine should be used with caution in patients whose conditions could be compromised by an increased heart rate or by an increase in blood pressure.

14.5 Other factors

In Scotland, antidepressants, particularly amitriptyline and other TCAs are frequently used in the treatment of chronic pain conditions, particularly neuropathic pain, fibromyalgia-type conditions and chronic musculoskeletal conditions. This practice is based on small, underpowered studies.

However, there is also a lack of evidence to suggest that antidepressants have no value as a treatment option for some people who continue to experience chronic pain symptoms and clinicians should consider each person in their individual circumstances and chronic pain experience *(see section 3.5)*.

Antidepressant medications may relieve both pain and depression through shared neurotransmitter pathways in the brain, hence there may be individuals with undiagnosed or unrecognised mood disorders where the beneficial effect on pain may be mediated by improvement in mood.

The SMC has accepted duloxetine for restricted use for the treatment of diabetic peripheral neuropathic pain in adults as second or third-line therapy *(see section 23.4)*. However, the evidence from the NMA reported in this guideline includes RCTs that recruited people with a wide range of chronic pain types (fibromyalgia, low back pain, hip, knee or hand osteoarthritis, pain associated with Parkinson's disease or neuropathic pain associated with chemotherapy, multiple sclerosis, diabetes, spinal cord injury or stroke)[144] and the GDG took this into account, along with the older SMC advice for duloxetine, which restricts use to people with painful diabetic neuropathy as second- or third-line therapy.

The NMA was not able to analyse efficacy of medicines by subtype of chronic pain but reported small-to-moderate effects for duloxetine on pain relief and pain intensity drawn from the pooled data of people with multiple pain types. The GDG considered that this increased the generalisability of the recommendation and concluded that it was appropriate for it to be considered in anyone with chronic pain, based on the evidence of clinical effectiveness and the likelihood of increased cost effectiveness as the medication is currently available as a generic drug. Prescribers should be aware of SMC advice for duloxetine in diabetic neuropathy and that use in people with chronic pain types other than diabetic neuropathy is off label.

Milnacipram is not licensed for use in the UK.

14.6 Recommendations

R **Consider a trial of 60 mg duloxetine in people with chronic pain.**

✓ Monitor blood pressure, especially during the first month of treatment, in people with chronic pain who are prescribed duloxetine and who have known hypertension and/or other cardiac disease.

Adopting a person-centred approach is critical. Pain is an individual experience, and certain medications may work for people at an individual level even while the research evidence at the population level is inconclusive or unavailable.

✓ Prescribers should engage in shared decision-making conversations and codevelop a management plan in partnership with the individual.

15 Antiepileptics

15.1 Introduction

Chronic neuropathic pain can be particularly challenging to manage and often does not respond to simple analgesics or opioids. Antiepileptic medicines are commonly prescribed for neuropathic pain, with mixed evidence of benefit to pain reduction, improved function or improved QoL. Antiepileptic medicines are also associated with several potential harms.

Antiepileptics are often prescribed for neuropathic pain associated with conditions such as fibromyalgia, diabetic neuropathy and postherpetic neuralgia. They are also sometimes used in patients with other conditions such as lower back pain and pelvic pain.

There are increasing concerns regarding potential harms from long-term use of antiepileptics, such as dependency on or addiction to gabapentinoids.

The analgesic action of antiepileptic drugs is thought to be a result of limiting neuronal excitation and enhancing inhibition.[155] Gabapentinoids (gabapentin, pregabalin, and mirogabalin) share a similar structure and mechanism of action. They target α-2-δ subunit of voltage-gated calcium (Ca^{2+}) channels leading to decreasing Ca^{2+} influx, subsequent neurotransmitter release (eg glutamate) that affects pain sensation, resulting in a reduction of neuropathic pain.[156] In Scotland, gabapentin and pregabalin are commonly used to manage neuropathic pain associated with a broad range of conditions. Mirogabalin does not have a marketing authorisation for use in the UK therefore evidence on this drug has not been included.

Carbamazepine is commonly prescribed for the management of trigeminal neuralgia. Oxcarbazepine is rarely prescribed in Scotland for neuropathic pain. The mechanism of action of both oxcarbazepine and carbamazepine is a modulation of voltage-gated sodium (Na^{+}) channels, leading to a decrease in neuronal activity.[157] Topiramate, sodium valproate, lamotrigine, lacosamide and levetiracetam are not commonly prescribed for chronic pain.

15.2 Evidence of benefit

Nine systematic reviews were identified that evaluated the effectiveness of antiepileptic drugs in adults living with chronic non-malignant pain. Four of the reviews were rated as acceptable quality[155,156,158,159] and five as high quality.[136,160-163] The number of trials included in the reviews ranged from three to 313, and the overall number of participants in the reviews ranged from 624 to 48,789. All trials were short or intermediate term with durations of six months or less. 1+ 1++

15.2.1 Lumbar radicular pain and lower back pain with or without radiating leg pain

A systematic review of the effects of antiepileptics for the treatment of non-specific lower back pain, with or without radiating leg pain, or lumbar radicular pain (sciatica or neurogenic claudication secondary to lumbar spinal stenosis) included trials of gabapentin at doses from 15 mg/kg/day to 3,600 mg/day. The review found that in people with low back pain with or without radiating leg pain gabapentin was not better than placebo in reducing pain (MD 0.0 on a 0–10 NPRS, 95% CI -0.8 to 0.7; three RCTs, 195 participants: high-certainty evidence) or disability (MD -0.2 on a 100-point ODI, 95% CI -5.9 to 5.5; one RCT, 71 participants) in the short term (up to three months). In contrast, a trial comparing 300 mg/day topiramate and placebo in people with lower back pain with or without radiating leg pain found topiramate effective in reducing pain (MD -11.4 on a 78-point scale, 95% CI -16.7 to -6.1), although not disability (MD -4.9 on a 100-point ODI, 95% CI -19.4 to 9.6; one RCT, 89 participants: moderate-certainty evidence) in the short term.[155] 1++

In people with lumbar radicular pain, there was no evidence of any effect from antiepileptics on pain compared with placebo in the immediate term (≤2 weeks after randomisation) (MD -0.1 on a 0–10-point NPRS, 95% CI -0.7 to 0.5; two RCTs, 255 participants: high-certainty evidence). The effects of antiepileptics on pain in the short term were inconsistent. One trial reported a statistically significant reduction in pain compared with placebo in people using up to 3,600 mg/day gabapentin (MD -0.8 on a 0–3-point NPRS, 95% CI -1.2 to -0.5; one RCT, 43 participants), but a further and larger trial reported no evidence of an effect from up to 600 mg/day pregabalin on pain compared with placebo (MD 0.6 on a 0- to 10-point NPRS, 95% CI -0.2 to 1.4; one RCT, 207 participants). There was no effect from antiepileptics on pain compared with placebo in the intermediate term (MD -0.1 on a 0- to 10-point NPRS, 95% CI -0.9 to 0.7, one RCT, 184 participants: high-certainty evidence) or long-term (MD 0.4 on a 0- to 10-point NPRS, 95% CI, -0.5 to 1.3; one RCT, 178 participants: moderate-certainty evidence).[155]

There was no effect from antiepileptics on disability over any follow-up period, including immediate-term (pooled SMD -0.1, 95% CI -0.3 to 0.2; two RCTs, 249 participants: high-certainty evidence); short-term (MD 0.6 on a 23-point RMDQ, 95% CI -1.5 to 2.7; one RCT, 182 participants: moderate-certainty evidence); intermediate-term (MD -1.4 on a 23-point RMDQ, 95% CI -3.6 to 0.8; one RCT, 172 participants: moderate-certainty evidence) and long-term (MD 0.8 on a 23-point RMDQ, 95% CI -1.5 to 3.1; one RCT, 162 participants: moderate-certainty evidence) durations.[155]

Similarly, 400 mg/day of topiramate did not reduce pain (MD -0.7, 95% CI -2.1 to 0.6 on a 0- to 10-point NPRS; one RCT, 58 participants: very low-certainty evidence) or disability (MD -2.0 on a 100-point ODI, 95% CI -10.0 to 6.0; one RCT, 58 participants: low-certainty evidence) in the intermediate term compared with placebo.[155]

1++

15.2.2 Pelvic pain

Mixed results were identified on the effectiveness of gabapentin compared with placebo in reducing pelvic pain. One systematic review found a significant reduction in pain at three months (MD -0.79, 95% CI -1.23 to 0.35; two RCTs, 76 participants) and six months (MD -1.68, 95% CI -2.30 to -1.05, two RCTs, 59 participants) when measured using VAS, but only at three months (MD -0.2, 95% CI -0.25 to -0.15; two RCTs, 256 participants) and not at six months (MD -0.27, 95% CI -0.80 to 0.26; two RCTs, 256 participants) when measured using a Numerical Rating Scale.[162] The certainty of evidence was not reported.

1++

15.2.3 Fibromyalgia

Trials comparing pregabalin or gabapentin with placebo in people with fibromyalgia found a small but statistically significant reduction in pain (MD -0.59 on a 0–10-point scale, 95% CI -0.75 to -0.43; nine RCTs, 5,081 participants: moderate-certainty evidence), improvement in function (SMD -0.21 on Fibromyalgia Impact Questionnaire 0 to 80 or 0–100, 95% CI -0.28 to -0.15, eight RCTs, 5,074 participants: moderate-certainty evidence), and sleep (various measures used: SMD -0.33, 95% CI -0.40 to -0.25; seven RCTs, participants and evidence certainty not reported) in the short to medium term (up to six months). Although, improvements were also seen on the Hospital Anxiety and Depression Scale for depression (SMD -0.11, 95% CI -0.18 to -0.03; five RCTs, participants and evidence certainty not reported) and anxiety (SMD -0.11, 95% CI -0.25 to -0.02; five RCTs, participants and evidence certainty not reported), these results fell below the threshold for a small effect and are unlikely to be clinically important.[136]

1++

15.2.4 Neuropathic pain (not otherwise specified)

A systematic review and meta-analysis analysed head-to-head trials of gabapentinoids (pregabalin or gabapentin) with other drug classes used in the management of chronic pain. The review included 30 RCTs that covered a range of neuropathic pain types, including one

1+

trial of cancer neuropathic pain. As the results were from pooled data from these trials, it was not possible to discriminate effects on individual pain types, or exclude data from the cancer trial.[159]

The review reported no evidence of a difference in pain severity in the short term (up to three months) between gabapentinoids and TCAs (MD 0.1, 95% CI -0.13 to 0.32; 10 RCTs, 920 participants), QoL (SMD -0.05, 95% CI -0.25 to 0.15; three RCTs, 372 participants), sleep scores (SMD -0.06, 95% CI -0.14 to 0.27; five RCTs, 570 participants) or symptoms of depression (SMD -0.09, 95% CI -0.31 to 0.13; two RCTs, 317 participants). The certainty of evidence was moderate for all comparisons. 1+

The review also reported a small effect of greater pain reduction with SNRIs compared with gabapentinoids (MD 0.36, 95% CI 0.01 to 0.70; five RCTs, 1,495 participants), but no evidence of a difference in QoL (SMD 0.06, 95% CI -0.11 to 0.22; three RCTs, 565 participants), sleep scores (SMD 0.33, 95% CI -0.30 to 0.95; three RCTs, 565 participants) or symptoms of depression (SMD 0.06, 95% CI -0.14 to 0.25; three RCTs, 1,314 participants). The certainty of evidence was low for all comparisons.

A systematic review and meta-analysis completed by the Neuropathic Pain Special Interest Group of IASP evaluated the effects of a wide range of pharmacological therapies in people with neuropathic pain. The authors suggest that a number needed to treat (NNT) of 10 or below is clinically significant. The review reported evidence of a small difference in 50% pain reduction with gabapentinoid use (gabapentin, mirogabalin and pregabalin) in the short to medium term (up to four months) compared with placebo (risk difference 0.11 (positive value favours gabapentinoids, ie a higher chance of achieving 50% pain reduction), 95% CI 0.09 to 0.13, 46 RCTs, 14,192 participants: moderate-certainty evidence). There was a similar difference in 30% pain reduction with gabapentinoids compared with placebo (risk difference 0.13 (no scale described), 95% CI 0.06 to 0.21, four RCTs, 860 participants: moderate-certainty evidence). The combined NNT across 56 studies was 8.9 (95% CI 7.4 to 11.1).[163] 1++

Evidence for carbamazepine/oxcarbazepine, lacosamide, lamotrigine and topiramate was assessed to be inconclusive (all low or very low-certainty evidence) and the authors did not make recommendations for or against their use.[163] A recommendation was made against use of sodium valproate (pooled effect estimate not available, authors noted teratogenicity and other adverse effects) and against use of levetiracetam (risk difference for 50% pain reduction or moderate pain relief 0.03, 95% CI -0.03 to 0.09, four RCTs, 130 participants: low-certainty evidence).[163]

Two further systematic reviews investigated the benefits of pregabalin or gabapentin for neuropathic pain without specifying the type of neuropathic pain.[136,156] Pregabalin or gabapentin provided significantly better pain relief compared with placebo when measured in percentage change in pain intensity or PGIC.[156] The level of pain relief provided by these drugs in the short to medium term (up to five months) was very similar (≥50% reduction in pain intensity from pregabalin RR 1.72, 95% CI 1.37 to 2.16; 15 RCTs, 4,247 participants: and ≥50% reduction in pain intensity from gabapentin RR 1.76, 95% CI 1.34 to 2.32; six RCTs, 1,851 participants: no evidence certainty rating).[156] A meta-analysis pooling data from 15 trials reported a small but statistically significant reduction in pain in the short to medium term (up to four months) in people using either pregabalin or gabapentin compared with placebo (MD -0.61 on a 0–10 scale, 95% CI -0.87 to -0.36; 15 RCTs, 4,832 participants: moderate-certainty evidence).[136] Based on three small head-to-head trials, there was no difference in pain reduction between pregabalin or gabapentin (effect size not reported; three RCTs, 433 participants: low-certainty evidence). Pregabalin or gabapentin compared with placebo also provided a small but significant improvement in sleep (MD -0.65 measured on a 0–10 scale, 95% CI -0.89 to -0.41; 15 RCTs, participants not reported: no evidence certainty rating) but not anxiety or depression 1+ 1++

measured with the Hospital Anxiety and Depression Scale (Anxiety: SMD -0.11, 95% CI -0.25 to 0.03; eight RCTs, participants not reported: no evidence certainty rating. Depression: SMD -0.01, 95% CI -0.14 to 0.11; eight RCTs, participants not reported: no evidence certainty rating).[136] 1+ 1++

One systematic review described trials comparing 600 mg daily pregabalin with placebo in people with human immunodeficiency virus (HIV) neuropathy, central neuropathic pain (which is caused by a lesion or disease affecting the central nervous system, such as stroke, multiple sclerosis or spinal cord injury), or mixed neuropathic pain. Pregabalin provided a significant reduction in pain intensity in the short to medium term (up to four months) for people with central neuropathic pain (≥50% reduction in pain intensity RR 1.62, 95% CI 1.28 to 2.03; three RCTs, 562 participants: low-certainty evidence), or mixed neuropathic pain (≥50% reduction in pain intensity RR 1.51, 95% CI 1.23 to 1.85; four RCTs, 1,367 participants: moderate-certainty evidence) but not HIV neuropathy (≥50% reduction in pain intensity RR 0.86, 95% CI 0.70 to 1.06; two RCTs, 674 participants: moderate-certainty evidence).[160] 1++

15.2.5 Diabetic peripheral neuropathic pain

A Cochrane systematic review reported that pregabalin provided a small but statistically significant reduction in pain intensity in people with diabetic peripheral neuropathic pain compared with placebo in the short to medium term (up to four months), with 600 mg daily dose providing slightly more benefit than 300 mg daily dose (≥50% reduction in pain intensity, (600 mg daily dose): RR 1.6, 95% CI 1.4 to 1.9; seven RCTs, 1,360 participants: moderate-certainty evidence, (300 mg daily dose): RR 1.3, 95% CI 1.2 to 1.5; 11 RCTs, 2,931 participants: moderate-certainty evidence). In contrast, 150 mg daily dose of pregabalin did not provide more reduction in pain intensity compared with placebo (RR 1.14, 95% CI 0.8 to 1.63; two RCTs, 359 participants: low-certainty evidence).[160] The results measured using PGIC showed a similar pattern. A further systematic review that investigated the effects of antiepileptics on chronic pain reported no difference in QoL between people taking pregabalin or placebo (EuroQol five-dimensional questionnaire (EQ-5D) SMD 0.24, 95% CI -0.07 to 0.54; three RCTs, 1,015 participants: low-certainty evidence).[136] 1++

Based on two trials where daily doses varied from 300 mg to 1,800 mg, oxcarbazepine provided a small but statistically significant reduction in pain compared with placebo (MD -0.89 measured on 0–10 scale, 95% CI -1.50 to -0.37; two RCTs, 493 participants: no evidence certainty rating). These trials reported mixed results for changes in quality of life and sleep disruption.[136]

One systematic review focused on the comparison of gabapentin (at doses of 300 mg to 3,600 mg daily) with duloxetine (at doses of 60 mg to 120 mg daily) in people with diabetic peripheral neuropathic pain in the short term (up to three months) and found no difference in pain intensity (SMD -0.26 on a 0–100-point VAS, 95% CI -0.53 to 0.02; seven RCTs, 624 participants: no evidence certainty rating), PGIC score (MD 0.07, 95% CI -0.20 to 0.35; two RCTs, 204 participants: no evidence certainty rating), or response rate (RR 1.05, 95% CI 0.92 to 1.20; three RCTs, 236 participants: no evidence certainty rating).[161] 1++

