Grŵp Strategaeth Meddyginiaethau Cymru Gyfan
All Wales Medicines Strategy Group

All Wales Analgesic Stewardship 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, 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).

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Development of this guidance

Analgesic stewardship aims to improve patient outcomes, reduce analgesic-related harm and ensure cost-effective use of analgesics to provide optimal pain management. Analgesic stewardship activities may include guideline development, monitoring of analgesic use, and trends and provision of education material to patients and practitioners[1].

This guidance has been adapted from the Quality Prescribing in Chronic Pain document by the Scottish Government and NHS Scotland[2]. Scottish guidance was developed by a multi-disciplinary working group of professionals, experts by experience, and third sector organisations[2].

This document has been adapted for Wales by a working group in Wales and the All Wales Prescribing Advisory Group (AWPAG), and adjusted based on additional guidance and recommendations from the All Wales Medicines Strategy Group (AWMSG), the National Institute for Health and Care Excellence (NICE), the Scottish Intercollegiate Guideline Network (SIGN) and comments received through national consultation. We are extremely grateful to our colleagues in Scotland and all those who contributed to the working group and to the review and development of this document.

In line with international evidence, there is a general shift away from a single condition approach to medicines strategy, and it is therefore important to consider this document in the broader context of a holistic approach to care[3,4].

Audits and reviews based on the recommendations in the document should be put in place as part of prescribing quality improvement programmes.

Why this guidance is important

Pain is one of the most common presenting symptoms in primary and secondary care. Between one-half and one-third of the adult population in the UK is affected by chronic pain, which in Wales could equate to as many as 1.3 million people, with symptoms ranging from mild discomfort to debilitating pain[5].

Wales spends more per capita on analgesic prescribing (medicines included in British National Formulary, Chapter 4.7) than England, Scotland or Northern Ireland[2]. Opioid prescribing in Wales increased by 30% in the 10-year period from 2008–2009 to 2018–2019[6].

There is increasing evidence that many analgesic medicines, including opioids, gabapentin and pregabalin, are not effective for many people but have significant potential for harm and misuse[7-9]. There are reports of an increasing street value, and cases of dependency have been described[10-12]. Evidence also highlights that over recent years, whilst the overall number of drug-related deaths has slightly reduced, there has been a significant increase in the number of deaths where both gabapentin and pregabalin have been involved[13].

Adopting the principles of analgesic stewardship into clinical practice across all sectors of healthcare aims to bring benefits including reduced incidence of analgesic-related harm as well as improved use of healthcare and economic resources[14].

Contents

Glossary

ADR	Adverse drug reaction
AWMSG	All Wales Medicines Strategy Group
AWPAG	All Wales Prescribing Advisory Group
BNF	British National Formulary
CD	Controlled drug
Chronic pain	Pain lasting longer than 12 weeks or which has persisted beyond normal tissue healing time
Chronic secondary pain	Pain caused by an underlying condition, for example: osteoarthritis, rheumatoid arthritis, ulcerative colitis, endometriosis
eGFR	Estimated glomerular filtration rate
Formulary	A list of medicines recommended for use within a health board
MED	Morphine equivalent
MHRA	Medicines and Healthcare products Regulatory Agency
Neuropathic pain	Pain from nerve damage, e.g. diabetes, shingles, multiple sclerosis, pain following stroke; it is likely to be a type of chronic secondary pain
NNT	Number needed to treat
NPI	National Prescribing Indicator
NSAID	Non-steroidal anti-inflammatory drug
OTC	Over-the-counter medication
PHN	Post-herpetic neuralgia
PNP	Peripheral neuropathic pain
Polypharmacy	The use of more than one medicine by a patient
Read Code	A code within primary care IT systems to indicate particular information
SIGN	Scottish Intercollegiate Guidelines Network
SNRI	Serotonin-noradrenaline reuptake inhibitor
SPIRA	Server for Prescribing Information Reporting and Analysis
TCA	Tricyclic antidepressants
UKMi	UK Medicines Information
WHO	World Health Organization

1.0 Introduction

1.1 What is the purpose of this guidance?

To provide evidence-based, prudently driven guidance for improving analgesic stewardship, through promotion of quality improvement and harm reduction in the prescribing of analgesic medicines in all sectors of healthcare in NHS Wales.

1.2 Who this guidance is for

- Healthcare professionals who prescribe or review analgesic medicines
- Medicines management units who are tasked with reviewing and monitoring analgesic prescribing
- Health board service managers involved in service development and reviewing service delivery and outcomes

1.3 What this guidance does not cover

- Analgesic or non-pharmacological interventions recommended by specialist practitioners including pain specialists and other secondary care practitioners.
  - It is expected that specialist recommendations for prescribing comply with national and local guidance where available.
  - Recommendations or prescriptions from specialist practitioners should be accompanied by sufficient information to explain the rationale and plan for review of efficacy as per GMC Good Practice guidelines for prescribers. This is especially important when medicines are being prescribed for unlicensed indications.

Welsh Government have produced guidance for health boards, healthcare professionals, and people living with pain and their carers, which is designed to support service improvement and increase access to pain management support[5].

