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A national clinical guideline

December 2013

Evidence

KEY TO EVIDENCE STATEMENTS AND GRADES OF 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

GRADES OF RECOMMENDATION	
Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.	
A	At least one meta-analysis, systematic review, or RCT rated as 1^{++}, and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}

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

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Scottish Intercollegiate Guidelines Network

Management of chronic pain

A national clinical guideline

December 2013

Scottish Intercollegiate Guidelines Network
Gyle Square, 1 South Gyle Crescent
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1 Introduction

1.1 THE NEED FOR A GUIDELINE

Chronic pain is a major clinical challenge: across Europe approximately 18% of the population are currently affected by moderate to severe chronic pain.[1] It has a considerable impact on quality of life, resulting in significant suffering and disability.[2-4] 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 measures. Chronic pain not only has an impact on affected individuals and their families, it also has substantial economic costs. For example, back pain alone was estimated to cost £12 billion per annum in the UK in 1998, and arthritis-associated pain costs around 2.5% of the gross national product of Western nations.[5,6]

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. It is vital that general practitioners (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. Within 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.[7]

A wide range of both pharmacological and non-pharmacological management strategies are available for chronic pain. The challenge is to understand the extensive published evidence for different treatments and to determine when and where to use them for the best long term outcomes for the patient. It is hoped that this evidence based guideline will provide the information needed to improve clinical outcomes and quality of life for patients with chronic pain.

1.2 REMIT OF THE GUIDELINE

1.2.1 OVERALL OBJECTIVES

This guideline provides recommendations based on current evidence for best practice in the assessment and management of adults with chronic non-malignant pain in non-specialist settings.

It does not cover:

- interventions which are only delivered in secondary care.
- treatment of patients with headache (*see SIGN 107, Diagnosis and management of headache in adults*).[8]
- children. While chronic pain occurs in children, some of their treatment options are different to those of adults, and evidence on the paediatric population has not been included in this remit.
- underlying conditions. Chronic pain is caused by many underlying conditions. The treatment of these conditions is not the focus of this guideline so the search strategies were restricted to the treatment of chronic pain, not specific conditions.

Details of the literature review are covered in section 12 and the key questions used to develop the guideline can be found in Annex 1. SIGN guidelines on other relevant topics are available on the SIGN website, **www.sign.ac.uk**.[8-12]

1.2.2 TARGET USERS OF THE GUIDELINE

This guideline will be of particular interest to all healthcare professionals involved in the assessment and management of patients with chronic pain, including general practitioners, pharmacists, anaesthetists, psychologists, psychiatrists, physiotherapists, rheumatologists, occupational therapists, nurses, patients, carers and voluntary organisations with an interest in chronic pain.

1.3 DEFINITIONS

In this guideline chronic pain is defined as pain that has been present for more than 12 weeks.

The non-specialist setting is 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.

1.4 REPORTING IN PAIN TRIALS

Difficulties in reporting make the interpretation of the evidence base challenging. Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[13] 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 there may be quite different pain mechanisms among patients. While changes in the peripheral pain processing might predominate in one patient, central changes may be much more important in the next patient.[14-16] While a particular treatment may work very effectively in one patient, it may not work at all in another patient with the same condition. 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 may not provide the best approach for developing a strong evidence base for pain management.[17-19]

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.

A number of factors need to be considered in order 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 (eg enriched enrolment) and duration of study, treatment groups (including active versus inactive placebo comparator), dosing strategies (fixed versus flexible) and type of trial (eg parallel, crossover).[17,20,21]

To allow comparison between studies a standardised approach to outcome measures, is recommended by IMMPACT.[17] Four key domains are recommended to adequately assess outcomes:

1. *Pain intensity*. A numerical rating scale 0-10 is recommended as 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 is recommended.
3. *Emotional functioning*. The Beck Depression Inventory and the Profile of Mood States are recommended.
4. *Patient rating of overall improvement*. The Patient Global Impression of Change scale can be used.

Side effects and detailed information about patient recruitment and progress through the trial should also be recorded.[22,23]

While much of the literature published to date does provide a sound evidence base for this guideline, it is hoped that future studies will follow the IMMPACT recommendations.

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. 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.[19]

Another important factor is how patients who drop out before completing the study are dealt with in the analysis. Using the last-observation-carried-forward (LOCF) for patients who drop out is based on the assumption that in a randomised controlled trial (RCT) drop-outs will occur randomly between the treatment groups. The active treatment may be an effective analgesic but if it has an unpleasant side effect profile then drop-outs are likely to be higher in a non-random manner in this treatment group. Pain scores prior to drop-out may therefore demonstrate efficacy, but in clinical practice this treatment is unlikely to be tolerated.

The majority of RCTs use the imputation method of LOCF, and may therefore potentially overestimate the treatment effect.[24]

While there are a number of good quality systematic reviews and meta-analyses that provide an evidence base for the management of patients with chronic pain, there are some limitations with the currently published literature. This has been taken into consideration by the guideline development group when appraising the evidence and, where there are areas of potential doubt, recommendations have been downgraded accordingly. Further details of the literature review can be found in section 12.

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 following discussion of the options 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 fully documented in the patient's case notes at the time the relevant decision is taken.

1.5.1 PATIENT VERSION

A patient version of this guideline is available from the SIGN website, **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 marketing authorisation
- 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 the off label use of medicines becomes necessary if the clinical need cannot be met by licensed medicines within the marketing authorisation. Such use should be supported by appropriate evidence and experience.[25]

"Prescribing medicines outside the conditions of their marketing authorisation alters (and probably increases) the prescribers' professional responsibility and potential liability".[25]

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

- be satisfied that such use would better serve the patient's needs than an authorised alternative (if one exists).
- be satisfied that there is sufficient evidence/experience of using the medicines to show its safety and efficacy, seeking the necessary information from appropriate sources.
- record in the patient's clinical notes the medicine prescribed and, when not following common practice, the reasons for the choice.
- take responsibility for prescribing the medicine and for overseeing the patient's care, including monitoring the effects of the medicine.

Non-medical prescribers should ensure that they are familiar with the legislative framework and their own professional prescribing standards.

Prior to any prescribing, the licensing status of a medication should be checked in the summary of product characteristics (SPC).[26] The prescriber must be competent, operate within the professional code of ethics of their statutory bodies and the prescribing practices of their employers.[27]

1.5.3 ADDITIONAL ADVICE TO NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

Healthcare Improvement Scotland processes multiple technology appraisals (MTAs) for NHSScotland that have been produced by the National Institute for Health and Care Excellence (NICE) in England and Wales.

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 and any major new indications for established products.

SMC advice relevant to this guideline is summarised in section 11.4.

2 Key recommendations

The following recommendations were highlighted by the guideline development group as the key clinical recommendations that should be prioritised for implementation. The grade of recommendation relates to the strength of the supporting evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

2.1 ASSESSMENT AND PLANNING OF CARE

✓ A concise history, examination and biopsychosocial assessment, identifying pain type (neuropathic/nociceptive/mixed), severity, functional impact and context should be conducted in all patients with chronic pain. This will inform the selection of treatment options most likely to be effective.

2.2 SUPPORTED SELF MANAGEMENT

✓ Healthcare professionals should signpost patients to self help resources, identified and recommended by local pain services, as a useful aide at any point throughout the patient journey. Self management may be used from an early stage of a pain condition through to use as part of a long term management strategy.

2.3 PHARMACOLOGICAL MANAGEMENT

✓ Patients using analgesics to manage chronic pain should be reviewed at least annually, and more frequently if medication is being changed, or the pain syndrome and/or underlying comorbidities alter.

B **Strong opioids should be considered as an option for pain relief for patients with chronic low back pain or osteoarthritis, and only continued if there is ongoing pain relief. Regular review is required.**

D **Specialist referral or advice should be considered if there are concerns about rapid-dose escalation with continued unacceptable pain relief, or if >180 mg/day morphine equivalent dose is required.**

2.4 PSYCHOLOGICALLY BASED INTERVENTIONS

C **Referral to a pain management programme should be considered for patients with chronic pain.**

✓ Clinicians should be aware of the possibility that their own behaviour, and the clinical environment, can impact on reinforcement of unhelpful responses.

2.5 PHYSICAL THERAPIES

B **Exercise and exercise therapies, regardless of their form, are recommended in the management of patients with chronic pain.**

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

3 Assessment and planning of care

3.1 ASSESSMENT TOOLS

There is consensus that it is good practice to assess severity, impact and type of pain before the initiation of treatment, to guide management and gauge its success.[28,29] No evidence was identified that the use of any assessments had any effect on clinically relevant outcomes. **4**

Brief and well validated tools are available for the assessment of pain in non-specialist settings. These include tools to measure severity of pain and/or its functional impact, tools to identify neuropathic pain, and tools to predict risk of chronicity in acute pain presentations.

One RCT of the STartBack tool stratified patients with back pain into low, medium and high risk of poor prognosis, to inform and evaluate treatment outcomes.[30] Those at medium risk were referred for physiotherapy and those at high risk were referred for psychologically augmented physiotherapy. Sixty per cent of patients in the intervention group and 58% in the control group had chronic pain. Outcome was measured using the Roland Morris Disability Questionnaire (RMDQ) scores, range 0 (no disability) to 24 (severe disability). At four months the intervention group reported an adjusted mean change of RMDQ score of 4.7 (standard deviation (SD) 5.9) compared to the control group (3·0 (SD 5·9)) with a between-group difference of 1.81 (95% confidence interval (CI) 1.06 to 2.57). Scores at 12 months were 4.3 (SD 6.4) versus 3.3 (SD 6.2), between-group difference 1.06 (95% CI 0.25 to 1.86).[30] **1++**

✓ A concise history, examination and biopsychosocial assessment, identifying pain type (neuropathic/nociceptive/mixed), severity, functional impact and context should be conducted in all patients with chronic pain. This will inform the selection of treatment options most likely to be effective.

A pathway for assessment can be found in Annex 2.

3.2 TIMING OF INTERVENTION

The specialist resource available for managing chronic pain is limited and long waits between the onset of pain, diagnosis of chronic pain, referral and seeing a specialist are common.

✓ Referral should be considered when non-specialist management is failing, chronic pain is poorly controlled, there is significant distress, and/or where specific specialist intervention or assessment is considered.

A systematic review of observational studies concluded that longer delays between specialist referral and specialist consultation result in poorer health and pain management by the time of this consultation. This deterioration starts as early as five weeks from referral and there is consensus that a delay of longer than six months is medically unacceptable.[31] **2++**

No RCT evidence was found that early or late initiation of specific treatments or early or late specialist referral influences outcome in patients with chronic pain.

3.3 CARE MANAGEMENT

Care management encompasses the assessment of a patient's needs, development of an individualised care plan, management of access to other services, and the monitoring and re-assessment of those needs.[32] Care management strategies are used in primary care for many chronic diseases and are intended to improve the quality of care and the use of resources.

A randomised controlled trial studied a collaborative care programme which included clinician education, patient assessment, education, goal setting and two-monthly telephone follow up by a primary care based pain team (who had minimal previous pain management experience), and communication of recommendations to GPs. This intervention led to statistically significant but modest reductions in the primary outcomes of mean pain-related disability, pain and depression scores. The number of patients with a 30% reduction in pain-related disability was clinically and statistically superior in the intervention group (21.9% versus 14% in the control group; p=0.04). This was a secondary outcome, however, and the results were not well reported.[33] **1++**

Another RCT studied an implementation strategy to promote a national guideline for management of back pain, with or without motivational counselling from practice nurses. This study showed improvements in outcomes but these were small, inconsistent and of unconvincing clinical significance.[34] **1+**

A review of nurse-led care identified only two RCTs in primary care which were of insufficient quality to support any recommendations.[35] **1-**

Another review found that evidence for the use of computerised clinical decision support systems was too weak to draw any conclusions.[36] **2-**

Many studies demonstrated that other care management approaches are feasible but with significant resource implications, and no evidence of clinically significant improvement in outcomes.

3.4 PATIENT-PROFESSIONAL INTERACTION

Studies suggest that, for patients with chronic pain, person-centred approaches, involvement in decision making, and concordance with professionals generally enhance the consultation experience. There is no high quality evidence directly linking the nature of the interaction between healthcare professionals and patients to outcomes in chronic pain management. Specific training of professionals in adopting these approaches might improve outcomes such as patient satisfaction with the interaction, reduction in anxiety and reduction in pain levels.[37-42] Further evidence that this effort and investment leads to long term improved health outcomes is required before their widespread adoption.[43] **3 1- 2+ 1+ 2++**

✓ A compassionate, patient-centred approach to assessment and management of chronic pain is likely to optimise the therapeutic environment and improve the chances of successful outcome.

4 Supported self management

Self management programmes are safe, low technology, community based and affordable interventions to help patients better manage their condition.[44] Patient or lay self help or self management therapies are distinct from simple patient education or skills training. They are structured programmes which aim to allow people to take an active part in the management of their own chronic condition.[45] These programmes are primarily educational, addressing self management and delivered by lay people. The form of delivery can be in groups or as individuals, face-to-face, by post, or electronically. The essential component is that it involves interaction between a participant and a tutor. **1+**

Participation in a self management programme was found to reduce pain (standardised mean difference (SMD) -0.14, 95% CI -0.23 to -0.04) and disability (-0.17, 95% CI -0.27 to -0.07) in patients with arthritis for up to twelve months. Insufficient evidence was found to determine the effectiveness in patients with chronic low back pain.[44] **1+**

The use of internet based self help materials can be a beneficial adjunct to clinical care for short term pain relief, reduction in perceived disability, and improvement in stress, coping and social support.[46-49] Outcomes for these studies varied, but overall improvements were small. **1+**

Studies on lay-led self management education programmes for patients with a variety of long term conditions have shown a small short term improvement in participants' confidence to manage their own health (SMD -0.3, 95% CI -0.41 to -0.19), adoption of aerobic exercises (SMD -0.2, 95% CI -0.27 to -0.12) and well-being (SMD -0.2, 95% CI -0.3 to-0.1). No evidence was found on the impact of the programmes on psychological health, symptoms or health-related quality of life.[45] **1+**

Patients require advice and specific instructions on appropriate exercise(s) and/or restoration of functional activities to promote active self management. Simple advice is not sufficient.[50] **1+**

C **Self management resources should be considered to complement other therapies in the treatment of patients with chronic pain.**

✓ Healthcare professionals should signpost patients to self help resources, identified and recommended by local pain services, as a useful aide at any point throughout the patient journey. Self management may be used from an early stage of a pain condition through to use as part of a long term management strategy.

Sources of further information for patients can be found in Section 10.

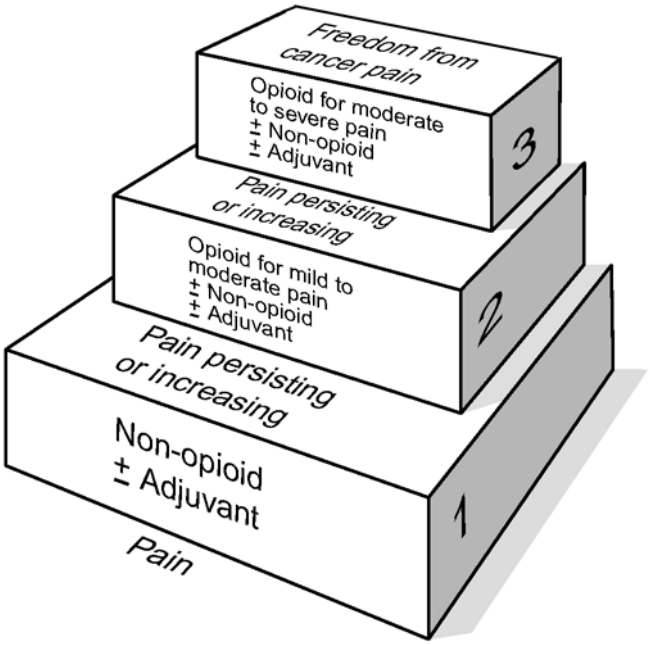
5 Pharmacological therapies

5.1 INTRODUCTION

A wide range of analgesics have been used in the treatment of chronic pain. This section addresses their individual use, but there are a number of more general aspects that should also be considered.

Although it was developed and validated only for the treatment of cancer pain, the World Health Organization analgesic ladder is widely used to guide basic treatment of acute and chronic pain.[51, 52] There is little good quality evidence for its use in chronic pain, but it does provide an analgesic strategy for non-specialists. Careful assessment and diagnosis is key to initiating appropriate pharmacotherapy. Continuing success requires regular, scheduled re-assessment of pain relief and side effects. *(See Annex 2 for pathways on assessment and managing care).*

Figure 1: World Health Organization analgesic ladder[53]



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There is considerable variation in patient responses to analgesia, both in terms of efficacy and side effects.[19] Even with the same chronic pain syndrome the underlying neurobiology will differ between individuals, influencing analgesic response.[16,54] There is also increasing evidence that variations in drug responses are linked to genetic factors (eg opioids).[55] Thus if a patient either fails to tolerate or has inadequate analgesia from a drug, then it is worthwhile considering a different agent from the same class of drug.

