Grŵp Strategaeth Meddyginiaethau Cymru Gyfan
All Wales Medicines Strategy Group

All Wales Pharmacological Management of Pain Guidance

November 2022

(April 2023 – updated with link to MHRA advice on antidepressants)

(July 2023 – updated with change to method for estimating renal function when prescribing pregabalin)

This document has been prepared by a multi-professional collaborative group, led by Emma Davies and Dr Sue Jeffs, with support from the All Wales Prescribing Advisory Group (AWPAG) and the All Wales Therapeutics and Toxicology Centre (AWTTC) and has subsequently been endorsed by the All Wales Medicines Strategy Group (AWMSG).

Please direct any queries to AWTTC:

All Wales Therapeutics and Toxicology Centre
The Routledge Academic Centre
University Hospital Llandough
Penlan Road
Llandough
Vale of Glamorgan
CF64 2XX

awttc@wales.nhs.uk
029 218 26900

The information in this document is intended to help healthcare providers make an informed decision. This document should not be used as a substitute for professional medical advice and although care has been taken to ensure the information is accurate and complete at the time of publication, the All Wales Therapeutics and Toxicology Centre (AWTTC) and All Wales Medicines Strategy Group (AWMSG) do not make any guarantees to that effect. The information in this document is subject to review and may be updated or withdrawn at any time. AWTTC and AWMSG accept no liability in association with the use of its content.

Information presented in this document can be reproduced using the following citation:
All Wales Medicines Strategy Group, Pain Prescribing Guidance. November 2022 (updated July 2023).

Contents

1.0 Introduction

This guidance has been developed to support prescribers in making the best choices in relation to medicines for pain.

Further aims are to allow timely exploration of the role of medicines for pain and reduce variation in prescribing across our health community.

The guidance also helps prescribers and health boards to understand how analgesic stewardship can be integrated into treatment pathways for a range of specialties.

The guidance does not include management of pain in end-of-life settings, or of disease-specific treatments which result in pain reduction (e.g., interventions for angina or autoinflammatory conditions). The guidance does not include treatment options that might be offered by specialist pain services, including interventional techniques that might be offered during hospital admission or via outpatient departments.

Adherence to general principles of good practice in prescribing underpin pharmacological management of pain:

- keep up to date with clinical evidence and relevant legislation;
- prescribe within your own competence;
- prescribing decisions should be supported by best clinical evidence;
- benefits and harms of treatments should be discussed with the patient.

You should not prescribe without:

- full knowledge of the patient's physical and emotional health;
- an understanding of how the proposed treatment meets the patient's needs;
- knowledge of other medicines the patient is taking, including over-the-counter (OTC), and recreational drugs including alcohol;
- making arrangements for monitoring and review;
- keeping clear records of prescribing decisions and the outcome of treatments.

If a decision is made to prescribe medicines for unlicensed indications, the rationale should be discussed with the patient, appropriate consent acquired, and all discussions clearly documented. Further information about prescribing unlicensed medicines is available from the General Medical Council[1].

If a medicine is not working, it should be carefully tapered and stopped

Note: Doses are oral and for adults aged 16 years and over unless otherwise stated. Please refer to British National Formulary (BNF) for further information.

[1] General Medical Council (2022): Ethical Guidance: https://www.gmc-uk.org/ethical-guidance?msclkid=b996885fc63611ec9699092677cfea32

2.0 Types of pain

Pain is usually classified depending on duration of symptoms. The overarching description of pain is of an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. The WHO International Classification of Diseases 11th edition (ICD-11) defines a number of pain conditions, including:

- **Acute pain is defined as pain with a duration of** less than 3 months. It usually results from injury, including operation, fracture or infection.

- **Chronic pain** is that which persists or recurs for longer than 3 months. Chronic pain is multi-factorial: biological, psychological and social factors can contribute to the pain experience. It can include low back pain and arthritis, and can sometimes develop from acute pain that persists.

The ICD-11 classification of chronic pain introduces new diagnoses, including chronic primary pain.

Chronic primary pain is chronic pain in one or more anatomical regions that is characterised by significant emotional distress (anxiety, anger/frustration or depressed mood) or functional disability (interference in daily life activities and reduced participation in social roles). The diagnosis is appropriate independently of identified biological or psychological contributors unless another diagnosis would better account for the presenting symptoms.

Potential chronic primary pain diagnoses include: chronic widespread pain or fibromyalgia; chronic primary musculoskeletal pain; chronic primary visceral pain; and complex regional pain syndrome. In these presentations, the priority will often be to manage emotional distress and so the use of standard analgesics and especially opioids is best avoided.

Chronic secondary pain is pain caused by an underlying condition, for example: osteoarthritis, rheumatoid arthritis, ulcerative colitis, endometriosis.

Chronic primary pain can co-exist with chronic secondary pain in conditions where there is underlying pathology that accounts for some of the symptoms described. Where the two co-exist, clinical decisions about symptomatic management should be guided by the level of emotional distress displayed and the degree to which pain is interfering with functioning.