1.4 Where this guidance fits

The advice in this document should be considered alongside existing clinical and policy guidance including:

AWMSG

- Chronic pain resources
- Polypharmacy: guidance for prescribing[15]

National Institute for Health and Care Excellence (NICE)

- NICE guideline 215: Medicines associated with withdrawal and dependence[16]
- NICE guideline 197: Shared decision making[17]
- NICE guideline 193: Chronic pain (primary and secondary) in over 16s: assessment of all chronic pain and management of chronic primary pain[18]
- NICE clinical guideline 173: Neuropathic pain in adults: pharmacological management in non-specialist settings[19]
- NICE guideline 59: Low back pain and sciatica in over 16s: assessment and management[20]
- NICE clinical guideline CG177: Osteoarthritis: care and management[21]

Royal College of Anaesthetists

- Core Standards for Pain Management Services in the UK[22]
- Opioids Aware[12]

Scottish Intercollegiate Guidelines Network (SIGN)

- Management of Chronic Pain[23]

- Quality Prescribing in Chronic Pain[2]

Welsh Government

- A Healthier Wales[4]
- Living with Persistent Pain in Wales[5]

1.5 Monitoring prescribing data

Prescribing data are available from the SPIRA dashboard for National Prescribing Indicators providing consistent metrics for health boards[24].

2.0 Benefits of improving analgesic stewardship

2.1 Benefits for people with pain

Medicines remain the most common intervention offered to people presenting with pain, despite evidence that they are often poorly effective and can cause adverse effects, which may worsen individuals' general health and well-being. Non-pharmacological management of pain can reduce analgesic burden and therefore, the incidence of associated short- and long-term adverse effects. Supported self-management can improve overall outcomes for people with pain, in line with Welsh Government guidance on Living with Persistent Pain in Wales[5].

This document can guide health boards and practitioners to consider:

- developing and agreeing a structured approach to analgesic prescribing for pain, to include:
  - appropriateness of analgesics for the individual's diagnosis, accounting for co-morbidities and polypharmacy;
  - trials of analgesics to ensure efficacy, functional benefit and tolerability before they are prescribed long term;
  - regular review of prescribed analgesics to ensure ongoing benefit and identify adverse effects before long-term harm is caused.
- promoting patient-centred care in all sectors of healthcare by:
  - improving access to individualised support for people with pain, including supported self-management and guidance for early referral to specialist services where appropriate;
  - developing local partnerships with representatives from third sector organisations and experts by experience to review and develop support services that meet the needs of people living with pain.

2.2 Benefits for clinicians

Pain is ubiquitous and people with pain present to all specialties and in all sectors of health and social care. Strengthening analgesic stewardship should benefit clinicians through:

- improved communication pathways between practitioners across sectors and specialties, which could include:
  - timely access to advice on analgesic prescribing for people with complex medical needs or polypharmacy;
  - services to support people who are identified with problematic prescribed analgesic use;
  - processes for convening case conferences where an individual's pain experience is identified as a barrier to other healthcare interventions including frequent attendance in primary care or out-of-hours services;

- wider availability of education and training on analgesic stewardship and basic pain management, leading to increased knowledge throughout the workforce.

2.3 Benefits for organisations

Through improved analgesic stewardship, implementation of this document can:

- improve quality of care for people with pain and reduce harm, adverse effects and ultimately, the burden on healthcare services;
- be used as an opportunity to review local pathways and services to ensure timely access to pain management support, and highlight service development needs;
- facilitate appropriate prescribing, in line with AWMSG National Prescribing Indicators:
  - e.g. since the introduction of the AWMSG tramadol educational resources and National Prescribing Indicator for tramadol, and its reclassification, tramadol prescribing in Wales has decreased[25,26].

3.0 Recommendations to improve analgesic stewardship

3.1 Actions for health boards and partner organisations[27]

3.1.1 Nominate local leads

Nominate local leads (e.g. one pharmacist and another healthcare professional with an interest in pain management) to drive delivery and implementation of the recommendations within this document across the health board.

- Part of this role should be to ensure appropriate links and communication between primary and secondary care clinicians, particularly around recommendations from specialist services, hospital discharge and medicines reconciliation.
  - Guidance and information is available on discharge planning in each health board and in the All Wales Multidisciplinary Medicines Reconciliation Policy[28,29].
  - Examining means of improving access to patient records and shared management plans between primary care and specialist services is encouraged.

3.1.2 Take a whole system approach to delivering improvement

This would include:

- Recognising the impact that pain, especially persistent pain, can have on individuals, carers and healthcare services in primary and secondary care.
- Ensuring that primary care clinicians and secondary care clinicians work collaboratively.
- Considering the role of community pharmacy in supporting analgesic stewardship initiatives locally and nationally.
- Working with third sector organisations to develop capacity for self-management and co-production as part of non-pharmacological management of chronic pain.
- Where provision is not in place, health boards should work towards providing appropriate supporting resources for clinicians to share with patients, for example:
  - information – help to navigate and understand their condition, including treatment plans and support tools;

  - emotional and psychological support – peer support, counselling at key stages;
  - support around employment – guidance for employers, support to stay in work;
  - access to online support – online chat, access to results, record symptoms.
- Consider the guidance within this document alongside available prescribing data.

