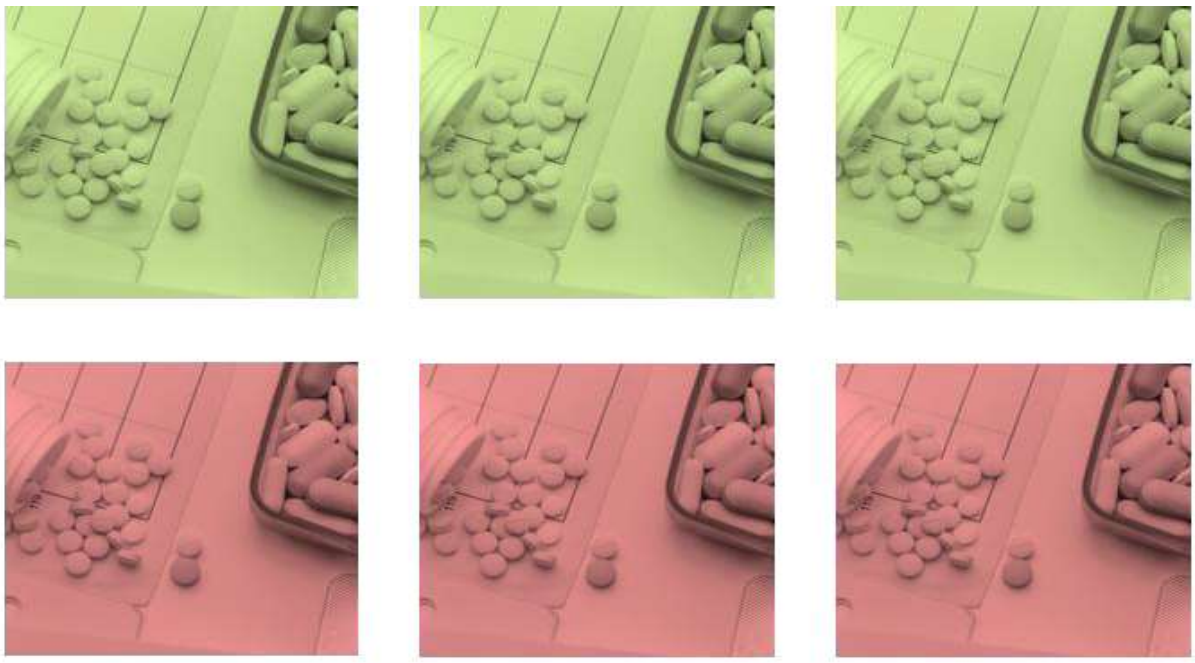
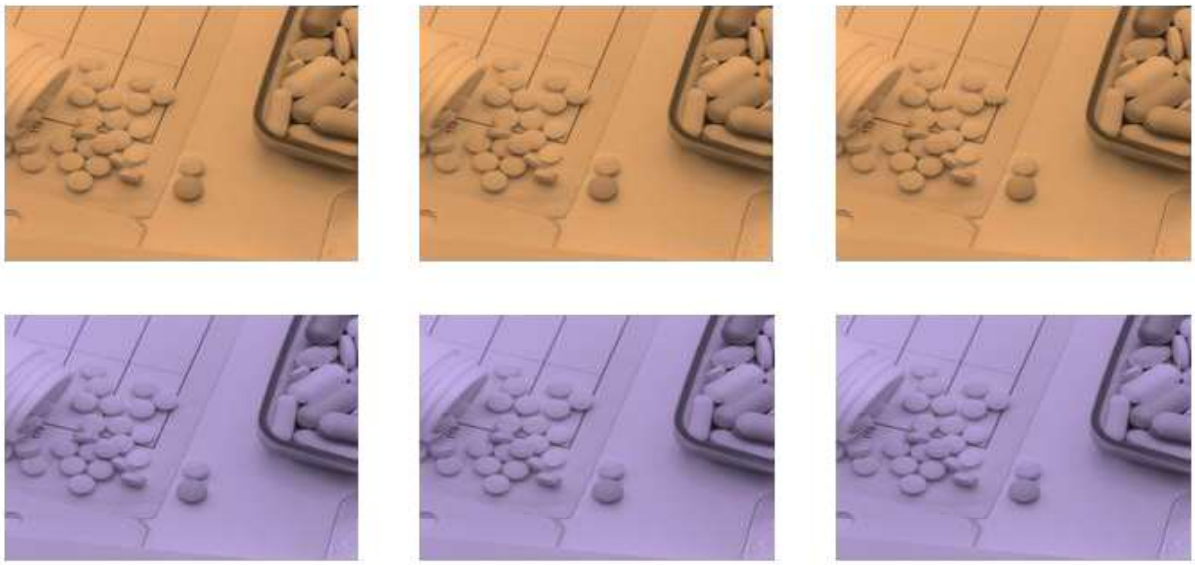


Opioid Prescribing for Chronic Pain

Medication Safety in opioid prescribing: A quality improvement resource for shared decision making



REALISTIC MEDICINE

Scottish Government
Riaghaltas na h-Alba
gov.scot

NHS SCOTLAND

Foreword

This resource has been written in collaboration with Scottish Government, colleagues from NHS, academia and with input from patients. The guidance contained in the resource aims to promote quality improvement in the prescribing of opioid pain relievers for treatment of chronic pain in Scotland, using a shared decision making approach. This shared decision making should be between the patient, whose life is most affected by the condition and the healthcare professional (HCP) or team with responsibility for that person's care. Opioid medication should not be the first option considered for the treatment of chronic pain.

This resource focuses on delivery of safe person centred care through promoting safe prescribing and practical review of opioids to prevent addiction and dependence. The guide also aims to promote shared decision making, self-management and non-pharmaceutical treatment of chronic pain in order for patients to be involved in all steps of their treatment. There is a need for HCPs to provide informed, effective oversight of opioid treatments and have honest conversations with patients or their carers about expectations from opioids. Opioids are relatively ineffective in treating chronic pain, although they do have a place in the treatment repertoire.