Neuropathic pain is pain from nerve damage, e.g. diabetes, shingles, multiple sclerosis, pain following stroke; it is likely to be a type of chronic secondary pain. It is normally described as electric, burning or shock like sensations. The pain may occur spontaneously, without provocation or be provoked by noxious or non-noxious stimuli.

Pain symptoms can fall into more than one category.

3.0 Pain intensity

Both acute and chronic pain can range from mild to severe. Intensity of acute pain is largely (but not completely) related to the degree of tissue injury: a big injury or operation hurts more than a small one. There is no similar relationship for chronic pain. The amount of tissue damage is a small contributor to pain intensity. Larger contributors are anxiety, distress, depression and concern about causes of pain.

Unpleasant thoughts, feelings and memories (even if unrelated to pain) can influence pain severity.

3.1 Red and yellow flags

Red and yellow flags in pain management were first described for acute low back pain but the underlying concept can be applied more broadly in the context of pain presentation of any cause.

Red flags are clinical indicators of possible serious underlying conditions requiring further medical intervention.

Table 1. Red flags (example uses acute low back pain as the presenting symptom)

Differential diagnosis	Red flags from patient history	Red flags from examination
Possible fracture	• Major trauma • Minor trauma in elderly or osteoporotic	• Evidence of neurological deficit (in legs or perineum in the case of low back pain)
Possible tumour or infection	• Age < 20 years or > 50 years • History of cancer • Constitutional symptoms (fever, chills, weight loss) • Recent bacterial infection • Intravenous drug use • Immunosuppression • Pain worsening at night or when supine	
Possible significant neurological deficit	• Severe or progressive sensory alteration or weakness • Bladder or bowel dysfunction	

The presence of red flags suggests the need for further investigation and specialist referral as part of the overall strategy. If there are no red flags present in this situation, it is safe to reassure the patient and move ahead with a multi-modal management approach.

Yellow flags are psychosocial indicators suggesting increased risk of progression to long-term distress, disability and pain. In principle, they can be applied more broadly to assess the likelihood of development of persistent problems from any acute pain presentation, which can be summarised as **distress, disability, dependence and drugs (4Ds).**

Table 2. Yellow flags

Attitudes and beliefs	• Pain is harmful or severely disabling • Expectation that passive treatment rather than active participation will help • Feeling that 'no-one believes the pain is real' – may relate to previous encounters with health professionals
Emotions and behaviour	• Fear-avoidance behaviour (avoiding activity due to fear of pain) • Low mood and social withdrawal
Other psychosocial factors	• Poor family relationships or history of abusive relationships • Financial concerns particularly related to ill health or ongoing pain • Work-related factors e.g. conflict over sick leave, ability to perform current job tasks • Ongoing litigation related to chronic pain condition

The presence of multiple biopsychosocial factors may highlight the need for a multidisciplinary approach to care.

3.2 The place of analgesics in pain management

Pain can be difficult to treat, especially pain that persists. The Faculty of Pain Medicine of the Royal College of Anaesthetists (UK) states that **most treatments help less than a third of patients with chronic pain**. Different treatments work for different patients. Medicines generally, and opioids in particular, are often ineffective for chronic pain, but some medicines are worth trying for neuropathic pain.

Medicines for pain should always be used as part of a wider treatment plan including advice on physical activity or physiotherapy, sleep and support in achieving improvements in emotional wellbeing and quality of life. Medicines for pain don't work for everyone and when they do work, they rarely take pain away completely.

The aim of pain management is to reduce the impact that pain has on a person's ability to perform activities of daily living. A holistic approach is needed. The patient's pain management plan needs to include supported self-management, strategies to reduce social isolation, manage employment and financial concerns, and improve mental health and resilience.

The aim of pharmacological treatment (analgesic medicines) is to reduce intensity of pain sufficiently to help patients function better and to help them to self-manage their pain.

The effectiveness of medicines for chronic pain should be regularly evaluated. Periodic dose taper will allow assessment of the natural history of the pain and confirm the usefulness of continued treatment.

4.0 A stepped approach to prescribing for pain

The WHO's analgesic ladder was developed to support patients with cancer pain. The underlying principle was that medications should be used sequentially, according to the patient's reported pain intensity, i.e. for mild pain non-opioid medication should be prescribed, and opioids used for moderate and severe pain.

Prescribing for chronic pain should not be determined by reported pain intensity alone (see section 3.0 above). In acute pain, it may be necessary to adjust analgesic medicines more rapidly, in order to reduce pain intensity sooner rather than later and reduce the risk of the individual becoming debilitated or progressing to a chronic pain state.

Generally, it is rational to start with non-opioid medicines, if these have evidence of efficacy for the condition being treated. For managing chronic pain, give non-opioid medicines with advice about exercise, sleep, pacing activity and strategies to improve function.

Trials of opioid therapy should be considered only if:

- there is a well-defined pain diagnosis;
- symptoms persist despite first-line treatments, including non-pharmacological management;
- the patient can be followed up within two to four weeks to evaluate effectiveness.

4.1 Reviewing analgesics

The timing of a review is partly dependent on the presenting complaint and the agreed goals of treatment.