3.1.3 Prioritise analgesic stewardship

Prioritise analgesic stewardship within prescribing action plans and use this document to drive improvement. This might include:

- developing support services for people who develop problematic behaviour due to dependence on prescribed analgesic medicines and advice and support for prescribers;
- developing health board policies to manage complaints resulting from the withdrawal of analgesic medicines when prescribers have concerns about an individual's use of medicines or harm resulting from them, and when withdrawal has been done in accordance with local or national guidance;
- support to develop public awareness campaigns locally to highlight the limitations and risks of analgesic medicines.

3.2 Actions for clinical practitioners, services and primary care

- Ensure patients presenting with pain are offered a person-centred assessment, to identify factors contributing to the pain and how the pain affects the person's life. This should take into account the impact pain can have on the person's ability to manage other physical and mental health conditions.
  - For primary care, consider encouraging practices to develop a disease register, following guidance in this document and using chronic pain Read Code 1M52 (Chronic Pain) to facilitate audit and review.
- Pursue non-pharmacological approaches wherever possible, either alone or in conjunction with medicines. Self-management should be encouraged and supported[5].
- Develop a clear management plan collaboratively with patients, including review dates. It is important that patients understand their pain and have realistic expectations. The plan should focus on patient-centred care[30] and improving function, not simply on pain reduction.
- Follow a clinically appropriate approach to initiation of analgesia, discussing expectations, risks and benefits and incorporating agreed criteria for stopping or continuing medication.
  - Analgesic medicines should be initiated as a trial, regardless of indication.
  - Functional goals should be agreed between the patient and prescriber at initiation, with a fixed time period and review date agreed.
  - An explanation of how analgesic medicines that are not assisting with attainment of functional goals will be reduced and stopped, should be given at initiation and again when medicines are reviewed.
  - Analgesic medicines should not be given as repeat prescriptions unless clear evidence of benefit is demonstrated at a review. Consider no more than 3 months of repeat prescribing each time, to encourage regular review.

- Determine features in the patient's history that may increase the likelihood of analgesic misuse, such as a history of substance misuse including alcohol.
  - Evaluate the risks of continued prescribing and make appropriate decisions regarding quantity of medicines prescribed and the intervals at which the patient should be reviewed.
  - Investigate any behaviours or patterns of prescription requests that may indicate a problem, such as excessive or early ordering, or repeated loss of prescriptions.
  - Care should be taken when co-prescribing medicines associated with dependence and withdrawal, e.g. opioids, gabapentinoids benzodiazepines, z-drugs, and other sedating agents.
- Review effectiveness, tolerability and compliance on an ongoing basis when analgesic medicines are prescribed long term (e.g. six months).
  - People prescribed analgesic medicines should have an annual pain management review to consider medicines and non-pharmacological aspects of management. Coding should be agreed locally for consistency and to improve opportunities for reporting, e.g. Read Code 66n (Chronic Pain Review) to record when a chronic pain review has been undertaken.
- The burden of medicines should be reduced where possible, in line with polypharmacy guidance. This is especially important where:
  - analgesic medicines are not supporting improvement or maintenance of function;
  - high levels of pain reporting continue despite the use of regular analgesic medicines;
  - high doses of opioids (> 120 mg oral morphine equivalence per day) or combinations of medicines associated with dependence and withdrawal (e.g., opioids, gabapentinoids and benzodiazepines) are being prescribed;
  - adverse effects from analgesics are demonstrated or where there are concerns about dependence or misuse.

4.0 Actions for medicines management units

Support clinicians in all sectors to follow national and local guidelines by:

- Providing regular feedback on prescribing patterns, e.g.:
  - including measures against National Prescribing Indicators;
  - developing audit cycles to analyse analgesic prescribing in all areas, against agreed standards; agree and implement change where needed and review outcomes of the process.
- Providing information and support to clinicians in all sectors on analgesic choices, safety and concerns. This could include:
  - wider dissemination of prescribing incidents, overdose-associated deaths, pertinent coroners' reports, in order to share learning and improve practice;
  - providing and developing opportunities for education and training on pain, pain management and particularly in regard of supporting self-management and non-pharmacological interventions, in all sectors.
- Working with specialist services to improve communication and shared practice.

- Working with specialist services and practitioners to ensure local guidelines and pathways are reflective of national guidance, evidence based and kept up to date.

5.0 Additional information

Why additional information has been included

The following information is provided to assist with the development of analgesic stewardship plans and reviews. It is not intended as guidance for clinical practice in this format.

Non-pharmacological therapies

- Healthcare providers should support patients to self-manage their pain.
- Self-management can be described as a set of approaches that aim to enable people to feel able to live well on their terms with a long-term condition(s) or being an unpaid carer, with support from a range of family, peer groups and professionals. It helps someone to learn about their condition, acknowledge the impact it has on their life, make changes and identify areas where they require support, for example Education Programmes for Patients.
- Supported self-management is a recognised intervention for persistent pain management in the document Living with persistent pain in Wales[5], but is important in all pain types.
    - It does not seek to cure, but helps patients manage their condition and minimise the impact pain has on their everyday life. Healthcare providers in all sectors and specialties should discuss self-management options with patients, and be able to direct patients to appropriate resources, where they can learn more about pain and what they can do for themselves.
    - There is evidence that brief education about pain can reduce sick leave and disability[31].
    - There is strong evidence for the benefits of physical exercise and activity as part of the management of chronic pain, and this is highlighted in NICE guidelines and SIGN 136[23]. Giving advice to participate in activity without any additional explanation or support is unlikely to be effective.