For the purposes of this resource, chronic pain is defined as per the SIGN guidance definition "pain that has been present for more than 12 weeks". Chronic pain affects one in five people in Scotland and is often associated with polypharmacy, with the risk of harm increasing with multiple medicines use and frailty.

The advice is based on existing clinical guidance, and each of the guides below should be considered as a companion document: "Quality Prescribing for Chronic Pain" Guide 2018;[1] SIGN 136: Management of Chronic Pain,[2] updated August 2019; and "Polypharmacy Guidance Realistic Prescribing" [3] (Appendix 2).

We are extremely grateful to all those who contributed to the working group, and to the review and development of this guide.

DRAFT

Acknowledgements

We would like to thank all the following members of the group that have worked together in the development of this guidance. This document has been produced by the collaborative efforts of the clinicians from multidisciplinary backgrounds, academics and patients. we have been supported by our colleagues in Public Health Scotland who have updated the prescribing data and indicators.

Guidance development membership:

Alex Kelso, Clinical Pharmacist, Effective Prescribing and Therapeutics Division, Scottish Government
Cara Richardson, Research Assistant in Chronic Pain, University of Dundee
Magdalena Laskawska, Research Assistant in Chronic Pain, University of Dundee
Professor Blair H Smith, Professor of Population Health Science, University of Dundee; Consultant in Pain Medicine, NHS Tayside; National Lead Clinician for Chronic Pain, Scottish Government
Professor Lesley Colvin, Professor of Pain Medicine, University of Dundee; Hon Consultant in Pain Medicine, NHS Tayside
Dr Paul Cameron, Pain Service Lead, NHS Fife; National Chronic Pain Coordinator, Scottish Government
Heather Harrison, Senior Prescribing Advisor, Central Prescribing Team, Pharmacy Principal Lead-Initial Education and Training for Pharmacists, NHS Education for Scotland (Pharmacy)
Richard Hassett, Senior Information and Prescribing Analyst, Effective Prescribing and Therapeutics Division, Scottish Government NHS Greater Glasgow and Clyde
Alpana Mair, Division Head, Effective Prescribing and Therapeutics, Scottish Government
Dr Iain Wilson, GP Clinical Lead, Effective Prescribing and Therapeutics, Scottish Government
Stuart Law, Head of Policy & Research , Effective Prescribing & Therapeutics, Scottish Government

With thanks to members of the SLWG for Prescription addiction and withdrawal
Aileen Bryson, Policy and practice lead for Royal Pharmaceutical Society Scotland
Kieran Dinwoodie, GP Advisor, Chronic Pain
Morris Fraser, Head of Alcohol, Tobacco and Drugs Branch, Scottish Government
Dr Lesley Graham, Clinical lead for Alcohol, Drugs and Health in Justice Settings
Duncan Hill, Specialist Pharmacist in Substance Misuse (SPiSM), NHS Lanarkshire
Emma Mair, Primary Care Clinical Lead, Chronic Pain
Dr Denise McFarlane, BMA SGPC representative
Dr Donald MacIntyre, Mental Health Clinical lead, NHS 24
Dr Baags Sharma, Royal College of Psychiatry
Tracy Stafford, NHS GGC
Alisa Stein, Healthcare Improvement Scotland
Anita Stewart, Team Leader - Neurological Conditions, Strategic Planning and Clinical Priorities, Scottish Government
Germaine Vonhof, Adult Mental Health - Mental Health Policy Team Leader, Scottish Government
Andrew Walker, NHS GGC

DRAFT

Executive Summary

As multimorbidity increases with ageing, chronic pain is often one of these co-morbidities. One of the pharmacological interventions commonly used in its treatment is the use of opioids. However, there is national and international concern about the associated harms with increased opioid prescribing. Evidence of a lack of effectiveness in treating chronic pain with opioids is growing. Both of these mean there is a requirement for guidance to promote quality improvement in the prescribing of opioid pain relievers for chronic pain. This resource focuses on delivery of safe, person centred care, promoting safe prescribing and practical review of opioids. This should sit alongside ensuring patients have the information required to make shared decisions to allow self-management and non-pharmaceutical management of their chronic pain. The overall aim should be safe effective treatment, reducing opioid dependence and withdrawal reactions. Patients currently prescribed a regular high dose of opioids ≥ 50mg daily morphine, or equivalent, should be reviewed at least annually as the risk of harm significantly increases at this dose or above.[4]

In addition, as part of a shared decision making process, this resource provides practical tools to support review of appropriate prescribing, along with monitoring and assessment support tools for withdrawal and audit.

The advice is based on the following existing clinical guidance: SIGN 136: Management of Chronic Pain - contains detailed information on pharmaceutical and non-pharmaceutical management of chronic pain, including the opioid update in August 2019. The resource also builds on:
"Quality Prescribing for Chronic Pain" Guide, and "Polypharmacy Guidance Realistic Prescribing" which contain a comprehensive model for medication review – the 7-Steps medication review model. The guidance in this Opioid Prescribing resource follows the framework of the 7-steps medication review process to provide a clear pathway for opioid prescribing and subsequent review, including how health care professionals (HCPs) can support patients throughout this process. The 7-steps process puts the patient at its core, asking *"what matters to you?"* and seeks to establish a clear and agreed plan with realistic, achievable actions, using a shared decision making process.

This Opioid Prescribing resource emphasises the following considerations, which should be noted by HCPs and are practical points to help reduce high dose opioids:

- Support the patient to understand the importance of reducing opioids and provide the information to make informed choices.
- Support the patient with shared decision making and provide information on non-pharmacological approaches to allow for self-management.
- Manage any symptoms that arise during reduction.