When trialling new medicines, a review of effectiveness should be undertaken within 2 to 4 weeks of initiation or dose changes. Review should include:

- a check of what analgesic medicines the patient is currently taking, to include:
    - how they are using prescribed medicines and any medicines they are purchasing or accessing from elsewhere;
    - any additional requests for medicines made in between agreed timings of prescriptions;
    - any new or changed symptoms which may be adverse effects of the medicines;
- a measure of function or pain interference:
    - ease of undertaking daily activities;
    - may include previously agreed functional goals e.g., increased walking time;
    - changes in sleep;
- reported changes in mood;
- patient-reported quality of life – do they think things are getting better, worse or much the same?

If the patient is not demonstrating benefit from the use of analgesic medicine(s), then the medicine(s) should be carefully reduced and stopped. A positive outcome of an analgesic trial does not indicate the medicine will continue to be helpful long term, therefore regular review (every 6 months to 1 year) is necessary to reduce the risk of continuing unhelpful or harmful medicines.

5.0 Opioids

5.1 A simple opioid prescribing guideline

Opioids should be prescribed in line with **general good practice in prescribing.**

- Keep up to date with clinical evidence and relevant legislation.
- Prescribe within your own competence.
- Prescribing decisions should be supported by best clinical evidence.
- Discuss the benefits and harms of treatments with the patient.
- Reduce doses in older people, those in frail health, low weight and in renal impairment (see BNF for advice).

You should not prescribe without:

- full knowledge of the patient's physical and emotional health;
- an understanding of how the proposed treatment meets the patient's needs; and
- knowledge of other medicines the patient is taking including OTC and recreational drugs.

You must make appropriate arrangements for regular monitoring and review. If a medicine is not working, it should be tapered and stopped.

Keep clear records of prescribing decisions and of outcome of treatments.

Key messages on opioids

Opioids are very good analgesics for acute pain and for pain at the end of life, but there is little evidence that they are helpful for chronic pain.

A small proportion of people may obtain good pain relief with opioids in the long term if the dose can be kept low and especially if their use is intermittent. However, it is difficult to identify these people at the point of opioid initiation.

The risk of harm increases substantially at doses above an oral morphine equivalent of 120 mg a day, but there is no increased benefit.

If a patient is using opioids but is still in pain, the opioids are not effective and should be discontinued, even if no other treatment is available.

Chronic pain is very complex and if patients have refractory and disabling symptoms, particularly if they are on high opioid doses, a very detailed assessment of the many emotional influences on their pain experience is essential.

Opioids Aware is an online resource for patients and healthcare professionals to support prescribing of opioids for pain.

5.2 Efficacy of opioids

Evidence from randomised controlled trials for effectiveness of opioids in chronic pain is lacking, although open-label trial data suggest that a small proportion of patients with chronic pain may demonstrate a sustained response from low-dose opioids. The relevance of these findings is uncertain as clinical trials exclude patients at risk from

long-term opioid use and supervision of medicines use in clinical trials is unlikely to be reflected in clinical practice.

Important practice points
It is not possible to identify which patients will benefit long term at initiation of therapy.

Patients who don't benefit from opioids within 2–4 weeks are unlikely to benefit from longer term prescribing.

Efficacy in the short term does not guarantee long-term efficacy. There are no conclusive data on improvements in quality of life with opioid therapy.

There is no evidence that any opioid is superior to morphine. Morphine should always be used first line unless a clear contraindication is noted.

When prescribing modified-release morphine, use the least costly option.

For patients with hepatic or renal impairment, consult the BNF.

Escalation of opioid dose beyond 120 mg morphine equivalent daily (MED) is unlikely to improve pain relief but is associated with increasing harms.

Transdermal (patch) opioids such as fentanyl and buprenorphine should not be used for unstable or changing pain levels or until the efficacy of an opioid has been established (see MHRA advice). They should generally be reserved for people who are unable to take oral medicines.

5.3 Harms of opioids

Constipation and itching usually persist. Other side effects, if experienced at initiation of opioid treatment or after dose increase, may improve with time.

Respiratory effects of opioids are more problematic during sleep. Patients with sleep apnoea are at risk from opioid therapy: these patients should have nocturnal respiratory function assessed according to local referral pathways and need to be compliant with treatment for sleep apnoea when recommended.

There is little evidence that different opioid preparations (in equianalgesic doses) have different side-effect profiles. The only reason to use an opioid other than morphine, is where benefit has been shown, but the patient is unable to manage side effects.

80% of patients are likely to experience at least one side effect from opioid treatment.

Co-prescription of benzodiazepines and gabapentinoids significantly increases risk of respiratory depression.

Oxycodone has been associated with higher rates of dependence and misuse than other opioids. It may be an option for opioid-responsive pain where morphine is not tolerated; however, its potential for misuse should be considered.

5.4 Long-term harms of opioid treatment

Harms associated with longer-term (e.g. > 6 months) use of opioids include:

- increased risk of fractures and falls;
- endocrine disturbance (reduced libido, amenorrhoea, erectile dysfunction, infertility, cortisol depression);
- immune disturbance, including effects on antimicrobial response and tumour surveillance.