Concerns about dependency and misuse of analgesic medicines

Prescribers should be supported to ensure:

- They have a complete list of medicines (including any over-the-counter products or illicit drugs) that patients are taking, so that hazardous medicine interactions can be minimised or avoided[10].
- Patients are given information on the potential benefits of their medicine, as well as the risks and reported side effects. This is particularly important for medicines that have the potential for dependence and withdrawal effects (including gabapentinoids and opioids).
- Patients are told about the potential for analgesic medicines to cause dependence and misuse.
- Individuals whose care may benefit from specialist support around dependence and withdrawal are able to access appropriate support.

Early intervention and identification of potential issues by primary care practitioners may help to prevent future problems[16].

Considerations in secure environments
The care of patients within secure settings carries many additional difficulties. The management of pain during imprisonment presents a serious challenge given the misuse potential of opioid analgesics and of high doses of medicines such as pregabalin and gabapentin. Clarity about the need for adequate and appropriate treatment of pain that takes account of both the context and risk of dependence, and the principles underlying pain treatment, is essential[32].

Resources to support the management and prescribing for pain in secure environments include the Royal College of General Practitioners' Safer prescribing in prisons: guidance for clinicians and Public Health England's Managing persistent pain in secure settings[33,34].

Driving advice
Provide advice to patients regarding the likely risk of their medicines causing side effects that may impair their driving. It is a driver's responsibility to decide whether they consider their driving is impaired, or they believe it might be impaired. Patients should be advised not to drive if any symptoms or signs develop suggesting that their driving may be impaired, such as sleepiness, poor co-ordination, impaired or slowed thinking, dizziness, or visual problems. Advise patients not to drive at the start of therapy, and when doses are increased (see Department for Transport Guidance for healthcare professionals on drug driving).

Pharmacological therapies
- Treatment options are dependent on patient assessment.
- A clear indication for the prescription of an analgesic medicine should be recorded in the patient's medical notes.
- Analgesic medicines should be started as a trial and only continued where there is evidence of benefit to the individual.
    - Functional outcomes should be agreed between the patient and the prescriber when the analgesic is initiated and used to review progress and decide whether the medicines should be continued.
- Clinicians should plan to trial intermittent dose tapering to establish continued efficacy.
- Many analgesic medicines are used off-label – clinicians should ensure this is properly recorded and discussed with the patient.

Paracetamol
The evidence of benefit from paracetamol varies depending on the type of pain present. There is high-quality evidence that paracetamol is ineffective in reducing pain and disability or improving quality of life in patients with low back pain and only offers a small but not clinically important benefit for pain and disability reduction in patients with hip or knee osteoarthritis[35].

The combination of paracetamol 1000 mg–4000 mg daily plus ibuprofen 400 mg has been shown to be significantly superior to paracetamol alone in patients with hip or knee osteoarthritis but is associated with a higher risk of gastrointestinal bleeding. Paracetamol dosing should be adjusted appropriately in patients weighing less than 50 kg or with other risk factors for hepatotoxicity such as acute malnutrition, or for those taking medicines that may affect liver function[36].

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 where co-morbidities and polypharmacy further increase the risk of inadvertent overdose and toxicity.
- **Malnourished patients** with nutritional deficiency and/or chronic debilitating illness and therefore likely to be glutathione depleted 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.

Safe prescribing of paracetamol[37]

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

Table 1. Paracetamol dose adjustment

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)

Oral 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.

Table 2. Risk factors and cautions for NSAID use[38]

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	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	

Topical NSAIDs

Topical NSAIDs are safe, may be effective and should be considered in the treatment of chronic pain from musculoskeletal conditions, particularly in patients who cannot tolerate oral NSAIDs[23].

Opioids

There is growing concern about the rise of prescribed opioid use, in the UK and internationally, not least because of the risk of dependence and the very limited evidence for their effectiveness in long-term pain conditions. Clinicians need to take

account of this when making decisions about treatment and advising patients and others involved in their care. This is especially pertinent when opioids are being considered for chronic pain conditions.

Not only is there a lack of evidence for efficacy of opioids in the long-term treatment of chronic pain there is also considerable risk, such as increased risk of overdose, fractures, misuse or dependence; this should be explicitly discussed with patients[39]. A recent Cochrane review found an increased risk of adverse events with opioids compared with placebo and compared with non-opioid active comparator[40]. There was also an increased risk of serious adverse events compared with placebo. The authors noted that "*based on the adverse events identified, clinically relevant benefit would need to be clearly demonstrated before long-term use could be considered in people with chronic non-cancer pain in clinical practice*"[40].

Despite limited evidence for use of co-codamol 8/500 mg, a small percentage of patients may not tolerate stronger opioids and co-codamol 8/500 mg may be appropriate in these patients. There may be some risk associated with co-codamol 8/500 mg, such as addiction and constipation; hence a step down to paracetamol alone should be trialled. Patients who are co-prescribed two opioids for mild to moderate pain should be reviewed.

Key points for prescribing opioids

- It is crucial that the potential benefits and potential risks are discussed with the patient.
- Side effects resulting from continuing use of opioids may include tolerance, withdrawal, weight gain, reduced fertility and irregular periods, opioid-induced hypopituitarism, erectile dysfunction, hyperalgesia, depression, dependence, addiction, reduced immunity, osteoporosis, and constipation.
- There is a variety of evidence regarding misuse of these medicines, and this should be considered particularly when prescribing to at-risk patients.