It is useful to have an indication of when to stop a medication, particularly for anti-neuropathic agents where there is a period of dose titration to response. If there has been no response to treatment within two-to-four weeks, after titration to adequate dose, patients are unlikely to develop a response thereafter. Integral to success is regular re-assessment of the patient and stopping medication that is not working effectively.

There is a scientific basis for the use of polypharmacy due to the complex nature of pain neurobiology, and evidence from acute pain where a combination of analgesics is used to improve postoperative pain control.[56] A Cochrane review of the use of combination therapies in patients with neuropathic pain found good evidence for improved efficacy from two-drug combinations, but drop-out rates tended to be higher because of increased adverse effects (*see section 5.6*).[57]

Regardless of which analgesia is used, regular review and reassessment to determine that there is continued value from using a particular medication is important in providing ongoing good quality chronic pain management.

✓ Patients using analgesics to manage chronic pain should be reviewed at least annually, and more frequently if medication is being changed, or the pain syndrome and/or underlying comorbidities alter.

Prescribing advice to NHSScotland from the Scottish Medicines Consortium can be found in Section 11.4.

5.2 NON-OPIOID ANALGESICS (SIMPLE AND TOPICAL)

5.2.1 NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Regular treatment with a non-steroidal anti-inflammatory drug (NSAID) has a modest beneficial effect in patients with non-specific low back pain compared with placebo, with an overall improvement of about 10%. No difference has been observed between different NSAIDs or between non-selective and cyclo-oxygenase (COX)-2 selective NSAIDs.[58] **1++**

A systematic review of six studies that compared various NSAIDs with paracetamol in low back pain found a trend in favour of NSAID (pooled SMD -0.21, 95% CI -0.43 to 0.02) but this was not significant.[58] One high quality RCT within the review found NSAIDs to be superior to paracetamol. Adverse effects were more common with NSAIDs than paracetamol (RR 1.76, 95% CI 1.12 to 2.76). **1++**

NSAID treatment is associated with a higher risk of adverse effects compared with placebo (relative risk (RR) 1.24, 95% CI 1.07 to 1.43).[58] Side effects were varied and included abdominal pain, diarrhoea, oedema, dry mouth, rash, dizziness, headache, and tiredness.[58-60] COX-2 selective NSAIDs had fewer side effects than traditional NSAIDs (RR 0.83, 95% CI 0.70 to 0.99).[58] **1++**

Gastrointestinal (GI) adverse effects are well established risks of long term regular NSAID treatment. This has been compounded by emerging evidence showing an increased risk of cardiovascular disease, stroke and heart failure. The risk of serious upper GI events differs significantly between NSAIDs.[61] The greatest risk of upper GI bleeding/perforation is seen with non-selective NSAIDs; those with a long half-life and slow-release preparations. The highest risk is with piroxicam (RR 9.94, 95% CI 5.99 to16.50) followed by naproxen (RR 5.57, 95% CI 3.94 to 7.87) whereas COX-2 inhibitors such as celecoxib (RR 1.42, 95% CI 0.85 to 2.3) are associated with the lowest risk.[61] **2+**

Meta-analyses of RCTs have shown that long term regular use of ibuprofen, diclofenac, celecoxib and etorocoxib are all associated with an increased risk of myocardial infarction and coronary heart disease death whereas this has not been observed with naproxen. In the same meta-analysis, all NSAIDs were associated with an increased risk of heart failure, but there was no evidence of an increased risk of stroke.[62] **1++**

B **NSAIDs should be considered in the treatment of patients with chronic non-specific low back pain.**

B **Cardiovascular and gastrointestinal risk needs to be taken into account when prescribing any non-steroidal anti-inflammatory drug.**

Further recommendations on the use of NSAIDs for specific conditions are available in guidelines focusing on rheumatoid arthritis, osteoarthritis and gout.[9, 63-66]

5.2.2 PARACETAMOL

There is insufficient evidence to determine the efficacy of paracetamol in the treatment of patients with generalised chronic low back pain.[59,67] Paracetamol showed slightly inferior pain relief to NSAIDs in patients with osteoporosis and chronic low back pain (SMD 0.3).[59] **1++**

Paracetamol (1,000 to 4,000 mg/day) showed a small benefit over placebo in treatment of patients with knee and hip osteoarthritis (OA) pain and could be considered in addition to non-pharmacological treatments.[68] One study showed high dose paracetamol (3,900 mg/day) to be more effective than placebo for pain relief and improved function in patients with OA of the knee.[68] NICE advise that paracetamol may be a suitable adjunct to other treatments such as education or exercise.[64] **1++ 4**

A combination of paracetamol 1,000 mg and ibuprofen 400 mg was significantly superior to regular paracetamol 1,000 mg alone for knee pain at 13 weeks but with an increased risk of gastrointestinal bleeding.[69] **1+**

C **Paracetamol** (1,000 mg/day) **should be considered alone or in combination with NSAIDs in the management of pain in patients with hip or knee osteoarthritis in addition to non-pharmacological treatments.**

5.2.3 NEFOPAM

The evidence identified on the use of nefopam for chronic pain relief is not sufficient to support a recommendation.[70] **1++**

5.2.4 TOPICAL NSAIDS

Topical NSAIDs were significantly more effective than placebo for reducing pain due to chronic musculoskeletal conditions.[71] The best evidence was for topical diclofenac in osteoarthritis, where the number needed to treat (NNT) for at least 50% pain relief over eight to 12 weeks compared with placebo was 6.4 for the diclofenac solution (four studies n=1,006), and 11 for the diclofenac gel (four studies, n=2,120). It was not possible to calculate NNTs of other individual topical NSAIDs compared with placebo. There was no difference in efficacy in a direct comparison of a topical NSAID with an oral NSAID. Local adverse events (mostly mild skin reactions) were more common with topical NSAIDs compared with placebo or oral NSAIDs, but there was no increase in serious adverse events. Gastrointestinal adverse events with topical NSAIDs did not differ from placebo, but were less frequent than with oral NSAIDs.[71] **1++**

A **Topical NSAIDs should be considered in the treatment of patients with chronic pain from musculoskeletal conditions, particularly in patients who cannot tolerate oral NSAIDs.**

5.2.5 TOPICAL CAPSAICIN

Topical capsaicin is available as low dose cream (0.025% or 0.075%) or as a high dose (8%) patch.

Few studies of low dose cream were identified but it appears to have no benefit over placebo cream for patients with neuropathic pain.[72] For patients with osteoarthritis three RCTs, ranging from four or twelve weeks in duration, found that low dose capsaicin cream is better than placebo.[73] **1++ 1+**

In studies of patients with postherpetic neuralgia (PHN) and patients with human immunodeficiency virus (HIV) neuropathy, application of an 8% patch gives significant benefit over placebo.[74] In patients with PHN the NNT was 7 (95% CI 4.6 to 15) for those who were better or very much better at 12 weeks. In patients with HIV neuropathy the NNT was 5.8 (95% CI 3.8 to 12) for those who were better or very much better at 12 weeks. Although of benefit, the cost and specialist application mean that it should be used when other therapies have failed. **1++**

A **Topical capsaicin patches** (8%) **should be considered in the treatment of patients with peripheral neuropathic pain when first line pharmacological therapies have been ineffective or not tolerated.**

5.2.6 TOPICAL LIDOCAINE

Topical lidocaine is better than placebo in treating patients with postherpetic neuralgia (p=0.003) based on results from three RCTs.[75,76] 1++

A systematic review on the use of lidocaine plaster for patients with refractory neuropathic pain (pain not responding to a number of standard treatments) concluded that little evidence is available, results of studies were inconsistent and there is not strong enough evidence on which to base a recommendation.[77] 1+

SMC accept the use of lidocaine plaster for patients with neuropathic pain when first line therapies have failed (*see section 11.4*).

B **Topical lidocaine should be considered for the treatment of patients with postherpetic neuralgia if first line pharmacological therapies have been ineffective.**

5.2.7 TOPICAL RUBEFACIENTS

Topical rubefacients are more effective than topical placebo for pain reduction (NNT 6.2, 95% CI 4.0 to 13) in patients with musculoskeletal conditions.[78] 1++

B **Topical rubifacients should be considered for the treatment of pain in patients with musculoskeletal conditions if other pharmacological therapies have been ineffective.**

5.3 OPIOIDS

Over the last few decades, opioids have been used increasingly in chronic pain management, with a number of potential reasons for this increase, including new preparations and formulations of opioids, changes in patient expectation, medical practice and societal attitudes.

There are a number of different classifications for opioids, but for the purposes of this guideline they are divided into weak opioids, with limited potency at the mu opioid receptor (MOR) and strong opioids, with greater potency at the MOR. Weak opioids include codeine and tramadol with defined upper dose limits in the BNF. Strong opioids include morphine, diamorphine, hydromorphone, oxycodone, fentanyl, buprenorphine and methadone, with some of the newer formulations allowing very low dosing, with an equivalent effect to weak opioids. There is limited evidence for the accuracy of dose equivalence tables and caution should be exercised in changing from one opioid to another (*see Annex 4 for a pathway for using strong opioids*).[11]

Another factor that must be considered when assessing opioid responses, is that several opioids, including codeine, tramadol, oxycodone and hydrocodone are affected by variations in metabolism, mediated by cytochrome P450 enzyme CYP2D6, resulting in unpredictable effects in individuals. As codeine is a pro-drug (its main effect relies on being metabolised to morphine), the five to ten per cent of the population who are poor metabolisers have very little analgesia, whereas the five to ten percent who are hyper-metabolisers will have an increased drug effect. There is considerable inter-ethnic variability in gene encoding for CYP2D6.[79] Tapentadol is a relatively new opioid preparation that is classed as a strong opioid, but also inhibits noradrenergic reuptake. This may have advantages in some chronic pain conditions such as neuropathic or mixed pains.

A number of systematic reviews identified RCTs of the efficacy of opioids, although none were judged as potentially free of bias.[59,80-84] One systematic review and meta-analysis of patients with chronic non-cancer pain on strong opioids for at least six months, identified only one RCT, with the remainder being non-RCTs or pre-post case series, reflecting the difficulty of carrying out long duration RCTs.[84] 1++ 2++

Although there was considerable heterogeneity, four studies of oral opioids found an SMD at six months of 1.55 (95% CI 0.85 to 2.25), suggesting a clinically important reduction in pain from baseline.[84] There was a high drop-out rate, indicating that those who either do not benefit or have unacceptable side effects drop out early. Transdermal opioids showed a large reduction in pain (SMD 7.56, 95% CI 4.65 to 10.19) although this was based on only two studies. Quality of life assessments were limited, with no clear evidence of clinically significant benefit from either oral or transdermal opioids. There was some improvement in physical function 1++ 1+

with transdermal opioids at 12 to 13 months.[84] Studies of transdermal buprenorphine in a relatively low dose (20 µg/hr), used an enriched enrolment design (the exclusion of non-responders or specific inclusion of responders) and found that the 20 µg/hr preparation was effective for up to 12 weeks compared to placebo, with conservative imputation methods and also had beneficial effects on quality of life.[85,86] **1++** **1+**

Another systematic review of RCTs of patients with chronic pain found moderate evidence for tramadol in patients with osteoarthritis, but found limited high quality evidence for other opioids, with most studies being of less than 12 weeks duration.[82] **1++**

There is no clear evidence that any particular opioid, including morphine, is better than any other in terms of efficacy for pain relief, although patients were more likely to discontinue buprenorphine than morphine because of lack of effect (odds ratio (OR) 2.32, 95% CI 1.37 to 3.95).[80] Compared to morphine, patients were more likely to discontinue methadone because of adverse effects (OR 3.0, 95% CI 1.14 to 8.36). Both fentanyl (OR 0.29, 95% CI 0.17 to 0.5) and buprenorphine (OR 0.3, 95% CI 0.16 to 0.53) were associated with fewer adverse effects than morphine.[80] A systematic review of methadone identified just two trials on patients with chronic pain which were only of eight weeks duration.[87] **1++**

There is limited evidence from systematic reviews for the efficacy and safety of tapentadol, as it has been licensed relatively recently. There have, however, been a number of large RCTs in osteoarthritis (mainly of the knee) and chronic back pain. These used an active comparator group (oxycodone) in addition to placebo. The drop-out rate was high in the studies with up to 65% of oxycodone treated patients failing to complete in one study and 40-45% dropping out in the placebo and tapentadol groups.[88] A pooled analysis of three RCTs of tapentadol (prolonged release, 100-250 mg, twice daily) versus placebo or oxycodone found evidence for efficacy of tapentadol (least squared mean difference (LSMD) versus placebo -0.6, 95% CI -0.80 to -0.39; p<0.001) and to a lesser extent, oxycodone (LSMD versus placebo -0.3, 95% CI -0.53 to -0.12; p=0.002) at 12 weeks.[89] Using conservative imputation methods, oxycodone did not demonstrate efficacy, possibly due to the high drop-out rates, with adverse effects being higher in the oxycodone group.[89] **1+**

Meta-analysis of data from 11,927 patients, using enriched enrolment design, showed efficacy from both weak opioids (effect size 0.55, 95% CI 0.45 to 0.66 for pain relief and 0.31, 95% CI 0.21 to 0.41 for function) and strong opioids (0.60, 95% CI 0.43 to 0.77 for pain relief and 0.37, 95% CI 0.22 to 0.52 for function).[90] **1+**

The clinical effectiveness of opioid therapy in any individual should be regularly assessed, with clearly defined stopping strategies, should there be inadequate pain relief or unacceptable side effects. There is a rationale for opioid rotation, if the initial choice of opioid is ineffective, and even more so if adverse effects are unacceptable.[80] **1++**

Three RCTs of tramadol for patients with chronic low back pain, of up to 90 days duration, with very strict entry criteria and high drop-out rates, found a modest benefit compared to placebo, with a reduction of 10.8 points on a 100-point visual analogue scale (VAS) (SMD 0.71, 95% CI 0.39 to 1.02), which is of unclear clinical benefit.[81] Similar results were found in the other reviews and meta-analyses, with a moderate effect size and improvements of between 10 to 20 on a 100-point VAS,[59, 60] although one good quality review found no significant reduction in pain compared to baseline and when opioids were compared to placebo or active controls there was limited evidence of efficacy.[83] **1++** **2++**

In elderly patients, opioids (average doses of 63 mg, 24-165 mg/day) are effective in reducing pain and physical disability, but have some adverse effects on mental health. Only five studies were of more than 12 weeks duration. In this patient group, there was a greater effect size for patients with neuropathic pain (-0.91, p<0.001) compared to patients with osteoarthritis (-0.46, p<0.001).[91] **1+**

No improvement in pain relief was found by adding short-acting opioids as rescue use medication for patients using long term opioids, but reported rates of nausea (25%) did not increase either.[92] **2++**

In elderly patients, the effect size of long-acting opioids was greater than immediate-release opioids for pain and physical functioning, but this was not significant.[91] **2++**

5.3.1 SIDE EFFECTS

One of the main reasons for high drop-out rates in clinical trials of opioids is side effects. Not only does this impact on analysis, but it also has implications for clinical practice, as side effects come with both a financial cost (in terms of treating them) and an adverse impact on quality of life.[93] **2⁻**

Two systematic reviews primarily examined adverse events, but this was restricted to reporting of nausea, constipation and somnolence.[92,93] Significantly less constipation was experienced with the use of tramadol and fentanyl than other opioids.[92] Patients using oxycodone experienced more somnolence than those using other opioids.[92] Other commonly reported adverse events with long term use of opioids include gastrointestinal effects (constipation, nausea, dyspepsia), headache, fatigue, lethargy, somnolence, and urinary complications (retention hesitancy, disturbance).[84] A few serious side effects such as sedation and respiratory depression were reported. Adverse effects led to discontinuation in 11% of patients on weak opioids and 35-39% on strong opioids.[84] **2⁻ 2⁺⁺**

Long term opioid therapy has a moderate increased risk of fractures (pooled RR 1.32 to 1.42), although this evidence is derived from meta-analysis of studies with considerable heterogeneity.[94] **2⁺**

5.3.2 OPIOID MISUSE

Reporting on opioid addiction is variable, with many studies of opioid use specifically excluding patients with a past history of substance misuse. Where addiction or abuse was reported an event rate of 0.27% (7 out of 2613 patients studied) was found.[84] In patients pre-selected to be at low risk, 0.19% of patients versus 3.27% in the non-selected group were found to meet criteria for addiction, with 0.59% versus 11.5% displaying adverse drug-related behaviour.[95] Lifetime prevalence estimates of substance use disorders in patients receiving opioids for chronic back pain did not differ markedly from those of the group not receiving opioids (current, 23% for both groups; lifetime, 54% versus 52%, respectively).[83] **2⁺⁺**

A systematic review of opioids in elderly patients found that older age was associated with a lower likelihood of abuse.[91] One large scale study of patients receiving opioids (n=15,160) found that fewer than one per cent of patients >60 years and four per cent of those <60 years had diagnosed opioid misuse.[91] **1⁺**

The use of validated tools or urine drug testing to identify patients at risk of developing iatrogenic opioid misuse has been studied. A systematic review found weak evidence from moderate quality studies that high scores on the Screener and Opioid Assessment for Patients with Pain (SOAPP Version 1) increased the likelihood for any future aberrant drug-related behaviour (positive likelihood ratios (PLR) 2.90, 95% CI, 1.91 to 4.39).[96] Low scores on the SOAPP Version 1 moderately decreased the likelihood of aberrant drug-related behaviours (negative likelihood ratio (NLR) 0.13, 95% CI 0.05 to 0.34). The revised SOAPP gave similar results. One poor quality study using the Opioid Risk Tool (ORT) found that categorisation of patients as high or low risk strongly affected the likelihood of future aberrant drug-related behaviours (PLR 14.3, 95% CI, 5.35 to 38.4, and 0.08, 95% CI, 0.01 to 0.62, respectively). The Current Opioid Misuse Measure (COMM) screening tool demonstrated a weak increase in the likelihood of current aberrant drug-related behaviours (PLR 2.77, 95% CI, 2.06 to 3.72) with high scores and reduced likelihood with lower scores (NLR 0.5, 95% CI, 0.24 to 0.52). There was no good evidence for the use of urine drug screening, pill counts or prescription drug monitoring programmes to detect misuse development.[96] **2⁺⁺**

5.3.3 OPIOID DOSE

Opioids are one of the few classes of analgesics where there is not always a maximum recommended dose for particular drugs, nor is there any agreed definition of what constitutes high dose opioid therapy. The American Pain Society Guidelines use a definition of >200 mg morphine equivalent per day, based on a review of the published literature, whereas the British Pain Society Guidelines recommend specialist referral for doses of 120-180 mg or greater.[96,97] The risk of overdose on higher doses may be greater, with a cohort study of a small number of overdoses finding a 0.2% annual risk in patients on <20 mg/day morphine and 1.8% risk in patients on >100 mg/day of morphine.[98] **4 2⁺⁺**

B **Strong opioids should be considered as an option for pain relief for patients with chronic low back pain or osteoarthritis, and only continued if there is ongoing pain relief. Regular review is required.**

B **Patients prescribed opioids should be advised of the likelihood of common side effects such as nausea and constipation.**

✓ All patients on strong opioids should be assessed regularly for changes in pain relief, side effects and quality of life, with consideration given to a gradual reduction to the lowest effective dose.