Worsening of pain (opioid-induced hyperalgesia; OIH) is well demonstrated in patients undergoing surgery given high-dose opioids perioperatively, patients receiving methadone maintenance for addiction, and in experimental pain. It is uncertain how often OIH occurs with routine clinical use of opioids for pain. Suspect OIH in patients taking opioids if a patient describes a relatively sudden and otherwise unexplained increase in pain which is often difficult to describe and seen as being different from their usual pain and is often widespread. Treat suspected OIH by dose reduction.

Opioids are associated with dependence. Dependence is characterised by tolerance (the need for increasing doses to maintain the same effect) and withdrawal symptoms if the dose is reduced or the medicine is stopped abruptly. Problematic dependence also features tolerance and withdrawal but has the additional characteristics of cravings, lack of control, overuse and continued use despite harm. There is considerable debate in relation to these definitions, and in practice, the terms are often used interchangeably.

Consider problematic dependence to opioids if:

- **continued opioid use becomes main priority for patient;**
- **continued desire to use opioids despite demonstrable physical, emotional, social harms;**
- **patient describes a craving for medicines;**
- **patient describes a lack of control over use of medicine.**

Risk of problematic dependence increases in patients who:

- have co-morbid mental health diagnoses including anxiety and depression;
- have current or past history of substance misuse;
- use multiple opioid preparations;
- are co-prescribed other psychoactive drugs e.g., benzodiazepines.

Analgesic dependence is a barrier to successful pain management. Patients who have both pain and dependence have complex needs and may need to be managed by multidisciplinary teams including pain specialists with expertise in dependence and drug and alcohol services.

5.5 Assessment of patients for opioid therapy

You may consider a trial of opioids for patients with well-defined pain syndromes with demonstrable physical pathology. If you are considering opioids for your patient you will need to assess for physical and emotional comorbidity that may influence outcome (includes respiratory, hepatic and renal function and assessment of mood, anxiety, substance misuse and significant emotional trauma which if unaddressed may complicate pain management).

5.6 The opioid trial

Explain that sustained pain relief is unlikely and when pain relief occurs it is usually modest.

- The aim of treatment should be to support specific functional improvement including sleep.
- Agree functional outcomes with the patient.
- Duration of the trial depends on the patient's pain. If the patient has continuous pain, effectiveness can be shown within 1–2 weeks. If a patient has intermittent pain or flare ups of disabling pain, observe effects of opioids on 2–3 episodes of pain.
- Explore effectiveness of opioids with short supply of immediate-release morphine liquid or tablets. Advise patients about dose range. If there is no obvious benefit from a single dose of morphine 20 mg it is unlikely that the patient is going to respond to opioids.
- Trial of modified-release regimens takes longer and needs close supervision: allow for one or two upward dose titrations.
- Ask the patient to keep a diary of opioid dose and effects of treatment on pain, sleep and function, and of side effects.
- If the opioid trial was unsuccessful, taper and stop opioids within one week.

5.7 Long-term prescribing of opioids

If the opioid trial is a success, consider longer-term prescribing.

Immediate-release opioid regimens or combinations of low-dose modified-release and standard-release preparations are associated with lower dose opioid use than fixed regimens. Modified-release regimens are often considered more appropriate for patients who are using opioids problematically.

If problematic opioid use is suspected or known, consideration should be given to slowly and carefully reducing the opioids. Seek advice from local misuse services or pain services.

5.8 Follow-up and monitoring

It is preferable to prescribe analgesic medicines using acute prescriptions rather than placing them on repeat, even if their use is prolonged for several months. Repeat prescribing is associated with increased incidence of adverse effects and healthcare utilisation in all sectors.

Patients receiving opioids for chronic pain conditions and receiving ongoing treatment, should be followed up monthly for three months and at least six-monthly thereafter. Concerns about efficacy or problematic use should prompt closer supervision.

Consider intermittent dose tapering to establish continued efficacy.

5.9 Opioids started in secondary care

There are significant concerns about prescribing of opioids during hospital admission and particularly in the peri-operative period. An international consensus statement has been agreed and UK-wide guidelines developed by the Royal College of Anaesthetists.

Whilst the full guidance discusses multidisciplinary collaboration and shared decision making, transitional pain services and the use of non-opioid treatment options, the main points that need to be considered are:

- Pre-operatively the patient should be reviewed to ensure optimal management of pre-operative pain, including the prescribing of opioids. Opioids should be used judiciously which may mean giving or weaning such medicines. Patients should be screened for chronic pain and opioid use before surgery.
- Perioperative multi-modal, balanced analgesic techniques should be used tailored to the individual patient. There should be a seamless transition from theatre to recovery.
- Post-operative management must promote return to normal function and this should be the measure by which analgesia is given rather than being driven by pain score.
    - The oral route in the form of standard-release morphine would be the chosen method of providing opioid-based medications.
    - The dose should be based on age and renal function rather than weight.
    - When analgesic requirements are reduced, opioids should be weaned first, then NSAIDs should be discontinued and finally paracetamol can be stopped.
    - At the time of discharge there should be protocols to ensure communication to primary care.
    - The discharge letter should explicitly state the name, dose and duration of any opioids. The prescribing should be reviewed or discontinued usually at 5 days post-discharge and no more than 7 days.
    - Those patients that were taking opioids before surgery should be reviewed with the plan to reduce to pre-surgical doses or lower.
- Post discharge, patients should be reviewed regularly if continuing to take opioids.