15.2.6 Postherpetic neuralgia

A Cochrane systematic review of pregabalin for neuropathic pain reported that pregabalin provided a significant dose-dependent reduction in pain intensity compared with placebo in the short to medium term (up to four months) in people with postherpetic neuralgia (≥50% reduction in pain intensity with 150 mg daily dose: RR 1.96, 95% CI 1.41 to 2.74; four RCTs, 360 participants: low-certainty evidence, with 300 mg daily dose: RR 2.52, 95% CI 1.86 to 3.42; four RCTs, 713 participants: moderate-certainty evidence, with 600 mg daily dose: RR 2.66, 95% CI 2.04 to 3.48; four RCTs, 365 participants: moderate-certainty evidence). Similar results were also found using the PGIC.[160] However, in a further systematic review, there was no 1++

difference in function measured using the Brief Pain Inventory interference scale between groups receiving gabapentin or placebo (MD -0.23, 95% CI -0.70 to 0.23; one RCT, 371 participants: low-certainty evidence).[136] 1++

15.3 Evidence of harms

15.3.1 Pregabalin and gabapentin

In a systematic review of head-to-head trials of medication used in the management of chronic pain, there was no statistically significant difference between groups receiving gabapentanoids or TCAs in number of withdrawals during active treatment (risk difference 0.02, 95% CI -0.03 to 0.07, nine RCTs, 953 participants: moderate-certainty evidence) or number of trial dropouts because of adverse events (risk difference -0.02, 95% CI -0.06 to 0.02, nine RCTs, 953 participants: moderate-certainty evidence). The most frequent adverse events for people receiving TCAs were dry mouth and dizziness. People receiving gabapentinoids most frequently reported somnolence and dizziness.[159] 1+

A meta-analysis pooling results from trials investigating pregabalin or gabapentin compared with placebo found no significant increase in the risk of having a serious adverse event (RR 0.94, 95% CI 0.63 to 1.40; 21 RCTs, 8,622 participants: low-certainty evidence). Subgroup analyses by pain condition, specific drug, dose and study quality did not alter these results. However, there was a moderate increase in withdrawals because of adverse events (RR 1.74, 95% CI 1.51 to 2.03; 28 RCTs, 10,148 participants: moderate-certainty evidence).[136] Similar findings were reported in other systematic reviews.[155,156,160,163]

Specific adverse events in which significant increases were noted included sedation, dizziness, cognitive effects, weight gain, and peripheral oedema (RR ranged from 2.32 for peripheral oedema to 3.57 for weight gain).[136] A further systematic review reported a variety of specific adverse events, with the highest risk being for inco-ordination in pregabalin trials (RR 7.21, 95% CI 1.36 to 38.25; three RCTs, 1,294 participants: evidence certainty not reported) and weight gain in gabapentin trials (RR 5.61, 95% CI 1.04 to 30.22; two RCTs, 504 participants: evidence certainty not reported). Trials did not report the incidence of gabapentinoid misuse disorder.[156] 1++

15.3.2 Oxcarbazepine

In one systematic review, oxcarbazepine did not significantly increase the risk of serious adverse events compared with placebo (RR 1.82, 95% CI 0.74 to 5.05; two RCTs, 493 participants: low-certainty evidence), but led to a large increase in withdrawals because of adverse events (RR 3.64, 95% CI 1.86 to 7.12; two RCTs, 493 participants: low-certainty evidence). Participants receiving oxcarbazepine reported more sedation (RR 3.13, 95% CI 0.74 to 16.08; two RCTs, 490 participants: low-certainty evidence) and/or hyponatremia (RR 5.93, 95% CI 0.55 to 63.8; two RCTs, 490 participants: low-certainty evidence) compared with participants receiving placebo, but the difference was not statistically significant.[136] 1++

In a further systematic review and meta-analysis that evaluated pooled effects of medications compared with placebo in people with neuropathic pain, the risk difference for study withdrawal was statistically significantly higher in groups using oxcarbazepine or carbamazepine than placebo (risk difference 0.18, 95% CI 0.13 to 0.23, five RCTs, 709 participants: very low-certainty evidence).[163] 1++

15.3.3 Topiramate

One systematic review of antiepileptics used in people with low back pain identified two RCTs where effects of topiramate were reported. One RCT comparing 400 mg/day topiramate with placebo found no significant increase in the number of participants reporting adverse events 1++

(RR 1.2, 95% CI 0.9 to 1.6, one RCT, 58 participants: very low-certainty evidence). A further RCT, where topiramate was titrated from 50 mg to 300 mg per day, found differences in the number of adverse events reported between topiramate (21 events among 48 participants) and placebo groups (10 events among 48 participants) however, effects were not calculated as the total number of participants who experienced an event was not reported.[155] 1++

In a further systematic review and meta-analysis, which evaluated pooled effects of medications compared with placebo in people with neuropathic pain, risk difference for study withdrawal was statistically significantly higher in groups using topiramate than placebo (risk difference 0.16, 95% CI 0.13 to 0.20, three RCTs, 1,668 participants: very low-certainty evidence).[163] 1++

15.4 Summary of benefits and harms of antiepileptics for chronic pain

Gabapentinoids are associated with statistically significant reductions in pain intensity compared with placebo in people with unspecified neuropathic pain, and specific types of neuropathic pain (as a result of diabetic neuropathy, postherpetic neuralgia and central neuropathic pain) with a risk ratio for ≥50% reduction in pain intensity ranging from 1.3 (treatment of diabetic peripheral neuropathic pain with 150 mg/day pregabalin) to 2.2 (treatment of postherpetic neuralgia with 600 mg/day pregabalin). There is evidence of higher efficacy at higher doses of gabapentinoids in people with diabetic neuropathic pain and postherpetic neuralgia. Reductions in pain severity, as well as secondary measures including quality of life, are likely similar for patients treated with gabapentinoids compared with patients treated with TCAs. There is some evidence of a beneficial effect on sleep in those with unspecified neuropathic pain. Gabapentinoids were not effective for pain relief in trials of HIV-related neuropathy.

Gabapentin and pregabalin are not more effective in reducing lumbar radicular pain or improving function than placebo. In women with chronic pelvic pain, there is limited evidence of the efficacy of gabapentin, with differing results in different studies using different measures of efficacy and at different timepoints. In people with fibromyalgia, there is evidence of a small statistically significant reduction in pain severity, although these effect sizes may not be clinically significant.

There is limited and inconsistent evidence of the efficacy of non-gabapentinoid antiepileptic medications in people with low back pain. One study of people with low back pain with or without radiating leg pain reported topiramate reduced pain intensity in the short term, while a further study reported no effects of topiramate on pain in the intermediate term in people with lumbar radicular pain. Oxcarbazepine is associated with a small reduction in pain in people with diabetic neuropathy, which is statistically significant but not clinically significant.

Gabapentin, pregabalin and oxcarbazepine were associated with study withdrawal because of adverse events. However, the rate of serious adverse events was not elevated compared with placebo. There was mixed evidence of harms associated with topiramate with one systematic review reporting increased risk of study withdrawal in people using topiramate compared with placebo, but a further review included a trial of topiramate that reported no increase in adverse events compared with placebo.

In clinical practice, oxcarbazepine commonly causes sedation, unsteadiness, irritability and weight changes. These may not have been observed because of the small sample size of the trials. No study reported risk of gabapentinoid misuse, or risks of use in combination with opioid medications.

15.5 Other factors

Specific antiepileptic drugs (currently sodium valproate and topiramate) may only be prescribed subject to restrictions, including a pregnancy prevention programme. Restrictions apply to both females and males. Prescribers should review current safety and educational information provided by the Medicines and Healthcare Products Regulatory Agency (MHRA). Information current at the time of writing is available on use of valproate in men and women under 55 years of age, use of valproate in men (additional fertility advice) and topiramate. Some patients may prefer not to enrol in a pregnancy prevention programme or agree to other restrictions, which may affect the range of medications available to them.

In 2021, MHRA published a safety leaflet, Epilepsy medicines and pregnancy, which supports people using these medicines to understand the risks during pregnancy. The leaflet explains the findings of a review of several epilepsy medicines and their risk of physical birth abnormalities and other harmful effects on the unborn baby. It reported that use of carbamazepine or topiramate during pregnancy increases the risk of physical birth abnormalities compared with the general population. It also noted that the risks of taking gabapentin or pregabalin during pregnancy were not yet fully understood.

A population-based cohort study examined perinatal outcomes of all singleton pregnancies in Scotland between 2010 and 2023 where the women and birthing people had used an antiepileptic medicine during pregnancy. In pooled analysis combining seven antiepileptic drugs, use of any antiepileptic during pregnancy increased the risk of pregnancy loss compared with matched unexposed pregnancies. This result was driven by the effects of valproate, gabapentin, pregabalin and topiramate, which all showed significantly increased risks of pregnancy loss. There was no significant increase in risk of congenital abnormalities in pooled analysis of all antiepileptics, with only valproate indicating a significant risk when analysed as a monotherapy. In pooled analysis, there was an increased risk of early childhood developmental concerns associated with any antiepileptic use driven by the effects of valproate, gabapentin and pregabalin, which all showed increased risks individually.[164]

Only one trial of long-term treatment was included in any systematic review identified and therefore there is insufficient evidence on the long-term efficacy and harms of antiepileptic drugs for the management of chronic pain to support recommendations beyond six months' duration.

The GDG notes that it is common practice for people with chronic pain to remain on these medicines long term and advises that patients should be reviewed appropriately to monitor efficacy and adherence. Scottish Government has published Manage My Meds for patients and carers to help support people to manage medical therapy and prepare for a medicines review.

Not all antiepileptic medications are licensed for use in the management of chronic pain. This does not preclude their use; however, clinicians should consider this when prescribing and obtain appropriate consent from the patient for their use.

Trigeminal neuralgia appears in the International Classification of Headache Disorders, and as headache is outwith the scope of this guideline, evidence for using carbamazepine to treat trigeminal neuralgia was not reviewed. Carbamazepine remains the only licenced treatment for trigeminal neuralgia and is commonly used in this indication.

The GDG notes that the potential for gabapentinoid misuse remains poorly characterised, and although this risk was not reported in the evidence, the potential for misuse should be subject to clinical judgement on an individual basis.

In April 2021 the MHRA updated advice on gabapentin, originally published in 2017, to include a similar warning for pregabalin, that both drugs have been associated with a rare (up to 1 in 1,000 patients) risk of severe respiratory depression even without concomitant opioid medications.

Dose adjustments may be necessary in those at risk of experiencing this reaction, including those:

- with compromised respiratory function or respiratory disease
- with neurological disease
- with renal impairment
- using concomitant central nervous system (CNS) depressants, and
- older people.

When prescribing gabapentin or pregabalin in those who require concomitant treatment with opioid medicines, patients should be carefully observed for signs of CNS depression, such as somnolence, sedation, and respiratory depression, and the dose of either the gabapentinoid or the opioid should be reduced appropriately. See section 21 for advice on combination pharmacological therapies.

In January 2026, the MHRA updated and strengthened the warnings regarding addiction, dependence, withdrawal and tolerance for gabapentin, pregabalin, benzodiazepines, and z-drugs. Strengthened warnings have been included in the SmPC, patient information leaflets and outer packaging of these medications. Full details, including current advice and information for communication with patients are available from the MHRA.

Gabapentinoids, both illicitly sourced and legally prescribed, are increasingly being implicated in drug-related deaths, especially when coprescribed with opioids.[165] Gabapentinoids can be abused in the community and, particularly, within the prison service. Consequently, caution should be exercised and alternatives considered when prescribing to patients with a history of substance misuse or who are detained within the prison service.

Further information on safe prescribing of medications associated with dependence, including gabapentinoids, is available in Scottish Government's Quality Prescribing for Chronic Pain Guide and in the NICE clinical knowledge summary on drug treatment for neuropathic pain.

It is common for people with chronic pain to use more than one medication to manage their pain or to manage other comorbidities. Careful consideration needs to be given to the increased risk of harm when using antiepileptic drugs in combination with other medicines, such as opioids and benzodiazepines *(see section 21)*.

15.6 Recommendations

R **Consider gabapentinoids (gabapentin and pregabalin) in patients with neuropathic pain, fibromyalgia or pelvic pain for up to six months. Treatment should only be continued if there is clear, documented evidence of ongoing benefit. It is not possible to recommend one drug over the other.**

✓ Individuals who are prescribed pregabalin or gabapentin should be regularly reviewed to monitor for adverse effects and reduced efficacy. Following medication review, use of these medications should be reduced and potentially withdrawn based on shared decision making with the patient.

R **Gabapentinoids should be started at a low dose and titrated to the lowest effective dose before efficacy is ruled out. Dose titration should include regular careful clinical review.**

✓
- Information about potential adverse effects of antiepileptic medications, including dose-dependent effects and their reversal on discontinuation, should be clearly explained to patients.
- Information about the potential adverse effects of antiepileptic medications should be shared with people planning pregnancy who may be prescribed these drugs.

16 Topical analgesics

16.1 Introduction

Topical analgesics are medications that are applied on or massaged into the skin to temporarily relieve superficial pain or pain of muscles or joints. Formulations include patches or plasters that are stuck directly to the skin surface and creams that are rubbed into the skin. Topical analgesics have the potential to benefit localised pain, while reducing the likelihood of systemic adverse effects. Some topical agents, such as NSAIDs and menthol can be obtained over the counter without prescription. Capsaicin cream (at 0.025% or 0.075% concentrations) is only available by prescription.

Topical analgesics, including NSAIDs and plant alkaloids, have been widely used in people with chronic pain, although there remains uncertainty about the supporting evidence for some agents. They often have to be applied frequently and may be inconvenient to apply, causing localised skin irritation.

16.2 Evidence of benefit

Three systematic reviews were identified that focused, respectively, on topical capsaicin for neuropathic pain,[166] capsaicin, diclofenac and lidocaine in people with chronic pain,[136] and topical diclofenac for chronic musculoskeletal pain.[167] A further systematic review was identified on use of the vasodilator topical clonidine,[168] which is licensed only for prevention of migraine or recurrent headache, or for the management of vasomotor conditions commonly associated with the menopause, therefore this evidence was not considered. All systematic reviews were of high quality, but the included RCTs varied from moderate to very low in the quality and certainty of evidence for outcomes of interest. 1++

16.2.1 Pain intensity

Topical capsaicin

Topical capsaicin is available in several formulations, that differ in terms of delivery method and concentration. Capsaicin cream is rubbed directly onto the skin at the area where the individual is experiencing pain and is available in the UK at two strengths – 0.025% (ie 250 micrograms per 1 g by weight), which is licensed for the symptomatic relief of pain associated with osteoarthritis, and 0.075%, which is licensed for the symptomatic relief of neuropathic pain associated with and following herpes zoster infections (postherpetic neuralgia) and for the symptomatic management of painful diabetic peripheral polyneuropathy.

Capsaicin patches are 14 x 20 cm and contain 179 mg of capsaicin (or 640 micrograms per cm^2 of patch, equivalent to 8% or 80 mg per 1 g of patch adhesive). Capsaicin patches are applied by healthcare professionals at the site of the pain and licensed for the treatment of peripheral neuropathic pain in adults. See sections 16.5 and 23.4 for SMC advice on topical capsaicin patches.

One systematic review reported no statistically significant participant-reported clinically meaningful response in people with diabetic neuropathy, postherpetic neuralgia or trigeminal neuralgia who received topical capsaicin cream or patch compared with placebo at four weeks or less (RR 1.60, 95% CI 0.93 to 2.75; two RCTs, 175 participants: no evidence certainty rating).

The review reported a clinically meaningful response (at least 30% improvement in pain) in people who received topical capsaicin cream or patch compared with placebo over six to 52-weeks follow-up (RR 1.40, 95% CI 1.26 to 1.55; ten RCTs, 2,344 participants: low-certainty evidence). Both low-dose capsaicin patches (at 0.625% or 1.25% by weight) or creams (at 1++

0.075% by weight), which were applied frequently (RR 1.56, 95% CI 1.20 to 2.03; seven RCTs, 534 participants: no evidence certainty rating) and high-potency capsaicin patches (8% by weight), which were applied less frequently (RR 1.36, 95% CI 1.22 to 1.52; six RCTs, 1,810 participants: no evidence certainty rating) provided a significant reduction in pain.[166] 1++

A further systematic review reported that while 8% topical capsaicin patches reduced pain severity in the short term in people with HIV-related neuropathy or postherpetic neuralgia, the magnitude of benefit fell below the prespecified level for a small effect (MD -0.33 on a 0–10-point scale, 95% CI -0.60 to -0.00; three RCTs, 1,051 participants: moderate-certainty evidence). There was no significant difference in pain response (≥30% reduction in pain) between people receiving topical capsaicin or controls (RR 1.17, 95% CI 0.98 to 1.37; three RCTs, 1,051 participants: moderate-certainty evidence).[136] 1++

Topical diclofenac

The same systematic review evaluated topical diclofenac for chronic pain in people with osteoarthritis of the knee. Diclofenac reduced pain severity in the short term (MD -0.58, 95% CI -0.81 to -0.35; four RCTs, 1,451 participants: moderate-certainty evidence). Meta-analysis of pain response (≥30% reduction in pain) also resulted in a small reduction in pain intensity (RR 1.20, CI 1.09 to 1.38; three RCTs, 1,232 participants: moderate-certainty evidence).[136] 1++

A further systematic review investigated use of topical diclofenac to manage pain in people with a range of chronic musculoskeletal conditions, mainly osteoarthritis of the knee. Based on studies with follow-up over two to six weeks, more participants had ≥50% pain reduction with topical diclofenac (NNT of five) compared with placebo (RR 1.86, 95% CI 1.50 to 2.31; five RCTs, 732 participants: moderate-certainty evidence). A smaller effect on ≥50% pain reduction (NNT of 9.5) compared with placebo was sustained in studies that were followed up over six to 12 weeks (RR 1.22, 95% CI 1.13 to 1.30; five RCTs, 2,652 participants: moderate-certainty evidence). There was no significant difference in pain reduction between topical diclofenac and an oral NSAID (diclofenac or ibuprofen) (RR 0.98, 95% CI 0.89 to 1.08; three RCTs, 1,230 participants: no evidence certainty rating).[167] 1++

Lidocaine patch

A systematic review identified two studies on topical lidocaine, one in participants with knee osteoarthritis, which was terminated early and one in people with diabetic peripheral neuropathic pain, in which all participants received pretreatment with lidocaine cream in addition to the lidocaine patch, limiting applicability to this evidence review. There is insufficient evidence available to draw conclusions about the effectiveness or lidocaine patches for the management of chronic pain.[136] 1++

16.2.2 Function

Topical capsaicin

No evidence was identified that reported on function in people with chronic pain who were treated with topical capsaicin.