Contents

Foreword 2

Acknowledgements 3

Executive Summary 4

Contents 5

Appropriate Prescribing of Opioids 6

Background information 7

Transitions of Care 12

Drug related deaths 12

Summary 12

Start, ongoing review, reduction and stopping of opioid therapy 13

Step 1: What matters to me, the patient. 14

Step 2: Together, identify essential drug therapy. 14

Step 3: Does the patient take drug therapy which is no longer necessary? 14

Step 4: Are therapeutic objectives being achieved? 17

Step 5: Is the patient at risk of ADRs or suffering from actual ADRs? 18

Step 6: Is drug therapy cost-effective? 19

Step 7: Is the patient willing and able to take drug therapy as has been agreed? 19

Appendices 20

Appendix 1 – Harms Associated with Opioids 20

Appendix 2 - The Polypharmacy Review Process: the '7-Steps' approach to medication review 21

Appendix 3 – Opioid Risk Tool to support the identification of abuse 23

Appendix 4 - Practice chronic pain pain-reliever protocol template 24

Appendix 5 – Adapted from SIGN 136 Management of Chronic Pain - pathways[2] 27

Appendix 6 – Opioid Care Bundle to assist in review and audit of opioid prescribing 33

Appendix 7 – Considerations for opioid reviews for Health Care Professionals 34

Appendix 8 – Clinical Opiate Withdrawal Scale 35

Appendix 9 – Examples of Symptomatic Relief in Opioid Withdrawal 38

Appendix 10 – Considerations when reducing strong opioids 39

Appendix 11 – Non-pharmaceutical support – resources 41

References 43

DRAFT

Appropriate Prescribing of Opioids

Introduction

What is the purpose of this resource?
Opioid prescribing and long term Opioid use is increasing. There is national and international concern about this prescribing and opioid associated harms which include possible side-effects, lack of efficacy, dependence, tolerance, withdrawal, and even death (see Appendix 1). The purpose of this resource is to promote quality improvement in prescribing for adults with chronic pain in Scotland, particularly focusing on shared decision making to deliver safe, person centred care.

The resource promotes self-management and non-pharmaceutical treatment of chronic pain. It provides tools to support the appropriate prescribing and practical review of opioids for chronic pain. There is also practical advice on how to support reducing dosing to a safe level, or stopping completely, where the decision is made with the patient to plan these courses of action.

The scope includes review of the pharmaceutical management for **adult** patients only, and encourages appropriate non-pharmaceutical approaches to the treatment of chronic pain. The resource is not intended to replace any current clinical guidance and should be used alongside the following:
"Quality Prescribing for Chronic Pain" Guide produced in 2018,[1] which contains detailed information on pharmaceutical management of chronic pain.
SIGN 136: Management of Chronic Pain.[2] Opioid section updated August 2019 to incorporate new evidence on efficacy and safety. This document contains detailed information on pharmaceutical and non-pharmaceutical management of chronic pain.
"Polypharmacy Guidance Realistic Prescribing",[3] which contains a comprehensive model for medication review – the 7-Steps medication review model (Appendix 2).

Reviewing Opioids with the patient
Patients currently prescribed a regular high dose of opioids ≥ 50mg daily morphine, or equivalent, should be reviewed jointly with the patient at least annually, primarily as the risk of harm significantly increases at this dose or above.[4] Joint review between the patient and healthcare professional (HCP) is to ensure prescriptions are appropriate and safe, and to agree a treatment plan. Proactive reviews, when patients are not experiencing crises or acute illness, are just as important in ensuring appropriate opioid prescribing and use. The frequency of these reviews may vary with the patient and their needs, for example, it may be appropriate to review the opioid pain relief after a recent discharge from hospital.

Background information

Data

Over the last two decades, there has been a large increase in rates of strong opioid prescribing for chronic pain in many countries.[5,6] This includes Scotland up to January 2017,[7] but since then the opioid prescribing rates for strong opioids has slightly decreased.

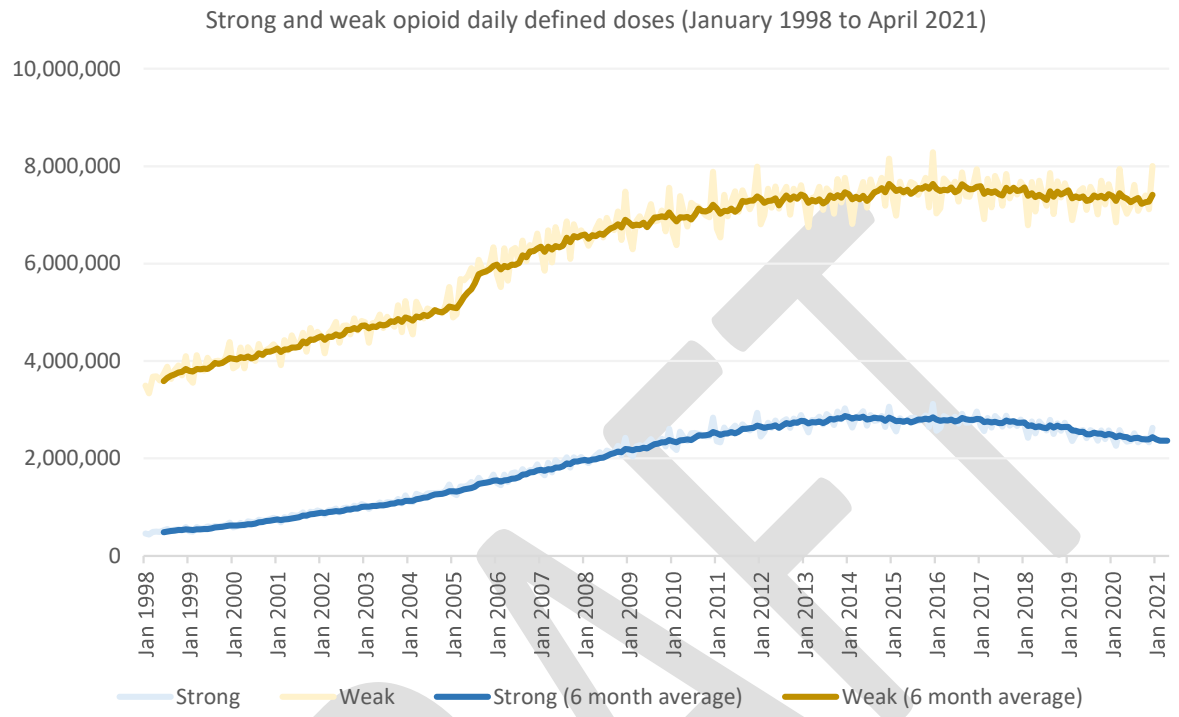


Figure 1 - rates of opioid prescribing in Scotland, as strong and weak opioid daily defined doses, from 1998 to 2020.