If a patient who prior to surgery was not on opioids but is continuing to take them 90 days post-surgery, then a clinical review should be triggered either in primary or secondary care as this might suggest that the patient has developed persistent postoperative opioid use (PPOU).

Do not put post-operative opioids on a "repeat prescribing" template.

6.0 Do not routinely prescribe

6.1 Tapentadol

Prolonged-release tapentadol (Palexia® SR) is recommended as an option for restricted use within NHS Wales, only in the following subpopulation within its licensed indication: patients with **severe chronic pain**, in whom modified-release morphine sulphate has failed to provide adequate pain control or is not tolerated.

Tapentadol prolonged-release (Palexia® SR) is not recommended for the management of severe chronic pain in adults, which can be adequately managed only with opioid analgesics, outside of the subpopulation described above.

Immediate-release tapentadol is not recommended for use within NHS Wales.

The MHRA warns tapentadol may increase seizure risk in patients taking other medicines that lower seizure threshold, for example antidepressants and antipsychotics. Serotonin syndrome has also been reported when tapentadol is used in combination with serotonergic antidepressants. Co-prescription of these medicines is best avoided.

6.2 Pethidine

Clinical experience suggests that pethidine is particularly unsuitable for patients with chronic pain. Its high lipid solubility and rapid onset and offset may predispose patients to problem drug use. Its active metabolite norpethidine can lead to serious neurotoxicity; this can occur even if a patient has used pethidine uneventfully for some time. It has similar effects on smooth muscle spasm as equipotent doses of other opioids and so confers no advantage for patients with visceral pain.

6.3 Co-proxamol

Do not initiate co-proxamol for acute or chronic pain.

Co-proxamol was withdrawn in 2005 on the advice of the Medicines and Healthcare products Regulatory Agency (MHRA) Committee on Safety of Medicines and has been identified as low value for prescribing in NHS Wales.

If patients prescribed co-proxamol continue to have pain, the medicine is not working so should be tapered and stopped.

If patients describe benefit from co-proxamol, try other therapies in the formulary and consider non-medicine interventions.

Patients who describe benefit and are unable to tolerate other medicines or describe other medicines as unhelpful will not continue to have access to the medicine. If the patient has derived no benefit from any other pain medicine, it is likely that a non-pharmacological approach is in the patient's best interest.

6.4 Nefopam

A Cochrane review of nefopam suggests there is no evidence for efficacy. No studies met methodological inclusion criteria, so the review concluded there was no confidence about using nefopam for painful conditions.

Nefopam is specifically not recommended in patients with seizures or patients on antidepressants.

6.5 Alfentanil and fentanyl

Alfentanil or **fentanyl** buccal, sublingual, and oral transmucosal preparations should **not** be used for the treatment of non-cancer pain.

7.0 Acute pain

Acute pain is usually self-limiting, and symptoms should resolve within days or weeks. Treatment needs to be given while healing occurs. Acute pain usually responds well to analgesic medicines. Severe acute pain, e.g. following major injury or surgery, will often need to be treated with opioids. Analgesic regimens need to be flexible, because choice of medicine and dose require adjustment as the patient recovers.

Always advise about general measures including elevation, immobilisation, and heat and cold.

Medicines for acute pain should not be put on repeat prescription because patients will need to be reassessed regarding changing analgesic requirements.

If acute pain remains severe and the patient's function remains limited after four weeks, consider underlying pathological processes. If these have been excluded, the patient may be developing complex or chronic pain and prescribing should be adjusted accordingly.

7.1 Medicines for acute pain

A word about paracetamol
Paracetamol is a useful medicine for the treatment of acute pain but has little role in the management of chronic pain.

1. Paracetamol	**Paracetamol 1 g tds or qds** (should be taken regularly before adding other medicines) **Dose adjust as appropriate – see Section 10**

2. Paracetamol and NSAID (if no contraindications)	**Paracetamol 1 g qds** plus **ibuprofen 400 mg tds** **Or**… **Paracetamol 1 g qds** plus **naproxen 500 mg bd** **Dose adjust as appropriate – see Section 10** Consider topical preparations first if pain is localised to joints, hands, feet etc. Licensed for short-term use: **diclofenac gel 1% tds** (supported by Cochrane review) or **ibuprofen gel 5% tds.**

If you have concerns about gastric side effects of NSAIDs, consider co-prescribing a proton pump inhibitor. See BNF for more information.

3. Paracetamol, NSAID and opioids for moderate pain	**Paracetamol 1 g qds** plus **ibuprofen 400 mg** plus **codeine phosphate 30–60 mg up to qds** (for 48 hours then reassess) **Or**… **Paracetamol 1 g qds** plus **naproxen 500 mg bd** plus **dihydrocodeine 30–60 mg up to qds** (for 48 hours then reassess; doses up to 240mg per day for severe pain) **Dose adjust as appropriate- see Section 10**

Dihydrocodeine may be more reliable and effective as it does not require metabolising to an active drug, unlike codeine.