Topical diclofenac

One systematic review reported no effect on short-term function in people after treatment with topical diclofenac compared with placebo (MD -0.51, 95% CI -1.06 to 0.04; four RCTs, 1,538 participants: moderate-certainty evidence).[136] 1++

Lidocaine patch

No evidence was identified that reported on function in people with chronic pain who were treated with lidocaine patches.

16.2.3 Quality of life

None of the systematic reviews reported evidence on the effects of any topical analgesic on QoL outcomes.

16.3 Evidence of harms

16.3.1 Adverse events and study withdrawal

Topical capsaicin

A systematic review of studies including people with diabetic neuropathy, postherpetic neuralgia or trigeminal neuralgia reported greater of risk application site burning, stinging and/or erythema (RR 1.63, 95% CI 1.50 to 1.79) and application site pain (RR 2.38, CI 1.99 to 2.84) in people using topical capsaicin compared with placebo. The review reported withdrawals because of adverse events occurred in 6% of participants using topical capsaicin, compared with 2% using control (RR 3.31; CI 1.56 to 7.01; three RCTs, 1,027 participants: low-certainty evidence).[166] 1++

A further systematic review of studies in people with HIV-related neuropathy or postherpetic neuralgia reported a greater risk of both application site erythema (RR 1.46, 95% CI 1.29 to 1.66; three RCTs, 1,075 participants: moderate-certainty evidence) and application site pain (RR 2.26, 95% CI 1.61 to 2.82; three RCTs, 1,075 participants: moderate-certainty evidence). The review reported no statistically significant increase in the likelihood of study withdrawal because of adverse events (RR 2.20, 95% CI 0.37 to 12.91; three RCTs, 1,075 participants: moderate-certainty evidence).[136] 1++

Topical diclofenac

The same systematic review also reported no evidence of increased risk of serious adverse events associated with use of topical diclofenac (RR 1.03, CI 0.29 to 27.01; two RCTs, 912 participants: low-certainty evidence) or withdrawal because of adverse events in studies involving people with osteoarthritis of the knee (RR 1.50, 95% CI 0.81 to 3.58; four RCTs, 1,549 participants: low-certainty evidence).[136] 1++

A further systematic review, which included studies of a range of chronic pain conditions, but mainly osteoarthritis of the knee, reported an increased risk of local adverse events, such as dry skin, redness or erythema and pruritis (RR 1.62, 95% CI 1.36 to 1.93; 12 RCTs, 3,774 participants: moderate-certainty evidence) and withdrawal because of adverse events (RR 1.50, 95% CI 11 to 2.0; ten RCTs, 3,093 participants: moderate-certainty evidence) associated with use of topical diclofenac compared with placebo.[167] 1++

Lidocaine patches

No evidence was identified that reported on adverse events or study withdrawal in people with chronic pain who were treated with lidocaine patches.

16.4 Summary of benefits and harms of topical analgesics for chronic pain

Moderate-certainty evidence from two systematic reviews showed a small reduction in pain severity in the short term for people with musculoskeletal pain after using topical diclofenac. There was no evidence of increased risk of serious adverse effects, and all reported harms were minor, self resolving and limited to local effects.

There was evidence of pain reduction from use of topical capsaicin in two systematic reviews, however, the clinical importance of the effects was unclear. While more people experienced a clinically meaningful response from treatment with capsaicin than placebo in one review (49% vs 34%), this represented less than half of those in the treatment group.[166]

There is little evidence available on the effect of topical analgesics on function, and no evidence of benefit.

Despite the absence of published evidence of benefit or harm compared with placebo, the GDG acknowledge that some individuals using lidocaine plasters experience pain relief and that it may be an option for people with neuropathic pain that has not responded to other treatments and where there are no further treatment options. There is no evidence or clinical rationale for the use of lidocaine plasters in those with musculoskeletal or non-superficial pain.

16.5 Other factors

In June 2026, the SMC advised that capsaicin cutaneous patch (Qutenza®) is accepted for restricted use within NHS Scotland for the treatment of peripheral neuropathic pain in diabetic adults either alone or in combination with other medicinal products for pain.

In October 2014, the SMC advised that capsaicin (Qutenza®) is accepted for restricted use within NHS Scotland for the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain.

In August 2008, the SMC advised that lidocaine 5% medicated plaster (Versatis®) is accepted for restricted use within NHS Scotland for the treatment of neuropathic pain associated with previous herpes zoster infection (postherpetic neuralgia).

See section 23.4 for details of SMC restrictions.

Scottish Government has published guidance to promote the effective use of medicines and minimise unwarranted variation in prescribing practice across NHS Scotland.[169] This guidance advises that rubefacients (with the exception of capsaicin and topical NSAIDs) are medications of low clinical effectiveness and should not be prescribed in primary or secondary care. This guidance also classifies lidocaine plasters as medications of limited clinical effectiveness, where prescribing may be appropriate in some exceptional circumstances. Specifically, they may be prescribed to individuals who have been treated in line with SMC guidance *(see section 23.4)* and are still experiencing neuropathic pain associated with previous herpes zoster infection (postherpetic neuralgia), or where the decision to prescribe is in line with the Scottish Palliative Care Guidelines, or where no other item or intervention is clinically appropriate or available. Consider deprescribing where safe and appropriate in individuals currently prescribed this item. Continued prescribing of these medicines should be subject to regular review.

Lidocaine patches are commonly prescribed and patients perceive benefits, however there is considerable variation in prescribing across Scotland and significant costs to health boards, while there is no conclusive evidence of an effect on pain or quality of life.

Topical diclofenac is commonly prescribed for musculoskeletal pain in Scotland and is also available over the counter.

Topical capsaicin patch (8%) is only available in secondary care and requires training for appropriate use.

There are a number of products available for topical pain relief over the counter. These may not necessarily be at the same concentrations or formulations as prescribed medications and individuals should consult with pharmacists or GPs for advice.

16.6 Recommendations

R **Consider topical diclofenac in people with chronic musculoskeletal pain.**

R **Consider topical capsaicin cream 0.025% and 0.075% in people with chronic neuropathic pain. If tolerated, treatment should be maintained for at least six weeks.**

R **Consider referral to secondary care pain management for assessment for treatment with 8% capsaicin patch.**

✓ Consider a trial of lidocaine 5% medicated plasters in people who are experiencing superficial neuropathic pain associated with previous herpes zoster infection or superficial neuropathic pain in a postoperative scar, where extreme pain to light touch (allodynia) is present.

17 Muscle relaxants

17.1 Introduction

Muscle relaxants are a broad range of drugs that include benzodiazepines (BZD), non-BZD antispasmodics and antispasticity agents, such as baclofen and methocarbamol. Although frequently prescribed in the UK for conditions involving acute muscle spasm,[170] their role in the management of chronic pain is less well understood. Benzodiazepines are indicated for short-term use (two to four weeks) to treat a range of conditions, including muscle spasms, severe anxiety and severe insomnia, each of which can occur with acute and chronic painful conditions.

Use of BZDs in people who have been prescribed other medication to manage chronic pain is particularly dangerous as the benzodiazepine-opioid combination, for example, can lead to potentially life-threatening respiratory depression.

17.2 Evidence of benefit

Two systematic reviews and one NMA were identified.

The first review assessed the efficacy of a range of skeletal muscle relaxants for the treatment of fibromyalgia in 14 RCTs, which included 1,851 participants. Most of the drugs reported in the systematic review are not licensed for use in NHS Scotland. The only available drug is alprazolam, which is licensed for the short-term symptomatic treatment of severe anxiety, therefore the GDG did not consider this evidence.[171] 1++

Another high-quality systematic review and meta-analysis assessed the efficacy, acceptability, and safety of muscle relaxants for adults with non-specific low back pain.[170] Of the trials included in the meta-analysis, two involved people with chronic pain. Antispastic muscle relaxants did not reduce chronic back pain intensity (MD -5.4, 95% CI -13.7 to 2.9; one RCT, 80 participants: very low-certainty evidence) or disability (MD -3.2, 95% CI -8.3 to 1.8; one RCT, 80 participants: very low-certainty evidence) at 3–13 weeks compared with control. A single RCT reported benefit from adding the sedative eszoplicone (described as a 'miscellaneous muscle relaxant' by the authors of this systematic review) as a treatment for insomnia to standard pain medication regimen (twice daily naproxen 500 mg). Participants receiving eszoplicone reported reduced chronic back pain intensity (MD -19.9 on a 0–100 point scale, 95% CI -31.5 to -8.3; one RCT, 52 participants: moderate-certainty evidence) but not disability (MD -5.6, 95% CI -20.6 to 9.4; 1 RCT, 52 participants: low-certainty evidence) at 3–13 weeks compared with control. 1++

An NMA identified 52 RCTs that compared two or more treatment modalities, including muscle relaxants, in patients with painful temporomandibular disorders of muscular origin. Overall, measured across all follow-up periods (two weeks to 12 months), muscle relaxants had no statistically significant effect on post-treatment pain (SMD -0.48, 95% CI -1.09 to 0.13, five RCTs, 161 participants: very low-certainty evidence). Based on short-term follow-up (less than five months), muscle relaxants had a small effect on pain (MD -0.73 (scale not reported), 95% CI -1.39 to -0.06; five RCTs, 161 participants: very low-certainty evidence).[83] Muscle relaxants were not ranked higher than tenth out of twelve interventions (which included manual therapy, counselling, local anaesthesia, and occlusal appliances) analysed for pain reduction. However, considering the limitations of the studies included, and the scarcity of high-certainty evidence, the authors suggest that their findings should be interpreted cautiously. sufficient

17.3 Evidence of harms

The systematic review of muscle relaxants for adults with non-specific low back pain reported no difference in the risk of experiencing an adverse event with miscellaneous muscle relaxants compared with control (RR 1.5, 95% CI 0.4 to 5.7; two RCTs, 95 participants: moderate-certainty evidence). The authors note that whilst muscle relaxants are typically prescribed for short-term use, the effects of long-term use are not known. This is particularly important when considering that a risk of dependency and misuse associated with muscle relaxants has been observed from indirect evidence.[170] 1++

17.4 Summary of benefits and harms of muscle relaxants for chronic pain

There is insufficient evidence to support the use of muscle relaxants that are available in the UK for treatment of chronic pain of any type. There is also an absence of long-term safety outcome data.

17.5 Other factors

Scottish Government has published a Quality Prescribing Guide on benzodiazepines and z-drugs, which aims to improve the care of individuals receiving these medicines and promote a holistic approach to person-centred care.[172]

In January 2026, MHRA updated and strengthened the warnings regarding addiction, dependence, withdrawal and tolerance for gabapentin, pregabalin, benzodiazepines, and z-drugs. Strengthened warnings have been included in the SmPC, patient information leaflets and outer packaging of these medications. Full details, including current advice and information for communication with patients are available from the MHRA.

17.6 Recommendations

✓ Prescribers should be familiar with up-to-date advice on the safe use of benzodiazepines, and z-drugs.

18 Medicinal cannabis

18.1 Introduction

There is a need for new, effective, safe pharmacotherapy for long-term management of chronic pain. Since the previous guideline was published in 2013, several medicinal cannabis products have become available for clinical use.

The hemp plant, *Cannabis sativa* (marijuana), produces up to 60 cannabinoid derivatives, of which delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD) are best known, with medicinal products available containing these compounds.[173] There is a potential neurobiological basis for analgesic effects of cannabinoids, with preclinical evidence of antinociception, through the endocannabinoid system, mediated by G-protein-coupled cannabinoid receptors (CB1 and CB2) in the peripheral and central nervous system (PNS, CNS). Both receptors may have a role in nociception, including in chronic pain.[174-176]

For new classes of analgesic drugs, such as cannabinoids, it is important to understand the evidence for analgesic use, and any related implications for clinical practice, particularly safety issues, with long-term use.

Currently in Scotland, there is no medicinal cannabis preparation licensed for treatment of chronic pain.

Delta-9-tetrahydrocannabinol and cannabidiol (Sativex®) is accepted by SMC for use within NHS Scotland as treatment for symptom improvement in adults with moderate to severe spasticity due to multiple sclerosis, who have not responded adequately to other antispasticity medication and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy.[177]

Any use for chronic pain would therefore be off label.

National Institute for Health and Care Excellence guideline 144 on cannabis-based medicinal products does not recommend the use of cannabinoids for the treatment of chronic pain, unless within the context of a clinical trial.[178] Subsequent to this, position statements from the Faculty of Pain Medicine (Royal College of Anaesthetists, London),[179] and the IASP (after a comprehensive evidence review for chronic pain)[180] did not recommend use for chronic pain due to the lack of high-quality evidence of efficacy and safety, particularly with long-term use. The need for robust clinical trials was highlighted by both organisations, as well as the importance of regulatory standards to ensure safety.

4

18.2 Evidence of benefit

Thirteen systematic reviews with meta-analyses, and one NMA, published between 2018 and 2023, were identified.[181-194] The number of included RCTs in the systematic reviews ranged from eight[185] to 65[181] (90 from the NMA comparing cannabinoids to opioids or placebo),[186] with six[182] to 57[191] observational studies. There was considerable overlap of included studies across the reviews. Four of the reviews focused specifically on chronic neuropathic pain. Most of the reviews (11/13) were rated as high quality, two acceptable quality, and the NMA was rated as sufficient. Overall, the quality of the studies included in the systematic reviews was mainly very low to low, with a high (or unclear) risk of bias, reducing our confidence in the conclusions.

1++
1+
sufficient

18.2.1 Pain severity

In most reviews (10/13), small reductions in pain were reported compared with placebo, to a level unlikely to be of clinical significance according to the authors. Three reviews reported no statistically significant improvement in pain. In the NMA, cannabis reduced pain on a 0–10 cm scale compared with placebo (WMD -0.60, 95% CI -0.87 to -0.33; 19 RCTs, 2,116 participants: low-certainty evidence). The authors note that the size of this effect fell below the 1 cm threshold for clinical significance using VAS, and was not significantly different to that seen with opioids (WMD 0.23, 95% CI -0.06 to 0.53; 82 RCTs, 19,693 participants: low-certainty evidence).[186] Although cannabinoids were compared with opioids in the NMA, most of these comparisons were indirect, with the only RCT directly comparing an opioid (dihydrocodeine) to a cannabinoid (nabilone) finding a statistically significant reduction in pain intensity for dihydrocodeine compared with nabilone in people with neuropathic pain.[195]

1+ sufficient

In a high-quality living systematic review and meta-analysis (minimum of one month of follow-up), a number of different preparations were included, with a reported MD in pain severity (0–10 scale) ranging from -0.54 (95% CI -0.95 to -0.19; seven RCTs, 702 participants: moderate-certainty evidence) to -1.97 (95% CI -5.91 to 1.21; two RCTs, 294 participants: insufficient certainty evidence) for cannabis products compared with placebo.[183]

1++

Meta-analysis of longer-term observational studies (up to 12 months) found that reductions in pain intensity did not meet predefined criteria of clinical significance with a WMD of pain intensity reduction of 1.75 (95% CI 0.72 to 2.78; six studies, 2,571 participants: very low-certainty evidence) on a 0–10 scale, compared with placebo,[182] with a further meta-analysis finding no evidence of sustained benefit in terms of reduced pain intensity, beyond six months.[183]

2++

None of the four systematic reviews that focused on chronic neuropathic pain, found a clinically significant reduction in pain severity, SMD -0.26, (95% CI -0.42 to -0.10; nine RCTs, 1,289 participants: low-certainty evidence),[184] SMD -0.44 (95% CI -0.69 to 0.19; eight RCTs, 893 participants: moderate-certainty evidence),[188] SMD -0.35 (95% CI -0.60 to -0.09; 14 RCTs, 1,837 participants: low-certainty evidence),[189] and MDs (0–100 scale) ranging from -6.62 (95% CI -9.15 to -4.09; five RCTs, 552 participants: moderate-certainty evidence) for THC/CBD to -8.68 (95% CI -10.97 to -6.38; seven RCTs, 332 participants: moderate-certainty evidence) for THC[190] with a calculated number needed to treat of 20 (11–100) for one person to benefit from a 50% reduction in pain intensity.[189]

1++
1+

18.2.2 Function, quality of life and sleep

Seven systematic reviews[181-183,186,190-192] reported on the effect of cannabinoids on functional abilities (for example, physical, emotional, social), with three of those finding very small to small benefits to physical function from cannabinoids compared with placebo. For example, one review found an MD (0–10 scale) ranging from -0.42 (95% CI -0.73 to -0.16; six RCTs, 616 participants: moderate-certainty evidence) to 1.75 (95% CI -0.46 to 3.98; one RCT, 16 participants: low-certainty evidence) in function with cannabis-based products compared with placebo, depending on the formulation of the cannabinoid.[183] A further review found a WMD of 2.52 (95% CI 0.37 to 4.91; 44 RCTs, 12,727 participants: moderate-certainty evidence) with cannabis compared with placebo (0–100 scale on the SF-36).[186] A systematic review of observational studies found moderate benefits from cannabis to disability compared with placebo, with a SMD 0.45 (95% CI 0.05 to 0.88; five RCTs, 2,201 participants: very low-certainty evidence).[182] There was little effect from cannabis compared with opioids on physical functioning on a 0–100 scale (SF-36), with a WMD 0.47 (95% CI -1.97 to 2.99; 44 RCTs, 12,727 participants: moderate-certainty evidence).[186]

1++
1+
2++ sufficient

Evidence on QoL was inconsistent, with either minor benefits (one study)[182] or no benefit (six studies)[181,183,185,188-190] reported when compared with placebo, with low-certainty evidence. 1++ 1+ 2++

For people experiencing neuropathic pain, there was a small, but statistically significant improvement in sleep quality compared with placebo (SMD 0.40, 95% CI 0.19 to 0.61; six RCTs, 744 participants: moderate-certainty evidence) in the one review where sleep quality was a primary outcome. However, there were also increases in daytime somnolence (SMD 2.23, 95% CI 1.32 to 3.74), nausea (OR 1.66, 95% CI 1.22 to 2.27) and dizziness (OR 3.80, 95% CI 2.52 to 5.73). All comparisons included seven RCTs with 867 participants and were rated as high-certainty evidence.[188] 1++

18.3 Evidence of harms

An increase in adverse events from cannabinoids compared with placebo at levels likely to be of clinical significance was consistently reported. Adverse events described were extensive, and included sedation, daytime somnolence, anxiety, mood disorder, suicidal thoughts, and nausea and vomiting.