B **It may be necessary to trial more than one opioid sequentially, as both effectiveness and side effects vary between opioids.**

✓ Opioid rotation should be considered for chronic pain that is likely to respond to opioids, if there are problems with efficacy or side effects.

C **Signs of abuse and addiction should be sought at re-assessment of patients using strong opioids. Routine urine drug testing, pill counts or prescription monitoring should not be used to detect problem use.**

B **Currently available screening tools should not be relied upon to obtain an accurate prediction of patients at risk of developing problem opioid use before commencing treatment.**

✓ There should be careful assessment of pre-existing risk factors for developing opioid misuse. In patients where opioid therapy is indicated, but there is an increased risk of iatrogenic opioid misuse, specialist advice should be sought. The minimal effective dose should be used to avoid increased problems of fracture and overdose that may occur on higher doses.

D **Specialist referral or advice should be considered if there are concerns about rapid-dose escalation with continued unacceptable pain relief, or if >180 mg/day morphine equivalent dose is required.**

5.4 ANTI-EPILEPSY DRUGS

5.4.1 GABAPENTIN

Using the IMMPACT definition of at least moderate benefit (at least 30% reduction in pain) gabapentin at daily doses of at least 1,200 mg is superior to placebo for pain relief in patients with postherpetic neuralgia, painful diabetic neuropathy or mixed neuropathic pain (NNT 6.8, 95% CI 5.6 to 8.7).[99] Adverse events occurred significantly more often with gabapentin, most commonly dizziness (21%), somnolence (16%), peripheral oedema (8%), and gait disturbance (9%). Serious adverse events (4%) were no more common than with placebo. **1++**

One RCT demonstrated a 30% reduction in pain over baseline, with 38/75 participants with fibromyalgia (49%) achieving the outcome with gabapentin compared with 23/75 (31%) with placebo. The relative benefit was 1.6 (95% CI 1.1 to 2.4) and the NNT was 5.4 (95% CI 2.9 to 31).[99] **1++**

Gabapentin was clinically and statistically superior to placebo in reducing pain reported by patients with chronic masticatory myalgia, masticatory muscle hyperalgesia and impact on daily functioning in a small RCT.[100] **1+**

A **Gabapentin** (titrated up to at least 1,200 mg daily) **should be considered for the treatment of patients with neuropathic pain.**

5.4.2 PREGABALIN

Pregabalin at doses of 300 mg, 450 mg, and 600 mg daily was effective in patients with various types of neuropathic pain. Pregabalin at 150 mg daily was generally ineffective.[101] The lowest NNT for each condition for at least 50% pain relief over baseline for 600 mg pregabalin daily compared with placebo were 3.9 (95% CI 3.1 to 5.1) for patients with postherpetic neuralgia, 5.0 (95% CI 4.0 to 6.6) for patients with painful diabetic neuropathy, 5.6 (3.5 to 14) for patients with central neuropathic pain, and 11 (95% CI 7.1 to 21) for patients with fibromyalgia.[101] Higher rates of substantial benefit (≥50% pain relief) were found in patients with postherpetic neuralgia and painful diabetic neuropathy than in patients with central neuropathic pain or fibromyalgia.[101] **1++**

One RCT found pregabalin to be an effective adjuvant therapy for patients with chronic pancreatitis after three weeks of treatment, with reduction in pain reported in 36% versus 24% placebo, (95% CI 22% to 2%, p=0.02) and a higher health status, Patient's Global Impression of Change (PGIC) score reported in the pregabalin group compared to placebo (44% versus 21%, p=0.048).[102] **1+**

With 600 mg pregabalin daily treatment was discontinued due to adverse events in 18% to 28% of patients.[101] Somnolence typically occurred in 15% to 25% of patients and dizziness occurred in 27% to 46%.[101] Adverse events related to cognition and co-ordination are commonly reported with the use of pregabalin, although none are considered to be serious, and they are dose related.[103] A flexible dosing strategy (150-600 mg per day based on clinical response and tolerability) may reduce discontinuations, facilitate a higher final dose and give slightly greater pain relief.[104] **1++** **1+**

Pregabalin is not helpful in the treatment of patients with chronic prostatitis, pelvic pain or HIV neuropathy.[105,106] **1++**

SMC restricts the use of pregabalin to adults with peripheral neuropathic pain where other first and second line pharmacological treatments have failed (*see section 11.4*).

A pathway for patients with neuropathic pain can be found in Annex 3.

A **Pregabalin** (titrated up to at least 300 mg daily) **is recommended for the treatment of patients with neuropathic pain if other first and second line pharmacological treatments have failed.**

A **Pregabalin** (titrated up to at least 300 mg daily*)* **is recommended for the treatment of patients with fibromyalgia.**

B **Flexible dosing may improve tolerability. Failure to respond after an appropriate dose for several weeks should result in trial of a different compound.**

Pregabalin does not have marketing authorisation for the treatment of patients with fibromyalgia.

5.4.3 CARBAMAZEPINE

In patients with neuropathic pain carbamazepine (any dose), is significantly better than placebo over four weeks using any definition of improvement (NNT 1.7). The trials were generally of short duration and with some design limitations, including small sample size. Results were similar in studies reporting a 50% pain reduction over baseline. Sixty six per cent of participants using carbamazepine reported adverse events, the most common of which was rashes.[107] **1++**

B **Carbamazepine should be considered for the treatment of patients with neuropathic pain. Potential risks of adverse events should be discussed.**

5.4.4 OTHER ANTI-EPILEPSY DRUGS

There is little evidence from a systematic review that sodium valproate is an effective first line treatment for patients with chronic pain.[108]

A systematic review found that lacosamide is not likely to be beneficial in treating patients with neuropathic pain.[109]

Lamotrigine was found to provide no benefit in the treatment of patients with chronic pain.[110]

No evidence was found to support the use of phenytoin in the treatment of patients with neuropathic pain or in fibromyalgia.[111]

There is no evidence to support the use of clonazepam in the treatment of patients with chronic neuropathic pain or fibromyalgia.[112]

One RCT investigating levetiracetam did not show it to be clinically effective in the treatment of pain in patients with polyneuropathy.[113]

1++

No evidence was found on the efficacy of topiramate for the treatment of patients with chronic pain.

5.5 ANTIDEPRESSANTS

Drugs that potentiate noradrenaline and serotonin or predominantly noradrenergic mechanisms (tricyclic antidepressants (TCA)/serotonin norepinephrine reuptake inhibitors (SNRI)), are more effective than selective serotonin reuptake inhibitors (SSRI) for treating neuropathic pain.[114] **1+**

There was insufficient evidence to determine the use of antidepressants in patients with temporomandibular disorders.[115] **1++**

✓ Patients with chronic pain conditions using antidepressants should be reviewed regularly and assessed for ongoing need and to ensure that the benefits outweigh the risks.

5.5.1 TRICYCLIC ANTIDEPRESSANTS

There is no significant difference between tricyclic antidepressants and placebo in pain relief for patients with chronic low back pain.[60,116] **1++**

Use of TCA for the treatment of patients with fibromyalgia can improve pain scores (SMD -0.43, 95% CI -0.55 to -0.30; p <0.001), depression (SMD -0.26, 95% CI, -0.39 to -0.12; p <0.001), sleep disturbances (SMD -0.32, 95% CI, -0.46 to -0.18; p < 0.001) and health-related quality of life (HRQOL) (SMD -0.31, 95% CI, -0.42 to -0.20; p <0.001).[117] **1++**

In patients with fibromyalgia amitriptyline was effective in reducing pain (SMD -1.64, 95% CI, -2.57 to -0.71; p < 0.001), fatigue (SMD -1.12, 95% CI, -1.87 to -0.38; p=0.003), and sleep disturbances (weighted mean difference (WMD) -1.84, 95% CI -2.62 to -1.06; p<0.001). The effect size on depression was not statistically significant and small in HRQOL.[117] **1++**

Nortriptyline combined with morphine had limited effectiveness in the treatment of patients with sciatica.[118] This small RCT had a very high drop-out rate. Amitriptyline is more efficacious than placebo in relieving neuropathic pain in patients with chronic spinal cord injury with either low or high grade depression.[119] Amitriptyline is sometimes used to treat arm pain related to repetitive use, but robust evidence of its benefit is lacking. An RCT found that low dose amitriptyline did not significantly decrease arm pain among these participants but did significantly improve arm function and well-being.[120] **1+** **1++**

Trials of amitriptyline (25 mg to 125 mg) reporting ≥30% reduction in pain demonstrated no evidence of effect in patients with HIV-related neuropathic pain. Analysis of combined results for patients with painful diabetic neuropathy, postherpetic neuralgia, post-stroke pain or fibromyalgia did show benefit (RR 2.3, 95% CI 1.8 to 3.1) compared to placebo.[121] The systematic review concluded that amitriptyline is effective for a minority of patients. **1++**

A **Tricyclic antidepressants should not be used for the management of pain in patients with chronic low back pain.**

A **Amitriptyline** (25 - 125 mg/day) **should be considered for the treatment of patients with fibromyalgia and neuropathic pain** (excluding HIV-related neuropathic pain).

✓ It may be appropriate to try alternative tricyclic antidepressants to reduce the side effect profile.

5.5.2 SEROTONIN NOREPINEPHRINE RE-UPTAKE INHIBITOR

There is some evidence to support the use of duloxetine 60-120 mg in patients with chronic low back pain. Mean changes in SF-36 bodily pain scores during treatment were 1.36 with placebo, 1.95 with duloxetine 60 mg ($p<0.05$ versus placebo), and 2.11 with duloxetine 120 mg ($p<0.05$ versus placebo). Mean changes in RMQD-24 were -1.3 with placebo, -2.7 with duloxetine 60 mg ($p<0.05$ versus placebo), and -2.9 with duloxetine 120 mg ($p<0.05$ versus placebo).[122] **1+**

Several studies and meta-analyses have shown benefit of duloxetine in patients with a variety of chronic pain conditions. A meta-analysis of pain control in fibromyalgia has shown that treatment with duloxetine was associated with better pain control (30% improvement in pain score, RR 1.52, 95% CI 1.24 to 1.86, $p<0.0001$ versus placebo; 50% improvement in pain score, RR 1.60, 95% CI 1.22 to 2.10, $p=0.0007$).[123] **1++**

Duloxetine 60 mg daily is effective in treating painful diabetic peripheral neuropathy in the short term to 12 weeks (RR for 50% pain reduction at 12 weeks 1.65 (95% CI 1.34 to 2.03), number needed to treat (NNT) 6 (95% CI 5 to 10).[124] **1++**

Pooled data analyses from two studies in patients with knee osteoarthritis show that 64.9% of patients in the duloxetine group, compared with 44.9% in the placebo group, reported improvement in pain from baseline to end point (RR 1.45, 95% CI 1.22 to 1.71; $p < 0.001$).[125] Treatment with duloxetine 60-120 mg daily is associated with significant pain reduction and improved function in patients with pain due to osteoarthritis of the knee.[126] In this study, the Brief Pain Inventory scale (BPI) average pain response rates (≥30% pain reduction from baseline to end point) were significantly higher in the duloxetine group versus placebo group (65.3% versus 44.1%, $p\leq0.001$). The 50% response rates of BPI average pain did not significantly differ between the two groups (duloxetine 43.8% versus placebo 32.3%, $p=0.068$). **1+** **1++**

Duloxetine was statistically superior to placebo in patients with chronic back pain on the primary endpoint objective of reduction in average weekly pain from weeks 3-12 but lost statistical significance at the final week.[122] Duloxetine showed a statistically significant reduction in BPI average pain compared with placebo.[127] **1++**

Duloxetine and milnacipran were effective in reducing pain by ≥50% in patients with fibromyalgia (SMD, -0.23, 95% CI -0.29 to -0.18) compared to placebo. There were no significant improvements in quality of life, reduction in fatigue or sleep disruption.[128] **1++**

Rates of reported adverse effects and drop-out due to adverse events did not differ between treatment and placebo groups.[117] **1++**

Forty per cent of patients with fibromyalgia reported ≥30% pain relief with milnacipran 100 mg or 200 mg compared with placebo (NNT 6 to 10). Adverse effects, such as nausea and constipation, were experienced by 87% of participants treated with milnacipran compared to 78% of the placebo group.[129] **1++**

SMC restricts the use of duloxetine as a second or third line therapy for adults with diabetic peripheral neuropathic pain (*see section 11.4*).

A pathway for patients with neuropathic pain can be found in Annex 3.

A **Duloxetine** (60 mg/day) **should be considered for the treatment of patients with diabetic neuropathic pain if other first or second line pharmacological therapies have failed.**

A **Duloxetine** (60 mg/day) **should be considered for the treatment of patients with fibromyalgia or osteoarthritis.**

Duloxetine does not have marketing authorisation for the treatment of patients with fibromyalgia or osteoarthritis. Milnacipran is not available in the UK.

5.5.3 SELECTIVE SEROTONIN RE-UPTAKE INHIBITOR

A meta-analysis reported evidence for the efficacy of SSRIs fluoxetine (20-80 mg/day) and paroxetine (12.5-62.5 mg/day) in reducing pain in patients with fibromyalgia (SMD -0.39, 95% CI, -0.77 to -0.01; p=0.04). Effects were small for depressed mood and HRQOL and there were no effects on fatigue or sleep. Data for paroxetine were from a single RCT.[117] 1++

B **Fluoxetine** (20-80 mg/day) **should be considered for the treatment of patients with fibromyalgia.**

5.5.4 CHRONIC PAIN WITH CONCOMITANT DEPRESSION

An RCT of patients with chronic pain and moderate depression given optimised antidepressant therapy for 12 weeks followed by a 12 week pain self management programme resulted in 37% of patients achieving a ≥50% reduction in depression compared to 16% receiving usual care (RR 2.3, 95% CI 1.5 to 3.2) after 12 months. There were also moderate reductions in pain severity (≥30% reduction in pain in 51% treatment group versus 17% usual care, RR 2.4, 95% CI 1.6 to 3.3) and disability.[130] 1++

B **Optimised antidepressant therapy should be considered for the treatment of patients with chronic pain with moderate depression.**

✓ Depression is a common comorbidity with chronic pain. Patients should be monitored and treated for depression when necessary.

5.6 COMBINATION THERAPIES

There is some evidence for combining therapies in patients with neuropathic pain, with a systematic review identifying 21 double blind RCTs comparing combinations of at least two drugs.[57] In four studies (n=578) the combination of opioid and gabapentin or pregabalin were studied. Other combinations included opioid plus a tricyclic antidepressant (n=776), gabapentin and nortriptyline (n=56), and a variety of topical medications (n=604). A high drop-out rate was common, with problematic side effects such as sedation and cognitive dysfunction, which may limit the utility of combination therapies. Meta-analysis of studies of opioid plus gabapentin (n=386) showed superiority for the combination over gabapentin alone.[57] 1++

One small trial suggests that a combination of nortriptyline and gabapentin is more efffective than either drug alone.[57] 1++

The addition of glyceryl trinitrate (GTN) spray to sodium valproate may improve pain control in diabetes although the evidence for valproate is poor.[57] 1++

A **Combination therapies should be considered for patients with neuropathic pain** (a pathway for patients with neuropathic pain can be found in Annex 3).