4. Paracetamol, NSAIDs and opioids for moderate to severe pain	**Paracetamol 1 g qds** plus **ibuprofen 400 mg or naproxen 500 mg** plus **morphine immediate-release 5–10 mg qds** initially adjusted according to response. Can use morphine solution 10 mg/5 ml or tablets (10 mg tablets can be halved). In elderly or frail patients start with 2.5 mg–5 mg dose then adjust according to response. Morphine unsuitable in CKD stage 5. **Or**… **Paracetamol 1 g qds** plus **ibuprofen 400 mg or naproxen 500 mg bd** plus **oxycodone immediate release 2.5–5 mg qds** adjusted according to response. Can use oxycodone solution 5 mg/5 ml or capsules. May have less accumulation in renal failure. **Only use if side effects of morphine cannot be tolerated or managed.** **Or**… **Paracetamol 1 g qds** plus **ibuprofen 400 mg or naproxen 500 mg bd** plus **sublingual buprenorphine 200–400 micrograms tds.** **Dose adjust as appropriate – see Section 10**

Transdermal opioid preparations (buprenorphine and fentanyl) are unsuitable for managing acute pain due to inflexible dosing and rapidly changing requirements. If transdermal preparations are used for people who are unable to take oral medicines, pain assessment should be done twice daily.

Avoid combinations of opioids unless advised and initially monitored by a specialist.

Tramadol should be very cautiously co-prescribed with antidepressants and/or gabapentinoids due to increased risks of serotonin syndrome, lowered seizure threshold and misuse.

If an opioid is genuinely indicated, consider codeine or dihydrocodeine for maximum 2 weeks as alternatives.

8.0 Chronic pain

Any medicine treatment results in a balance between benefits and harms. If a medicine doesn't relieve the symptoms for which it is being prescribed, then **the result of taking the medicine is harm only.**

Chronic pain, or pain that persists, has many consequences including lack of mobility, low mood, poor sleep, irritability and interruption of work and social activities. Anxiety, depression, post-traumatic stress disorder, and previous emotional trauma or other mental health diagnoses will make the pain feel worse and make it more difficult to treat.

8.1 Medicines for chronic pain, including chronic primary pain

There is little evidence for the **efficacy of paracetamol** for chronic pain. If there are no contraindications, ambulant patients can be advised to try OTC paracetamol 1 g qds but should **stop taking it if there is no effect within 3 days.**

If a patient is already taking paracetamol and is reporting benefit, encourage the patient to reduce the dose where possible to minimise toxicity.

1. NSAIDs (if no contraindications)	Consider topical preparations first if pain is localised to joints, hands, feet etc. Licensed for short-term use: **Diclofenac gel 1% tds** (Cochrane review supports) or **ibuprofen gel 5% tds.** **Ibuprofen 400 mg tds** **Or**… **Naproxen 500 mg bd** **Dose adjust as appropriate – see Section 10** May be useful for osteoarthritis, rheumatoid arthritis, musculoskeletal pain. Can be continued with other medicine classes if effective.

If you have any concerns about gastric side effects of NSAIDs, consider co-prescribing PPIs.

Be aware of potential renal and cardiovascular side effects of extended use of NSAIDs, particularly in older people.

2. Medicines used in the treatment of depression (if no contraindications, dose reduce in older people) Do not co-prescribe with tramadol.	**Amitriptyline initially 10 mg increasing to 50 mg taken once daily between 6–8pm** but effectiveness for pain is dose related so may need **50-125 mg** (see: SIGN guideline). **Or...** **Duloxetine 30 mg increasing to a maximum 120 mg per day** (do not co-prescribe with an SSRI). **Or…** **SSRIs** **Citalopram 20 mg increasing to maximum 40 mg** once daily. **Fluoxetine 20 mg increasing to maximum 60 mg** once daily. **Paroxetine 20 mg increasing to maximum 50 mg** once daily. **Sertraline 50 mg increasing to a maximum 200 mg** once daily. Can be continued with other medicine classes if effective. Amitriptyline is usually used for neuropathic pain but may be helpful for other types of pain if sleep is disturbed by pain.

Do not co-prescribe multiple classes of antidepressants unless recommended by a mental health specialist prescriber.

Prescribers are reminded of MHRA advice relating to the use of antidepressants in patients at risk of harming themselves, including those aged less than 25 years.

Gabapentin and **pregabalin** should not be prescribed for pain that is **not neuropathic.**

9.0 Neuropathic pain

Medicines are usually the first-line treatment for neuropathic pain but are typically not highly effective and work for only a small proportion of patients. Complete pain relief is very unlikely.

Different medicines work for different people so you may need to try a number of medicines in succession.

If a patient has no response after four weeks of being on a therapeutic dose of a medicine for neuropathic pain, they are unlikely to respond, and the medicine should be tapered and stopped (see SIGN guideline). Appropriate follow-up arrangements should be in place (e.g. telephone follow-up) to minimise the use of medicines that are ineffective.