One systematic review reported RRs of dizziness ranging from 2.52 (95% CI 1.20 to 4.82; three RCTs, 360 participants: moderate-certainty evidence) to 8.34 (95% CI 4.53 to 15.34; one RCT, 277 participants: low-certainty evidence); and of sedation from 1.60 (95% CI 1.01 to 2.95; four RCTs, 386 participants: low-certainty evidence) to 5.04 (95% CI 2.10 to 11.89; six RCTs, 866 participants: low-certainty evidence), for different cannabinoids compared with placebo.[183] 1++

In a further systematic review, pooled event rates for all-cause adverse events were 81.2% for cannabinoids compared with 66.2% for placebo, (OR 2.33, 95% CI 1.88 to 2.89) with a number needed to harm (NNTH) of 6 (95% CI 5 to 8; 10 RCTs, 1,959 participants: moderate-certainty evidence).[191] A Cochrane review of neuropathic pain found that nervous system adverse events were higher in people receiving cannabis-based medication compared with placebo (61% vs 29%, risk difference 0.38 (95% CI 0.18 to 0.58; nine RCTs, 1,304 participants: low-certainty evidence)).[189] 1++

One high-quality systematic review of 39 observational studies which included 12,143 participants with median duration of 24 weeks (interquartile range 12 to 33.8 weeks),[194] used long-term and serious harms from cannabinoids as the primary outcome. Prevalence of any adverse events was 26% (95% CI 13.2% to 41.2%) with a prevalence of psychiatric adverse events of 13.5% (95% CI 2.6% to 30.6%). Evidence was of low certainty, with high risk of bias. Prevalence of serious adverse events was lower at 1.2% (95% CI 0.1 to 3.1) with very low-certainty evidence. 2++

Four systematic reviews specifically considered dependence or psychosis as secondary outcomes.[181,182,189,196] One review identified a single 32-week open-label extension study (n=124) where one participant displayed mild signs of cannabis dependence. There was no other evidence reported in any of the other studies on dependence. Many of the studies in the systematic reviews excluded people with dependence or substance use issues, or psychosis or severe mental health problems. 1++

18.4 Summary of benefits and harms of medicinal cannabis for chronic pain

In conclusion, although there were some statistically significant small reductions in pain severity, there was no strong evidence of clinically relevant pain reduction from cannabinoids. Overall, there was no improvement in QoL, or clinically significant improvement in function. While one review found a small improvement in sleep quality there was also an increase in daytime somnolence and other adverse events.

The evidence for increased adverse events or harms from cannabinoids compared with placebo was consistent (in all the reviews that reported on this, except one[184]), with generally much larger effect sizes than found for any benefits. A wide range of harms were reported, (even in short- to medium-duration studies) including sedation, anxiety, dizziness and nausea. There was insufficient evidence to comment on long-term dependence or mental health issues.

While the systematic reviews were mainly of high quality, the included studies had limitations in quality and risk of bias.

18.5 Other factors

While there are a considerable number of clinical studies on medicinal cannabis, from a broad geographical area (including Scotland and the UK), and a range of research groups or institutions, there are a number of major limitations with these studies, including:

- Duration: The majority of the studies included in the reviews were of short duration, with only six observational studies identified that had follow-up for >6 months and the majority of RCTs having follow-up for <6 months. As chronic pain is a long-term condition, longer-term follow-up is needed to ensure studies reflect the clinical population.
- Comorbidities were not consistently reported, with many of the studies identified in the systematic reviews excluding people with a history of substance use, and major medical diseases, including mental health conditions. Reporting on dependency and substance use was limited, and often not specifically reported.
- Risk of bias, where assessed, was moderate to high, and study quality was very low to low in the majority of studies included in the systematic reviews. All the authors of one systematic review on neuropathic pain declared links with the manufacturers of nabiximols.[184] Of the 16 studies included in the Cochrane review on cannabis in neuropathic pain, 12 declared potential conflicts or funding from the manufacturers of the studied drugs.[189] There was overlap of inclusion of these studies with other systematic reviews.
- Only two of the reviews specifically mentioned input from people with lived experience, who were included on the guideline panels.[192,194]

1++
1+

18.6 Recommendations

R **Medicinal cannabis-based products are not recommended for use in the management of chronic pain outside of the context of a clinical trial.**

19 Opioids

19.1 Introduction

In recent decades, there has been a significant increase in opioid prescribing for people living with chronic pain, despite limited evidence for long-term efficacy. There is international concern around the rise in opioid prescribing and opioid-associated mortality rates in the United States of America (USA), Australia and Europe.[197-199] Between 2012 and 2016 Scotland and England saw similar increases.[200,201] Meanwhile, there has been growing awareness and concern about the harms caused by long-term use of opioids and their adverse effects.[165,202] As a result, monitoring of National Therapeutic Indicators has been able to demonstrate a fall of 10% in opioid prescribing rates between 2017 and 2024 (excluding a slight increase during the coronavirus disease (COVID-19) pandemic.[203,204]

These concerns prompted the Faculty of Pain Medicine (Royal College of Anaesthetists) 'Opioids Aware' campaign, which provides evidence-based resources and advice for clinicians and patients on the use of opioids for pain (including chronic pain). In 2018 the IASP produced a statement on the use of opioids in people with chronic pain, which concluded that, 'There may be a role for medium-term, low-dose opioid therapy in carefully selected patients with chronic pain who can be managed in a monitored setting. However, with continuous longer-term use, tolerance, dependence and other adaptations compromise both efficacy and safety'.[205] (The IASP did not define 'medium-term', 'low-dose' or 'longer-term' in this statement.) Evidence from the USA indicates that opioid use around the time of surgery (peri-operative opioid use) may have contributed to the large increase in prolonged opioid use.[206]

Opioids have been used for their analgesic effects for centuries. For the majority of clinically used opioids, this effect is predominantly, although not exclusively, via the mu opioid receptor (MOR). The potency of different opioids at this receptor varies. Some opioids, such as codeine, dihydrocodeine, tramadol and tapentadol, have defined upper dose limits in the British National Formulary (BNF). Among these, the BNF classifies codeine and dihydrocodeine as 'weak opioids', with the other commonly used opioids being classed as 'strong opioids'.[207] Tramadol and tapentadol have additional actions on pain systems through noradrenergic mechanisms; tramadol also acts through serotoninergic reuptake inhibition. These additional actions on pain systems may have advantages in some chronic pain conditions, such as neuropathic or mixed pains, but they can also limit upward dose titration and increase the range of adverse effects. Strong opioids listed in the BNF include morphine, diamorphine, hydromorphone, oxycodone, tramadol, fentanyl, buprenorphine and methadone.[207]

19.2 Evidence of benefit

High-quality evidence was identified comparing the clinical effectiveness of opioids with placebo or non-opioids, including a systematic review published in 2020 pooling data from 74 RCTs (20,502 participants),[208] with additional studies providing surveillance from August 2019 to March 2022,[209-211] and a systematic review and NMA pooling data from 82 RCTs (22,619 participants).[212]

There were no RCTs comparing opioids with placebo for longer than six months' follow-up, and only one that compared opioids with non-opioids for up to one year's follow-up.[213]

19.2.1 Opioids versus placebo

Comparing opioids with placebo in the short term (1 to <6 months) opioids were associated with a slightly lower pain intensity score (MD -0.79 on a scale from 0 to 10, 95% CI -0.93

1++

to 0.67; 71 RCTs, 19,616 participants: high-certainty evidence).[208] This difference of less than one point on an 11-point scale is unlikely to be clinically significant. When only trials with three to six months' follow-up were included, there was no difference in pain intensity between opioids and placebo (MD -0.30, 95% CI -0.83 to 0.23; eight RCTs, 2,243 participants: no evidence certainty rating). When considering all studies regardless of follow-up duration, there was evidence of a pain response (typically defined as a 30% or greater pain reduction, though definitions across studies varied) from opioids when compared with placebo (RR 1.35, 95% CI 1.24 to 1.48; 44 RCTs, 12,481 participants: high-certainty evidence). When restricted to studies with follow-up periods between 3 and 6 months, there was no significant difference in the likelihood of pain response from opioids compared with placebo (RR 1.19, 95% CI 0.68 to 2.17; five RCTs, 1,503 participants: no evidence certainty rating). There was evidence of better function and physical health status for people who received opioids in the short term (1 to <6 months). Greater improvement in physical health status was seen with opioids (1.64/100, 95% CI 1.10 to 2.17; 23 RCTs, 8,005 participants: high-certainty evidence) compared with placebo, although this improvement was small and not clinically significant, and there was no difference in mental health status (0.48/100, 95% CI -1.39 to 0.44; 21 RCTs, 7,586 participants: high-certainty evidence). No studies had longer than six months' follow-up. — 1++

Greater short-term benefit from opioids (versus placebo) has been reported for people with neuropathic pain (-1.15 points on an 11-point scale, 95% CI -1.43 to 0.91; 20 RCTs, 2,568 participants: no evidence certainty rating) compared with those with musculoskeletal pain (-0.67 points on an 11-point scale, 95% CI 0.81 to 0.54; 50 RCTs, 16,979 participants: no evidence certainty rating).[208] The difference of 0.48 points is statistically significant (p=0.009), although of uncertain clinical importance *(see section 1.4.1)*. Although the difference in pain intensity reduction with enriched enrolment RCTs (which ensure that only responders who experience considerable pain relief and no or acceptable side effects on a predefined or titrated dose during a selection phase are included in the randomised double-blind experimental phase) compared with non-enriched enrolment RCTs was non-significant (-0.86 vs -0.75), with enriched enrolment resulting in a significantly lower relative risk of discontinuation due to adverse events (RR 1.35, 95% CI 1.02 to 1.78; 25 RCTs, 8,011 participants: no evidence certainty rating) compared with non-enriched RCT designs (RR 3.06, 95% CI 2.50 to 3.81; 36 RCTs, 11,983 participants: no evidence certainty rating). — 1++

A well-conducted systematic review with NMA evaluated 14 opioids either against placebo or against each other.[212] Seventy-eight trials that included 21,906 participants reported on pain relief. Using the surface under the cumulative ranking curve (SUCRA) rankings suggested that modified-release (MR) codeine, MR oxymorphone, and immediate-release (IR) oxycodone were the best opioids for pain relief with reduction in pain scores ranging from 0.99 to 2.03 cm on a 10 cm scale but these findings were supported by evidence rated by the authors as low to very low certainty.

There was high to moderate-certainty evidence that IR tramadol, MR morphine, sublingual buprenorphine, MR tapentadol, and MR tramadol were superior to placebo, with pain reduction ranging from 0.80 to 1.09 cm on a 10 cm scale.

For physical function, the evidence (39 studies, 13,134 participants) was rated low to very low quality and according to the SUCRA rankings the most effective opioids for improving function were MR codeine and MR hydromorphone. — sufficient

19.2.2 Opioids versus non-opioid medication

Comparing opioids with non-opioids (medications used across trials included NSAIDs, antiarrhythmic drugs, antiepileptics and antidepressants), no significant difference was reported in pain reduction (MD -0.29 on a 0 to 10 scale, 95% CI -0.61 to 0.03) at short-term follow-up — 1++

(1 to <6 months; 14 RCTs, 2,195 participants: moderate-certainty evidence), nor for likelihood of a pain response (RR 1.28, 95% CI 0.90 to 1.85; 12 RCTs, 2,886 participants; moderate-certainty evidence).[208]

Pooled analysis of 11 RCTs, which included 2,010 participants, found that there was no difference in functional ability between opioids and non-opioids (SMD 0.00, 95% CI -0.14 to 0.12: high-certainty evidence).

Only one study that followed participants up for longer than six months, the Strategies for Prescribing Analgesics Comparative Effectiveness (SPACE) trial,[213] was identified in a meta-analysis.[208] The trial compared outcomes in 106 people with chronic musculoskeletal pain who received opioids with 115 receiving non-opioid medicines and found no difference in function between the groups, but a greater reduction in pain severity among those receiving opioids (4.0/10 vs 3.5/10) at 12 months. The size of this effect did not meet the minimum clinically important difference established by the trial authors *(see section 1.4.1)*. 1++

No data were reported on quality of life in studies comparing opioid and non-opioid use.

19.2.3 Specific chronic pain conditions

It is not possible to draw conclusions about opioid effectiveness in different chronic pain conditions. Analysis of studies of specific pain types in one systematic review compared the effects of opioids in participants with neuropathic pain and those with musculoskeletal pain.[208] They found that, compared with placebo, opioids were associated with a slightly larger improvement in neuropathic pain compared with those with musculoskeletal pain, (low back pain and osteoarthritis). There was only one RCT identified in participants with fibromyalgia, where no effect was demonstrated. The most frequently assessed neuropathic pain conditions were diabetic neuropathy and postherpetic neuralgia. There were no interactions between pain type and risk of discontinuation due to adverse events or of serious adverse events. 1++

19.2.4 Summary of effectiveness

Evidence based on high-quality systematic reviews consistently found little or no reduction in pain severity among people with chronic pain who were treated with opioids, compared with placebo or non-opioid medications. Where improvements in pain severity and function were seen with opioids, these were small and not clinically significant, and there was no evidence of opioid efficacy when treatment was given beyond three months.

The low certainty of evidence and the calculated rankings of relative efficacy from the NMA shows that individual opioids are similarly ineffective with no opioid showing superior short-term effectiveness.

19.3 Evidence of harms

19.3.1 Opioids versus placebo

Opioids were associated with a greater risk (RR 2.25, 95% CI 1.86 to 2.73; 61 RCTs, 19,994 participants: high-certainty evidence) of participant discontinuation due to adverse events compared with placebo. There were significantly greater risks of all recorded adverse events (nausea, vomiting, constipation, somnolence, dizziness, pruritus), except for headache which showed no difference at short-term follow-up.[208] 1++

In the NMA, 53 studies (n=20,283) reported on vomiting. Modified-release oxycodone was found to result in greater risk of vomiting than placebo (OR 7.12, 95% CI 5.42 to 9.35; nine RCTs, 3,091 participants: moderate-certainty evidence). Analysis of 67 trials with 22,681 participants found that MR oxycodone, MR tramadol and MR tapentadol resulted in increased sufficient

nausea compared with placebo (high to moderate-certainty evidence). Analysis of 64 studies with 22,531 participants found that MR oxycodone, MR hydromorphone, and MR tramadol resulted in increased risk of constipation compared with placebo (high- to moderate-certainty evidence).[212] — sufficient

19.3.2 Opioids versus non-opioid medication

Pooled analysis of 12 RCTs with 3,637 participants found that opioids were more likely than non-opioids to be associated with discontinuation due to adverse events (RR 2.18, 95% CI 1.48 to 3.08; moderate-certainty evidence). The most common adverse events were vomiting, pruritis, constipation, nausea, drowsiness and headache. Risk of adverse events, drug reactions and discontinuation did not differ between low and high opioid doses. There were also associations between opioid use and fractures, falls, cardiovascular events, and endocrine outcomes, but not with self harm.[208] — 1++

19.3.3 Long-term adverse events

No systematic review of RCTs has identified studies that investigate the long-term (>12 months) adverse events of opioids. Observational studies identified in one systematic review found that, compared with people taking opioids, people not taking opioids were more likely to report lower pain intensity at one year,[208] and were less likely to experience severe pain-related interference with activities at two years.[214] — 2++

The SPACE trial, which followed participants up for 12 months, found that those receiving opioids experienced more (1.8 vs 0.9), and more frequent (p=0.03) medication-related symptoms than those receiving non-opioid medicines.[213]

19.3.4 Dose- and duration-related adverse events

A systematic review and its associated surveillance reports noted consistent evidence from observational studies on associations between increasing opioid dose and increasing risk of overdose and opioid-related mortality.[209] Similarly, observational studies report a dose-dependent association between opioid prescription and opioid use disorder (OUD), with both a higher daily dose, and, particularly, a longer duration of therapy associated with a greater risk of subsequent OUD. One case-control study reported that doses of opioids greater than 20 mg/day morphine-equivalent dose (MED) taken by drivers were associated with increased odds of injuries related to road trauma.[208] — 2++

A 10-year longitudinal study followed up over one million adults (mostly in the UK) who were prescribed opioids for non-cancer pain. They found that UK adults who were prescribed morphine had a 12-fold risk of all-cause mortality compared with those who had been prescribed codeine HR 12.58, 95% CI 11.87 to 13.32). This risk was dose dependent, and rose with age. All-cause mortality risk was greater among those prescribed >50 mg/day MED, and in the presence of multimorbidity and/or a history of substance misuse.[215] — 2+

19.3.5 Dependence and opioid use disorder

A systematic review of studies involving individuals treated with opioids for chronic non-malignant pain (148 studies, >4.3 million participants) reported that 9.3% experienced dependence and opioid use disorder (D&OUD), with a further 12.4% at risk of this, and a total of 29.6% showing signs and symptoms of D&OUD.[216]

The authors of a large systematic review with meta-analysis of opioid treatments for chronic pain noted that most trials excluded people with substance use history or mental health disorders or did not describe these characteristics, meaning that differential effects according to comorbidities could not be assessed.[208] However, they identified a large UK cohort study — 2++

estimating risk of overdose (98,140 participants), that reported a dose-dependent increase of hazard ratio for overdose (≥50 mg MED/day compared with no opioid (HR 3.81, 95% CI 2.50 to 5.80).[217] 2++

Although screening tools exist to predict D&OUD, evidence for their effectiveness is weak, and their effect size has been modest at best. A systematic review identified no reliable evidence for the effectiveness for the use of urine drug screening, pill counts or prescription drug monitoring programmes to predict subsequent misuse.[218]

There is, therefore, consistent evidence of adverse events associated with opioid treatment, and this association appears to be dose dependent.