The patient should be reviewed within two to four weeks of initiation of opioid treatment whatever the indication. The frequency of review once the opioid regimen has been established will depend on the early effectiveness of treatment, the frequency of troublesome side effects, the timing of additional interventions to control pain (e.g., surgery) and the presence of concerns in relation to problematic use of opioids. When a regimen is stable, the patient reports substantial relief of symptoms and additional concerns do not dictate otherwise, opioids should be reviewed at least six-monthly[23].

- Faye's story illustrates how opioid prescribing can potentially have serious, unintended consequences[41].

Continue opioids only after confirming clinically meaningful improvements in pain and function without significant risks or harm. Various thresholds are quoted where the risk of harm outweighs the benefits. Opioids Aware, produced by the Faculty of Pain Medicine, is a resource for patients and healthcare professionals to support prescribing of opioid medicines for pain[12]. Opioids Aware states: "*There is no good evidence of dose–response with opioids, beyond doses used in clinical trials, usually up to 120 mg/day morphine equivalent. There is no evidence for efficacy of high-dose opioids in long-term pain. The risk of harm substantially increases at doses of ≥ 120 mg morphine equivalent dose (MED)/day with no increase in benefit*"[12].

There is evidence to suggest that the majority of patients taking opioids for moderate to severe pain will develop opioid-induced constipation; tolerance does not develop to this side effect[23]. Refer to local formularies for guidance on specific agents for the management of opioid-induced constipation.

Opioid prescribing points

Opioids are not effective in every patient, and this should be discussed with the patient prior to commencing treatment. Opioids are not routinely recommended for managing acute or chronic lower back pain[20], fibromyalgia or migraine[42-45]. If opioids are deemed appropriate, then a realistic aim should be for a minimum of a 30% improvement in pain and/or a significant improvement in functional ability; complete pain relief is rarely achieved with opioids.

A maximum four-week trial is recommended when prescribing opioids, to observe efficacy, tolerability and suitability. Morphine is the recommended drug for opioid trials (to determine if a person has a positive response to an opioid medicine), rather than another opioid (Opioids Aware)[12]. An alternative opioid should only be used where morphine is beneficial but produces intolerable side effects.

'Starting low' and 'going slow' is a good strategy for newly prescribed opioids to help minimise side effects. Before starting treatment with opioids, agree with the patient a treatment strategy which should include functional outcomes and plan for end of treatment if those outcomes are not acheived[8].

As a general rule, it is perhaps better to consider the oral morphine equivalence of the prescribed opioid rather than the drug. However, opioids for mild to moderate pain are considered to include codeine, dihydrocodeine and low doses of buprenorphine (sublingual up to 200 micrograms and transdermal preparations up to 20 micrograms per hour). Opioids for moderate to severe pain include tramadol, buprenorphine (sublingual up to 400 micrograms and transdermal from 20 micrograms per hour), morphine, oxycodone, fentanyl and tapentadol. They should be prescribed instead of, not alongside, opioids for mild to moderate pain. They are best used in conjunction with non-opioid analgesic medication to reduce dosing and side effects.

Dose equivalence charts and tapering guides are available to facilitate switching or discontinuing opioids (Table 3). However, it is important to point out that equivalent analgesic dose conversions are only estimates and patients may be more sensitive to the new opioid than expected. This may lead to life-threatening over-sedation, and/or ventilatory impairment. If switching, ensure the dose of the new agent is reduced by 20–50%.

Table 3. Opioid equivalence tables

Oral opioids[12]	Potency ratio with oral morphine	Equivalent dose to 10 mg oral morphine
Codeine phosphate	0.1	100 mg
Dihydrocodeine	0.1	100 mg
Morphine	1	10 mg
Oxycodone	1.5	6.6 mg
Tapentadol	0.4	25 mg
Tramadol	0.1	100 mg

Transdermal opioids	Patch strength (microgram/h)	Oral morphine equivalent dose
Buprenorphine[12]	5	12 mg
	10	24 mg
	20	48 mg
	35	84 mg
	52.5	126 mg
	70	168 mg
Fentanyl[12,46]	12	30 – 45 mg
	25	60 – 90 mg
	50	120 – 180 mg
	75	180 – 270 mg
	100	240 – 380 mg

Note: Table 3 is to be used as a guide rather than a set of definite equivalences. Refer to the Summary of Product Characteristics for further details. Most data on doses are based on single-dose studies so may be less accurate in chronic use where similar data are unavailable. Consider that individual patients may metabolise different medicines at varying rates. **The advice is to always calculate doses using morphine as standard and to adjust them to suit the patient and the situation – consider making a reduction in morphine equivalence dose of 20–50% when changing medicines.** Caution should be used in renal and hepatic failure. Avoid patch use in unstable pain[47].

Tramadol

The number of deaths where an opioid (especially tramadol), is mentioned on the death certificate continues to increase, despite some reductions in prescribing rates. In 2019, there were seven deaths related to tramadol in Wales, which accounted for around 5.8% of all opioid-associated deaths. Tramadol has been classified as a Schedule 3 controlled drug since 2014.