Did you know?

If a decision is made to prescribe medicines for unlicensed indications, the rationale should be discussed with the patient, appropriate consent acquired, and all discussions clearly documented. N.B: the licensing of newer medicines reflects the stringent modern trial design.

Amitriptyline is licensed for neuropathic pain.
Duloxetine is licensed for use in diabetic neuropathy.
Carbamazepine is licensed for use in trigeminal neuralgia.
Gabapentin is licensed for peripheral neuropathic pain.
Pregabalin is licensed for peripheral and central neuropathic pain.

9.1 Medicines for neuropathic pain

1. Medicines used in the treatment of depression	**Amitriptyline 10 mg increasing to 50 mg between 6–8pm** initially but effectiveness for pain is dose related so may need **50–125 mg** (between 6–8pm) **Or...** **Duloxetine 30 mg increasing to a maximum 120 mg** once daily (do not co-prescribe with an SSRI).

2. Medicines with antiepileptic action	**Gabapentin 900–1200 mg daily in three divided doses.** **Dose adjust as appropriate – see Section 10** Doses greater than 600 mg tds should be prescribed only when some benefit has been demonstrated at lower doses. **2nd line – if unable to tolerate side effects of gabapentin:** **Pregabalin 100–400 mg daily in two divided doses.** **Dose adjust as appropriate – see Section 10** Doses greater than 200 mg bd should only be prescribed where some benefit has been demonstrated at lower doses.

9.1.1 Gabapentin and pregabalin

Gabapentin and pregabalin are structurally similar medicines acting through the alpha-2-delta subunit of voltage-gated calcium channels. Bioavailability of gabapentin decreases as the dose increases whereas pregabalin bioavailability is largely independent of dose, which explains the **increased risk associated with high-dose pregabalin use**.

There are no trials that compare efficacy of gabapentin with that of pregabalin. The side effects of both medicines occur with similar frequency although an individual may tolerate one medicine more than the other. Both medicines can cause unsteadiness and should be used **with caution in patients at risk of falls**.

Gabapentin should be tried before pregabalin. Be extremely cautious about prescribing gabapentin and pregabalin with other sedating medicines, particularly benzodiazepines.

Professionals prescribing gabapentin and pregabalin should not only be aware of the potential benefits of these medicines to patients, but also the risk of dependence, misuse and diversion.

Practitioners should prescribe gabapentin and pregabalin appropriately to minimise the risks of misuse and dependence and should be able to identify and manage problems of misuse if they arise. Most patients who are given these medicines will use their medicines appropriately without misuse.

Patients who are offered these medicines need to have sufficient information to consent to the treatment plan. Patients should be aware of the likely efficacy of the medicines for management of their symptoms and also about the risk of harms, including dependence.

9.1.2 Topical treatments for neuropathic pain

Capsaicin cream 0.025% or 0.075%	**To be regularly applied four times daily.** Much less effective if used intermittently. If no response after first tube, then **stop.** If evidence of benefit, arrange regular review to establish continued efficacy. Consider for the following conditions when no response to oral therapy or when side effects of oral therapy limit use: • post-herpetic neuralgia; • discrete surface neuropathic pain of clear origin. Consider starting with 0.025% capsaicin cream for any indication and use 0.075% to optimise response in people who report good effect.

Lidocaine 5% plaster	**1 to 2 patches to be applied for 12 out of 24 hours.** Consider when no response to oral therapy or when side effects of oral therapy limit use, for: • **post-herpetic neuralgia only.** **Stop if no clear benefit within 28 days.** Patches can be cut to size for smaller areas of pain to allow multiple use per patch. Lidocaine plasters have been identified as low value for prescribing in NHS Wales.

10.0 Dose adjustments

Prescribers must ensure that the choice and dose of all analgesic medicines are appropriate for the patient and take into account their age, weight, frailty and polypharmacy.

10.1 Paracetamol

Risk factors for paracetamol toxicity:

- **Body weight less than 50 kg**
- **Alcohol dependency**
- **Severe liver disease**
- **Increasing age and/or frailty** where paracetamol might have been prescribed for significant periods and who have morbidities and polypharmacy, which can further increase their risk of inadvertent overdose and toxicity
- **Malnourished patients** with nutritional deficiency and/or chronic debilitating illness and therefore likely to be glutathione deplete e.g. acute or chronic starvation (patients not eating for a few days), eating disorders (anorexia **or** bulimia), cystic fibrosis, AIDS, cachexia, alcoholism, cirrhosis
- **Chronic dehydration**
- **Hepatic enzyme induction or evidence of ongoing liver injury** e.g. long-term treatment with liver enzyme-inducing drugs such as carbamazepine, phenobarbital, phenytoin, primidone, rifampicin, rifabutin, efavirenz, nevirapine, St John's wort; regular consumption of ethanol in excess of recommended amounts, particularly if nutritionally compromised