19.4 Summary of benefits and harms of opioids for chronic pain

There may be limited short-term benefits associated with short-term use of opioids in terms of pain intensity and some aspects of function. These benefits appear to be small and to reduce or disappear with longer-term use (beyond three months). The possibility that some people who use opioids may experience greater short-term benefits cannot be excluded. This suggests that individualised treatment may be considered. There is no evidence suggesting that opioids may be more effective than a placebo after six months, and some evidence suggesting that pain-related and functional outcomes may be worse with long-term (>12 months) opioid use, compared with not taking opioids.

There are strong associations between opioid therapy and adverse events (minor and serious) irrespective of dose, with approximately two- to threefold greater relative risk of specific adverse events (GI symptoms, drowsiness, dizziness, and itching) versus placebo. Observational evidence consistently shows dose-dependent associations between opioid therapy and subsequent OUD, overdose and death, as well as evidence that taking opioids for longer duration is associated with OUD. The risk of harm increases substantially at doses above an oral morphine equivalent of 50 mg/day.

Although most of the evidence includes studies undertaken in the UK, many studies were conducted elsewhere, particularly North America. Factors such as access to healthcare and prescribing regulations may affect the availability of opioids but are less likely to affect the evidence relating to benefits and harms.

19.5 Other factors

19.5.1 Prescribing opioids

The evidence suggests that for most people with chronic non-cancer pain, opioid treatment provides minimal-to-no benefit and is likely outweighed by adverse events, especially after three months, both in terms of pain intensity and overall function. In most people presenting with chronic non-malignant pain, therefore, opioids are unlikely to be appropriate.

If a trial of an opioid is considered, then measurable treatment goals should be agreed between the clinician and person with chronic pain before opioids are started and a strategy for deprescribing put in place if these goals are not achieved.[219] This can be achieved through a comprehensive biopsychosocial assessment, consideration of personal goals, knowledge, previous experience and preferences and shared decision making, involving individuals, families and carers as well as the healthcare team. Resources, including information for patients, are available through Opioids Aware. The lack of good evidence for specific risk prediction tools means that clinical judgement, based on assessment, discussion and information, is important from the outset.

19.5.2 Risk of opioid dependence

A systematic review and meta-analysis found that those who were younger, were male, and/or reported a history of, or current substance use or mental health diagnosis were at a greater risk of developing opioid misuse.[220] A NICE clinical knowledge summary describes a number of risk factors for opioid dependence, including:[221]

- availability of drugs
- peer substance use
- adverse childhood experiences
- history of mental illness
- social disadvantage
- genetic predisposition, and
- younger age and male gender.

The National Institute for Health and Care Excellence has published guidance on safe prescribing and withdrawal of medicines associated with dependence or withdrawal symptoms.[143]

19.5.3 Reviewing opioid use

Clinicians should work with patients to incorporate strategies to mitigate risk in management plans. This should include regular (<3-month) review of their medication, and consideration given to changes in their status (for example, infection, or changing comorbidities) which may increase the risk of opioid toxicity, including confusion, respiratory depression and overdose.

People who are already being prescribed long-term opioids also need regular review, and assessment of benefits (pain reduction, function, quality of life) and harms, potentially with a view to safe reduction and withdrawal of treatment, if appropriate.[222] It is important to consider the possibility of stigmatising people who have been taking opioids on long-term prescription, and to avoid this. The Scottish Government Quality Prescribing for Chronic Pain Guide contains information on medication review and opioid management including practical steps to reduce high-dose opioids, deprescribing tips and advice on addressing challenges during reduction. Prescribers should note the additional risks from facilitating the dispensing of opioids in the community, where their potential illicit use may lead to more widespread harms.

19.6 Recommendations

The following recommendations are based on high-level evidence (for limited clinical effectiveness and risk of adverse events or drug reaction) during the first six months, and on low-level evidence for benefits and harms after six months and the risk of overdose and other adverse events. These recommendations cover both IR and MR opioids.

R **Opioids should not be considered routinely for people with chronic non-malignant pain.**

R **In carefully selected individuals, and only when other pain therapies have been fully explored, opioids can be considered for short-term treatment (up to 3 months), if it is considered that the potential benefits outweigh the risks of serious harms such as addiction, overdose and death.**

R **If prescribing opioids, undertake early and frequent review to identify any benefits and potential or actual adverse events or drug reactions. If necessary, the dose should be adjusted or treatment stopped.**

R **All people receiving opioid doses of >50 mg MED/day should be reviewed regularly (at least annually and preferably more often) to detect emerging harms and consider ongoing effectiveness.**

R **Pain specialist advice or review should be sought at doses >90 mg MED/day.**

✓ For people who are already on long-term opioids, consider a review to assess the benefits and potential or actual harms, with a view to reducing or stopping the prescription.

✓ If an individual has pain that remains severe despite opioid treatment consider stopping opioids, with appropriate support, even if no other pharmacological treatment is available as the risks of continuation are likely to outweigh the benefits.

✓ At initiation of opioid prescribing, and at subsequent reviews, patients should be informed about the risks and potential harms of taking opioids. Any opioid prescribing must be based on the patient's fully informed understanding and agreement to the potential risks and benefits.

20 Naloxone

20.1 Introduction

Naloxone is an opioid antagonist that can be used to temporarily reverse the CNS and respiratory depressant effects of an opioid overdose. Naloxone is licensed for lay administration in the event of a suspected opioid overdose; legislation allows for anyone to administer naloxone for the purpose of saving a life.

Naloxone is a prescription-only medicine, however specific legislation is in place in the UK that allows the supply of intramuscular and intranasal formulations to people at risk of an opioid overdose without the need for a prescription, under certain circumstances.

A national naloxone programme was established in Scotland in 2011 in response to increasing numbers of drug-related deaths. After training, naloxone kits suitable for community administration are supplied to people at risk of opioid overdose, their friends, family and service workers to help reduce drug-related deaths in Scotland. From October to December 2025 9,552 naloxone kits were issued across Scotland.

While the supply of naloxone has been successfully established in Scotland, the focus of the programme is to target those at increased risk of opioid overdose due to substance misuse. Current practice in Scotland does not proactively identify people who are prescribed opioids for chronic pain who may be at an increased risk of opioid overdose *(see sections 19.3.4–5)*.

20.2 Evidence of benefit

There is limited evidence around coprescribing naloxone when opioids are indicated for chronic pain. One systematic review was identified that included evidence on risk mitigation strategies for people who are prescribed opioids.[208]

The review identified one observational study that assessed the association between coprescribing of intranasal naloxone for people taking daily opioids for chronic pain and the use of emergency departments (ED) in a safety-net healthcare setting in the USA.[223] Safety-net hospitals provide healthcare for individuals regardless of their insurance status or ability to pay. These hospitals typically serve a proportionately higher number of uninsured, low-income, and other vulnerable individuals. While in Scotland, the risk of being prescribed an opioid is higher in areas of high deprivation,[201] differences in the healthcare systems and other sociodemographic factors may make this study population less representative of the Scottish target population.

The mean age of the study participants was 56.7 years (± 10.8), 58.6% were male, and the majority of patients were Black. The most commonly prescribed opioid was oxycodone and the median dose was 53 mg MED/day. The study does not provide any information about comorbidities or polypharmacy within this population. Notably, they were unable to determine whether the patients included in the analysis had any history of substance use, however, people taking opioids for OUD at the time of the study were excluded. 2+

The study suggested benefit from coprescribing naloxone when opioids are indicated for chronic pain. The study found that, on average, coprescribing naloxone was associated with 6% fewer ED visits per month (incidence rate ratio (IRR) 0.94, 95% CI 0.89 to 0.998, p=0.044), a 47% reduction in ED visits per month after six months (IRR 0.53, 95% CI 0.34 to 0.83, p=0.005) and 63% reduction after one year (IRR 0.37, 95% CI 0.22 to 0.64, p<0.001).

When advised to offer naloxone to all people receiving long-term opioids, clinicians were found to be more likely to prescribe naloxone to those whom they considered to be at higher risk of opioid overdose, including individuals receiving higher doses of opioids and those who had previously had an opioid-related ED admission. There is no information about whether naloxone prescribed was actually dispensed, and no investigation of outcomes other than ED attendance. 2+

20.3 Evidence of harms

The study hypothesises that prescribing naloxone may change patient behaviour with respect to opioids. However, the authors also caution that there may be hazards to risk stratifying users of opioids to be offered naloxone, including stigma and concerns about identifying an individual's elevated risk for overdose.

See section 21.3 for further information about harms associated with coprescription of opioids with medications which have a depressant effect on the CNS.

20.4 Summary of benefits and harms of naloxone coprescription with opioids for chronic pain

There is limited evidence to support widespread coprescribing of naloxone to people prescribed opioids for chronic pain. However, learning from other at-risk groups may be applied and where additional risk factors for opioid overdose are identified, clinicians should consider offering naloxone in a suitable formulation intended for lay person administration, ie provided in a ready-to-use kit with needles for intramuscular administration or an appropriate nasal spray.

The supply of naloxone to those at higher risk of opioid overdose does not negate the need for safe prescribing of opioids. Clinicians should work with patients to incorporate strategies to mitigate risk in management plans, this should include regular (<3-months) review of their medication, and consideration given to changes in patient status, which may increase the risk of overdose.

20.5 Other factors

Public Health Scotland has reported that the supply of naloxone for use in the community is feasible in the Scottish context as it is already established for other at-risk groups, such as those receiving opiate substitution treatment.

When considering overdose risk among people who misuse drugs, additional risk factors include a history of opioid-related hospital admissions, previous near-fatal overdoses, a history of substance use (including alcohol), coprescribing of depressant medicines (for example, gabapentinoids, benzodiazepines), high-dose opioid prescribing, and multimorbidity that increases the risk of opioid toxicity *(see section 19.5.2)*.[224,225]

It is recognised as good practice to offer training to people who are prescribed opioids for chronic pain and their significant others to recognise the signs of an opioid overdose and about appropriate interventions, including naloxone administration.[219]

Further information on naloxone coprescription with opioids is included in the Scottish Government Quality Prescribing for Chronic Pain Guide. Details on accessing and using naloxone appropriately can be found in section 22.2.

20.6 Recommendations

R **Consider prescribing naloxone for people with chronic pain who are prescribed opioids and who may be at risk of an opioid overdose.**

✓ Offer a naloxone product that is suitable for use in the community, for example, an intranasal formulation or prefilled syringe.

✓ Coprescribing of naloxone to those at higher risk of opioid overdose does not negate the need for safe prescribing of opioids. Clinicians should work with patients to incorporate strategies to mitigate risk in management plans, this should include regular (<3-months) review of their medication.

21 Combination pharmacological therapies

21.1 Introduction

Management of chronic pain is challenging because of the multifactorial influences that can modify pain responses, such as stress, sleep, diet, relaxation, relationships, etc. Therefore, pharmacological management is part of the many options available to support pain management.

In clinical trials, analgesics are considered effective if they demonstrate a reduction in pain intensity by 30% or 50%, and many are limited by adverse effects. Consequently, people may continue to have ongoing pain despite treatment. Many clinical conditions are managed by multiple medicines, for example, hypertension, which can increase the risk of adverse effects. Individuals are often commenced on a second or third analgesic, without the first being stopped at the time of initiation or after trial of the second, which can increase the risk of adverse effects, and many will continue the first analgesic even if ineffective.

The evidence of benefit and harms of simple analgesic *(see section 13)*, antidepressant *(see section 14)*, antiepileptic *(see section 15)*, topical analgesic *(see section 16)*, muscle relaxant *(see section 17)*, medicinal cannabis *(see section 18)* and opioid *(see section 19)* monotherapy are considered separately. This section considers the evidence for combination pharmacological therapies and the potential harms associated with these.

Combination pharmacological therapies are either a combination of analgesics, for example, morphine and amitriptyline (ie an opioid and an antidepressant), or an analgesic and another therapy which may reduce pain perception or alter other factors affecting pain, for example, amitriptyline and melatonin.

As with the initiation of any analgesic, efficacy should be regularly assessed and if there is no reduction in pain intensity, or improvement in function, then the therapy should be stopped or reduced to stop, to minimise adverse effects and medication interactions.

Non-pharmacological pain management options should always be considered in conjunction with analgesia.

21.2 Evidence of benefit

Three systematic reviews were identified that assessed the effectiveness of combination pharmacological therapies compared with single pharmacological therapies, using pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events, drug reactions or dependency (physiological or psychological).

The reviews considered neuropathic pain,[226] fibromyalgia,[227] and low back pain and sciatica[228] in adults.

21.2.1 Pain intensity

Neuropathic pain

A systematic review and meta-analysis examining combination pharmacotherapy for treatment of neuropathic pain in adults included 40 RCTs.[226] Although the studies were of acceptable quality, they were downgraded because of incomplete outcome data, short duration of treatment (10 studies had durations of less than three weeks), small sample sizes (nine studies had fewer than 30 participants), and high risk of bias (in 35 studies). 1+

Because of heterogeneity across many studies, meta-analysis was completed for only three combinations: opioids and gabapentinoids, opioids and antidepressants, and gabapentinoids and antidepressants. 1+

Opioid and gabapentinoid combination

Combination treatment with an opioid and gabapentinoid provided at least moderate/good pain relief (defined as ≥30% pain reduction) compared with gabapentin monotherapy in the short to medium term (RR 1.27, 95% CI 1.01 to 1.59; two RCTs, 452 participants: no evidence certainty rating) but no statistically significant difference compared with opioid monotherapy (RR 1.06, 95% CI 0.80 to 1.40; three RCTs, 548 participants: no evidence certainty rating).[226] 1+

Opioid and antidepressant combination

Combination treatment with an opioid and antidepressant provided at least moderate/good pain relief (defined as ≥30% pain reduction) compared with antidepressant monotherapy in the short to medium term (RR 1.29, 95% CI 1.03 to 1.65; two RCTs, 214 participants: no evidence certainty rating), but no statistically significant difference compared with opioid monotherapy (RR 1.22, 95% CI 0.97 to 1.52; two RCTs, 214 participants: no evidence certainty rating).[226] 1+

Gabapentinoid and antidepressant combination

Combination treatment with a gabapentinoid and antidepressant provided at least moderate/good pain relief (defined as ≥30% pain reduction) (RR 1.34, 95% CI 1.02 to 1.76; three RCTs, 502 participants: no evidence certainty rating) and more substantial pain relief (defined as ≥50% pain reduction) (RR 1.76, 95% CI 1.25 to 2.47; two RCTs, 390 participants: no evidence certainty rating) compared with antidepressant monotherapy in the medium term. There was no significant difference between combination treatment with a gabapentinoid and antidepressant compared with gabapentinoid monotherapy for at least moderate/good pain relief (defined as ≥30% pain reduction) (RR 1.40, 95% CI 0.93 to 2.10; three RCTs, 527 participants: no evidence certainty rating), nor substantial pain relief (defined as ≥50% pain reduction).[226] 1+

Authors of the systematic review concluded that there is no compelling evidence that combination therapies offer greater pain relief when compared with both constituent monotherapies.

The GDG notes that where there was a benefit in combination therapy, the choice of second agent was important in relation to the first with addition of antidepressant having no benefit, but addition of opioid yielded greater intensity reductions than gabapentinoid. However, this should be balanced against the harms of these medicines *(see sections 14.3, 19.3 and 21.3)*.

Table 6: Effects of combination pharmacological therapies compared with monotherapies on pain relief in treatment of people with neuropathic pain[226]

	Opioid monotherapy (95% CI)	**Gabapentinoid monotherapy** (95% CI)	**Antidepressant monotherapy** (95% CI)
Opioid and gabapentinoid combination	RR 1.06 (0.80 to 1.40) p=0.68 three RCTs (548 participants) Does not favour adding a gabapentinoid to an opioid	**RR 1.27 (1.01 to 1.59)** **p=0.04** **two RCTs** **(452 participants)** Favours adding an opioid to a gabapentinoid	Not applicable
Opioid and antidepressant combination	RR 1.22 (0.97 to 1.52) p=0.08 two RCTs (214 participants) Does not favour adding an antidepressant to an opioid	Not applicable	**RR 1.29 (1.03 to 1.63)** **p=0.03** **two RCTs** **(214 participants)** Favours adding an opioid to an antidepressant
Gabapentinoid and antidepressant combination	Not applicable	RR 1.40 (0.93 to 2.10) p=0.11 three RCTs (527 participants) Does not favour adding an antidepressant to a gabapentinoid	**RR 1.34 (1.02 to 1.76)** **p=0.03** **two RCTs** **(390 participants)** Favours adding a gabapentinoid to an antidepressant

RR relative risk, CI confidence interval, RCT randomised controlled trial

Fibromyalgia

A systematic review evaluated combination pharmacotherapy for the treatment of adults with fibromyalgia. Most of the included studies are of low or very low quality because of methodological bias or poor design (for example limited comparisons to monotherapies, low numbers, short duration).[227]

Many combinations in the systematic review are not commonly used in clinical practice and were not considered relevant to the guideline target population, for example, the combinations of carisoprolol, paracetamol and caffeine (carisoprolol is not licensed in the UK), or NSAID and benzodiazepine (which are avoided because of known risks of long-term benzodiazepines). Heterogeneity of study outcomes and the specific drugs used in combination meant that meta-analysis was not possible. The authors note that none of the combinations of drugs provided sufficient data for analysis compared with placebo or other comparators for any outcome and they provide a narrative description of results. They note that three RCTs provide evidence of benefit for different drug combinations on pain outcomes compared with monotherapy. 1++

Evidence certainty was not reported as no pooled effects were calculated although the quality of these studies was low or very low.