Tramadol is considered to be an opioid used for moderate pain[48]. The dose range is 50–100 mg every 4–6 hours, maximum 400 mg in 24 hours. If converting to or from tramadol and another opioid, be aware of the wide range of morphine equivalence. It is similar in adverse effect profile to codeine and dihydrocodeine, but has a greater potential for medicine interactions. It should not be combined with other opioids for mild to moderate pain. Clinicians should be aware of potentially serious side effects (e.g. serotonin syndrome) that may result from prescribing tramadol with other serotonin enhancing drugs such as selective serotonin reuptake inhibitors.

Medicines for neuropathic pain

It is important to assess whether there are elements of neuropathic pain. Screening tools such as the Leeds Assessment of Neuropathic Symptoms and Signs can be used to assist in making a diagnosis[49]. Neuropathic pain has been defined by the International Association for the Study of Pain as pain caused by a lesion or disease of the somatosensory nervous system. All Wales Chronic Pain Resources and NICE guidelines recommend amitriptyline, duloxetine, pregabalin or gabapentin as first-line pharmacological treatment for neuropathic pain[19]. The medicine to use first mainly depends on clinical preference and patient factors. If the initial treatment is not effective or is not tolerated, offer one of the remaining three medicines, and consider switching again if the second and third medicines tried are also not effective or not tolerated.

A meta-analysis of pharmacotherapy for neuropathic pain in adults showed that outcomes were relatively modest, and were generally not dependent on the aetiology of the underlying disorder[50]. Despite a low number needed to treat (NNT) for opioids (including tramadol), the quality of evidence was moderate and therefore the authors proposed first-line use of tricyclic antidepressants (TCAs), serotonin and norepinephrine reuptake inhibitors (SNRIs), pregabalin and gabapentin. Weak recommendations were made for lidocaine patches, capsaicin patches and tramadol as second-line treatments, and for opioids (particularly oxycodone and morphine) as third-line treatment. However, there is no consideration of health economics in these recommendations and current acquisition costs would support the NICE recommendation of amitriptyline, duloxetine, pregabalin or gabapentin first line in neuropathic pain (excluding trigeminal neuralgia)[50].

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.

Prescribing points

Amitriptyline

Amitriptyline should be started at a low dose and slowly titrated up from 10 mg to 125 mg[23].

Gabapentinoids

Gabapentin typical initiation dose is 300 mg at night, and titrated upwards usually by 300 mg per week. Evidence suggests that a minimum of 1,200 mg is needed and doses may need to be increased to the maximum of 3,600 mg. Doses above 1,200 mg per day should only be prescribed where there is some evidence of benefit (at the lower doses). Older people may require dosage adjustment due to declining renal function (see below).

Pregabalin typical initiation dose 75 mg twice daily, increased up to a maximum of 300 mg twice daily. This would be managed according to side effects and clinical effectiveness. Older people may require dosage adjustment due to declining renal function (see below).

There are risks of misuse for gabapentin and pregabalin. In April 2019, gabapentin and pregabalin were reclassified as Schedule 3 Controlled Drugs (CDs) under the Misuse of Drugs Regulations 2001, and the Safe Custody Regulations 1973[51]. Drug-related deaths involving gabapentin and pregabalin in Wales have risen from 0 in 2009, to 13 in 2019[52]. Clinicians should ensure patients treated with these medicines are reviewed at least annually.

Table 4. Example of equivalent doses of gabapentin and pregabalin[53]

Example of equivalent doses of gabapentin and pregabalin	
Gabapentin 300 mg three times a day	Pregabalin 75 mg twice a day
Gabapentin 600 mg three times a day	Pregabalin 150 mg twice a day
Gabapentin 900 mg three times a day	Pregabalin 225 mg twice a day
Gabapentin 1,200 mg three times a day	Pregabalin 300 mg twice a day
NB – Patients with renal impairment should have their dose of gabapentin or pregabalin reduced per BNF recommendation in Table 5.	

For further information please see UKMi Q&A on 'How do you switch between pregabalin and gabapentin for neuropathic pain, and vice versa?'

Patients with renal impairment should have their dose of gabapentin or pregabalin reduced per BNF recommendation (see Tables 5 and 6).

Table 5. Renal dose adjustments for gabapentin[54]

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

Table 6. Renal dose adjustments for pregabalin[55]

Creatinine clearance (ml per minute)	Total pregabalin dose	
	Starting dose	Maximum dose
30–60	75 mg	300 mg
15–30	25–50 mg	150 mg
<15	25 mg	75 mg

Duloxetine
Duloxetine is licensed for the treatment of diabetic peripheral neuropathic pain, and is included in the NICE clinical knowledge summary guidance for neuropathic pain[56]. Start with 30 mg per day for two weeks and titrate up to a maximum of 120 mg per day. In patients with known hypertension and/or other cardiac disease, blood pressure monitoring is recommended, especially during the first month of treatment.

Carbamazepine
Carbamazepine can be used as first-line treatment for trigeminal neuralgia. Initial dose of 100–200 mg daily, increasing slowly in increments of 100–200 mg at weekly intervals. Usual maintenance dose range 600–1200 mg in 24 hours. Maximum dose of 1600 mg per day. There are several significant adverse drug reactions associated with carbamazepine including hyponatraemia. There are also several clinically significant drug interactions with carbamazepine. Check product Summary of Product Characteristics, BNF and Stockley's Drug Interactions for information about interactions with other medicines.