A **In patients with neuropathic pain who do not respond to gabapentinoid** (gabapentin/pregabalin) **alone, and who are unable to tolerate other combinations, consideration should be given to the addition of an opioid such as morphine or oxycodone. The risks and benefits of opioid use need to be considered.**

No evidence was identified on other combinations of therapies for treating patients with chronic pain.

6 Psychologically based interventions

It has long been recognised that the perception of pain, and the disability that often arises from it, is inextricably linked to an individual's emotional, cognitive and social functioning.[131] Living with chronic pain can also significantly affect an individual's mental health and, consequently, their response to treatment.[132]

✓ Healthcare professionals referring patients for psychological assessment should attempt to assess and address any concerns the patient may have about such a referral. It may be helpful to explicitly state that the aims of psychological interventions are to increase coping skills and improve quality of life when faced with the challenges of living with pain.

6.1 MULTIDISCIPLINARY PAIN MANAGEMENT PROGRAMMES

Multidisciplinary biopsychosocial treatment, also known as a pain management programme (PMP), addresses the complexities experienced by patients with chronic pain.[133] The definition of multidisciplinary biopsychosocial treatment of patients with chronic pain is variable amongst studies. Three systematic reviews used the inclusion of one physical dimension and one or more psychological, social or occupational dimensions as a minimum for their definition.[134-136] Another defined multidisciplinary treatment as including at least three of the following categories: psychotherapy, physiotherapy, relaxation techniques, medical treatment, patient education or vocational therapy.[137] Inconsistencies in the reported results may be due to the differences in the definition of multidisciplinary treatment, the treatment combinations, treatment intensity, setting and heterogeneity of the study populations and control groups.

Positive results were found in a systematic review addressing non-specific musculoskeletal conditions which grouped outcome domains into primary (pain, mood, quality of life (QoL), function and coping) and secondary (physical capacity, return to work rate, sick leave, use of healthcare system, medication, pain behaviour, quality of sleep and other domains (eg subjective improvement).[137] An intervention was judged as successful if it showed itself to be superior to the control condition on at least two primary outcomes or on one primary and two secondary outcomes. Thirteen of fifteen studies had positive results that multidisciplinary programmes are superior to no treatment or standard medical treatment. The differences after treatment were maintained in those studies which included long term follow up. Multidisciplinary treatment was also superior to other unidisciplinary treatments (eg physiotherapy or education) in ten of the 15 studies identified. This was maintained in follow up. Patients with low back pain or fibromyalgia had greater benefits than those with diverse origins of chronic pain diagnoses. **1++**

Of the systematic reviews that looked at outcomes separately, two concluded that there is no demonstrable effect that multidisciplinary treatment reduces pain for clients with non-specific chronic low back pain (CLBP) compared to no treatment or usual care.[134,136] In contrast a third systematic review found moderate evidence that multidisciplinary treatment is superior compared to no treatment (WMD -9.47, 95% CI -13.87 to -5.87) or other active treatments (eg physiotherapy, WMD -11.55, 95% CI -19.68 to -3.43) for reduction in short term pain intensity but moderate quality evidence of no differences in long term pain (WMD compared to no treatment -9.27, 95% CI -27.86 to 9.12; WMD compared to active control -3.34, 95% CI -11.64 to 4.97).[135] **1++**

There is no demonstrable effect that multidisciplinary treatment improves functional status or disability for patients with CLBP (WMD -8.84, 95% CI -18.49 to 0.82).[134-136] **1++**

One systematic review cited two high quality studies which addressed long term quality of life in patients who received intensive (≥30 hours/week) multidisciplinary treatment. Only one of the studies reported significant improvements in the multidisciplinary treatment group compared to controls.[136] **1++**

In patients with fibromyalgia with a risk profile for heightened psychological distress, the intervention, (described as targeted cognitive behavioural therapy, but also including physiotherapy, therefore multidisciplinary treatment) was found to be significantly effective in both the short and long term (six month follow up) in reducing pain intensity, fatigue, disability, negative mood and quality of life, compared to a waiting list control group.[138] **1++**

One small study examined the effects of a pain management programme on outcomes for individuals with neuropathic pain following spinal cord injury.[139] Compared to waiting list controls, the intervention group experienced significant changes in two out of four secondary outcome domains not seen in the control group; a reduction in anxiety and an increase in participation in activities. There were no significant differences on pain intensity, pain-related disability, depression and life satisfaction. 1+

C **Referral to a pain management programme should be considered for patients with chronic pain.**

6.2 UNIDISCIPLINARY EDUCATION

Persistent pain differs from acute pain that everyone experiences occasionally. It has therefore been considered beneficial to educate patients about these differences in order to help them understand and manage their pain and reduce any unwarranted concerns that they may have. Educational interventions have varied in terms of length, topics covered, the profession of those delivering them and whether or not they were combined with other therapies.

6.2.1 BRIEF EDUCATION

Brief education for patients with CLBP is effective in reducing sick leave and disability when compared to usual care.[140] Brief education in a clinical setting (defined as "examination, information, reassurance and advice to stay active") was not shown to be any more effective at reducing pain than usual care alone.[140] 1++

There is limited evidence that brief education compared to other active interventions, such as spinal stabilisation, yoga, physiotherapy treatment, exercise, acupuncture and massage, is effective for pain or disability in either the short- or the long-term.[140,141] 1++

No evidence was found on the effects of brief education on emotional outcomes, such as depression.

C **Brief education should be given to patients with chronic pain to help patients continue to work.**

6.2.2 PAIN NEUROPHYSIOLOGY EDUCATION

Pain neurophysiology education (PNE) compared to a biomechanically focused education programme, produces statistically significant but clinically small improvements in pain intensity. When PNE was added to a pain management programme and compared to a PMP with education based on *The Back Book* there was evidence that the PNE group had significantly greater reductions in pain in the short-medium-and long-terms.[142,143] Although the amount of evidence is limited, PNE appears to be associated with short term reduction in pain intensity. Reading a book of stories and metaphors related to pain neurophysiology, however, did not produce benefits in terms of pain reduction, but did reduce the level of catastrophising and increased participants understanding of pain neurophysiology when this was compared to reading a book of traditional pain management advice.[144] 1+ 1++

Results are more mixed for the effects of PNE on disability with only one study finding small, short term effects on disability, whilst the other study that examined PNE in combination with a PMP failed to find any differences either in the short-, medium- or long-term.[142] Similarly, reading a book of metaphors and stories relating to pain neurophysiology did not decrease disability when compared to reading a book of traditional pain management advice.[144] 1+ 1++

There is some evidence that PNE produces reliable short term improvements in measures of attitudes towards pain. In combination with a PMP, PNE produced greater benefits than a PMP with *The Back Book* education, in terms of work status at medium- and long-term, but not in the short term. More research is required to improve the confidence in these results.[142] 1+

6.3 BEHAVIOURAL THERAPIES

6.3.1 RESPONDENT BEHAVIOURAL THERAPIES

Respondent treatment aims to modify the physiological response system to pain, through reduction of muscular tension. The theoretical basis of this approach is the assumption of the existence of a pain-tension cycle, where pain is viewed as both a cause and a result of muscular tension. Respondent treatment attempts to interrupt this cycle by using a tension-incompatible reaction, such as relaxation. Electromyographic (EMG) biofeedback, progressive relaxation, and applied relaxation are used to reduce the assumed muscular tension, relieve anxiety, and subsequently pain.[145]

There is low quality evidence that progressive relaxation is effective for short term pain relief compared to no treatment and comparing pain intensity before and after treatment, in patients with chronic low back pain (WMD -19.77, 95% CI -34.34 to -5.20 and WMD -19.74, 95% CI -34.32 to -5.16).[135,145] It also improved short term functional status and disability.[135,145] Two small RCTs (n=58) suggest that progressive relaxation is not effective for depression in the short term.[145] **1++**

EMG biofeedback is also effective for short term pain relief, although this conclusion is based on low quality studies.[135, 145] One systematic review found EMG biofeedback to be effective when disability was measured pre- and post-treatment (WMD -7.33, 95% CI -21.38 to 6.73),[135] but in another, two small RCTs suggest that it does not improve short term functional status (SMD -0.17, 95% CI -1.56 to 1.22).[145] **1++**

There was no difference between progressive relaxation and cognitive therapy on post-treatment pain intensity, disability, long term pain or long term disability over any length of follow up, although these conclusions are based on RCTs with a small number of participants.[135,145] **1++**

One systematic review identified one small RCT which found EMG biofeedback to be as effective as cognitive behavioural therapy (CBT) post-treatment and at six month follow up for pain and behavioural outcomes.[135] Another small RCT found it to be more effective than progressive relaxation for short term pain relief.[145] Adding EMG biofeedback to CBT for patients with chronic low back pain did not confer any further benefit.[146] **1++**

A systematic review which compared self regulatory treatments (SRTs), defined as biofeedback, relaxation and hypnosis, to waiting list control concluded SRTs are effective at reducing post-treatment pain intensity (effect size 0.75, $p<0.001$) and reducing depression, immediately post treatment (effect size 0.81, $p<0.05$).[147] **1++**

Respondent therapy is as effective as CBT in improving pain relief immediately post treatment, and functional status immediately post treatment and up to six month follow up. Results for depression were superior for respondent therapy immediately post-treatment, but there was no significant difference at six month follow up.[145] **1++**

C **Progressive relaxation or EMG biofeedback should be considered for the treatment of patients with chronic pain.**

6.3.2 OPERANT BEHAVIOURAL THERAPIES

Operant therapy is based on the notion that unhelpful responses can be reinforced, either by the individual's own behaviour, or through the behaviour of others. For example, the avoidance of pain through the avoidance of activity is one type of natural reinforcement. Alternatively, overly concerned family, friends or healthcare professionals may inadvertently reinforce excessive rest, with negative consequences. Operant approaches delivered on their own are uncommon in Scotland but frequently form part of multidisciplinary rehabilitation programmes that are based on cognitive behavioural principles.

Two systematic reviews of patients with chronic low back pain identified RCTs of varying size and quality.[135,145] Compared to waiting list controls, pain intensity was reduced post treatment following an operant behavioural therapy intervention (SMD -0.43, 95% CI -0.75 to -0.11, and WMD -7.00, 95% CI -12.33 to-1.67). There was no evidence of short term improvement in functional outcomes. **1++**

Evidence on the effect of operant behavioural therapy on mood is mixed. One review combined outcomes from two RCTs (described as low quality) and found no significant difference between operant therapy and **1++**

waiting list controls on depressive symptoms in the short term.[145] A second systematic review identified one study, with a low risk of bias, which found a significant reduction in negative effect immediately post-treatment that favoured the operant therapy group.[135] 1++

Both reviews suggest that combining operant therapy with exercise confers no reliable benefit over exercise therapy alone for reduction in pain intensity, depression and improved functional status.[135, 145] 1++

Evidence of moderate quality showed no significant difference in pain intensity between patients receiving operant therapy compared to those receiving cognitive therapy in the short- to medium-term. There was no significant difference between operant therapy and combined behavioural treatments for improved pain relief in the short-, medium- or long-term.[145] 1++

✓ Clinicians should be aware of the possibility that their own behaviour, and the clinical environment, can impact on reinforcement of unhelpful responses.

6.4 COGNITIVE BEHAVIOURAL THERAPY

Although many PMPs are based on cognitive behavioural principles CBT can also be delivered as a unidisciplinary intervention, facilitated by appropriately qualified staff.

A systematic review found no short term benefit of CBT compared to usual care in patients with orofacial pain, but at three month follow up there was significant improvement in pain reduction, depression, activity interference and disability.[148] 1++

Adding cognitive behavioural principles to exercises for chronic neck pain within unidisciplinary physiotherapy treatment yielded no additional benefit in terms of disability. Similarly there were no differences between groups in terms of numerical pain ratings, quality of life, patients' ratings of treatment efficacy or patients' satisfaction with the treatment.[149] 1+

In patients with CLBP CBT is effective in reducing pain intensity immediately post treatment compared to waiting list controls. There was no difference in depression or health-related quality of life.[147] 1++

Compared to waiting list controls, CBT and CBT combined with biofeedback in patients with chronic back pain both showed benefit in:[146]

- reducing pain intensity, CBT; effect size 0.47 (95% CI 0.19 to 0.7), CBT plus biofeedback; 0.67 (95% CI 0.39 to 0.95)
- reducing consumption of analgesic medicines, CBT; effect size 0.46 (95% CI 0.18 to 0.74), CBT plus biofeedback; 0.31 (95% CI 0.06 to 0.56)
- reducing pain-related disability, CBT; effect size 0.38 (95% CI 0.10 to 0.66), CBT plus biofeedback; 0.44 (95% CI 0.18 to 0.70) 1++
- improvement in health-related quality of life, CBT; effect size 0.47 (95% CI 0.19 to 0.75), CBT plus biofeedback; 0.39 (95% CI 0.13 to 0.65)
- improvement in adaptive coping strategies, CBT; effect size 0.82 (95% CI 0.51 to 1.13), CBT plus biofeedback; 0.61 (95% CI 0.34 to 0.88)
- reducing depression, CBT; effect size 0.29 (95% CI 0.02 to 0.56), CBT plus biofeedback; 0.35 (95% CI 0.09 to 0.61)
- reducing the number of doctor visits, CBT; effect size 0.33 (95% CI 0.06 to 0.60), CBT plus biofeedback; 0.38 (95% CI 0.12 to 0.64).

These results were maintained at six month follow up with the exception of depression and number of doctor visits in the CBT group and consumption of analgesic medicines in the combined therapies group.

One small study of individuals with rheumatoid arthritis compared behavioural therapy (BT) to cognitive therapy (CT) and to CBT.[150] Although this study had a small number of participants, where there were differences, these tended to favour therapies with a cognitive component. Improvements were noted in C-reactive protein immediately post treatment and tender joint count. Similar improvements were found in the CT and CBT groups at six month follow up. Anxiety was improved in the CT and BT groups, post treatment, but not in the CBT and waiting list group. 1+

Significant improvements in self rated global health were found after telephone-delivered CBT compared to usual care in patients with widespread chronic pain, at six- and nine-month follow up.[151] At six months sleep had also improved for patients receiving telephone CBT. Combining telephone CBT with exercise brought a wider range of benefits at six month follow up compared to usual care including self rated global health, fatigue, self rated physical health, and active and passive pain coping, but this combined treatment was no better than usual care when it came to sleep, self rated mental health, combination measure of pain and functioning and emotional well-being. These differences were maintained in only two measures (self rated global health and passive pain coping) at nine month follow up. **1++**

A small RCT of internet-based CBT showed improvements in the quality of life and pain catastrophising subscale on the pain coping measure at 12 weeks. Other outcomes were not significantly different to the control group.[152] **1+**

Compared to education alone, CBT appears to be more effective in improving depression and pain catastrophising, in patients with chronic pain, although this result was not statistically significant after intention-to-treat analysis.[153] **1+**

C **Cognitive behavioural therapy should be considered for the treatment of patients with chronic pain.**

6.5 MINDFULNESS MEDITATION AND ACCEPTANCE AND COMMITMENT THERAPY

Mindfulness meditation has become an increasingly popular intervention for chronic pain and other long term conditions. Through encouraging participants to pay attention in a particular way, it is thought to foster a greater willingness to accept what are sometimes aversive experiences. Mindfulness meditation is often delivered as part of a manualised educational package. The most commonly used package is mindfulness based stress reduction (MBSR). This is a structured programme that combines various meditation practices with modified yoga exercises and mind-body education.

Like mindfulness meditation, acceptance and commitment therapy (ACT) encourages participants to re-evaluate their relationship with their experiences, including learning to develop a greater distinction between themselves and their thoughts. These changes are used to help individuals to become more psychologically flexible. In essence, ACT changes the agenda away from controlling aversive experiences and instead facilitates a focus on setting values-based goals.

A systematic review of mixed study types found that less well controlled studies showed larger effects and significant improvements from the use of MBSR across outcome measures: pain (SMD 0.48, 95% CI 0.25 to 0.71), depression (SMD 0.50, 95% CI 0.12 to 0.89), anxiety, physical well-being and quality of life.[154] Results from the randomised controlled trials showed small but significant improvements in pain (SMD 0.25, 95% CI 0.01 to 0.49) and depression (SMD 0.26, 95% CI 0.05 to 0.47) and small to moderate improvements in measures of physical well-being. No significant improvements were found in anxiety or quality of life. The authors found some evidence of a publication bias when depression was used as an outcome measure which suggested that small studies that found negative results were not being published.[154] Some of the studies included may have been underpowered as sample sizes were small. Two further RCTs concluded that MBSR provided no benefit compared to controls or an educational programme.[155,156] **2++** **1++**

A review of trials of mindfulness based interventions (MBI), which included MBSR in six of the 10 trials, showed that MBI produced superior results in terms of pain control when compared with an educational control group and a control group who received massage. CBT was, however, better at reducing pain than MBI.[157] **2+**

Comparisons between patients on an ACT based programme and a CBT programme showed no significant differences in terms of pain intensity, pain interference, depression, pain-related anxiety, general activity on the Multidimensional Pain Inventory (MPI), and mental and physical related quality of life rating on the SF-12 scale. The within-groups analysis showed significant improvements in both the ACT and CBT groups following treatment in terms of pain interference, depression, and pain-related anxiety, but not in pain severity, the MPI or the SF-12 subscales compared to treatment as usual.[158] **1++**

7 Physical therapies

7.1 MANUAL THERAPY

7.1.1 LOW BACK PAIN

Manual therapy (MT) is an umbrella term that has increasingly been adopted to encompass various forms of hands-on treatment, including both manipulation and mobilisation.