The authors of this systematic review concluded that there are too few high-quality trials evaluating the efficacy of combination pharmacological therapies in the management of fibromyalgia to support a recommendation for their use. 1++

Melatonin and amitriptyline combination

One RCT (63 participants), assessed to be at moderate or low risk of bias for most aspects of methodology except size of study and similarities of baseline characteristics (high risk of bias), compared the combination of melatonin and amitriptyline with each drug as a monotherapy. There were no results reported for patient-reported pain relief of ≥30% or ≥50%. Participants receiving melatonin and amitriptyline in combination had significantly lower VAS pain scores compared with participants receiving amitriptyline monotherapy and significantly larger improvements in FIQ score (which measures pain, fatigue, rest or sleep, stiffness, anxiety, and depression) compared with both monotherapies (effect sizes not reported).[227]

The GDG notes that pain is multifactorial and improved sleep quality can improve pain, therefore it is not unexpected that melatonin may reduce pain intensity through sleep improvement. This is supported by the study authors' conclusion that melatonin, alone or in combination, was effective in improving FIQ scores.

Amitriptyline and fluoxetine

One RCT (31 participants) compared the combination of amitriptyline and fluoxetine with both monotherapies and placebo. There were no results reported for patient-reported pain relief of ≥30% or ≥50%. Considering secondary outcomes, combination therapy with amitriptyline and fluoxetine produced significantly greater improvements in VAS scores of pain, sleep and global wellbeing and improved FIQ scores compared with both monotherapies (effect sizes not reported).[227]

Pregabalin and duloxetine

One RCT (41 participants: very low-certainty evidence) compared the combination of pregabalin and duloxetine with both monotherapies and placebo. Combination therapy with pregabalin and duloxetine reduced pain scores from baseline (28%) statistically significantly more than pregabalin monotherapy (1.4%) or placebo (7.1%). Participants receiving combination therapy experienced at least moderate pain relief (68%) significantly more than with pregabalin monotherapy (42%), duloxetine monotherapy (39%) or placebo (18%) (effect sizes not reported).[227]

Chronic low back pain

One systematic review assessed the combination of two or more different drugs compared with constituent drug monotherapy or placebo for low back pain with or without sciatica.[228]

Of 27 RCTs, one small study reported a clinically significant benefit of combination pharmacotherapy (44 participants: low-certainty evidence). The combination of transdermal buprenorphine (35 microgram/hour) and pregabalin (300 mg daily) showed a clinically important reduction in pain intensity measured by VAS for chronic back pain in the immediate term, (two weeks or less) (MD -23.30 on a 0–100 mm scale, 95% CI -27.68 to -18.92; one RCT) and short term, (>2 weeks but ≤12 weeks) (MD -27.60 on a 0–100 mm scale, 95% CI -31.70 to -23.50; one RCT) compared with buprenorphine monotherapy. 1+

A buprenorphine 35 micrograms/hour patch is the morphine equivalent daily dose of 84 mg, and recommendations on medication review and pain specialist advice regarding the prescribing of opioids should be considered *(see section 19)*.

The authors concluded that there was no clear evidence to support any combination drug therapy for the management of low back pain because of the limited number of studies and overall low quality of evidence.

21.3 Evidence of harms

Neuropathic pain

A systematic review and meta-analysis examining combination pharmacotherapy for treatment of neuropathic pain reported higher rates of adverse events in participants using combination therapy with an opioid and gabapentinoid (constipation, dry mouth, nausea, dizziness, fatigue, and somnolence) compared with groups using monotherapy (no effect size reported). A higher proportion of people using opioid and gabapentinoid combination (9.2%) dropped out of studies because of adverse events than those using opioid monotherapy (8.2%, no statistical comparison reported; four RCTs, 531 participants: no evidence certainty rating). A higher proportion of people using opioid and gabapentinoid combination (14.5%) also dropped out of studies because of adverse events than those using gabapentinoid monotherapy (4.6%, no statistical comparison reported; two RCTs, 395 participants: no evidence certainty rating).[226]

A lower proportion of people using opioid and antidepressant combination (8.4%) dropped out of studies because of adverse events than those using opioid monotherapy (12.1%, no statistical comparison reported; two RCTs, 107 participants: no evidence certainty rating). While a higher proportion of people using opioid and gabapentinoid combination (7.3%) dropped out of studies because of adverse events than those using antidepressant monotherapy (3.3%, no statistical comparison reported; three RCTs, 123 participants: no evidence certainty rating).

Study withdrawal because of adverse events was similar between those in gabapentinoid plus antidepressant (5.4%), antidepressant monotherapy (4.4%) and gabapentinoid monotherapy (5.7%) groups (no statistical comparison reported; three RCTs, 472 participants: no evidence certainty rating).

1++

Fibromyalgia

One systematic review reported that adverse events were common in groups receiving combination therapies and controls, with no serious adverse events reported. Common adverse events were nausea, dizziness, somnolence, and headache.[227]

1++

Low back pain

The systematic review, which focused on combination therapies for people with low back pain, reported no serious adverse events in groups receiving either the combination of transdermal buprenorphine (35 microgram/hour) and pregabalin (300 mg daily) or buprenorphine monotherapy. There was no statistically significant difference in incidence of any adverse event between groups receiving combination therapy and buprenorphine monotherapy (54.5% vs 63.6%, RR 0.86, 95% CI 0.52 to 1.41; one RCT; 44 participants: low-certainty evidence), although in both groups over 50% of those receiving any pharmacological treatment experienced adverse events.[228]

1+

Chronic pain in general

A further systematic review explored the safety of gabapentinoids in the context of opioid use.[229] The review incorporated studies from a range of clinical settings including perioperative, cancer pain and chronic non-cancer pain. As the review included two RCTs, four case reports, three case-control studies, 14 cohort studies, and two cross-sectional studies, the data were analysed using narrative synthesis only.

1+

All three case-control studies show evidence of an association between concurrent opioid and gabapentinoid use and opioid-related death. The first two studies reported, respectively, that concurrent prescribing of opioids and gabapentin (adjusted odds ratio (aOR) 1.49, 95% CI 1.18 to 1.88) or pregabalin (aOR 1.68, 95% CI 1.19 to 2.36) in the 120 days before death was associated with opioid-related death. Both studies noted that the highest doses of gabapentin (for ≥1,800 mg daily: aOR 1.58, 95% CI 1.09 to 1.27) and pregabalin (for >300 mg daily: aOR 2.51, 95% CI 1.24 to 5.06) were linked to higher risks of drug-related death. 1+

The third nested case-control study was carried out in the UK and linked medical records from the Clinical Practice Research Database (CPRD) 1987–2015 of opioid analgesic users aged over 18 years with Office for National Statistics (ONS) death registrations 2000–2015 of opioid-related deaths.[230] The persistence of opioid utilisation (POU) was examined across three patient years. Persistent opioid use within one patient-year was defined as receiving an annual dose greater than or equal to oral morphine equivalent 4,500 mg covering three or more quarters in the year.

Individuals who were prescribed opioids persistently had a higher risk of opioid-related death compared with those who were not, and those who were also prescribed psychotropics concurrently had a greater risk *(see Table 7)*.

Table 7: Association between persistent opioid prescribing and opioid-related deaths after adjusting for concurrent psychotropics

Use of medication	**Adjusted odds ratio of opioid-related death** (95% CI)
POU and concurrent DDD >1 of benzodiazepines	6.5 (4.0 to 10.4), p<0.001
POU and concurrent DDD >1 of gabapentinoids	6.2 (2.9 to 13.5), p<0.001
POU and concurrent antipsychotics	4.3 (2.5 to 7.3), p<0.001
POU and concurrent DDD 0 to ≤1 of benzodiazepines	3.6 (2.1 to 6.2), p<0.001
POU and concurrent DDD >0.5 tricyclic antidepressants	2.0 (1.2 to 3.5), p=0.034
POU in any of three patient-years	1.9 (1.2 to 2.9), p=0.006

DDD defined daily dose

Note: for each comparison the accompanying reference value is an adjusted odds ratio of 1, representing no concurrent medication use, or, in the final row, no persistent opioid prescribing.

Adapted with permission from Chen TC, Knaggs RD, Chen LC. Association between opioid-related deaths and persistent opioid prescribing in primary care in England: a nested case-control study. Br J Clin Pharmacol. 2022;88(2):798–809.[230]

These findings align with the evidence of harms in the opioid section of this guideline *(see section 19.3)*, and the MHRA warnings issued in 2017 regarding the increased risk of respiratory depression with the combination of opioids and gabapentinoids. For recommendations and information on use of naloxone to reverse respiratory depressant effects of an opioid overdose see section 20.

21.4 Summary of benefits and harms of combination pharmacological therapies

Although commonly used in practice, there is limited evidence to support combination therapy over constituent monotherapies in the management of chronic pain. However, the GDG acknowledges that despite the lack of evidence, combination therapy is used, and it is common for people to be prescribed an antidepressant and gabapentinoid.

Clinicians should be aware that combination therapy may be used for outcomes other than chronic pain reduction, for example, antidepressants may be required for the management of depression or anxiety, and therefore each person should be considered as an individual and any additions to existing treatments should consider the potential risks. See the prescribing guides developed by Scottish Government on chronic pain, antidepressants and polypharmacy for pragmatic advice on using combination pharmacological therapies.

While some combinations did show benefit compared with some monotherapies in people with neuropathic pain (the addition of an opioid to a gabapentinoid or an antidepressant, or addition of a gabapentinoid to an antidepressant), in general, combinations with opioids were not more effective than opioid monotherapy and combination gabapentinoid plus antidepressant was not more effective than gabapentinoid alone.

There is insufficient high-quality evidence to determine the effectiveness and safety of combination therapies in the management of low back pain and/or sciatica, and the management of fibromyalgia.

Evidence for harms were poorly reported, inconsistent and it was not always reported whether differences in adverse events were statistically significant. Studies had small numbers of participants or were of low or very low quality. These studies should be used as the basis for further research.

Where combinations are used, clinicians should consider the potential harms of monotherapy and the potential for additive effects of combinations, and consult MHRA advice for any alerts.

21.5 Other factors

While the included evidence considers some people with chronic pain, there is an absence of information for populations with multimorbidity and the frail or elderly and conclusions may not be as applicable to these groups.

Clinicians should be aware of SMC restrictions and licensed indications of the combinations being prescribed, and any items of limited clinical value listed in the document released December 2024 Achieving Value and Sustainability in Prescribing.

Individuals may choose to purchase analgesics over the counter including paracetamol, NSAIDs and codeine-containing products, which may confer increased risks of harm to the individual. The risk of divergence of medication, either to the individual or by the individual, should be considered, especially if there are unexpected adverse effects or lack of efficacy. A good therapeutic relationship between the clinician and individual is required to identify these.

21.6 Recommendations

R **In management of neuropathic pain, clinicians should carefully consider the addition of an opioid to gabapentinoid or antidepressant monotherapies, or addition of a gabapentinoid to an antidepressant, but not other combination therapies. Clinicians should note the limitations of evidence for long-term management of chronic pain for these medications.**

✓ Prescribing the combination of opioids and gabapentinoids should be carefully considered because of limited evidence of benefit and the increased risk of respiratory depression and death.

22 Provision of information

This section reflects the issues likely to be of most concern to patients and their carers. These points are provided for use by health professionals when discussing chronic pain with patients and carers and in guiding the development of locally produced information materials.

22.1 Publications from SIGN

SIGN presents recommendations and rationales, created for health and social care professionals, in plain language to be easily understood and used by the public. This information aims to:

- help people understand the latest evidence around diagnosis, treatment, and self care
- empower people to actively participate in decisions about managing their condition in discussions with health and social care professionals
- highlight areas of uncertainty for people, making them aware of where more information or research is needed.

The plain language version of this guideline is available from www.sign.ac.uk/patient-public-involvement/plain-language-versions-of-guidelines/chronic-pain

Patients may also find the following booklet helpful: Migraine: a booklet for patients and carers (2023).

22.2 Sources of further information

Information for people with chronic pain

Flippin' Pain®
www.flippinpain.co.uk

Flippin' pain is a public health campaign that aims to change the way people think about, talk about and treat persistent pain. It includes information on chronic pain, real life stories and resources to help understand pain and move towards recovery.

Health Experience Insights
hexi.ox.ac.uk/chronic-pain/overview

Health Experience Insights provides written and filmed personal health stories about what it's really like to live with a health condition. Formerly known as Dipex and Healthtalk, it includes views on pain management approaches, medical treatments and the impact of living with chronic pain.

Live Well with Pain
livewellwithpain.co.uk/resources-for-people-with-pain

Live Well with Pain provides knowledge about, and support for, self managing persistent pain. The website offers a range of materials and a step-by-step online guide to living well with pain, including videos, tips and tools and links to trusted resources.

Manage my meds
rightdecisions.scot.nhs.uk/manage-my-meds-for-patients-and-carers

This online toolkit helps people to build knowledge and understanding of their medicines, manage medicines more confidently and prepare for a medication review with a healthcare professional.

Naloxone
naloxone.org.uk

This website provides information on access and use of naloxone in the UK. It also contains practical information about how to spot signs of opioid overdose and how to put an individual into the recovery position.

www.sdftraining.org.uk/e-learning

A free e-learning module is available from the Scottish Drugs Forum which includes how to administer naloxone.

NHS Greater Glasgow and Clyde: Information and resources for people living with chronic pain
live.nhsggc.scot/hospitals-services/services-a-to-z/chronic-pain/information-and-resources-for-patients

A large collection of resources developed for people with chronic pain includes information about the NHS Greater Glasgow and Clyde Pain Service, More Harm Than Good leaflets (information about opioids), a library of mindfulness resources and links to further online information.

NHS Highland Chronic Pain Management Service
www.nhshighland.scot.nhs.uk/your-services/all-services-a-z/chronic-pain-management/how-you-can-help-yourself-with-your-pain

A collection of resources to help people living with chronic pain to manage their condition. The set includes videos, booklets and links to further resources and information.

NHS Inform
www.nhsinform.scot/illnesses-and-conditions/brain-nerves-and-spinal-cord/chronic-pain

This resource provides information about chronic pain symptoms, pain management strategies to live better with chronic pain, how to cope with a flare up of chronic pain and a self-help guide.

Pain Association Scotland
painassociation.co.uk/online-self-management-wellbeing-videos

Pain Association Scotland is a national charity that aims to improve the quality of life for chronic pain sufferers by supporting and empowering them to live independently in the community. It promotes a reduced reliance on clinical services through collaborative working with health and social care professionals and encourages access to self management at an early stage of the clinical journey. The charity has developed a range of videos on topics such as stress management, pacing, relaxation and flare ups.

Pain Concern
painconcern.org.uk/product-category/leaflets

Pain Concern provides information and support about pain, helping people understand what they can do to help themselves. It collaborates with the NHS to provide education sessions. Podcasts and expert-led publications bridge the gap between professional and public education. Their website provides a comprehensive guide to understanding and navigating daily life with pain; there is a helpline and an online support community.

Helpline: 0300 123 0789
help@painconcern.org.uk
painconcern.org.uk/the-navigator-tool/

The interactive navigator tool guides people towards a positive and focused dialogue with healthcare professionals during consultations about living with chronic pain. It contains forms that cover pain concerns, questions the individual may like to ask their healthcare professional, goals to help manage pain and self-management options.

Scottish Families Affected by Alcohol and Drugs
www.sfad.org.uk

Scottish Families Affected by Alcohol and Drugs is a national charity that supports anyone affected by someone else's alcohol or drug use in Scotland, whether they are still actively using substances, are in recovery, or are bereaved. The charity provides both national and local support services, befriending, bereavement support, a learning hub, listening and advice.

They offer access to injectable or nasal naloxone via a click and deliver service from www.sfad.org.uk/naloxone.

The Pain Toolkit
www.paintoolkit.org

The Pain Toolkit is an interactive and simple information booklet, that provides readers or listeners with handy tips and skills to support people self managing their pain or long-term health condition. It offers a tailored set of 12 tools to help pain self management, plus a suite of resources for both healthcare professionals and people living with persistent pain.

West of Scotland Chronic Pain Education Group
www.paindata.org

The Chronic Pain Education Group is a multidisciplinary group of NHS pain specialists working in the West of Scotland. It includes doctors, physiotherapists, nurses, pharmacists, psychologists, and a patient representative. The website includes a wide range of resources for patients with chronic pain, including information about commonly prescribed medications, non-pharmacological treatments and practical guidance to support self management.

Women's Health Concern
www.womens-health-concern.org

Women's Health Concern is the patient arm of the British Menopause Society and provides independent advice to inform and reassure women about their gynaecological, sexual and postreproductive health. They provide evidence-based factsheets on a wide range of topics, including endometriosis.

#StopTheDeaths
www.stopthedeaths.com

#StopTheDeaths encourages all members of the public, including people who use drugs, their families and communities as well as services, policymakers and wider Scottish society, to act to prevent overdose deaths. In addition to campaign information to raise awareness of drug harms, it includes information and advice on how to access and use naloxone.

Occupational health support

Access to Work
www.gov.uk/access-to-work

Access to Work can help individuals to get or stay in work if they have a physical or mental health condition or disability. It can support some adjustments being made when costs are a barrier to providing these.