Capsaicin
Capsaicin 0.025% – 0.075% cream can be used for people with localised neuropathic pain who wish to avoid, or cannot tolerate, oral treatments.

Capsaicin 8% patch is restricted to specialist use in pain management for the treatment of post-herpetic neuralgia (PHN) and peripheral neuropathic pain (PNP) in non-diabetic adults who have not achieved adequate pain relief from, or who have not tolerated, conventional first- and second-line treatments.

Lidocaine
Prescribing of lidocaine plaster 5% should be reviewed. **Within NHS Wales it is recommended that the prescribing of lidocaine plasters in primary care should be restricted to the licensed indication of post-herpetic neuralgia in patients for whom alternative treatments have proved ineffective or where alternative treatments are contra-indicated**[57].

Patients on long-term therapy with lidocaine plasters should be assessed for continued need, with the view to discontinuing treatment or having a longer plaster-free period between applications.

Off-label use should only be initiated by pain specialists in secondary care and should be in line with MHRA guidance on the use of off-label and unlicensed medicines[58].

Patients being prescribed lidocaine plasters for an unlicensed indication should be reviewed with the intention of discontinuing treatment or switching to a licensed alternative wherever possible.

Also refer to NICE Clinical Guideline 173: Neuropathic pain in adults: pharmacological management in non-specialist settings.

Table 7. Principles for prescribing for patients with pain (developed in collaboration with NHS Greater Glasgow and Clyde Chronic Pain Primary Care Guideline Development Group)

Early assessment	Early assessment and characterisation of pain type is crucial in guiding treatment. Many medicines that are specifically effective in neuropathic pain are ineffective in other types, and vice versa[50]. Consider high-risk patient groups and patient risk factors, including misuse/abuse potential.
Planning and patient understanding	It is important that patients understand their condition and have appropriate expectations. Medication should be considered as **part** of the management of pain: patients should understand that medication will not "cure" pain and they need to engage in self-management: see resource list for examples of sources for self-management support. It is vital the short- and long-term treatment plans, and any changes, are discussed with and agreed by the patient along with arrangements for repeat prescribing.
Realistic aims	It is important to discuss patients' aims for pharmacological treatment. Realistic aims may include pain reduction (≥ 30%) and/or functional goal improvement (assessment tools include the Brief Pain Inventory)[59]. An exit plan and plans for stepping down should be discussed as part of initiation. Patient understanding can be explored using teach-back.
Record consumption	Record **all** analgesic consumption, including OTC medication, and identify complementary therapies. Recording of the Read Code 66n is **strongly recommended** for audit, review and quality improvement[60].
Stepped approach	Apply a stepped approach to pain management and review regularly. Remember that there is both a *step up* **and** *step down* approach and that patients should be empowered to safely reduce their medications where appropriate.
Early review	Any medicine initiated for persistent pain should be subject to early, frequent and recorded review with the patient. It should be titrated up to a dose that balances maximum clinical efficacy with minimal risk, and gradually stopped if found to be ineffective or if adverse effects outweigh benefits. This particularly applies to medicines with common serious adverse effects or abuse potential, or that are expensive to prescribe[60].
Ongoing review	Once the dose is stable and effectiveness has been established, ongoing recorded review should occur at least every six months - more frequently if needed, for example, due to flare-ups. This review should: confirm ongoing need for and effectiveness of medication; screen for side effects; and adjust dose or discontinue prescription as appropriate. A holistic polypharmacy approach is recommended.
Effective care	Multimodal analgesia is most effective but requires using medicines with different mechanisms of action to deliver additional or synergistic impact: inappropriate polypharmacy should be avoided. Use the minimum effective or tolerated dose and step up as required. Start low and go slow.

The polypharmacy review process

The Welsh National Standards for Medication Review were endorsed by AWMSG in 2020 and aim to ensure a consistent approach, resulting in high-quality medication reviews by:

- involving patients and carers;
- considering medicines safety;
- reviewing all prescribed and non-prescribed medicines;
- reducing waste;
- updating patient records and completing documentation[61].

The '7-Steps' approach to medication review

NHS Scotland provide a structured approach to medication review but are flexible enough to allow the review to be tailored to the patient[62].

The following seven steps are intended as a guide to structure the review process.

Step 1: **What matters to the patient**
Identify aims and objectives of medicine therapy by asking the patient what matters to them. Before embarking on a clinical medication review it is helpful to establish the aims and objectives of medication on the basis of the information available, i.e. patient demographics, medical and medication history, laboratory markers, social situation. Based on this information, likely treatment objectives can often be identified, and will require agreement with the patient (see Step 7).

Step 2: Identify essential medicines
A rational first step of the medication review is to separate the list of medicines the patient is currently taking into those that are essential and should usually not be stopped, from those that could potentially be stopped. Essential medicines in this respect are those that have a replacement function or may cause rapid symptomatic decline or loss of disease control if stopped, and should only be stopped on specialist advice.

Step 3: Does the patient take unnecessary medicines?
For the remaining medicines, it should be verified that each has a function in achieving the above defined therapeutic objectives and whether their use is supported by a sufficient up-to-date evidence base. In addition to stopping medication with expired indications, the continued need for prophylactic treatments in patients with a short life expectancy should be considered.