Mobilisation techniques involve the therapist applying slow, passive movements to a joint; typically the patient cannot perform these movements independently but they are within the normal physiological range of motion of the joint. Manipulation is a passive technique where the therapist applies a specifically directed manual thrust to a joint, at or near the end of the physiological range of motion. This may be accompanied by an audible 'crack' or 'pop'.

Manual therapy as a treatment option in the management of pain is an intervention that is practised by a variety of healthcare professionals including physiotherapists, osteopaths and chiropractors. Philosophical differences exist both within and between the various professions regarding the possible mechanisms of action of manual therapy.

Whilst there is extensive, although generally poor quality literature, with regards to the effectiveness of various MT approaches these are usually compared to placebo. There are few head-to-head trials of different approaches.

For the purpose of the guideline studies were included if they encompassed an intervention that could be described as including a manual therapy treatment arm.

A Cochrane review found high quality evidence that spinal manipulation therapy (SMT) is as effective as other interventions, in the short term, for pain relief (SMD -4.16, 95% CI -6.97 to -1.36) and functional status (SMD -0.22, 95% CI -0.36 to -0.07) for patients with chronic low back pain.[159] It was not found to be significantly more effective than sham or inert interventions, although these studies were of poor quality.[159] **1++**

A mixture of RCTs of varying quality show that SMT has a statistically significant, short term difference on pain relief and functional status when combined with another intervention.[159] **1++**

Evidence from poor quality studies show that there is no statistically significant difference in effect on pain intensity and disability, from exercise compared to manual therapy at short and long term follow up.[135] **1++**

Massage provides short term pain relief for patients with chronic low back pain, although this conclusion is based on studies of low quality.[160] **1++**

B **Manual therapy should be considered for short term relief of pain for patients with chronic low back pain.**

7.1.2 NECK PAIN

Manual therapy combined with exercise demonstrated long term improvements in pain (pooled SMD -0.87, 95% CI -1.69 to -0.06), function/disability, and global perceived effect compared to no treatment in patients with neck pain, although this conclusion is based on low quality studies.[161] The same systematic review identified better quality evidence which demonstrated that manual therapy and exercise provides greater short term relief compared with exercise alone (pooled SMD -0.50, 95% CI -0.76 to -0.24). There were no long term differences across multiple outcomes.[161] Combined therapy resulted in greater pain reduction and improved quality of life compared to manual therapy alone (pooled SMD -0.31, 95% CI -0.61 to -0.02); heterogeneity: p=0.04, I^2=0%).[161] **1++**

Manual therapy may provide short term relief compared with control (pooled SMD -0.90, 95% CI -1.78 to -0.02).[162] Nine or 12 sessions were superior to three for reduction in pain, disability and cervicogenic headache. These results are based on low quality studies.[162] **1++**

Low quality evidence supported a single session of thoracic manipulation for immediate pain reduction compared to placebo for patients with chronic neck pain (NNT 5, 29% treatment advantage).[162] 1++

B **Manual therapy, in combination with exercise, should be considered for the treatment of patients with chronic neck pain.**

7.2 EXERCISE

Evidence identified on exercise as a treatment intervention for patients with chronic pain revealed heterogeneous studies, and a relatively small number of good quality systematic reviews. A lack of clear definition of the exact format of exercise interventions made direct comparison difficult. Recommendations can be made relating to exercise approaches and the format of delivery.

7.2.1 EXERCISE APPROACH

Aerobic and strength conditioning exercises

In patients with fibromyalgia aerobic-only exercise training at the recommended intensity levels had positive effects on global well-being (SMD 0.49, 95% CI 0.23 to 0.75) and physical function (SMD 0.66, 95% CI 0.41 to 0.92) and possibly on pain (SMD 0.65, 95% CI -0.09 to 1.39) and tender points (SMD 0.23, 95% CI -0.18 to 0.65). Supervised aerobic exercise training was also found to have some benefits on fibromyalgia symptoms.[163] 1++

Movement facilitation and stabilisation exercises

Unloaded movement facilitation exercise compared to no exercise is effective for improving pain and function in patients with non-specific chronic low back pain. Compared to other types of exercise, including effort-intensive trunk strengthening and time-intensive specific stabilisation, the effects are comparable. For many people with non-specific chronic low back pain, unloaded exercise is as helpful as quite vigorous exercise against resistance.[164] 1++

High quality trials support the use of stabilisation exercises in patients with chronic back pain. Overall the evidence was conflicting and significant differences favouring stabilisation exercises were less likely when they were compared with active treatment control groups rather than inactive control groups.[165] 1++

Walking

A systematic review identified moderate evidence that walking alone does not have a positive effect in the management of patients with low back pain compared with individual based exercise. Additionally there was poor quality evidence for treadmill walking as an effective management strategy.[166] 2+

T'ai Chi, pilates and yoga

Pooled data from poor quality studies showed T'ai Chi has a small positive effect for reducing pain and improving disability in people with chronic arthritis. Duration of these effects was not reported.[167] 1++

Pilates was superior to minimal intervention for reduction of pain in individuals with persistent non-specific low back pain, but no more effective than other forms of exercise to reduce pain. In this instance the pilates component of the exercises that were used was not defined.[168] 1++

Yoga can be a useful supplementary approach to treatment with moderate effect sizes on pain and associated disability. The yoga interventions used in and between trials included in the meta-analysis were not defined.[169] 1+

Therapeutic Aquatic Exercise

Therapeutic aquatic exercise may be beneficial for patients with chronic low back pain.[170] 1+

Exercise therapy

A systematic review on the effectiveness of physical and rehabilitation interventions for patients with chronic non-specific low back pain of more than 12 weeks duration comparing exercise therapy with usual care and advice to stay active showed a significant decrease in pain intensity and disability in favour of the exercise therapy.[135] 1++

Statistical pooling of three studies showed a significant decrease in pain intensity and disability in favour of the exercise group (WMD -9.23, 95% CI -16.02 to -2.43 and -12.35, 95% CI -23.00 to -1.69, respectively). One study found a statistically significant difference at intermediate (five-month) follow up in pain relief for the exercise group compared to the usual care group. Three studies reported on pain and/or disability at long term follow up. The pooled WMD for pain was not statistically significant (-4.94, 95% CI -10.45 to 0.58); the WMD for disability was statistically significant in favour of the exercise group (WMD -3.17, 95% CI -5.96 to -0.38).[135] **1++**

No difference in pain reduction and disability was found in short term results of poor quality studies comparing exercise therapy with waiting list controls, but there was some evidence that it improved pain intensity and disability compared to usual care.[135] **1++**

7.2.2 ADVICE

The addition of interventions based on CBT to physiotherapy programmes may be effective for people with whiplash-associated disorder.[171] **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/or functional activities.[50] **1++**

7.2.3 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.[171] **1++**

Performance accuracy is improved by refresher sessions or by providing audiotapes or videotapes of exercises.[171] **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.[172] **2+**

7.2.4 HETEROGENEITY OF EXERCISE

One study identified on the effect of exercise on pain and disability in patients with CLBP aimed to explain between-trial heterogeneity.[173] When all types of exercise were analysed, small but significant reductions in pain and disability were observed compared with minimal care or no treatment. Despite many possible sources of heterogeneity in exercise trials, only the dosage (intensity, duration, amount) was significantly associated with effect sizes. **1++**

7.2.5 EXERCISE ADHERENCE

A Cochrane review considering adherence to exercise in patients with chronic musculoskeletal conditions identified moderate quality evidence that:[171] **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/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.

B **Exercise and exercise therapies, regardless of their form, are recommended in the management of patients with chronic pain.**

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

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

B • **supervised exercise sessions**

B • **individualised exercises in group settings**

C • **addition of supplementary material**

B • **provision of a combined group and home exercise programme.**

7.3 TRACTION

There is strong evidence that there is no statistically significant difference in outcome between traction as a single treatment against placebo, sham or no treatment for patients with acute, subacute or chronic low back pain with and without sciatica. The addition of continuous traction to standard physiotherapy practice did not affect outcomes either.[174] **1++**

Conflicting evidence was found when comparing autotraction with placebo, sham or no treatment; other forms of traction with other forms of treatment and different forms of traction compared to each other.[174] **1++**

7.4 ELECTROTHERAPY

Active transcutaneous electrical nerve stimulation (TENS) treatments have shown a positive analgesic outcome in patients with chronic pain. Little difference was found between high and low frequencies.[175] **1++**

There is conflicting evidence about whether the use of TENS for chronic low back pain is beneficial in reducing pain intensity, but consistent evidence from two studies showed that it did not improve functional status.[176,177] **1+** **1++**

There is low quality evidence that pulsed electromagnetic field therapy, repetitive magnetic stimulation and transcutaneous electrical nerve stimulation are more effective than placebo in reducing neck pain.[178] **1++**

The use of TENS in patients with peripheral diabetic neuropathy reduces pain intensity.[176] **1+**

Studies of low level laser therapy (LLLT) have shown statistically significant but clinically unimportant pain relief compared to sham therapy for patients with sub-acute and chronic low back pain at short term and intermediate term follow up (up to six months).[179] In one study LLLT was more effective than sham at reducing disability in the short term. LLLT or the addition of LLLT to exercise was not better than exercise alone, with or without sham in reducing pain or disability in the short term.[179] **1++**

The relapse rate in the LLLT group was significantly lower than in the control group at the six-month follow up. No side effects were reported.[179] **1++**

B **Transcutaneous electrical nerve stimulation should be considered for the relief of chronic pain. Either low or high frequency TENS can be used.**

B **Low level laser therapy should be considered as a treatment option for patients with chronic low back pain.**

8 Complementary therapies

8.1 ACUPUNCTURE

Systematic reviews have identified RCTs of varying quality which show a small clinically relevant benefit from acupuncture for short term pain relief for patients with chronic knee pain, compared to sham and chronic low back pain versus waiting list control or when added to another intervention.[180,181] At six to twelve months follow up patients with knee pain were still reporting significant improvements in pain reduction, while results were inconsistent for those with back pain. **1++** **1+**

Meta-analysis of acupuncture versus no acupuncture studies (with various end points) showed overall benefit of acupuncture for pain relief and functional status in patients with back and neck pain (SD 0.55, 95% CI 0.51 to 0.58) and osteoarthritis (SD 0.57, 95% CI 0.50 to 0.64).[182] **1++**

For patients with osteoarthritis pain, acupuncture showed improvement in pain relief compared to sham at short term (SMD -0.28, 95% CI -0.45 to -0.11), and at six month follow up (SMD -0.10, 95% CI -0.21 to 0.01). Compared to waiting list controls acupuncture demonstrated a clinically significant improvement in short term pain relief (SMD -0.96, 95% CI -1.19 to -0.72).[183] An additional RCT of patients with osteoarthritis of the knee or hip reported a significant difference at three months between acupuncture and routine care, (SF-36 bodily pain scores SD 50.7 ±23.5 compared to SD 36.3 ±18.3).[184] **1++** **1+**

Many studies used sham acupuncture, which may have a physiological effect, as a control which may result in smaller effect sizes.[183] **1++**

A systematic review of acupuncture for patients with chronic non-bacterial prostatitis/chronic pelvic pain syndrome identified nine RCTs which suggested that acupuncture is effective as part of a multi-interventional approach. The findings are based on poor quality trials.[185] **1++**

Meta-analysis of five studies showed auricular acupuncture can be an effective treatment for various types of pain or as an adjunct to other therapies (compared to sham, placebo or usual care, overall change in pain score SMD 1.84, 95% CI 0.60 to 3.07).[186] **1++**

No benefit was found for patients with rheumatoid arthritis, and there was insufficient evidence to support the use of acupuncture in patients with fibromyalgia.[187] **1++**

Acupuncture delivered by qualified practitioners is not associated with serious adverse events.[182, 183, 187] **1+** **1++**

A **Acupuncture should be considered for short term relief of pain in patients with chronic low back pain or osteoarthritis.**

8.2 HERBAL MEDICINE

A systematic review of the use of herbal medicines in patients with chronic low back pain found few studies and those identified were small and of low quality. Two small RCTs found willow bark (salic alba) to have significant short term effects on pain relief but not recovery.[181] In patients with osteoarthritis it was not found to be more effective than placebo in one trial, while in another, 14% of patients reported reduction in pain compared to 2% on placebo.[188] **1++**

Limited evidence has shown the following interventions to be effective for patients with osteoarthritis.[188]

- Four small RCTs reported improvement in pain with Indian frankincense.
- Ginger was reported as being more effective than placebo, but not as effective as ibuprofen in three RCTs of short term and up to six months duration.
- Three studies found devil's claw to improve osteoarthritis related symptoms to similar levels to conventional therapies. There is a risk of side effects and interaction with anticoagulants, NSAIDs, cardiovascular and gastric acid drugs.

1+

Two studies showed no benefit in the use of harpagophytum over placebo.[181] **1++**

No good quality studies were identified in a Cochrane review of Chinese herbal medicine for patients with chronic neck pain.[189] | 1++

8.3 OTHER THERAPIES

A Cochrane review of music therapy for all types of pain identified three studies of adults with chronic pain. The trials were small, of poor quality and reported inconsistent results.[190] | 1++

Two RCTs of aromatherapy in patients with fibromyalgia showed no difference in efficacy between the treatment and control groups.[187] | 1++

Results from trials of homeopathy in patients with rheumatoid arthritis, osteoarthritis and fibromyalgia were inconsistent.[187] | 1++

One RCT of patients with low back pain found no significant difference between those who received reflexology and those who received group based relaxation or usual care.[187] | 1++

No good quality studies were identified to evaluate the efficacy of hypnotherapy or reiki.

9 Dietary therapies

Few good quality RCTs are available on diet supplementation to treat patients with chronic pain symptoms.[191] | **4**

A Cochrane review looking at the impact of various types of diet, such as vegetarian, Mediterranean, and elimination diets, on pain and functional status in patients with rheumatoid arthritis concluded that the studies identified were too small and not of sufficient quality to determine efficacy.[192] | **1++**

A Cochrane review of vitamin D supplementation for patients with chronic pain identified four studies. Only one of the studies reported a benefit in terms of reduction in analgesics used, but was considered to be methodologically poor.[193] | **1++**

Dietary interventions were most effective when combined with deep breathing techniques and acupuncture. The naturopathic approach was linked to improved quality of life, reduced body mass index and reduced back pain (-6.89, 95% CI -9.23 to -3.54, p <0.0001) when compared to physiotherapy.[194] | **1+**

Omega-3 fatty acid taken as a fish oil is effective in reducing joint pain.[188] | **1+**

Green lipped mussel extract was no better than placebo in patients with rheumatoid arthritis.[188] | **1+**

Limited evidence has shown the following interventions to be effective for patients with osteoarthritis:[188] | **1+**

- S-adenosylmethionine (SAMe). A systematic review and two RCTs reported that SAMe (400 mg, 600 mg or 1,200 mg per day) had similar effects on pain reduction and functional ability as treatment with NSAIDs for up to 12 weeks duration (effect size for pain 0.12; 95% CI, -0.029 to 0.273).
- Bioflavinoids (pine bark extracts). One RCT (n=156) reported a reduction in pain in 56% of the treatment group compared to 10% in the placebo group.
- Rosehip. A systematic review found trials reporting that 5 g of rosehip showed a reduction in pain and in painkiller use compared to placebo.

10 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 production of locally produced information materials.

10.1 SOURCES OF FURTHER INFORMATION

British Complementary Medicine Association
P.O. Box 5122, Bournemouth, BH8 0WG
Tel: 0845 345 5977
www.bcma.co.uk

A professional umbrella organisation which provides a 'find a therapist' service.

British Pain Society
Third Floor, Churchill House, 35 Red Lion Square, London WC1R 4SG
Tel: 020 7269 7840
www.britishpainsociety.org • Email: info@britishpainsociety.org

A multidisciplinary professional organisation which aims to promote education, training, research and development in all fields of pain. It endeavours to increase both professional and public awareness of the prevalence of pain and the facilities that are available for its management. Provides pathways for patient care. The website includes a list of UK based organisations that specialise in helping patients with specific underlying conditions that cause chronic pain.

Chronic Pain Policy Coalition
Policy Connect, CAN Mezzanine, 32-36 Loman Street, Southwark, London, SE1 0EH
Tel: 020 7202 8580
www.policyconnect.org.uk/cppc • E-mail: rachel.downing@policyconnect.org.uk

A forum to unite patients, professionals and parliamentarians in a mission to develop an improved strategy for the prevention, treatment and management of chronic pain and its associated conditions.