The support that is available will depend on the individual's needs. Through Access to Work, people can apply for:

- a grant to help pay for practical support with work
- support with managing mental health at work
- money to pay for communication support at job interviews.

Advisory, Conciliation and Arbitration Service (Acas)
www.acas.org.uk/advice
Helpline: 0300 123 1100

Acas is an independent public body that receives funding from the UK Government to provide free and impartial advice to employers, employees and their representatives on:

- employment rights
- best practice and policies
- resolving workplace conflict.

The website includes advice about equality, health and well-being at work and access to a free telephone helpline.

Citizens Advice Scotland

www.citizensadvice.org.uk/scotland/law-and-courts/discrimination/check-what-type-of-discrimination-youve-experienced/asking-for-reasonable-adjustments-if-youre-disabled

Citizens Advice Scotland is the largest independent advice network in Scotland. It is a network of independent charities that offers impartial and confidential advice about justice, human rights, debt and money, digital inclusion, energy, housing, social security and many other topics.

It supports individuals with access to benefits and employment rights, including asking for reasonable adjustments if they're disabled.

Equality Advisory Support Service
www.gov.uk/equality-advisory-support-service

The Equality Advisory Support Service provides information about disability discrimination and the Equality Act.

Arthritis UK
www.arthritis-uk.org/information-and-support/living-with-arthritis/work-benefits-and-finances/work-and-arthritis

Arthritis UK is a charity that provides information, supports research and healthcare and influences decision makers to understand and take account of arthritis and musculoskeletal conditions. It offers information and advice on managing musculoskeletal chronic pain in the workplace and making appropriate decisions about work, education, careers and benefits that are focused on individuals' needs.

Information for healthcare professionals

Quality Prescribing for Chronic Pain: A Guide for Improvement 2026–2029
www.gov.scot/publications/quality-prescribing-chronic-pain-guide-improvement-2026-2029

This guide promotes the importance of good communication between individuals living with chronic pain and the clinician, to enable an understanding of 'what matters to them' in line with the 7-Steps medication review process.

Faculty of Pain Medicine of the Royal College of Anaesthetists
fpm.ac.uk/patients/patient-info

The Faculty of Pain Medicine has a series of leaflets, created with the help of many professionals as well as patient representatives, intended to be handed out to patients when they are prescribed medications or undertake procedures. The leaflets can be used within a variety of clinical settings including Pain Management Services, GP practice, community pharmacies and physiotherapy clinics.

Grampian Pain Management
www.gpm.scot.nhs.uk

The Pain Management Service in Grampian is made up of a multidisciplinary team, offering a range of services to help people living with persistent pain to improve their quality of life. Their website offers information leaflets and videos for people living with chronic pain, referral information and useful links to further resources.

Live Well with Pain
livewellwithpain.co.uk/professional-tools

Live Well with Pain has produced self-management tools and techniques for use by clinicians and other practitioners working with people with pain. These include videos, tools and guidance on skills and knowledge for practitioners, medicines management and written information for sharing with people with chronic pain.

National Trauma Transformation Programme
www.traumatransformation.scot

The National Trauma Transformation Programme is a multiagency training and implementation resource to support services to respond in ways that prevent further harm, support recovery, address inequalities and improve life chances for people affected by trauma and adversity. It includes a wide range of learning resources, guidance and implementation support for all sectors of the workforce, including leaders, to develop staff to the appropriate level of trauma-informed and responsive practice and to embed and sustain this model of working.

National Wellbeing Hub
wellbeinghub.scot/resource/supporting-your-wellbeing-free-apps-and-online-programmes

The National Wellbeing Hub is an evidence-led resource to promote, enhance and support the psychosocial well-being of everyone working in health, social care, and social work in Scotland, as well as unpaid carers. It provides access to free online apps and programmes, which support good mental health, relaxation, anxiety improvement and sleep quality.

NHS Education for Scotland Motivation, Action and Prompts (MAP): Health Behaviour Change Learning Programme
www.nes.scot.nhs.uk/our-work/behaviour-change-for-health

The MAP Learning Programme aims to equip health, care and third sector staff with the knowledge, skills and confidence to talk to people about behaviour change and to deliver theory-based interventions that are person centred and will promote positive health and well-being outcomes.

NHS Education for Scotland: Chronic Pain Knowledge Hub
learn.nes.nhs.scot/74191

The Chronic Pain Knowledge Hub, developed by NHS Education for Scotland, provides an interactive chronic pain learning toolkit for all health and social care professionals providing support and management for people living with pain. The toolkit consists of four practice levels capturing what health and social care workers in different service contexts can do to make a positive difference to people with chronic pain.

(Access to this resource requires a Turas Learn account).

Primary Care Chronic Pain Management Multidisciplinary Team sway
sway.cloud.microsoft/szyeuKXg7Z8Jv0Is?

This sway for primary care staff includes a multidisciplinary flowchart and example letters for medication reviews.

The Institute of Psychosexual Medicine
www.ipm.org.uk

The Institute of Psychosexual Medicine is a professional organisation, registered as a charity, which provides education, training and research in psychosexual medicine for qualified registered practitioners. It focuses on training based on psychoanalytic skills and which can be applied in primary care, secondary care or community settings.

The Matrix – A Guide to Delivering Evidence-Based Psychological Therapies and Interventions in Scotland
www.matrix.nhs.scot/evidence-summaries/populations-requiring-special-considerations-and-adjustments/chronic-pain

The Matrix is a resource developed by NHS Education for Scotland and the Scottish Government to guide NHS boards in planning and providing effective psychological therapies. The Matrix provides information on the current evidence base for various therapeutic approaches, guidance on well-functioning psychological therapies services, and advice on governance issues.

The Pain Toolkit
www.paintoolkit.org

The Pain Toolkit is an interactive and simple information booklet, that provides readers or listeners with handy tips and skills to support people to self manage their pain or long-term health condition. It offers a tailored set of 12 tools to help pain self management, plus a suite of tailored resources for both healthcare professionals and people living with persistent pain.

West of Scotland Chronic Pain Education Group
www.paindata.org

The Chronic Pain Education Group is a multidisciplinary group of NHS pain specialists working in the West of Scotland. It includes doctors, physiotherapists, nurses, pharmacists, psychologists, and a patient representative. The website includes a wide range of resources for healthcare professionals supporting people with chronic pain, including an opioid converter, opioid tapering calculator, videos, training modules, guidelines, audits and links to further information.

23 Implementing the guideline

This section provides advice on the resource implications associated with implementing the key clinical recommendations, and advice on audit as a tool to aid implementation.

23.1 Implementation strategy

Implementation of national clinical guidelines is the responsibility of each NHS board, including health and social care partnerships, and is an essential part of clinical governance. Mechanisms should be in place to review care provided against the guideline recommendations. The reasons for any differences should be assessed and addressed where appropriate. Local arrangements should then be made to implement the national guideline in individual hospitals, units and practices.

Quality improvement methodologies can be used locally to implement the guidelines. The Quality Improvement Journey contains generic advice and tools for using quality improvement methods to support local implementation. NHS Education for Scotland also delivers the Scottish Improvement Leaders programme and Scottish Quality and Safety Fellowship programme to develop individuals to lead local implementation projects to improve the quality of care.

Implementation of this guideline will be encouraged and supported by SIGN. The implementation strategy for this guideline encompasses the following tools and activities.

Use of naloxone – while anyone can use naloxone legally in an emergency, training is recommended to ensure correct administration. A range of training courses is provided for health and social care professionals in territorial boards, such as NHS Lothian, NHS Greater Glasgow & Clyde and NHS Tayside. The charity, Scottish Drugs Forum, has developed a range of training for people who may respond to opioid overdoses. An e-learning module on opiate overdose prevention, intervention and using naloxone is focused at members of the public seeking overdose response skills or health and social care professionals working in harm reduction services.

23.2 Resource implications of key recommendations

No recommendations are considered likely to reach the £5 million threshold that warrants resource impact analysis.

23.3 Auditing current practice

A first step in implementing a clinical practice guideline is to gain an understanding of current clinical practice. Audit tools designed around guideline recommendations can assist in this process. Audit tools should be comprehensive but not time consuming to use. Successful implementation and audit of guideline recommendations requires good communication between staff and multidisciplinary team working.

The guideline development group has identified the following as key points to audit to assist with the implementation of this guideline:

- the proportion of adults with chronic pain who have been considered for a peer support intervention and who complete these.
- the proportion of adults with chronic pain who have been considered for digital self-management interventions and who complete these.
- the proportion of adults with chronic pain that seek psychological support who receive CBT or ACT from a healthcare professional with appropriate training.

- the proportion of adults with chronic pain who have been assessed by a multidisciplinary team and who have a documented consideration for a comprehensive pain management programme.
- the proportion of people with chronic pain who have received information about possible use of TENS.
- the proportion of people who are prescribed oral NSAIDs for chronic pain and who have an increased risk of harm (for example, chronic kidney disease or previous gastric bleed).
- the proportion of adults with chronic pain prescribed opioids who have a documented exploration of other therapeutic approaches for pain management before confirmation of opioid treatment.
- the proportion of adults with chronic pain prescribed opioids who receive an initial review of opioid medication within four weeks of starting treatment (in line with advice in the Scottish Government Quality Prescribing for Chronic Pain Guide (2026–2029)).
- the proportion of adults with chronic pain prescribed >50 mg/day MED who have received a review of opioid medication within the previous 12 months.
- the proportion of adults with chronic pain who are assessed for the risk of an opioid overdose in advance of being prescribed opioid therapy. (This helps to monitor implementation of the recommendation for the consideration of naloxone).
- the proportion of adults with chronic pain prescribed duloxetine who have known hypertension or other cardiac disease and who have blood pressure monitoring at baseline and during treatment with duloxetine.
- the proportion of antiepileptic drug prescriptions for adults with chronic pain where prescription is in line with current Government prescription guidance or restrictions.
- the proportion of people who are prescribed a gabapentinoid for chronic pain for longer than six months and who have not had a medication review.

23.4 Health technology assessment advice for NHS Scotland

In October 2014, the SMC advised that capsaicin (Qutenza®) is accepted for restricted use within NHS Scotland for the treatment of peripheral neuropathic pain in non-diabetic adults either alone or in combination with other medicinal products for pain. It is restricted to use in patients who have not achieved adequate pain relief from, or have not tolerated, conventional first- and second-line treatments.

In June 2026, the SMC advised that capsaicin cutaneous patch (Qutenza®) is accepted for restricted use within NHS Scotland for the treatment of peripheral neuropathic pain in diabetic adults either alone or in combination with other medicinal products for pain. It is restricted to use alone or in combination with other medicinal products for the treatment of painful diabetic peripheral neuropathy in patients who have not achieved adequate pain relief from, or have not tolerated, conventional first- and second-line treatments.

In September 2006, the SMC advised that duloxetine (Cymbalta®) is accepted for restricted use for the treatment of diabetic peripheral neuropathic pain in adults. It is restricted to initiation by prescribers experienced in the management of diabetic peripheral neuropathic pain as second- or third-line therapy.

In June 2008, the SMC advised that glucosamine (as hydrochloride) (Alateris) is not recommended for use within NHS Scotland for relief of symptoms in mild to moderate osteoarthritis of the knee.

In August 2011, the SMC advised that glucosamine sulphate (Glusartel®) is not recommended for use within NHS Scotland for relief of symptoms in mild to moderate osteoarthritis of the knee, and, in the absence of a submission from the holder of the marketing authorisation, advised that glucosamine sulphate (Dolenio®) is not recommended for use within NHS Scotland for the symptomatic treatment of mild to moderate osteoarthritis of the knee.

In August 2008, the SMC advised that lidocaine 5% medicated plaster (Versatis®) is accepted for restricted use within NHS Scotland for the treatment of neuropathic pain associated with previous herpes zoster infection (postherpetic neuralgia). It is restricted to use in patients who are intolerant of first-line systemic therapies for post-herpetic neuralgia or where these therapies have been ineffective.

24 The evidence base

24.1 Systematic literature review

The evidence base for this guideline was synthesised in accordance with SIGN methodology. A systematic review of the literature was carried out using an explicit search strategy devised by a Healthcare Improvement Scotland Information Scientist. Databases searched include Medline, Embase, PsycINFO and the Cochrane Library. The year range covered was 2018–2025. Internet searches were carried out on various websites for relevant guidelines. The main searches were supplemented by material identified by individual members of the development group. Critical appraisal of relevant evidence was carried out by Healthcare Improvement Scotland Health Service Researchers and NHS Research Scotland Pain researchers. Each of the selected papers was evaluated by two reviewers using standard SIGN methodological checklists before conclusions were considered as evidence by the guideline development group.

The search strategies and further details of the methodology used are available on the SIGN website, www.sign.ac.uk.

24.2 Recommendations for research

There are significant limitations in the design, quality and certainty of evidence supported by many studies in the pain medicine literature.

Innovative approaches to the methodology of clinical pain trials are needed, taking into consideration a number of factors, including entry criteria (for example, baseline pain scores),[231] and individual variation in treatment response.[232] Pragmatic clinical trials that bridge the translational gap between tightly controlled explanatory clinical trials and real-world clinical effectiveness may be one approach to be considered.[32] Furthermore, ensuring robust involvement of people with chronic pain throughout the research cycle has been recognised as important[233] to ensure the relevance of study questions, appropriate study design and meaningful outcome measures, including consideration of composite measures (that reflect not just pain intensity but its wider impact).[234]

A number of factors need to be considered to optimise the design of trials studying chronic pain. These include patient selection (pain diagnosis, duration, intensity) and sample size, different phases within the trial (for example, enriched enrolment) and duration of study, treatment groups (including active versus inactive placebo comparator), dosing strategies (fixed versus flexible) and type of trial (for example, parallel, crossover).[32,34,235]

The guideline development group was not able to identify sufficient evidence to answer all of the key questions asked in this guideline *(see Annex 1)*. The following areas for further research have been identified.

24.2.1 Self-help interventions

- Studies to quantify the impact of peer support on both peer supporters and recipients, including emotional well-being, social connectedness, and QoL, for both groups.
- Studies examining the qualities and skills that contribute to successful peer support, such as empathy, active listening, and problem-solving abilities.
- The design and implementation of effective training programmes to equip peer supporters with the necessary knowledge and skills.
- Long-term follow-up studies to assess the sustainability of the effects of peer support interventions and to measure any potential long-term benefits or harms.

- Studies to evaluate the effectiveness of digital self-help interventions in people experiencing pain conditions other than musculoskeletal pain.
- Research to improve the understanding of the acceptability, engagement, and adherence in digital support interventions.

24.2.2 Physical therapies (hands-off)

- Further evidence to identify which types of hands-off physical therapies and at what intensity and duration are effective for the treatment of people with chronic pain.
- Further evidence on the effects of hands-off physical therapies on quality of life in people with chronic pain.
- Further evidence on the effect of mobility aids on chronic pain.
- Further evidence to identify barriers to exercise interventions for the treatment of people with chronic pain and how best to mitigate these.

24.2.3 Physical therapies (hands-on)

- Further evidence on the intermediate-term and long-term safety and effectiveness of physical therapies for the treatment of people with chronic pain.
- Further evidence on effects of physical therapies on quality of life and healthcare utilisation outcomes for the treatment of people with chronic pain.

24.2.4 Psychological interventions

In general, studies of psychological interventions should establish greater standardisation of control conditions.

- Any research on the impact of psychological interventions should actively involve people with lived experience of chronic pain.
- To establish the generalisability of interventions, high-quality RCTs that include adults with a wide variety of chronic pain conditions.
- Studies that include long-term follow-up periods of all outcomes (including acceptance, self efficacy, psychological flexibility and cost effectiveness, where appropriate).
- Studies using appropriate outcome measures that match the goals of the intervention (for example, daily functioning). More specifically, studies which assess acceptance and valued activity as outcome measures, as these better align with ACT focus.
- Studies to establish adverse events using clearer, consistent definitions and standardised reporting on adverse events (including long-term adverse events).
- Studies that compare intervention delivery modes directly with each other (ie, face-to-face versus remote delivery, and delivery by psychologists versus non-psychologists).

24.2.5 Occupation-based interventions

- Studies to establish the effectiveness of the wide range of occupation-based interventions, including and not limited to, energy conservation strategies, postural and positional strategies, sensory integration, advocacy skills, community reintegration strategies, environmental adaptations or equipment provision, meaningful engagement in daily occupations.
- High-quality studies to establish the effectiveness of return-to-work interventions. Researchers should consider defining a core outcome set and/or comparative outcomes to be used in trials to enable comparability across multiple studies.
- Studies in people with chronic pain who are unemployed and want to return to work, and people who are struggling to manage their pain condition while in work.

- Studies to capture the impact of interventions on the person's satisfaction with their work-life balance and confidence to manage their pain condition in the workplace.
- Researchers should consider investigating activity management (activity regulation, activity pacing) beyond osteoarthritis or fibromyalgia, including the diagnosis of chronic pain itself, to improve the generalisability of evidence. Also, to use valid and reliable outcome measures and justification of sample size to improve the quality of studies.
- Studies of activity management interventions for people with chronic pain delivered using a psychologically informed approach to investigate the effectiveness of this approach and how this intervention might be delivered in a consistent way.
- Additional research to investigate the effectiveness of activity management as a learned strategy in the activity and participation outcome domains in determining the impact this intervention can have on a person's ability to participate in daily occupational and life roles.

24.2.6 Pain management programmes

The GDG is aware of individual UK PMPs having presented outcome data at national meetings, but this valuable data is then not submitted or does not reach publication. We propose a collaborative research network of PMP providers within the UK. This pooled, multicentre and international approach may lead to better data for a wider variety of outcomes. A national audit is proposed which should include the audit points suggested in this guideline *(see section 23.3)*.