Dosing and use

There is no good quality evidence to support the effectiveness of long-term opioid therapy for chronic pain,[5] with limited evidence of effectiveness in neuropathic pain where opioids are not first line therapy (Box 1).[8] Current evidence shows that chronic opioid therapy is associated with serious adverse effects (Appendix 1)[6,7] and higher doses of opioids are associated with poorer functional outcomes, worse pain and lower mood,[9] with various thresholds quoted where the risk of harm outweigh the benefits.[4] The US Department of Health suggests prescribers should consider

Number Needed to Treat (NNT) and **Number Needed to Harm (NNH)**

The NNT is a measure used in assessing effectiveness of a treatment, and is the average number of patients who require to be treated for one to benefit, compared with a control.

The NNH is the average number of people taking a medication for one to suffer an adverse event.

Box 1 **- NNT and NNH figures for opioids used to treat neuropathic pain (1,8):**

Tramadol	**Oxycodone, Morphine**
NNT 4.7 (3.6-6.7)	NNT 4.3 (3.4-5.8)
NNH 12.6 (8.4-25.3)	NNH 11.7 (8.4-19.3)

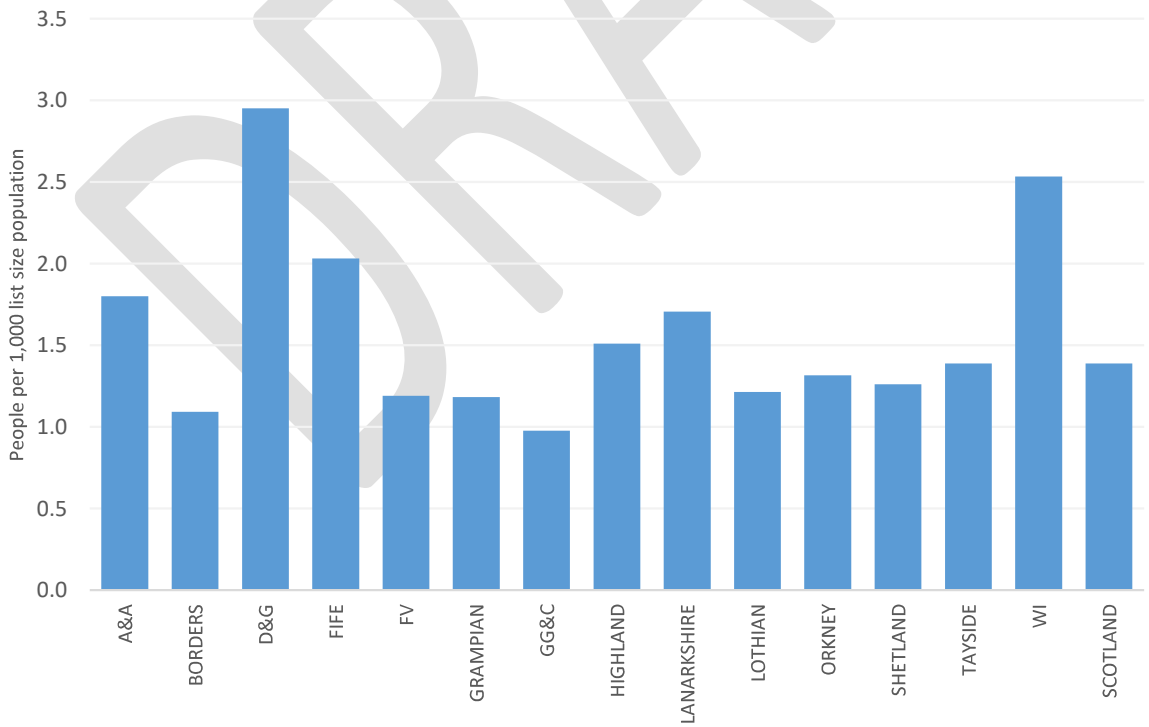
These figures suggest evidence is weak/inconclusive for strong opioids in *neuropathic* pain. However, they provide a general **guide** to the relative effectiveness in chronic pain.

DRAFT

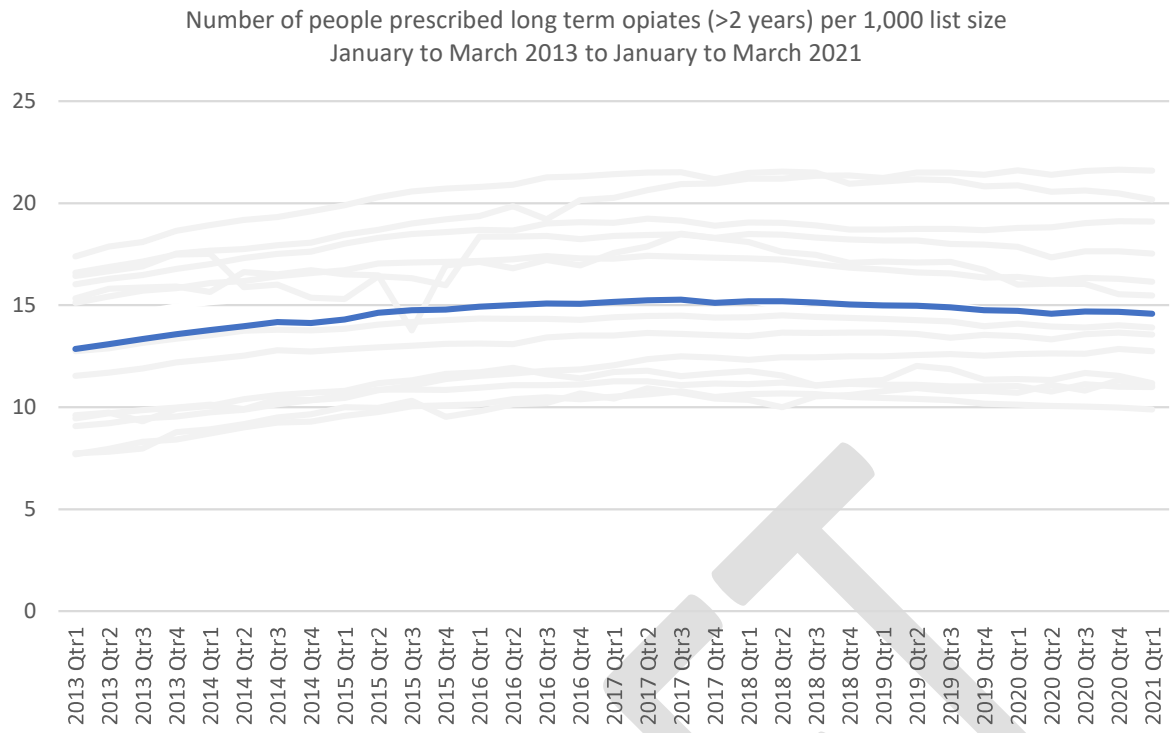
"the individual benefits and risks when increasing dosage to ≥50mg Morphine Equivalent Dose (MED)/day, and should avoid increasing dosage to ≥90mg MED/day, or carefully justify a decision to titrate dosage to ≥90mg MED/day".[10] The risk of harm substantially increases at doses of ≥120mg MED/day with no increase in benefit.[11,12] Review would be required in order to ensure safe prescribing in these cases (Figure 2).