Health and Social Care Alliance Scotland
Venlaw Building, 349 Bath Street, Glasgow, G2 4AA
Tel: 0141 404 0231 • Fax: 0141 246 0348
www.alliance-scotland.org.uk • E-mail: info@alliance-scotland.org.uk

The national third sector health and social care intermediary. It brings together over 270 organisations to ensure the voice of people and unpaid carers, and the expertise of the third sector, are influential in shaping policy and practice.

Healthtalkonline Database
www.healthtalkonline.org

An online database of patient's experiences and information on around 50 health conditions.

National Chronic Pain Website for Scotland
www.chronicpainscotland.org

A website which provides information, advice, education and resources for people with pain, for families and carers as well as for healthcare professionals and Service Improvement Groups. It provides details of specialist pain management services in Scottish NHS Boards and voluntary organisations.

NHS Inform
www.nhsinform.co.uk

The national health information service.

Pain Association Scotland
Suite D, Moncrieffe Business Centre, Friarton Road, Perth, PH2 8DG
Tel: 0800 783 6059
www.painassociation.com • Email: info@painassociation.com

An organisation which develops and delivers self management training for people with chronic pain, addressing the non-medical issues, particularly the disabling effects of chronic pain which impact on people's lives. The focus is to introduce people to, and quickly build self-management skills, thereby creating practical, positive change leading to an improved quality of life and well-being.

Pain Concern
Unit 1-3, 62-66 Newcraighall Road, Fort Kinnaird, Edinburgh, EH15 3HS
Tel: 0131 669 5951 • Helpline: 0300 123 0789
www.painconcern.org.uk • Email: info@painconcern.org.uk
Facebook facebook.com/painconcern • Twitter @PainConcern

Pain Concern provides information and support to people with pain and their carers and aims to raise awareness about pain and improve the provision of pain management services. Their Airing Pain radio show is a series of audio podcasts featuring the experiences of those managing their everyday pain and interviews with top, internationally recognised experts. Their magazine Pain Matters contains news, features and comment on topics including self-management techniques, research into pain treatments and personal experiences of living with pain. They run a helpline and an online community on HealthUnlocked which provides members with a forum to share experiences.

Pain Support
www.painsupport.co.uk

Pain Support provides pain relief techniques for those with chronic pain. There is also a regular email newsletter, a discussion forum and a contact club for making new friends, plus a shop for books, relaxation CDs and downloads.

Pain UK
www.painuk.org

Pain UK aims to bring together pain charities in the UK to speak up about the common needs of the people they represent. It aims to provide training and support to member charities, signpost support for people living with pain and raise awareness for new forms of support, when needed.

10.1.1 SELF MANAGEMENT TOOLS

Arthritis Care
www.arthritiscare.org.uk/LivingwithArthritis/Self-management

Centers for Disease Control and Prevention
www.cdc.gov/arthritis/interventions/self_manage.htm

Chronic Disease Self-Management Program (CDSMP)
http://patienteducation.stanford.edu

Expert Patient Programme
www.nhs.uk/NHSEngland/AboutNHSservices/doctors/Pages/expert-patients-programme.aspx

Pain Association Scotland
www.painassociation.com

Pain Tool Kit
www.paintoolkit.org

10.2 CHECKLIST FOR PROVISION OF INFORMATION

This section gives examples of the information patients/carers may find helpful at the key stages of the patient journey. The checklist was designed by members of the guideline development group based on their experience and their understanding of the evidence base. The checklist is neither exhaustive nor exclusive. Patient pathways can be found in Annexes 2 to 4.

Assessment
• Explain the mechanism of pain and the benefits of a holistic approach to managing the pain. • Encourage the patient to return within an agreed timescale if the initial planned treatment/s are not having the desired effect, and explain that there are other treatments that may be more effective. • Provide information on self management and where to access resources suitable to the individual. • Give advice on exercise and encouragement to stay active.
Pharmacological management
• Give advice on the treatment being given, the reasoning behind the treatment, the potential side effects and periodically review the medicines prescribed.
Psychological therapies
• Ensure the patient is aware that pain management programmes are a group based treatment to improve quality of life.
Complementary therapies
• Advise patients seeking therapies outwith the NHS to ensure the practitioner is a member of the appropriate professional regulatory body. • Advise patients to inform their GP/healthcare professional of any complementary therapies or supplements they may be taking.

11 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.

11.1 IMPLEMENTATION STRATEGY

Implementation of national clinical guidelines is the responsibility of each NHS Board 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.

Implementation of this guideline will be encouraged by SIGN and actively supported by the Chronic Pain Service Improvement Groups. The Scottish Government is supporting NHS boards to establish local Service Improvement Groups in a two year development programme that aims to implement the Scottish service model for chronic pain across Scotland (*see Annex 5*).

11.2 RESOURCE IMPLICATIONS OF KEY RECOMMENDATIONS

No recommendations were identified as having significant budgetary impact.

11.3 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 number of patients presenting with chronic pain
- the number of patients using analgesics to manage chronic pain who receive an annual review
- the number of patients on strong opioids and gabapentinoids who receive an annual review of their medications
- the number of patients on >180 mg/day morphine or equivalent referred for specialist assessment
- the number of patients referred for self management.

A core national dataset for audit for chronic pain services in Scotland is also available at www.chronicpainscotland.org.

11.4 ADDITIONAL ADVICE TO NHSSCOTLAND FROM HEALTHCARE IMPROVEMENT SCOTLAND AND THE SCOTTISH MEDICINES CONSORTIUM

- Capsaicin cutaneous patch is accepted for restricted use by the Scottish Medicines Consortium for the treatment of adults with post herpetic neuralgia who have not achieved adequate pain relief from, or who have not tolerated, conventional first and second line treatments. Treatment should be under the supervision of a specialist in pain management (February 2011).
- Lidocaine 5% medicated plaster is accepted for restricted use within NHSScotland for the treatment of patients with 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 postherpetic neuralgia or where these therapies have been ineffective (August 2008).
- Pregabalin is accepted for restricted use within NHSScotland for the treatment of peripheral neuropathic pain in adults who have not achieved adequate pain relief from, or have not tolerated, conventional first and second line treatments for peripheral neuropathic pain. Treatment should be stopped if the patient has not shown sufficient benefit within eight weeks of reaching the maximally tolerated therapeutic dose (May 2009). Pregabalin oral solution should be prescribed only for patients who find it difficult to, or are unable, to swallow tablets (June 2012).
- Duloxetine 30 mg and 60 mg is accepted for restricted use for the treatment of diabetic peripheral neuropathic pain in adults (September 2006). Duloxetine is restricted to initiation by prescribers experienced in the management of diabetic peripheral neuropathic pain as second or third line therapy.

12 The evidence base

12.1 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 SIGN Evidence and Information Scientist. Databases searched include Medline, Embase, Cinahl, PsycINFO and the Cochrane Library. The year range covered was 2007-2012. Internet searches were carried out on various websites including the US National Guidelines Clearinghouse. The main searches were supplemented by material identified by individual members of the development group. Each of the selected papers was evaluated by two members of the group using standard SIGN methodological checklists before conclusions were considered as evidence.

12.1.1 LITERATURE SEARCH FOR PATIENT ISSUES

At the start of the guideline development process, a SIGN Evidence and Information Scientist conducted a literature search for qualitative and quantitative studies that addressed patient issues of relevance to management of patients with chronic pain. Databases searched include Medline, Embase, Cinahl and PsycINFO, and the results were summarised and presented to the guideline development group.

12.2 RECOMMENDATIONS FOR RESEARCH

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:

- Studies to examine the effect on treatment outcomes of assessing the type, severity and impact of chronic pain using current validated instruments in primary care.
- Studies to help identify, at the time of diagnosis, which patients are likely to have poorer outcomes and whether referring them at an early stage improves outcomes and reduces harms.
- Investigation of the efficacy of simple approaches to enhancing professional-patient interactions in consultations in non-specialist settings to improve long term health outcomes in patients with chronic pain.
- RCTs on the efficacy of paracetamol in patients with chronic low back pain.
- A study into patterns of opioid prescribing and factors indicating good practice to consider how opioid prescribing can be optimised.
- RCTs on the long term effects of opioid use to measure efficacy and adverse events, including effects on endocrine and immune function.
- Studies into factors that contribute to the inter-individual variation in response to different treatments (clinical, genetic, pharmacokinetic, neurobiological) and clinical biomarkers for predicting response to treatments.
- RCT on the efficacy of opioid rotation.
- Studies on the development of predictive tools for risk of misuse of opioids.
- Studies on whether the patient's age has an impact on the use of opioids.
- Investigation of strategies for combining drug therapies for optimal efficacy, safety and cost effectiveness.
- RCTs on the efficacy of pain neurophysiology education.
- RCTs on the efficacy of acceptance and commitment therapy.
- Large RCTs on the use of acupuncture compared to standard care or other therapies in reducing pain and improving quality of life. Researchers should ensure that the acupuncture is carried out by practitioners who have received professional training. Sham acupuncture is not a suitable comparator.
- Economic modelling into the cost effectiveness of an acupuncture service.
- Studies into the use of music in combination with other non-pharmacological therapies in patients with chronic pain to determine the outcomes of reduction in pain intensity, reduction in use of pharmacological therapies, and cost effectiveness.
- RCTs into the use of hypnosis for pain relief.

- Studies into the use of herbal medicines, such as harposogide, for pain relief.
- Investigation into which specific dietary interventions may be beneficial to both specific (eg diabetic neuropathic pain) and chronic pain conditions in general.
- Studies into the effect of vitamins A, B6, C, E, omega-3 fatty acids, salts (Ca, Mg, Se, Zn, Fe) and lactic ferments) in pain relief.

12.3 REVIEW AND UPDATING

This guideline was published in 2013 and will be considered for review in three years. Any updates to the guideline in the interim period will be noted on the SIGN website: **www.sign.ac.uk**

13 Development of the guideline

13.1 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**

13.2 THE GUIDELINE DEVELOPMENT GROUP

Dr Lesley Colvin *(Chair)*	*Consultant in Pain Medicine, Western General Hospital, Edinburgh*
Dr Rachel Atherton	*Clinical Psychologist, Chronic Pain Management Service, NHS Highland*
Dr Jonathan Bannister	*Consultant in Anaesthesia and Pain Medicine, Ninewells Hospital, Dundee*
Ms Janette Barrie	*Nurse Consultant for Long Term Conditions, NHS Lanarkshire*
Dr Heather Cameron	*Physiotherapy Professional Lead, Western Infirmary, Glasgow*
Mr Paul Cameron	*Clinical Lead Pain Specialist Physiotherapist, NHS Fife Integrated Pain Management Service*
Dr Alan Carson	*Consultant Neuropsychiatrist, Royal Edinburgh Hospital*
Dr Martin Dunbar	*Consultant Clinical Psychologist, The Pain Management Team, Glasgow*
Dr Steve Gilbert	*Consultant in Anaesthesia and Pain Medicine, Queen Margaret Hospital, Dunfermline*
Dr John Hardman	*General Practitioner, Dalhousie Medical Practice, Bonnyrigg*
Ms Melanie Hutchison	*Advanced Occupational Therapist, NHS Fife Integrated Pain Management Service*
Mr Malcolm Joss	*Specialist Occupational Therapist, Occupational Health and Safety Advisory Services, Rosyth*
Professor Arduino Mangoni	*Professor of Clincial Pharmacology, Flinders University, Australia*
Mr Peter McCarron	*Patient representative, Kelty*
Mr Ronald Parsons	*Patient representative, Leven*
Miss Deborah Paton	*Lead Pharmacist, Pain Management, Lynebank Hospital, Dunfermline*
Ms Kathleen Powderly	*Member of the British Acupuncture Council and Member of the Register of Chinese Herbal Medicine, Aberdeen*
Professor Stuart Ralston	*Professor of Rheumatology, Western General Hospital, Edinburgh*
Dr Mick Serpell	*Consultant in Pain Medicine, Gartnavel General Hospital, Glasgow*
Professor Blair H Smith	*Professor of Population Science, University of Dundee*
Mrs Lynne Smith	*Evidence and Information Scientist, SIGN*
Ms Ailsa Stein	*Programme Manager, SIGN*
Dr John Wilson	*Consultant in Anaesthesia and Pain Medicine, Royal Infirmary of Edinburgh*

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 which are available in the Supporting Material section at **www.sign.ac.uk.**

Guideline development and literature review expertise, support and facilitation were provided by the SIGN Executive. All members of the SIGN Executive make yearly declarations of interest and further details of these are available on request.

Mrs Lesley Forsyth	*Events Coordinator*
Mrs Karen Graham	*Patient Involvement Officer*
Miss Gemma Hardie	*Distribution and Office Coordinator*
Mr Stuart Neville	*Publications Designer*
Miss Gaynor Rattray	*Guideline Coordinator*

13.2.1 ACKNOWLEDGEMENTS

SIGN is grateful to the following people who have contributed to the development of the guideline.

Mr Mark Bovey	*Coordinator, Acupuncture Research Resource Centre, British Acupuncture Council, London*
Professor Andrew Moore	*Deputy Editor, Cochrane Pain, Palliative and Supportive Care Group, Oxford*

13.3 CONSULTATION AND PEER REVIEW

13.3.1 NATIONAL OPEN MEETING

A national open meeting is the main consultative phase of SIGN guideline development, at which the guideline development group presents its draft recommendations for the first time. The national open meeting for this guideline was held on 12 December 2012 and was attended by 226 representatives of all the key specialties relevant to the guideline. The draft guideline was also available on the SIGN website for a limited period at this stage to allow those unable to attend the meeting to contribute to the development of the guideline.

13.3.2 SPECIALIST REVIEWERS INVITED TO COMMENT ON THIS DRAFT

This guideline was also 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. All expert referees made declarations of interest and further details of these are available on request from the SIGN Executive.

SIGN is very grateful to all of these experts for their contribution to the guideline.

	The Association of British Neurologists, London
Dr David Carroll	*Associate Specialist in Palliative Care and GP Locum, Aberdeen*
Mr David Falconer	*Director, Pain Association Scotland, Perth*
Dr Jonathan Hill	*Research Physiotherapist, Keele University*
Mr Simon Land	*Royal College of Physicians, London*
Mrs Kirsty MacFarlane	*Prinicipal Pharmacist, Scottish Medicines Consortium, Glasgow*
Dr Hugh MacPherson	*Senior Research Fellow in Health Sciences, University of York*
Professor Chris Main	*Professor of Clinical Psychology (Pain Management), Keele University*
Ms Cecilia McQuade	*Patient representative, Glasgow*
Dr Barry Miller	*Consultant in Pain Medicine, Royal Bolton Hospital*
Professor Steve Morley	*Professor of Clinical Psychology, University of Leeds*
Mr Paulos Quadros	*Chief Executive, Intlifepain, Strathaven*
Ms Judith Rafferty	*Lead Advanced Nurse Specialist Pain Management, Ninewells Hospital, Dundee*

Mr Ian Semmons	*Chairman, Action on Pain, Norfolk*
Mrs Heather Wallace	*Chairman, Pain Concern, Haddington*
Dr David Watson	*General Practitioner, Hamilton Medical Group, Aberdeen*
Dr Mike Winter	*Medical Director, National Services Division, NHSScotland*

13.3.3 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 the SIGN Editorial group make yearly declarations of interest and further details of these are available on request from the SIGN Executive.

Dr Jenny Bennison	*Royal College of General Practitioners*
Professor Keith Brown	*Chair of SIGN; Co-Editor*
Dr Roberta James	*SIGN Programme Lead; Co-Editor*
Dr Rajan Madhok	*Royal College of Physicians and Surgeons of Glasgow*
Ms Fiona McMillan	*Royal Pharmaceutical Society*
Professor Mark Strachan	*Royal College of Physicians of Edinburgh*
Dr Sara Twaddle	*Director of SIGN; Co-Editor*

Abbreviations

ACT	acceptance and commitment therapy
BNF	British National Formulary
BPI	Brief Pain Inventory
BT	behavioural therapy
CBT	cognitive behavioural therapy
CI	confidence interval
CLBP	chronic low back pain
COMM	Current Opioid Misuse Measure
COX	cyclo-oxygenase
CT	cognitive therapy
CYPD	cytochrome P450 2D6
EMG	electromyographic
GI	gastrointestinal
GMC	General Medical Council
GP	general practitioner
GRIPS	Getting Relevant Information on Pain Services in Scotland
GTN	glyceryl trinitrate
HIV	human immunodeficiency virus
HRQOL	health-related quality of life
IMMPACT	Initiative on Methods, Measurement and Pain Assessment in Clinical Trials
LLLT	low level laser therapy
LOCF	last-observation-carried-forward
LSMD	least squared mean difference
MA	marketing authorisation
MBI	mindfulness based interventions
MBSR	mindfulness based stress reduction
MOR	mu opioid receptor
MPI	Multidimensional Pain Inventory
MT	manual therapy
MTA	multiple technology appraisal
NICE	National Institute for Health and Care Excellence
NLR	negative likelihood ratio
NNT	number needed to treat
NSAID	non-steroidal anti-inflammatory drug
OA	osteoarthritis
OR	odds ratio

ORT	Opioid Risk Tool
PGIC	Patient's Global Impression of Change
PHN	postherpetic neuralgia
PLR	positive likelihood ratio
PMP	pain management programme
PNE	pain neurophysiology education
QoL	quality of life
RCT	randomised controlled trial
RMDQ	Roland Morris Disability Questionnaire
RR	relative risk
SAMe	S-adenosylmethionine
SD	standard deviation
SF-36	short-form with 36 questions
SIGN	Scottish Intercollegiate Guidelines Network
SMC	Scottish Medicines Consortium
SMD	standardised mean difference
SMT	spinal manipulation therapy
SNRI	serotonin norepinephrine re-uptake inhibitor
SOAPP	Screener and Opioid Assessment for Patients with Pain
SPC	summary of product characteristics
SRT	self regulatory treatment
SSRI	selective serotonin re-uptake inhibitor
TCA	tricyclic antidepressant
TENS	transcutaneous electrical nerve stimulation
VAS	visual analogue scale
WMD	weighted mean difference

Annex 1

Key questions

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.