Step 4: Are therapeutic objectives being achieved?
The next step is to check whether the remaining medicines are the most effective for the indication they are used for and whether they are actually achieving what they are intended to achieve. If this is not the case, the possibility of patient non-adherence should be investigated as a potential explanation. Otherwise, the need for intensifying doses or adding or replacing medicines may also be considered.

Step 5: Is the patient at risk of adverse drug reaction (ADR) or suffers actual ADRs?
The presence of ADRs can sometimes be identified from laboratory data (e.g. hypokalaemia from diuretic use), alternatively, the patient may report specific symptoms. However, ADR identification often requires a more proactive approach of identifying ADR risks (including drug–drug and drug–disease interactions, but also the patient's ability to self-medicate) and asking the patient specific questions (e.g. about the presence of anticholinergic symptoms, dizziness or drowsiness).

Step 6: **Is medication cost-effective?**
Opportunities for cost minimisation should be explored, but changing medicines for cost reasons should only be considered if effectiveness, safety or adherence are not comprised.

Step 7: **Is the patient willing and able to take medication as intended?**
Assessment of adherence has been mentioned in Steps 4 and 5 as a way to explain medication failure or identify medication risks. This step aims to facilitate optimisation of the drug regimen so that adherence is as easy as possible. In order to maximise their involvement and cooperation, patients should be explicitly asked what they hope to achieve from medication and be empowered to make decisions regarding effectiveness versus safety as well as symptom control versus longevity.

Useful resources

PrescQIPP

Registration required: Login to PrescQIPP. PrescQIPP is an NHS-funded not-for-profit organisation that supports quality, optimised prescribing for patients. It produces evidence-based resources and tools for primary care commissioners. Subscribers are provided with a range of data and intelligence tools, webinars and events.

www.Paintoolkit.org

Self-management support devised by Pete Moore, who himself lives with persistent pain. Includes a long list of links to a variety of charities and support for long-term conditions. (https://www.paintoolkit.org/resources/links)

www.my.livewellwithpain.co.uk

Supported self-management resources developed by people living with pain and professionals working with them. Includes links to the 10 Footsteps – can be used to support education programmes for patients or as an alternative for people who feel able to work through things on their own or with a little support from their healthcare team.
10 Footsteps https://my.livewellwithpain.co.uk/resources/ten-footsteps/
10 Footsteps for Carers: Cover - Ten Footsteps for Carers (livewellwithpain.co.uk)
Resources for healthcare professionals, wellbeing co-ordinators, health trainers are available from www.livewellwithpain.co.uk.

https://painconcern.org.uk

Pain Concern is a charity based in Scotland which provides information for people living with pain, their carers and healthcare professionals. They have a regular podcast which highlights various areas of pain management as well as getting experts (professional and lived-experience) to talk about topics of interest and new developments in research.
The Navigator tool (https://painconcern.org.uk/the-navigator-tool/) can help people to make the most of their appointments with healthcare professionals where they will be discussing their pain.

https://livingwellpain.net

A website created by Tina, who lives with persistent back pain and sciatica. Provides information about sciatica and methods of managing and living better with it. Tina also shares her experience of navigating healthcare services and communicating with professionals about her condition which can be really helpful for other people to learn from.

https://healthtalk.org/chronic-pain/overview

A repository of videos of people talking about living with a range of different health conditions. There is a section on chronic pain. Living with pain can be an isolating experience and so sharing experience can be valuable to help people feel less on their own, as well as learning about different things which others have found helpful (or not).

https://flippinpain.co.uk

Flippin Pain's mission is to bring pain neuroscience to public awareness to change the way we think about, talk about and treat persistent pain. The team provides webinars that can be accessed by people with pain, their carers and healthcare professionals as well as live events featuring experts from all over the world.
The Flippin Pain work is based on the work of Pain Revolution from Australia (https://www.painrevolution.org/) – they have a useful short film called "Tame the Beast", that explains persistent pain mechanisms (https://www.youtube.com/watch?v=ikUzvSph7Z4).

British Pain Society

The British Pain Society is a multi-disciplinary organisation that promotes best practice and research in pain. They have a helpful section for people living with pain with lots of links to other resources and information developed by the British Pain Society as well. https://www.britishpainsociety.org/people-with-pain/

Retrain Pain

Free online course for people living with pain. Designed to aide understanding and start on the path to self-management. https://www.retrainpain.org/.

NHS Online Studio

A range of videos are available to help and encourage people to move, including Tai Chi and yoga-based exercise. https://www.nhs.uk/conditions/nhs-fitness-studio/

Some useful books

An Introduction to Living Well with Pain – Frances Cole
ISBN-10:147213771X

Manage Your Pain – Michael Nicholas, Alan Molloy, Lois Tonkin and Lee Beeston
ISBN: 0-75380-997-4

The Pain-free Mindset – Deepak Ravindran
ISBN: 978-1-78504-339-0

Short films for people with pain

- How does your brain respond to pain? https://www.youtube.com/watch?v=I7wfDenj6CQ
- Pain and me https://www.youtube.com/watch?v=ZUXPqphwp2U
- Understanding pain in less than 5 minutes https://www.youtube.com/watch?v=OYOi1AD5mOk
- Why things hurt https://www.youtube.com/watch?v=gwd-wLdIHjs

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