Figure 2 - Opioid dependency: Number of people prescribed an opioid at an average daily dose equivalent of at least 120mg of morphine per day over the previous six months per 1,000 list size population, October 2020 to March 2021

NHS Board	People per 1,000 list size population
NHS AYRSHIRE & ARRAN	1.80
NHS BORDERS	1.09
NHS DUMFRIES & GALLOWAY	2.95
NHS FIFE	2.03
NHS FORTH VALLEY	1.19
NHS GRAMPIAN	1.18
NHS GREATER GLASGOW & CLYDE	0.98
NHS HIGHLAND	1.51
NHS LANARKSHIRE	1.71
NHS LOTHIAN	1.21
NHS ORKNEY	1.32
NHS SHETLAND	1.26
NHS TAYSIDE	1.39
NHS WESTERN ISLES	2.53
SCOTLAND	1.39



DRAFT



The Scottish Therapeutics Utility (STU) allows identification of specific indicators (Primary care National Therapeutic Indicators) with a trigger set at opioid equivalent to >50mg morphine for example (Figure 3). The full list of National Therapeutic Indicators can be found at https://scotland.shinyapps.io/nhs-prescribing-nti/ and a list of available Opioid related indicators for each NHS board, Health and Social Care Partnership and Practice are shown below;

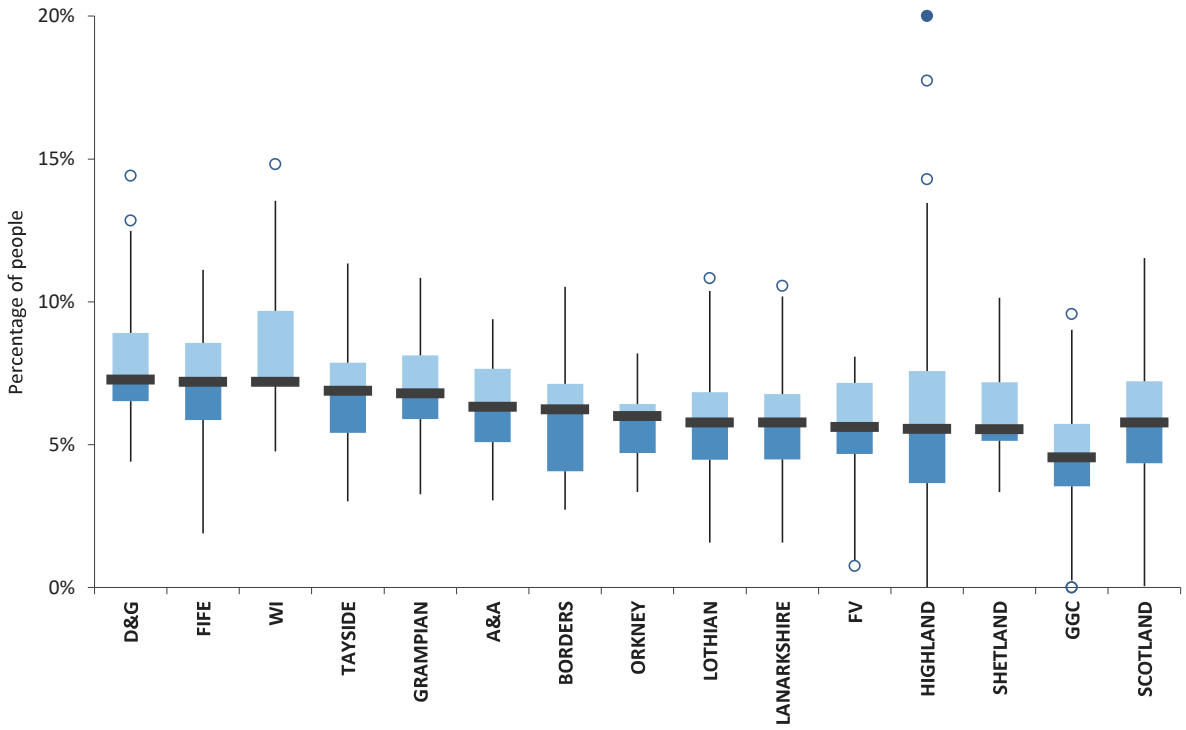
Opioid related Indicators:

National Therapeutic Indicators can be found at https://scotland.shinyapps.io/nhs-prescribing-nti/

- Analgesics (opioid DDDs)
- Analgesics (opioid DDDs) opioids excluding tramadol
- Analgesics (opioid DDDs) tramadol only
- Analgesics (opioid DDDs) weighted
- Analgesics (opioid DDDs) opioids excluding tramadol (weighted)
- Analgesics (opioid DDDs) tramadol only (weighted)
- Opioid and gabapentinoid dependency (high dose opioids %) 120mg
- Opioid and gabapentinoid dependency (high dose opioids %) 50mg
- Opioid and gabapentinoid dependency (long term opioids %)
- Opioid and gabapentinoid dependency (high dose gabapentinoid %)

Figure 3: Example of National Therapeutic Indicator data visualisation.