Key question	See guideline section
1. In patients with chronic non-malignant pain presenting in a non-specialist setting, does the use of assessment tools lead to improvement in any of the core outcomes of treatment compared with not using assessment tools? Outcomes: pain scores (30% reduction and 50% reduction), functional ability, quality of life (mood, sleep), adverse events	3.1
2. In patients with chronic non-malignant pain being managed by any intervention is there any evidence that timing of that intervention impacts on pain scores (30% reduction and 50% reduction), functional ability, quality of life (mood, sleep), adverse events?	3.2
3. In patients with chronic non-malignant pain is there any evidence to show that a managed care approach can improve pain scores (30% reduction and 50% reduction), functional ability, quality of life (mood, sleep), adverse events? Consider: managed care (ie coding chronic pain, call and recall systems, structured protocol-driven care delivered by nurses or clinicians with a special interest, with active management and regular reviews of pharmacological treatments, considering when to refer)	3.3
4. In patients with chronic non-malignant pain is there any evidence that the nature of interaction with healthcare professionals affects pain scores (30% reduction and 50% reduction), functional ability, quality of life (mood, sleep), adverse events? Consider: communication, empathy, relationship	3.4
5. In patients with chronic non-malignant pain are opioids effective compared with placebo or other interventions in pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events/drug reactions, dependency (physiological or psychological)? Interventions: morphine, oxycodone, hydromorphone, buprenorphine, fentanyl, methadone, meptazinol, tapentadol, targinact, codeine, dihydrocodeine, tramadol, cocodamol and codydramol Exclude: parenteral and neuraxial administration	5.3, 5.6
6. Are there benefits and harms associated with high dose opioid versus low dose opioid use in patients with chronic non-malignant pain? Consider: efficacy, pain potentiation, addiction, adverse drug reactions	5.3
7. In patients with chronic non-malignant pain what are the most effective 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, dependency (physiological or psychological)? Interventions: a. NSAIDs, COX inhibitors, COX-2s b. paracetamol c. nefopam	5.2

8. In patients with chronic non-malignant pain what is the effectiveness of anti-epilepsy drugs compared with placebo or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse drug reactions, dependency (physiological or psychological)? Interventions: a. gabapentin b. pregabalin c. sodium valproate d. carbamazepine/ oxcarbazepine e. topiramate f. lamotrigine g. lacosamide h. levetiracetam	5.4, 5.6
9. In patients 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, dependency (physiological or psychological)? Interventions: a. lidocaine patch b. capsaicin cream c. capsaicin patch d. topical non-steroidals	5.2
10. In patients 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, dependency (physiological or psychological)? Interventions: a. tricyclic antidepressants (amitriptyline, nortriptyliine, clomipramine, imipramine) b. SSRIs(fluoxetine, citalopram) c. SNRIs (duloxetine, mirtazapine, venlafaxine)	5.5
11. In patients with chronic non-malignant pain what is the effectiveness of combination pharmacological compared to single pharmacological therapies on pain scores (pain 30% reduction and 50% reduction), functional ability, quality of life, adverse events/drug reactions, dependency (physiological or psychological)?	5.6
12. In patients with chronic non-malignant pain what is the effectiveness of physical therapies compared with no physical therapy or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events? Interventions: manual therapy, exercise, massage, traction, electrotherapy	7

13. In patients with chronic non-malignant pain what is the effectiveness of complementary and alternative therapies compared with no treatment or other interventions on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events? Interventions: a. aromatherapy b. music therapy c. acupuncture d. reflexology e. reiki f. hypnotherapy g. homeopathy h. herbal medicine	8
14. In patients with chronic non-malignant pain what is the effectiveness of expert/clinician guided self help management advice/ programmes/ psychological treatments compared with no treatment or other interventions on pain scores, functional ability, mood, QoL and adverse events. Interventions: a. multidisciplinary pain management programmes basedon biopsychosocial principles b. unidisciplinary education (excluding exercise) c. first wave psychological treatments: behavioural therapies (i) respondent behavioural therapies (1) biofeedback (2) relaxation (ii) operant behavioural therapies d. second wave psychological treatments: cognitive behavioural therapy e. third wave psychological treatments: acceptance and commitment therapy and mindfulness based interventions Consider: unidisciplinary versus multidisciplinary programmes, mode of delivery, as above; intensity; who delivers intervention	6
15. 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, adverse events? Interventions: a. bibliotherapy b. computer-guided self help c. structured or guided self help d. self help groups versus one-to-one interventions e. shorter, structured, educational classes Consider: intensity of programmes, mode of delivery (ie is telephone/video contact as effective as face-to-face)	4

16. In patients with chronic non-malignant pain is there any evidence for the effectiveness of dietary interventions compared with usual care on pain scores (30% reduction and 50% reduction), functional ability, quality of life, adverse events? Interventions: a. vitamins (B, C, D) b. omega-3 c. antioxidants d. glucosamine e. chondroitin f. dietary/nutritional supplements or replacements	9
17. In patients with chronic non-malignant pain what is the effectiveness of occupational based interventions on pain scores (30% reduction and 50% reduction), functional performance, physical capacity, engagement in personally meaningful occupations, return to work rates, quality of life, adverse events? Interventions: a. analysis of activity/occupational performance b. purposeful activity as a treatment modality c. pacing education d. energy conservation advice e. establishment of daily routines to improve health and well-being f. environmental assessment g. adaptations/equipment provision h. work/vocational assessments Consider: Increased independence in activities of daily living, rehabilitative approaches, participation in occupation, compensatory techniques, occupational performance (self care/work/leisure), return to employment/vocational rehabilitation	No evidence identified

Annex 2

Pathway for chronic pain assessment, early management and care planning in non-specialist settings

This pathway is drawn from evidence identified in the guideline, information extrapolated in the research for the guideline and the clinical experience and consensus of the guideline development group. More detailed pathways on pain assessment and management are available from the British Pain Society.[195]

Chronic pain management should focus on non-pharmacological strategies just as much as the use of analgesic drugs. The prescription of medication is the most convenient element of care but is potentially the most harmful and sometimes the least effective.

Step 1 Initial assessment	**Divide assessment and initial management over multiple consultations** *Investing time at the initial presentation may improve outcomes for patients and minimise unhelpful use of resources in future.*	
	Use a patient-centred, culturally sensitive approach • Explain the treatment options. • Encourage patients' involvement in decision making.	
	Consider red flags • Consider serious pathology and investigate and refer if necessary. • Avoid further investigations unless serious pathology is suspected. • Identify the stage at which no more investigations are planned and explain this clearly to the patient.	
	Identify the duration of pain • Make a clear diagnosis of chronic pain where appropriate. *Pain that has been present for more than 12 weeks.* • Record the diagnosis and code it electronically in the patient record.	
	Identify if there may be an element of neuropathic pain *Typical features: character of pain (burning, shooting), allodynia (pain due to a stimulus that does not normally provoke pain), hyperalgesia (exaggerated response to a painful stimulus) unpredictable pain, other abnormal sensations, sensory abnormalities and/or skin changes on clinical examination; symptoms and signs neuroanatomocally consistent with underlying cause.* *Brief validated tools are available to aid diagnosis (eg LANSS, DN4, painDETECT)[196] but there is insufficient evidence to support a recommendation for their routine use.*	
	Assess the severity of pain at different sites • Use a narrative clinical history to clarify the complexity and intensity of pain. • Consider using a visual analogue scale or numerical score to help gauge the response to treatment.	
	Assess functional impact as part of a bio-psychosocial assessment • Consider work, relationships, sleep, mood, disability etc. *The depth of the assessment will depend on the severity of the problem and it may be completed over multiple consultations.*	
	Identify patients at increased risk of poor outcomes • Use clinical judgement. • Consider the use of evidence based tools (eg Keele STarT Back Tool). • Be aware of the presence of significant comorbidities. *Mental health problems (including depression, anxiety, personality disorder, post-traumatic stress disorder), cognitive impairment, substance misuse, pregnancy, polypharmacy, significant renal or hepatic impairment* • Be aware of the presence of yellow flags.	
	Biomedical yellow flags	*Severe pain or increased disability at presentation, previous significant pain episodes, multiple site pain, non-organic signs, iatrogenic factors.*
	Psychological yellow flags	*Belief that pain indicates harm, an expectation that passive rather than active treatments are most helpful, fear avoidance behaviour, catastrophic thinking, poor problem solving ability, passive coping strategies, atypical health beliefs, psychosomatic perceptions, high levels of distress.*
	Social yellow flags	*Low expectation of return to work, lack of confidence in performing work activities, heavier work, low levels of control over rate of work, poor work relationships, social dysfunction, medico-legal issues.*

Step 2 Interventions	**Listen, validate, educate, reassure** • Acknowledge that pain may never entirely resolve.	
	Encourage a self management approach *(see section 4)*. *Signposting patients to self management resources should be considered at any stage of their treatment. The healthcare professional needs to consider which approaches will suit each patient and signpost them appropriately (see section 10.1). Involve an advocate or carer where possible and relevant, to help understanding and motivate for change.*	
	Advise the patient to stay active • Consider referral for: ○ exercise therapy where available (*see section 7.2*) ○ manual therapy (eg physiotherapy, TENS; *see sections 7.1, 7.4*), or ○ acupuncture where available (*see section 8.1*).	
	Support the patient to stay at work • Consider occupational health referral and benefits advice.	
	Treat the underlying cause of pain where possible • Encourage appropriate use of over-the-counter analgesics (*see section 5.2)*. • Be aware that treatment of moderate or severe depression (where present) may reduce pain (*see section 5.5.4)*.	
Step 3 Additional interventions	**Conduct a more comprehensive biopsychosocial assessment, where possible, for patients at increased risk of poor outcomes**	
	Biomedical assessment	*Thorough pain history assessing each discrete pain experienced by the patient (site, character, intensity, onset, precipitants, duration, intensity, exacerbating and relieving factors, night pain, perceived cause), systemic symptoms, past medical history, physical examination (including behavioural response to examination); previous investigations (and patient's understanding); previous and current treatment (including response, specialist treatments, side effects, misconceptions, fixed beliefs, messages from other health professionals).*
	Psychological assessment	*Consider low mood, anxiety or depression; psychiatric history, alcohol and illicit drug use, misuse, dependence or addiction, history of physical or sexual abuse; identify yellow flags (see above), loss of confidence, poor motivation, reluctance to modify lifestyle, unrealistic expectations of self and others.*
	Social assessment	*Ability to self care, occupational performance, influence of family on pain behaviour, dissatisfaction at work, secondary gain (family overprotection, benefits, medico-legal compensation).*
	Agree a pain management plan *eg verbal agreement of a single goal, and how to achieve it, or a self directed written plan.* • Consider early referral to secondary care where pain is severe, not responding adequately to management, or for specific specialist assessment and/or treatments.	

Step 4 Analgesic drugs	**Before prescribing analgesic drugs** • Offer non-pharmacological strategies in addition to, or as alternative to, analgesic drugs. • Agree the goals of therapy eg reduction in pain, improved mood, improved function. • Agree the length of the initial trial. • Discuss the potential side effects of all drugs prescribed. • Discuss the significant risks of specific drugs, especially NSAIDs and opioids. • Discuss the short term benefits and potential loss of efficacy over time before prescribing opioids. • Avoid co-prescription of sedative and hypnotic medication where possible and be aware of concomitant alcohol use. • Be aware of concomitant use of over-the-counter treatments, and advise accordingly.
	For patients who continue to have poorly controlled pain • Schedule review appointments rather than allowing them to be dictated by pain levels. • Plan management of exacerbations. • Consider trialling two or three other drugs from the same class if the first is ineffective. • Down-titrate or withdraw ineffective treatments. • Consider rational multimodal analgesia: avoid coprescription of drugs from within the same class, consider the safety and logic of the prescribing regimen when combining drug treatments.
	After commencing drug treatment • Increase to the recommended starting dose then titrate against response where appropriate, up to the recommended maximum dose, unless limited by side effects. • Review the efficacy of all drugs after an initial trial at the optimum dose, usually after two weeks (up to four weeks for antidepressants), using the narrative clinical history, a visual analogue scale or numerical scores. *Most individuals respond in one of two ways: either a good response (at least 30% improvement) or no response.*
	Choice of drug • Use the WHO ladder pragmatically and do not continue prescribing drugs that are ineffective. • If neuropathic pain appears to be present follow the pathway for patients with neuropathic pain (*see Annex 3).* *Choice of individual drug or combination will be influenced by:* - *severity of pain* - *presence of neuropathic pain* - *comorbidity and coprescribing* - *risk of drug misuse* - *previous drug efficacy* - *previous adverse effects* - *interactions with other prescribed medication* - *clinician experience.* • Use as first line: ○ paracetamol (*see section 5.2)* ○ NSAIDs (*see section 5.2)* • Also consider: ○ weak opioids (see *section 5.3)* ○ topical NSAIDs (*see section 5.2)* ○ topical rubefacients (*see section 5.2.7).* • If pain still not controlled: ○ reconsider non-pharmacological strategies (*see sections 6,7 and 8*) ○ refer to the pathway for using strong opioids (*see Annex 4*).

Step 5 **Referral**	**Consider onward referral** • To psychologically based therapies (includes CBT, behavioural therapies, mindfulness meditation, acceptance and commitment therapy); (*see section 6*) when the patient: ○ has moderate to high levels of distress ○ has difficulty adjusting to a life with pain ○ is struggling to change their behaviour to maintain normal activities. *For patients with pre-existing emotional problems, discuss any proposed referral with their current care provider or with the team who will be providing the new therapy. The discussion should review the outcomes of previous therapeutic interventions and consider whether the patient is likely to benefit.* *Selection of a particular therapeutic approach is likely to be determined by local availability, but consider the patients' preferences where a choice is available.* • To specialist pain service if: ○ there is treatment failure after trial of four drugs for neuropathic pain ○ the opioid dose is greater than 180 mg morphine per day or equivalent ○ there is an inadequate response to non-specialist management. • To a multidisciplinary pain management programme (*see section 6.1*) when the patient has: ○ poor functional capacity ○ moderate to high levels of distress ○ social and occupational problems related to pain ○ failed to benefit from other, less comprehensive therapies ○ a preference for a self management rather than a medical approach. *Delaying referral until other treatment avenues are exhausted can be dispiriting and unhelpful. Ensure that patients are aware that PMP will be a group based treatment focused on improving quality of life and participation in normal activities. It is also important that the patient understands the likely composition of the PMP team.*
Step 6 **Review**	**Initial review** • Once stability is achieved an initial review should take place no more than six months later.
	Subsequent reviews • Subsequent reviews should be at least annual. • At each review re-assess medication concordance and efficacy, adverse effects, alcohol and illicit drug use, mood, function and review the management plan if appropriate. • Consider using a recall system to facilitate annual reviews.
Step 7 **Exacerbations**	**Re-assessment** • Consider re-assessment for new or worsening pathology and the possible need for further investigation. • Plan for the use of non-pharmacological strategies. • Avoid the use of short-acting strong opioids. *Routine use during exacerbations may increase tolerance and may lead to dose escalation.* • Down-titrate analgesics between exacerbations.
	Reassurance • Reassure the patient that exacerbations are common, are not necessarily indicative of a worsening of their underlying condition and are likely to settle quickly. *Reviewing previous episodes may be helpful.* • Reassure the patient that it is safe to maintain normal activities of daily living at a moderate level. • Discourage patients from resting excessively during an exacerbation.