- Studies to investigate how best to capture behavioural change following participation on a PMP. (In practice PMPs are designed to promote behavioural change in the service of improving QoL in the presence of persistent pain. Changes that individuals report following completion of a PMP are often not reflected in changes in the outcome measures used to quantify effects in the historical research evidence. Individual items on the outcome measures currently used can mean different things to people living with chronic pain and clinicians. The use of less relevant outcome measures makes it harder to properly evaluate the role of PMPs).
- Studies to assess long-term clinical and cost effectiveness of PMPs measured in terms of effects on mood, anxiety, QoL, medication usage, activity levels, fear of movement, disability, pain intensity, psychological flexibility and measures of primary and secondary healthcare utilisation, in addition to qualitative descriptions of change in activity, well-being and behaviour.
- Further information is required on qualitative outcomes associated with PMPs. Published evidence commonly does not reflect lived experience of change and there is a need for greater incorporation of the perspective of people living with chronic pain, including local viewpoints that take into account cultural and societal differences.
- Further information is required on factors that affect the suitability of people for CPMPs, and how to target a population who are likely to benefit and systematically comparing individual and group-based PMPs to better understand how different modes of delivery, intervention components and dose characteristics influence outcomes and subjective experiences.

24.2.7 Dietary interventions

- Further evidence on the safety and effectiveness of anti-inflammatory diets, high-fibre diets, Mediterranean diets and FODMAP diets
- Further evidence on the effects of turmeric on chronic pain, investigating its role in pain reduction and functional improvement as a dietary component, or as a supplement. Studies should investigate possible dose effects.

- Further evidence on the effects of different doses of PUFA on pain intensity and function in people with chronic pain. Studies should carefully control comparators to avoid interference from other oils that may impact inflammation.

24.2.8 Electrotherapy

- Further evidence on the role of ESWT/LiST in NHS Scotland, including the cost effectiveness of the intervention, service delivery factors (including training, knowledge and workforce specialisation) required to support it).
- Further evidence on the safety and effectiveness of electrotherapies, with particular attention to function, quality of life and healthcare utilisation outcomes for the treatment of people with chronic pain.

24.2.9 Complementary therapies

- Further evidence, including reporting of longer-term outcomes, on the safety and effectiveness of all complementary interventions in people with chronic pain.
- Further evidence on the safety and effectiveness of herbal products on pain intensity and function in people with chronic pain. Studies should aim to recruit larger samples, and include a wider range of herbal products.
- Further evidence on the effectiveness of acupuncture, herbal products and hypnotherapy on function in people with chronic pelvic pain.

24.2.10 Simple analgesics

- Further evidence on intermediate-term and long-term safety and effectiveness of NSAIDs for the treatment of people with chronic pain
- Further evidence on the safety and effectiveness of oral NSAIDs for the treatment of people with chronic lower back pain
- Further evidence on the head-to-head comparison between oral NSAIDs for the treatment of people with chronic pain

24.2.11 Antidepressants

- Studies to assess the safety and efficacy of antidepressants used for longer than three months in the treatment of chronic pain.
- Studies to assess the safety and efficacy of antidepressants in people with chronic pain comparing effects between those with and without a diagnosis of clinical depression.

24.2.12 Antiepileptics

- Further evidence on the intermediate-term and long-term safety and effectiveness of antiepileptics for the treatment of people with chronic pain
- Further evidence on the effectiveness of carbamazepine for pain relief in people with trigeminal neuralgia.
- Further evidence on the effectiveness of topiramate for lower back pain and lumbar radicular pain.
- Studies to quantify the risk of overdose and substance use disorder in patients prescribed antiepileptics for chronic pain management.

24.2.13 Topical analgesics

- Further evidence on the safety and effectiveness of all topical analgesics, including analysis of effects on pain reduction and function.
- Establishment of the clinical significance of the pain reduction associated with topical capsaicin.

24.2.14 Muscle relaxants

- Further evidence on the intermediate-term and long-term safety and effectiveness of muscle relaxants for the treatment of people with chronic pain.

24.2.15 Medicinal cannabis

- High-quality UK-based RCTs with appropriate duration of follow-up are needed to identify clinically relevant harms and benefits of medicinal cannabis in the treatment of chronic pain, with outcome measures aligned to IMMPACT recommendations. Where standard RCT designs may be inappropriate to adequately address the question(s) other robust trial designs should be considered.
- Studies to assess effects in specific populations, for example those with neuropathic pain; older adults; those with multimorbidity; polypharmacy, recruited from populations that reflect the characteristics of people with chronic pain in Scotland.
- Longer-term studies to identify harms that may take time to develop, such as dependence and mental health issues.
- Studies to assess potential interactions between different formulations of medicinal cannabis and medications commonly used by people living with chronic pain.

24.2.16 Opioids

- Studies to quantify the risk of adverse events, including overdose and substance use disorder in people being prescribed opioids for pain management, and to develop accurate risk prediction tools. These should include assessment of risks associated with coprescribed medications.
- Studies of comparisons of benefits and harms experienced according to different personal and pain characteristics, and different types of opioids.
- Studies to determine effective risk mitigation strategies in people who are prescribed opioids.
- Studies to identify the efficacy and adverse events of long-term (>12 months) opioid use.
- Studies to identify optimal opioid tapering or deprescribing strategies, and the type of support and services, and also assess the benefits and harms associated with deprescribing.

24.2.17 Naloxone

- Studies to assess the impact of naloxone prescribing on the incidence of fatal and non-fatal overdose events in people prescribed opioids for chronic pain, with a particular focus on other factors that may increase an individual's risk of overdose (for example comorbidity, polypharmacy, demographics).
- Studies to evaluate the acceptability of naloxone use, including the willingness of this population and their families, and how this may change management of their chronic pain and use of opioids.

- Studies to assess the efficacy of naloxone in people using opioids for chronic pain with a range of comorbidities commonly seen in Scotland. A larger observational study could stratify results according to specific combinations of concurrent medications, which would give useful feedback on the relative efficacy of naloxone in the context of commonly used analgesia and medicines prescribed for comorbid conditions.

24.2.18 Combination pharmacological therapies

- Further evidence on effectiveness and safety (including appropriate dosage) of combination therapies in pain conditions other than neuropathic pain.
- Further evidence on effectiveness and safety (including appropriate dosage) of combination therapies other than opioid plus gabapentinoid, opioid plus antidepressant or gabapentinoid plus antidepressant.
- Further evidence on effectiveness and safety (including appropriate dosage) of combination therapies in people with multimorbidities.

24.3 Review and updating

This guideline was issued in 2026 and will be considered for review in three years. The review history, and any updates to the guideline in the interim period, will be noted in the update report, which is available in the supporting material section for this guideline on the SIGN website: www.sign.ac.uk

Comments on new evidence that would update this guideline are welcome and should be sent to SIGN (email: sign@sign.ac.uk).

25 Development of the guideline

25.1 Introduction

SIGN is a collaborative network of clinicians, other healthcare professionals and patient organisations and is part of Healthcare Improvement Scotland. SIGN guidelines are developed by multidisciplinary groups of practising healthcare professionals using a standard methodology based on a systematic review of the evidence. Further details about SIGN and the guideline development methodology are contained in 'SIGN 50: A Guideline Developer's Handbook', available at www.sign.ac.uk

This guideline was developed according to the 2025 edition of SIGN 50.

25.2 The guideline development group

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The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest. A register of interests is available in the supporting material section for this guideline at www.sign.ac.uk

Guideline development and literature review expertise, support and facilitation were provided by SIGN and Healthcare Improvement Scotland staff. All staff members make yearly declarations of interest. A register of interests is available on request from SIGN.

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Karen Graham	Patient and Public Involvement Advisor
Domenico Romano	Publications Designer
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25.2.1 Acknowledgements

SIGN is grateful to the following former members of the guideline development group and others who have contributed to the development of the guideline.

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25.3 Consultation and peer review

A report of the consultation and peer review comments and responses is available in the supporting material section for this guideline on the SIGN website. All expert referees and other contributors made declarations of interest and further details of these are summarised in the report.

25.3.1 Specialist review

This guideline was reviewed in draft form by the following independent expert referees, who were asked to comment primarily on the comprehensiveness and accuracy of interpretation of the evidence base supporting the recommendations in the guideline. The guideline group addresses every comment made by an external reviewer, and must justify any disagreement with the reviewers' comments.

Mr Neil Clark	Chronic Pain Physiotherapist, NHS Borders
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25.3.2 Public consultation

The draft guideline was also available on the SIGN website for a month to allow all interested parties to comment. Responses were received from 29 individuals and nine organisations.

25.3.3 SIGN editorial group

As a final quality control check, the guideline is reviewed by an editorial group comprising the relevant specialty representatives on SIGN Council to ensure that the specialist reviewers' comments have been addressed adequately and that any risk of bias in the guideline development process as a whole has been minimised. The editorial group for this guideline was as follows. All members of SIGN Council make yearly declarations of interest. A register of interests is available on the SIGN Council page on the SIGN website www.sign.ac.uk

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Abbreviations

Acas	Advisory, Conciliation and Arbitration Service
ACT	acceptance and commitment therapy
AD	adjusted difference
AHRQ	Agency for Healthcare Research and Quality
aOR	adjusted odds ratio
aRR	adjusted relative risk or risk ratio
BNF	British National Formulary
BRAN	Benefits, Risks, Alternatives, doing Nothing
BZD	benzodiazepine
CBD	cannabidiol
CBT	cognitive behavioural therapy
CCC	Cremor Capsici Compositus
CI	confidence interval
CKD	chronic kidney disease
CNS	central nervous system
COVID-19	coronavirus disease 2019
COX	cyclo-oxygenase
CPMP	comprehensive pain management programme
CPRD	Clinical Practice Research Database
CrI	credible interval
D&OUD	dependence and opioid use disorder
DDD	defined daily dose
ED	emergency department
EQ-5D	EuroQol five-dimensional questionnaire
ESWT	extracorporeal shockwave therapy treatment
FIQ	Fibromyalgia Impact Questionnaire
FODMAP	fermentable oligosaccharides, disaccharides, monosaccharides and polyols
GDG	guideline development group
GDP	gross domestic product
GI	gastrointestinal
GMC	General Medical Council
GP	general practitioner
HIV	human immunodeficiency virus
HLLT	high-level laser therapy

HR	hazard ratio
HRQL	health-related quality of life
HSF	hot sand fomentation
IASP	International Association for the Study of Pain
IBS-QoL	Irritable Bowel Syndrome Quality of Life Instrument
ICD	International Classification of Diseases
IMMPACT	Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
IPMP	integrated pain management programme
IQR	interquartile range
IR	immediate-release
IRR	incidence rate ratio
IT	interferential therapy
LiST	low-intensity shockwave therapy
LLLT	low-level laser therapy
MA	marketing authorisation
MAP	Motivation, Action and Prompts
mARS	modified Anticholinergic Risk Scale
MBSR	mindfulness-based stress reduction
MCID	minimum clinically important difference
MCS	mental component summary
MD	mean difference
MED	morphine-equivalent dose
mHealth	mobile health
MHRA	Medicines and Healthcare Products Regulatory Agency
MOR	mu opioid receptor
MPI	Multidimensional Pain Inventory
MR	modified-release
NDI	Neck Disability Index
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIH-CPSI	National Institutes of Health-Chronic Prostatitis Symptom Index
NMA	network meta-analysis
NNT	number needed to treat
NNTH	number needed to harm
NPQ	Northwick Park Neck Pain Questionnaire
NPRS	Numerical Pain Rating Scale

NSAID	non-steroidal anti-inflammatory drug
ODI	Oswestry Disability Index
ONS	Office for National Statistics
OR	odds ratio
OUD	opioid use disorder
PCS	physical component summary
PGIC	Patient Global Impression of Change
PMP	pain management programme
PNE	pain neuroscience education
PNS	peripheral nervous system
POMS-SV	Profile of Mood States Short Version
POU	persistence of opioid utilisation
PUFA	polyunsaturated fatty acid
QoL	quality of life
RCT	randomised controlled trial
RD	risk difference
RDS	Right Decision Service
RMDQ	Roland-Morris Disability Questionnaire
RR	relative risk or risk ratio
RTW	return to work
SAE	serious adverse event
SD	standard deviation
SDi	shortwave diathermy
SF-12	12-item Short Form Survey
SF-36	36-item Short Form Survey
SIGN	Scottish Intercollegiate Guidelines Network
SMART	specific, measurable, achievable, relevant, and time bound
SMC	Scottish Medicines Consortium
SMD	standardised mean difference
SmPC	Summary of Product Characteristics
SNRI	serotonin-noradrenaline reuptake inhibitor
SPACE	Strategies for Prescribing Analgesics Comparative Effectiveness trial
SRL	a homeopathic gel containing *Symphytum officinale, Rhus toxicodendron* and *Ledum palustre*
SSRI	selective serotonin reuptake inhibitor
SUCRA	surface under the cumulative ranking curve
TAU	treatment as usual

TCA	tricyclic antidepressant
TENS	transcutaneous electric nerve stimulation
THC	tetrahydrocannabinol
TMD	temporomandibular disorder
TPMT	trigger point manual therapy
TU	therapeutic ultrasound
UK	United Kingdom
USA	United States of America
VAS	visual analogue scale
WAE	withdrawal due to adverse events
WHO	World Health Organization
WMD	weighted mean difference
WOMAC	Western Ontario and McMaster Universities Osteoarthritis Index

Annex 1

Key questions addressed in this guideline

This guideline is based on a series of structured key questions that define the target population, the intervention, diagnostic test, or exposure under investigation, the comparison(s) used and the outcomes used to measure efficacy, effectiveness, or risk. These questions form the basis of the systematic literature search.

Section(s)	Key questions
4	In patients with non-malignant chronic pain what is the effectiveness of patient and lay self-help advice compared with no treatment or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life or adverse events? Interventions were considered that had no or minimal ongoing healthcare professional input (which can potentially reach large numbers of patients) and are generally self-led, with or without intermittent supportive contact, including • apps (mobile and web-based/mHealth, eHealth), • computer-based programmes • monitoring devices, eg exercise trackers • automated reminders, brief telephone support to follow programme or take actions • bibliotherapy, advice booklets or manuals • lay self-help or support groups, eg third-sector groups • mentoring or support by peers.
5	In patients with chronic non-malignant pain what is the effectiveness of hands-off based interventions (exercise, physical activity or mobility aids) compared with comparators (placebo, waiting list, usual care, other hands-off treatments or no treatment)) on pain scores (30% reduction and 50% reduction), functional ability, quality of life or adverse events?
6	In patients with chronic non-malignant pain what is the effectiveness of hands-on based interventions (manual therapies or massage) compared with comparators (placebo, waiting list, usual care, other hands-on treatments or no treatment) on pain scores (30% reduction and 50% reduction), functional ability, quality of life or adverse events?
7	In patients with chronic non-malignant pain what is the effectiveness of psychological interventions (cognitive behavioural therapy, acceptance and commitment therapy, mindfulness-based interventions, biofeedback or relaxation) compared with no treatment or other interventions on pain scores (30% reduction and 50% reduction), functional ability, mood, quality of life or adverse events?
8	In people with chronic non-malignant pain what is the effectiveness of occupation-based interventions on pain scores (30% reduction and 50% reduction), occupational performance, engagement in personally meaningful occupations, return to work rates, quality of life or adverse events?

Section(s)	Key questions
9	In people with chronic non-malignant pain, what is the effectiveness of pain management programmes (as defined in the guideline) compared with no treatment or other interventions on pain scores (30% reduction and 50% reduction), functional ability, mood, quality of life and adverse events?
10	In people with chronic non-malignant pain what is the evidence for the effectiveness of dietary interventions compared with usual care on pain scores (30% reduction and 50% reduction), functional ability, quality of life or adverse events?
11	In people with chronic non-malignant pain what is the effectiveness of electrotherapy-based interventions (TENS, interferential, laser therapy, pulsed-shortwave diathermy, ultrasound, microcurrent therapy, or shockwave therapy) compared with comparators (placebo, waiting list, usual care, other electrotherapy treatments or no treatment) on pain scores (30% reduction and 50% reduction), functional ability, quality of life or adverse events?
12	In people with chronic non-malignant pain what is the effectiveness of other/complementary interventions (acupuncture, aromatherapy, homeopathy, herbal medicine, hypnotherapy, music therapy or Reiki) compared with comparators (placebo, waiting list, usual care, other complementary interventions or no treatment) on pain scores (30% reduction and 50% reduction), functional ability, quality of life or adverse events?
13	In patients with chronic non-malignant pain what is the effectiveness of simple analgesics compared with placebo or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events/drug reactions or dependency (physiological or psychological)?
14	In people with chronic non-malignant pain what is the effectiveness of antidepressants compared with placebo or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events/drug reactions or dependency (physiological or psychological)?
15	In people with chronic non-malignant pain what is the effectiveness of antiepileptics compared with placebo or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse drug reactions or dependency (physiological or psychological)?
16	In people with chronic non-malignant pain what is the effectiveness of topical analgesics compared with placebo or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events/drug reactions or dependency (physiological or psychological)?
17	In people with chronic non-malignant pain what is the effectiveness of muscle relaxants compared with placebo or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse drug reactions or dependency (physiological or psychological)?
18	In people with chronic non-malignant pain what is the effectiveness of medicinal cannabis compared with placebo or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse drug reactions or dependency (physiological or psychological)?

19	In people with chronic non-malignant pain are opioids more likely than placebo or other interventions to improve pain scores (30% reduction and 50% reduction), functional ability, and/or quality of life, and/or to cause adverse events/drug reactions, or dependency (physiological or psychological)?
20	Should naloxone be coprescribed when opioids are used for chronic pain (or when long-term/high-dose opioids are prescribed)?
21	In people with chronic non-malignant pain what is the effectiveness of combination pharmacological therapies compared with single pharmacological therapies on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events/drug reactions or dependency (physiological or psychological)?

Further details on the populations, interventions, comparators and outcomes used for each key question, the revision history of the questions and additional questions can be found in the methodology supplement on the SIGN website.

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