Opioid dependency: Number of people prescribed an opioid at an average daily dose of opioid equivalent to at least 50mg per day of morphine over the previous six months as a percentage of all people prescribed step 2 and strong opioids (October 2020 to March 2021)



For more information about STU and NTIs go to: www.therapeutics.scot.nhs.uk/resources, the NTI shiny app, or contact your local Primary Care Prescribing Team.

Suggested approaches for prescribing

Non-pharmacological therapies that focus on improving quality of life for the patient are the preferred methods for treating chronic pain.[13] There is a place for short-term (<3 months) opioid use for some pain conditions with appropriate monitoring and review.[13] Evidence supports the effectiveness of psychological and physical approaches in improving the patient's quality of life,[14] and opioids should only be used as a part of a wider treatment plan as a shared decision between the HCP and the patient.[1]

Review of Opioids

SIGN 136 recommends a minimum annual assessment of patients on strong opioids with more frequent review if required for changes in pain relief, side effects, quality of life or if considering a gradual reduction to the lowest effective dose.[2] This should be a jointly agreed plan.

During the review with the patient the reviewer should assess for any signs of misuse and addiction prior to prescribing strong opioids (Box 2), and while continuing to use strong opioids (Box 3).

Routine urine drug testing, pill counts, or prescription monitoring are not of proven value in detecting misuse of prescribed medication. Screening tools to identify risk of dependence or misuse are available, but these tools have limited evidence of benefit (Box 4).[15]

Box 2 **- Individuals at increased risk of misuse BEFORE starting opioids are those who:**

- Have a history of heroin and/or alcohol abuse and/or stimulant use.[2]
- Have a history of, or are currently experiencing, mental health problems.[2]
- Have a history of preadolescent sexual abuse.[16]

Box 3 **- Possible flags of developing problematic use when opioids are already prescribed are:**[17]

- Making early prescription requests
- Reporting misplaced prescriptions
- Requesting a dose increase

Box 4 – Examples of various assessment tools available for assessing initial risk of misuse. Note the lack of evidence supporting or validating these:[15]

- **The Opioid Risk Tool** (Appendix 3)[1, 16] - assists in making decisions about the risk of misuse prior to initiating opioids.
- **The Pain Medication Questionnaire (PMQ)**[15, 18] - used to evaluate risk of drug related behaviours which are out of the normal, in patients prescribed opioids.
- **Screener and Opioid Assessment for Patients with Pain (SOAPP)**[15,19] - used to evaluate risk of drug related behaviours which are out of the normal, in patients prescribed opioids.
- **The Current Opioid Misuse Measure (COMM)**[15,20] - used for regular monitoring, screens for developing misuse of prescribed opioids over the past 30 days.

Transitions of Care

Post-surgery is a time when opioids are often started and patients can potentially end up on these longer term. A US study found that the incidence of new persistent use of opioids amongst patients undergoing surgery was common. Specifically, it has been found that 6% of patients undergoing surgery continued to use opioids 90 days after surgery.[21] In addition, in the USA, opioid prescribing for minor surgery has increased: up to 75% of patients are prescribed opioids at hospital discharge, with the risk of misuse increasing by 44% for each week and repeat prescription thereafter.[22]

TRANSITIONS OF CARE

If a patient has been discharged from hospital on an opioid, then it is important to review this with them before further prescriptions are issued. Ideally the discharging team should provide clear guidance on how long the opioid should be continued for. It is important that when a prescribing issue is addressed, work is undertaken across the health system to ensure linking across transitions of care to avoid lack of clarity around decisions which have been made.

Drug related deaths

According to official figures published by the National Records of Scotland there were 1,339 drug-related deaths registered in Scotland in 2020, an increase of 59 (5%) drug-related deaths over 2019. This figure was the largest ever recorded in Scotland, 765 (133%) more than the figure for 2008 (574 deaths). One or more opioids including morphine and methadone were implicated in, or potentially contributed to, 1,192 (89%) of the total drug-related deaths for 2020. It is important to note that any figures also include non-prescribed opioids such as heroin, and that "related" does not equate to "caused". Other drugs frequently implicated were benzodiazepines and/or z-hypnotics including novel psychoactive substances such as etizolam (974 deaths, (73%)) and gabapentinoids (pregabalin, gabapentin) (502 deaths, (37%)).

Combination prescribing

Extreme care should be taken when co-prescribing opioids with benzodiazepines, z-hypnotics or gabapentinoids due to the risks of respiratory depression and increased risk of overdose.[23]

Summary

There is a lack of evidence regarding the efficacy of long-term use of opioids in treating chronic pain,[1] and recent evidence of relative ineffectiveness.[24] There are also considerable risks involved with their use, such as increased risk of overdose, fractures, abuse and dependence alongside associated withdrawal difficulties. All of these should be discussed with the patient before prescribing and at reviews to allow informed choices to be made about treatment.[25] Tools and resources such as the ones contained in this guide can help facilitate discussions around the potential risks and benefits of opioid therapy and allow informed choices to be made about initiation or continuation of treatment. Review is essential with all patients prescribed opioids and should also include consideration of other non-pharmacological approaches. Suggested approaches to prescribing, reviewing, reducing and stopping opioid medication is provided below and should be considered at the transitions of care.

Start, ongoing review, reduction and stopping of opioid therapy

It is important that the need for opioid medicines are assessed at initiation and reviewed regularly to ensure ongoing benefit. This should be reviewed by the HCP and the patient using the 7-steps process outlined in the box below and described in Appendix 2.