Annex 3

Pathway for patients with neuropathic pain

This pathway is drawn from evidence identified in the guideline, information extrapolated in the research for the guideline and the clinical experience and consensus of the guideline development group. More detailed pathways on pain assessment and management are available from the British Pain Society.[195]

Step 1 **Diagnosis**	• **Make a clinical diagnosis based on history, signs and symptoms** • **Screening questionnaires can be used to aid the process** (*see Annex 2 for pathway on assessment and early management of chronic pain*)
	Diagnosis of neuropathic pain is a clinical diagnosis but may be aided by one of the various available questionnaires. Common causes are postherpetic neuralgia and diabetic peripheral neuropathy but there are many other causes including post-surgical nerve dysfunction, cancer, trigeminal neuralgia, HIV, post amputation pain, multiple sclerosis etc. Once a diagnosis is made, then it is usual to start an initial systemic drug. Review should be frequent to optimise drug dosage and to improve tolerability. Drugs that are having little useful effect after a dose titration should be stopped and an alternative tried.
Step 2 **Initial agents**	• **Amitriptyline** • **Gabapentin**
	The drug to use first depends mainly on clinical preference. There is no strong evidence to choose one over the other. Prescriber preference, experience and patient factors should all be considered. If the first agent chosen is not helpful, then an alternative may be used either as a sole agent or in combination. In clinical practice the usual step one systemic drug is a tricyclic antidepressant such as amitriptyline or a gabapentinoid. **Amitriptyline** (*see section 5.5*) The suggested efficacious dose range for amitriptyline is 25-125 mg. In many patients it may be beneficial to start with only 10 mg and titrate upwards. The dose should be increased by 10 mg per week until either efficacy is achieved or the patient cannot tolerate the drug. Dosages higher than 125 mg are sometimes used in clinical practice but evidence for these doses is lacking. Amitriptyline, in common with the other TCAs, has a number of side effects. One of the common reasons for discontinuation is excessive drowsiness. **Gabapentinoids** (*see section 5.4*) Gabapentin is normally the gabapentinoid of choice. It is usually started at 300 mg at night and titrated upwards (increasing by 300 mg per week is suggested). Evidence suggests that a minimum of 1,200 mg is needed. Doses may need to be increased as high as 3,600 mg. This is consistent with published clinical trials. **Pregabalin** (*see section 5.4.2*) Pregabalin is an alternative in patients who have have found no benefit from or not tolerated amitriptyline or gabapentin. It is usually started at a dose of 75 mg per day. In some patients smaller starting doses may be used but doses of 150 mg daily are generally ineffective. The drug may be titrated up until a maximal dose of 300 mg per day is reached. The dose should be titrated according to effect and with the side effects in mind as a flexible dosing has been shown to be better. Common side effects are somnolence and dizziness. (The SMC recommends that pregabalin is reserved for patients who have not tolerated or who have failed on a conventional first or second line agent, for example a TCA or gabapentin; *see section 11.4*).

Step 3 **Alternative agents**	• **Alternative tricyclic antidepressants** • **SNRI antidepressants**
	Alternative systemic drugs (*see section 5.6*) If initial agents do not help it is appropriate to change to an alternative agent, either as a sole agent or in combination with one or more drugs known to be effective in neuropathic pain, such as a gabapentinoid (or opioid in appropriate cases). Generally two types of antidepressant are not given together unless one is in low dose (eg amitriptyline 25 mg) or on specialist advice. **Alternative TCAs** (*see section 5.5.1*) If amitriptyline does not produce effective results, then an alternative TCA such as impramine or nortriptyline may be used. These may be less sedating and better tolerated but are not any more efficacious. Dosages are normally in the range of 25-75 mg daily. **SNRI antidepressants** (*see section 5.5.2*) Duloxetine is the SNRI most commonly used for neuropathic pain. The recommended dose of duloxetine is 60 mg per day in a single dose (doses up to 120 mg have been used). **Alternative anti-epilepsy drugs** (*see sections 5.4.3 and 5.4.4*) Although many anti-epilepsy drugs have been used in the treatment of neuropathic pain, apart from carbamazepine, there is little evidence to support their use. Carbamazepine should be used as a first line agent in patients with trigeminal neuralgia. It may also be used in patients with general neuropathic pain. In both cases the initial dose should be 100-200 mg daily increasing slowly in increments of 100-200 mg biweekly. Doses up to 1,600 mg daily have been used.
Step 4 **Topical agents**	• **Topical lidocaine plasters**
	In patients with localised neuropathic pain it may be appropriate to use a topically acting agent (*see sections 5.2.4 to 5.2.7*). **Topical lidocaine plasters** (*see section 5.2.6*) Topical lidocaine plasters are the topical agent of choice (in the non-specialist setting) in patients who prefer a topical treatment. Up to three plasters can be used at a time. These are worn 12 hours on and 12 hours off. There are few side effects apart from some skin reddening and irritation. If there is no improvement after four weeks, then they should be discontinued. **Low dose topical capsaicin** There is no good evidence for the use of low dose topical capsaicin (*see section 5.2.5*; see *Step 6* regarding high dose capsaicin patch).
Step 5 **Opioids**	• **Opioids**
	Opioids (*see section 5.3*) • Use only in carefully selected and screened patients • Use long acting preparations only. Avoid breakthrough dosing • Prescribe no higher than 180 mg morphine (or equivalent) without specialist advice • Discontinue if not effective • Follow the pathway for using strong opioids (*see Annex 4*).
Step 6 **Specialist referral**	• **Tertiary drugs** (capsaicin 8% patch, ketamine) • **Specialised interventions** • **Multidisciplinary assessment with appropriate psychological therapies**
	Patients with refractory pain (pain unresponsive after four or more conventional drug therapies) or patients failing on opioids should be referred for specialist advice. Tertiary options include the use of capsaicin 8% patch (*see section 5.2.5*), interventional procedures, drugs such as ketamine and a robust multidisciplinary approach which includes appropriate psychological therapies.

Annex 4

Pathway for using strong opioids in patients with chronic pain

This pathway is drawn from evidence identified in the guideline, information extrapolated in the research for the guideline and the clinical experience and consensus of the guideline development group. More detailed pathways on pain assessment and management are available from the British Pain Society.[195]

Strong opioids should only be considered after a full assessment and as part of a wider management plan, rather than as sole agents. Prescribers should have knowledge of opioid pharmacology and be competent and experienced in the use of strong opioids.

Step 1 **Assessing suitability for strong opioid**	**Assess pain** • Likely to respond to opioid, eg nociceptive; some benefit from weak opioids, consider opioid trial. • Less likely to respond to opioid, eg neuropathic; no analgesia at all from weak opioids, consider specialist advice before opioid trial OR avoid opioids.
	Assess patient for • Relevant psychosocial factors: ○ children in house ○ other family members with a history of substance misuse problems. • Increased risk of misuse or developing iatrogenic dependency: ○ history of heroin abuse ○ history of alcohol abuse ○ history of stimulant use ○ mental health problems. • Other comorbidities: ○ cognitive impairment; cognitive side effects are more likely; concordance and safety may be an issue ○ renal impairment; accumulation of active metabolites with some opioids ○ gastrointestinal pathology; adverse effect on bowel function. • Other analgesics; use simple analgesics, topical therapies and anti-neuropathic agents (if appropriate) for opioid sparing effect.
	Discuss the plan with the patient before starting opioids • Provide information leaflets (eg SIGN patient leaflet, British Pain Society patient leaflet). • Establish goals of treatment: ○ primary: pain relief (define the degree that would be acceptable to the patient) ○ secondary: improved function, sleep, mood. *Be aware that opioids should NOT be used as anxiolytics.* • Discuss the side effects/potential problems. The patient needs to be aware of the potential side effects and they need to be acceptable to the patient, eg: ○ GI dysfunction; nausea, vomiting, constipation ○ central nervous system; memory and cognitive impairment, nightmares, hallucinations, visual disturbance ○ endocrine; fertility, sexual function ○ immune function ○ misuse potential ○ tolerance ○ opioid-induced hyperalgesia.

Step 1 **Assessing suitability for strong opioid**	**Define and discuss how the trial will work** • Set a timescale; discuss the expected duration of trial, frequency of review. • Set a dose; including upper dose limit; aim for lowest effective dose. • Agree stopping rules with the patient before starting: ○ if treatment goals are not met ○ if there is no clear evidence of dose response ○ if rapid tolerance develops necessitating high dose opioids. In this situation proceed to reduction and cessation, or consider specialist referral/advice. • Consider opioid rotation if the pain is opioid responsive but efficacy and dose titration is limited by side effects. *The suggested dose conversion ratios table (see box 2) is for guidance only and should be used with caution.* If the patient is on a high dose before conversion consider phased conversion to avoid withdrawal. Short acting opioids may need to be used during conversion until the correct dose is established.
Step 2 **Starting a strong opioid**	**Factors to consider** • Route of administration; oral or transdermal are the main routes for chronic non-malignant pain. • Choice of opioid *(see boxes 1 and 2 on choice of opioid and suggested dose conversion ratios).* • Dose; there is considerable variability in the dose needed to effectively treat pain. Careful titration to the lowest effective dose, balanced against side effects requires regular review.
	There are two potential options for starting strong opioids: • Start with low dose of long-acting preparation. If the patient is already on cocodamol or dihydrocodeine, then they are not opioid naive, particularly if they are on the maximum dose or more than one of these agents. OR • While establishing dose, use an immediate release preparation for short term use, only to determine approximate dose range, then convert to equivalent long-acting preparation as soon as possible. This may be more appropriate if the patient has multiple comorbidities. Aim to establish the patient on long-acting opioid with no immediate release opioid if the chronic pain is stable. For patients with mild 'breakthrough pain' consider non-opioids (eg paracetamol, NSAIDs) or weak opioid.
Step 3 **Monitoring opioid trial**	**Monitor adverse effects** • Gastrointestinal: ○ nausea/vomiting; tolerance usually develops. Consider use of an antiemetic at initiation of therapy. Due to the abuse potential of cyclizine, avoid if possible. ○ constipation: tolerance often does not develop to this. Use stool softeners/stimulant laxatives or a combination. Consider opioid preparations less likely to cause GI effects. • Central nervous system: *If these do not resolve, then either dose reduction or rotation will be needed.* ○ impaired memory, concentration ○ hallucinations, milder visual disturbance ○ sedation, confusion, cognitive impairment ○ myoclonic jerks. • Other: ○ sweating ○ reduced libido, fertility; consider stopping, testosterone replacement, possible opioid rotation; may need endocrine review ○ respiratory depression; stop opioid until resolves; consider factors contributing to event ○ tolerance; rotate opioid or reduce and stop ○ opioid induced hyperalgesia - rotate opioid or reduce and stop; seek specialist advice.

Step 3 **Monitoring opioid trial**	**Assess pain relief** • If there is good pain relief on a stable dose of opioid without unacceptable side effects continue with at least annual review. • If pain relief is inadequate due to: ○ dose titration not being possible due to adverse effects, try opioid rotation ○ no/minimal evidence of opioid responsiveness, reduce and stop opioid ○ intolerable side effects, try opioid rotation. Short-acting opioids may need to be used during the conversion both to reduce physical withdrawal and while optimum dose is being established. If the patient is on a large dose of opioid, consider phased conversion (eg reduce the current opioid dose by 50% and introduce the new opioid dose at less than the morphine equivalent dose replacement dose (because of incomplete cross-reactivity). Continue with reduction of the old opioid and increase in new opioid as indicated by response.
	At all times before and during opioid treatment signs of iatrogenic substance misuse should be sought and if problems arise, then consider early specialist advice/referral.
Step 4 **Continuing opioid therapy**	**Regular review, ideally with one prescriber:** • At least annual, more frequently if problems arise. • Have a clear plan for flare-up management (including availability to out of hours service).

Box 1: Choice of opioid

OPIOID	ROUTE	COMMENTS
Morphine	Oral	Most commonly used; very variable bioavailability (15 - 65%), no evidence that it is better than other opioid; active metabolites can accumulate in renal impairment, some may cause hyperalgesia.
Tramadol	Oral	weak MOR agonist (~1/6000th that of morphine) with additional effects on noradrenergic and serotonergic systems. Metabolism is via the CYPD, with one of the active metabolites: O-desmethyltramadol having considerably more potency at the MOR.
Oxycodone	Oral	More reliable bioavailability than morphine (60 - 87%); metabolism involves CYPD.
Fentanyl	Transdermal	Useful if problems with oral administration.
Buprenorphine	Transdermal	Useful if problems with oral administration; minimal active metabolite accumulation in renal impairment.
Hydromorphone	Oral	Potent strong opioid, metabolised in the liver. Wide inter-individual patient variability.
Tapentadol	Oral	New opioid with additional activity on the noradrenergic systems; may have a role in neuropathic pain; some evidence of improved side effect profile and drop-out rates from RCTs compared to other strong opioids.
Oxycodone/ Naloxone	Oral	Combined preparation where naloxone binds preferentially to MORs in the GI tract, with potential reduction in opioid-related adverse GI effects. Maximum recommended dose 80 mg oxycodone/40 mg naloxone.
Methadone	Oral	Very unpredictable pharmacokinetics with considerable inter-individual variation. NOT recommended for use without specialist advice.

Box 2: Suggested dose conversion ratios		
(converting from) Current opioid	**(converting to) New opioid and/or new route of administration**	**Divide 24 hour dose* of current opioid (column 1) by relevant figure below to calculate initial 24 hour dose of new opioid and/or new route (column 2)**
Example 120 mg oral morphine in 24 hours	subcutaneous diamorphine	**Divide by 3** (120 mg / 3 = 40 mg subcutaneous diamorphine in 24 hours)
ORAL TO ORAL ROUTE CONVERSIONS		
oral codeine	oral morphine	**Divide by 10**
oral tramadol	oral morphine	**Divide by 5**
oral morphine	oral oxycodone	**Divide by 2**
oral morphine	oral hydromorphone	**Divide by 7.5**
ORAL TO TRANSDERMAL ROUTE CONVERSIONS		
oral morphine	transdermal fentanyl	*Refer to manufacturer's information***
oral morphine	transdermal buprenorphine	*Seek specialist palliative care advice*
ORAL TO SUBCUTANEOUS ROUTE CONVERSIONS		
oral morphine	subcutaneous morphine	**Divide by 2**
oral morphine	subcutaneous diamorphine	**Divide by 3**
oral oxycodone	subcutaneous morphine	**No change**
oral oxycodone	subcutaneous oxycodone	**Divide by 2**
oral oxycodone	subcutaneous diamorphine	**Divide by 1.5**
oral hydromorphone	subcutaneous hydromorphone	*Seek specialist palliative care advice*
OTHER ROUTE CONVERSIONS RARELY USED IN PALLIATIVE MEDICINE		
subcutaneous or intramuscular morphine	intravenous morphine	**No change**
intravenous morphine	oral morphine	**Multiply by 2**
oral morphine	intramuscular morphine	**Divide by 2**

Conversion ratios between strong opioids: Strong evidence for converting between opioids is lacking, with the majority of studies being single dose, small sample size pharmacokinetic studies, usually in healthy volunteers *(see section 12.2)*. A number of dose conversion charts are available and can be useful, but there is significant inter-individual variability and they should be used with caution, particularly in the elderly; if there are significant other co-morbidities (eg hepatic or renal impairment); or with polypharmacy.

* The same units must be used for both opioids or routes, eg mg morphine to mg oxycodone

** The conversion ratios of oral morphine:transdermal fentanyl specified by the manufacturer(s) vary from around100:1 to 150:1

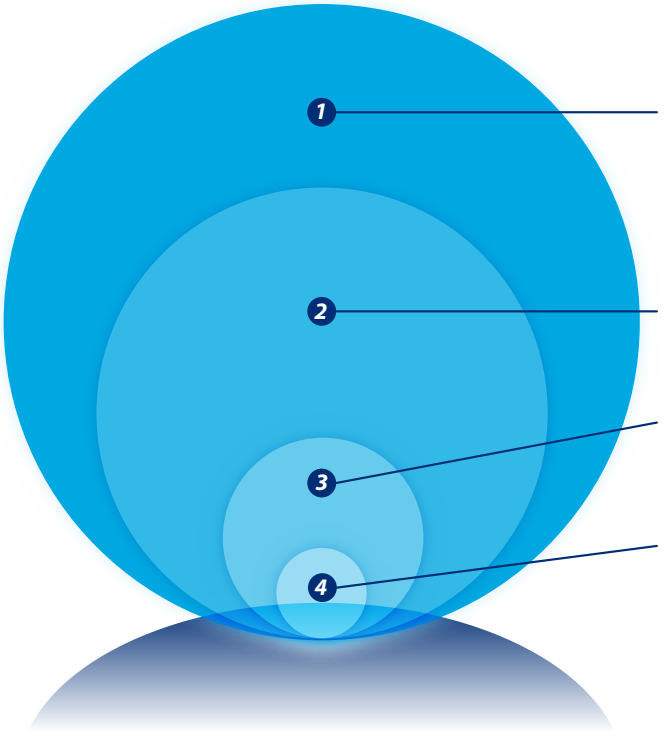
Annex 5

Scottish service model for chronic pain

NHS SCOTLAND

Chronic Pain Scotland Service Model

Most people get back to normal after pain that might come on after an injury or operation or for no apparent reason. Sometimes the pain carries on for longer than 12 weeks despite medication or treatment – this is called chronic or persistent pain.



Level 1 - Advice and information about pain and what to do about it. Anyone can access these services from home or community settings

Level 2 - When help from a GP or therapist is needed

Level 3 - For those needing more specialist help from a chronic pain management service

Level 4 - Highly specialised help

Information and guidance supporting all levels
Visit www.chronicpainscotland.org

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Edinburgh Office | Gyle Square |1 South Gyle Crescent | Edinburgh | EH12 9EB
Telephone 0131 623 4300 Fax 0131 623 4299

Glasgow Office | Delta House | 50 West Nile Street | Glasgow | G1 2NP
Telephone 0141 225 6999 Fax 0141 248 3776

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