Table 3. Paracetamol dosing

Dose of ORAL paracetamol in ADULT patients WITHOUT risk factors	
500 mg – 1 g four times daily (minimum 4 hours between doses) **Maximum 4 g in 24 hours**	
Dose of ORAL paracetamol in ADULT patients WITH risk factors Note: Low body weight is a risk factor on its own and requires dose reduction	
Body weight	Dose reduction is required normally to 15 mg/kg body weight, per dose (body weight up to 50 kg).
33 – 39 kg	**Maximum 2 g in 24 hours** (minimum 6 hours between doses) Oral suspension may be required for an accurate dose.
40 – 50 kg	500 mg – 1 g up to four times a day **Maximum 3 g in 24 hours** (minimum 6 hours between doses)
> 50 kg	500 mg – 1 g up to four times a day **Maximum 3 g in 24 hours** (minimum 4 hours between doses)

Safe prescribing of paracetamol

1. Record patient weight.
2. Assess the patient for risk factors for toxicity.
3. If risk factors are present, **REDUCE** the total daily dose.
4. Prescribe dose in multiples of 500 mg of paracetamol – do not prescribe a range.
5. Do not exceed four doses of paracetamol in 24 hours.

10.2 Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs have an established place in the treatment of rheumatoid arthritis and gout and confer some benefit in chronic low back pain and some forms of osteoarthritis. They are associated with cardiovascular and gastrointestinal risk factors. Lower-risk agents should be prescribed first line at the lowest effective dose for the shortest duration necessary to control symptoms. Ibuprofen in doses up to 1.2 g daily or naproxen 0.5 g –1 g daily, have not been associated with significant thrombotic or cardiovascular risks.

Where one medicine is ineffective, a switch to a different NSAID may be helpful. Extra caution is required for the use of NSAIDs in frail patients with an increased risk of acute kidney injury with dehydrating illness – refer to CEPP National Audit. There are numerous cautions and contraindications to the use of NSAIDs – see below. Consider dose reductions in people who are low weight (< 50 kg), frail, aged > 65 years, and in those who are receiving multiple medicines (polypharmacy). In all cases, NSAIDs should be used at the lowest possible dose for the shortest time needed.

Example dose reductions

- **Ibuprofen** – 200 mg up to three times a day
- **Naproxen** – 250 mg twice daily up to twice daily

See BNF for further advice on prescribing.

Table 4. Risk factors and cautions for NSAID use

At risk groups	Key common drug interactions
Older people (aged over 65 years) Renal or hepatic impairment Heart failure (contraindicated) Ischaemic heart disease (IHD) Peripheral arterial disease (PAD) Cerebrovascular disease Uncontrolled hypertension Pregnant or breastfeeding Active gastrointestinal ulceration or bleeding (contraindicated) History of gastrointestinal ulceration, bleeding or perforation	Angiotensin Converting Enzyme (ACE) inhibitors Angiotensin II receptor antagonists Anti-platelets Oral anticoagulants Ciclosporin Oral corticosteroids Diuretics Pentoxifylline Lithium Other NSAIDS or COX II inhibitors Selective serotonin reuptake inhibitors Tacrolimus Venlafaxine
Potential high-risk combinations	
NSAID plus ACE inhibitor or ARB and diuretic NSAID and a diagnosis of heart failure NSAID plus eGFR < 60 mg/min NSAID plus warfarin NSAID in patients aged over 75 years without a PPI COX II inhibitor or diclofenac and a diagnosis of IHD, PAD or cerebrovascular disease	

10.3 Gabapentinoids

The dose of gabapentin and pregabalin should be reduced for patients with impaired renal function, for frail or older people, or those who have previously demonstrated a predisposition to adverse effects or are prescribed other sedating medicines.

Examples of adjusted titrations are included here. Weekly titrations are preferred in primary care settings and can be slower if needed. Refer to BNF for more information.

Gabapentin

Titration	Week 1	Week 2	Week 3
Standard dose	300 mg in the evening	300 mg morning and evening	300 mg three times a day
Reduced dose	100 mg in the evening	100 mg morning and evening	100 mg three times a day

Pregabalin

Titration	Week 1	Week 2	Week 3
Standard dose	75 mg in the evening	75 mg twice a day	75 mg morning and 150 mg evening
Reduced dose	25 mg in the evening	25 mg twice a day	25 mg morning and 50 mg evening

Renal dose adjustments for gabapentin

Creatinine clearance (ml per minute)	Total gabapentin dose
50–79	600–1800 mg daily in 3 divided doses
30–49	300–900 mg daily in 3 divided doses
15–29	150–600 mg daily in 3 divided doses*
<15 ǂ	150–300 mg daily in 3 divided doses*

* 150 mg daily dose to be given as 300 mg in 3 divided doses on alternate days.

ǂ For patients with creatinine clearance < 15 ml/min, the daily dose should be reduced in proportion to creatinine clearance (e.g. patients with a creatinine clearance of 7.5 ml/min should receive one-half the daily dose that patients with a creatinine clearance of 15 ml/min receive).

Renal dose adjustments for pregabalin

Creatinine clearance (ml per minute)	Total pregabalin dose	
	Starting dose	Maximum dose
30–60	75 mg	300 mg daily in 2 or 3 doses
15–30	25–50 mg	150 mg daily in 1 or 2 doses
<15	25 mg	75 mg once daily