Summary of the 7-steps review process (for more detail, see appendix 2)

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

- STEP 1 – Assess diagnosis & identify therapeutic objectives with the patient
- STEP 2 – Identify if medication (including the opioid) is essential
- STEP 3 – Identify what medication should be reviewed (may include the opioid)
- STEP 4 – Does the dose of the opioid (or other medication) need to be increased?
- STEP 5 – Identify any risks to patient – patient safety, adverse effects
- STEP 6 – Check if therapy is cost effective and is formulary choice
- STEP 7 – Ensure review outcomes are understood & therapy will be taken as intended

The "Practice chronic pain pain-reliever protocol" (Appendix 4) provides further information on safe and effective prescribing of opioids for GP practices.

Practice codes

All patients who suffer from chronic pain should be allocated with a read code of **1M52** (**"Chronic Pain"**). Similarly, the following read code: **66n** ("**Chronic Pain Review"**) should be recorded when a chronic pain review has been undertaken. This creates a clear audit trail and ensures visibility of these patients to the practice.

SIGN 136 provides assessment algorithms and the pathways for chronic pain assessment,[2] early management and care planning (see Appendix 5 for more detail). The opioid care bundle was developed to assist with the audit and review of patients who have been prescribed opioids (please see Appendix 6). This aims to ensure that opioids are safely prescribed and reviewed, with reviews taking place even if pain reliever response has been good and side effects have been acceptable.

Step 1: What matters to me, the patient.

The HCP should identify the aims and objectives of drug therapy by asking the patient "what matters to you?"

Before embarking on a clinical medication review it is helpful to mutually establish the aims and objectives of drug therapy, in this case the objectives of pain relief. It is useful to consider the available information as part of that decision making e.g. patient demographics, drug history, social situation. Choices can also be made that fit in with the patient's lifestyle, for example around the need to **drive**. Information on opioids, driving and the law can be found here, with updates and changes here.

Realistic objectives may include:
a reduction in pain intensity by at least 30% and/or improvement in functional ability.

*Note that complete pain relief is rarely achieved with opioid therapy [1,26]

In patients with chronic pain there is a need to assess the patient's pain when initiating or reviewing opioid therapy, the pain duration, intensity, impact and likely cause. This is both to provide a baseline, and to assess the ongoing appropriateness of opioids.

Initiation and ongoing review of Opioids
A review should take place with the patient **within four weeks of starting opioid treatment or sooner if required**.[1] The frequency of review once the opioid regimen is established depends on the factors mentioned, but should be, **at minimum**, **annually**, in order to evaluate the effectiveness and tolerance of the opioid treatment. A review can be more frequent as desired or if required, for example with difficult side-effects, or if patient circumstance require individual tailoring. Appendix 7 provides a summary of the practical considerations of a review. As noted previously, the GP practice should record an appropriate pain diagnosis and any pain reviews in patients treated with opioids.

Step 2: Together, identify essential drug therapy.

The rational next step of the medication review is to separate the list of drugs the patient is taking into those that are clinically essential and should usually not be stopped, from those that could potentially be stopped. Essential drugs in this respect are those that may cause rapid symptomatic decline or loss of disease control and should only be stopped on specialist advice.

Opioids are not essential medicines and their on-going need should be reviewed. This is to ensure that other pain relievers had been considered prior to starting opioids. Strong opioids should only have been considered after a full assessment and as part of a holistic management plan, rather than as the sole treatment option.

Step 3: Does the patient take drug therapy which is no longer necessary?

For the remaining drugs it should be verified that each has a function in achieving the defined therapeutic objectives and whether their use is supported by a sufficient up to date evidence base. If these establish that the medicine may no longer be required discuss this with the patient. When this objective is agreed, reduce, or where possible discontinue the medicines by jointly instigating a plan to do so.

If opioids for chronic pain are no longer necessary **abrupt discontinuation should be avoided** to prevent severe withdrawal symptoms. Reducing and stopping should be considered if the therapeutic goals have not been reached, the medication is ineffective, no longer necessary or if side effects have become unacceptable.

Trials of reduction should also be considered periodically with the patient even if pain is well managed to assess continuing or stopping opioid therapy in partnership with the patient.

The rationale for any dose reduction and strategy for achieving such a reduction must be fully discussed and agreed with the patient (see step 7 for detail).

The Clinical Opiate Withdrawal Scale (COWS) (Appendix 8) can be used in both inpatient and outpatient settings. This tool can reproducibly rate common signs and symptoms of opioid withdrawal and help monitor these symptoms over time. This will aid healthcare professionals in determining the stage or severity of opioid withdrawal and in assessing the level of physical dependence on opioids. This helps a shared plan to be made on how to manage dependence or withdrawal after an appropriate conversation around the issue.
Suggestions to help manage the symptomatic relief of opioid withdrawal can be found in Appendix 9.

Prescriptions of opioids to patients with chronic pain are usually limited to a 30 day supply; when reducing opioids it may be appropriate to consider further supply management e.g. adding a review date on the prescription, or using the dose instruction 'dispense weekly', which may be beneficial for additional monitoring and ensuring safety of the patient.

A. Opioid reduction – medication aspects

Dose equivalence calculators can assist in the switching between different opioids and the tapering tool in the reduction and discontinuation. These tools also provide the basis for discussing the detail of a planned reduction/cessation with the patient, so that informed joint decisions can be made around the treatment plan.

It is important to point out that equivalent pain reliever dose conversions are only estimates. Patients may be either more sensitive to the new opioid than expected, which may cause life threatening over sedation and/or respiratory suppression;[2] or be less sensitive to the new opioid with associated under dosing.
If switching, the aim should be to have the opioid in a form which enables the most straightforward reduction regime, to aid the dose reduction of the agent according to the agreed plan.[2]

Guidance for healthcare professionals is based on specialist centres such as the Oxford Pain Management Clinic who emphasise the following considerations to aid reduction of a patient's high dose opioids. These are expanded on in **Appendix 10** [27]

and a link for the current advice can be found here; https://www.ouh.nhs.uk/services/referrals/pain/opioids-chronic-pain.aspx :

a. Education: it is most helpful if the patient has the information to understand the importance of reducing their opioids.
b. Engagement: there should be as much choice as possible around how the patient will reduce their opioids.
c. Effecting the weaning plan – agree and stick to the "how" but be as flexible as necessary noting the **rate and size of reduction** (taper tool). There should also be planning for short term pain flares and for any opioid withdrawal effects.
d. Emotional impact: it is helpful for the patient to be aware that anxiety is to be expected during opioid reduction, and that this can be managed together. Resources such as patient information leaflets and those found on NHS inform (Mental health | NHS inform) can be useful to help individuals manage these symptoms.
e. Expectations: it is also helpful to ensure the individual understands that the pain is likely to worsen in the short term during opioid weaning, and again, that this can be managed together.

B. Opioid reduction - non-pharmacological support

Plans should also be agreed jointly with individuals to support self-management of their pain by non-medicinal means. Healthcare professionals should discuss these non-drug self-management plans with the individuals and signpost to relevant resources (Appendix 11),[1] which will aid with informed joint decision making.

Despite a lack of evidence-based non-pharmacological approaches to opioid reduction in individuals with chronic pain,[28] psychologically-based pain management programmes may be effective in reducing opioid use in the short term.[29] Non-pharmaceutical approaches should be encouraged, either alone or in conjunction with medicines as agreed with the individual and as part of their overall treatment plan. This includes resources that offers digital and mental health wellbeing support, such as online CBT that can be accessed via SCI Gateway referral from General Practice in Scotland. A list of locally available resources may be available on your local Health Board pain team website to aid with these discussions. Useful links (nhslothian.scot)

It is important for the patient to be aware of the effect their emotions can have on their pain and vice versa. Relaxation, mindfulness and enjoyable activities can help to ease distress.[1] Mindfulness based stress reduction packages, which include yoga, meditation and guided meditation apps can also be used to reduce the distress associated with chronic pain.

Self-care, with education and a clear plan, is recommended to support the patient in carrying out reduction of their opioids. This can include advice on limiting bedrest, diet and physical activity[30] where the following strategies can be suggested: low-impact aerobic exercise, brisk walking, water aerobics or cycling[30] where the patient should be adequately supported and encouraged in their exercise regime.[2] Natural approaches may also be beneficial such as those advocated by the Natural Health Service.

Step 4: Are therapeutic objectives being achieved?

The next step is to check whether the medications being taken are the most effective for what they are being used for, and whether they are actually achieving what is intended.
The possibility of patient non-adherence (not taking the medication) should be investigated by the healthcare professional as a potential explanation. Otherwise, the need to intensify doses or add or replace drugs may be considered. There is also a need to intensify the non-medicine approaches already mentioned above. The actions agreed as part of the treatment plan should once again be carried out after discussion and agreement with the patient.

Use of a validated tool such as the Brief Pain Inventory (BPI) is recommended during follow-up to assess response and adjust regimes accordingly. Note that some patients are less likely to respond to opioids e.g. patients with neuropathic pain.[6]

If opioids are no longer effective, they should be reduced and stopped as described in step 3, following discussion and agreement with the patient. If the patient is taking the medication at the prescribed dose with some benefit, it may also be necessary to discuss with the patient if there is an identified need to ***increase*** the opioid to assess for further benefit. In this case the following factors should form part of the discussion, and jointly decided in the plan:

- Expected duration of increase and when this should be reviewed
- Expected effectiveness of pain control e.g. that being completely pain free is unlikely
- Any further associated risks – e.g. Adverse Drug Reactions (ADRs)
- Possible dependence developing and subsequent withdrawal issues
- Opioid rotation can be considered if the pain is opioid responsive, but effectiveness is compromised by side effects

DRAFT

Step 5: Is the patient at risk of ADRs or suffering from actual ADRs?

The presence of opioid Adverse Drug Reactions (ADRs) can be identified by the healthcare professional. These can be seen from laboratory data (e.g. endocrine effects), or in patient reported symptoms e.g. constipation.
However identifying ADRs often requires a more proactive approach. Identifying ADR risks, including drug-drug and drug-disease interactions can be assessed and predicted.
Too much of the opioid being taken (either deliberately, or if the prescribed amount is too high) is also something which can be assessed and form the basis of a discussion.
Asking the patient specific questions, e.g. about the presence of gastro-intestinal symptoms, dizziness or drowsiness, can help identify problems not raised by the patient as being associated with the opioid.

Monitoring for ADRs by HCP, once opioids are initiated:

- When starting opioid therapy, the lowest possible dose which provides pain relief with acceptable side effects should be prescribed (considering drug interactions, age, renal function, other co-morbidities and previous experience of opioids).
- Once started, the aim is to titrate the opioid dose up gradually, until the pre-determined therapeutic goals agreed with the patient are reached or side effects prevent a higher dose.
- Careful monitoring of pain relieving response and side effects should always accompany any titrated dose. Also any dependence which may develop.
- Patients should also be assessed for their risk of misuse and other comorbidities.
- Please see Box 3 (page 9) and Appendix 3 for more information on how to evaluate the risk of misuse in patients who suffer from chronic pain.

ADRs are more fully described in Appendices 1 and 5. The Medicines Health Regulatory Agency's Yellow Card scheme is a voluntary reporting scheme for ADRs associated with, or suspected to be from, any prescribed medicine.

Step 6: Is drug therapy cost-effective?

Opportunities for cost minimisation should be explored but changing drugs for cost reasons should only be considered if effectiveness, adherence or safety are not compromised. In any case, this needs done in full discussion with the patient, and with their agreement and understanding.

Step 7: Is the patient willing and able to take drug therapy as has been agreed?

This step is to ensure that there has been an appropriate joint decision making discussion, between the patient and the prescriber, and that everyone involved understands the outcomes of the review and benefit from any non-pharmacological treatments.
Patients should have been explicitly asked what they hoped to achieve from drug therapy at step one. After information has been shared, and appropriate discussion has taken place, plans can be agreed in step 7 so that the patient is empowered to make decisions around effectiveness versus safety or symptom control versus longevity**.**

The following need to have been considered, discussed and agreed with the patient:

- Route of administration
- Choice of opioid
- Dose and duration of treatment
- Timing of additional interventions, such as surgery, to control pain
- Presence of concerns in relation to problematic use of opioids
- Additional conditions
- Change in pain

Information to help with user understanding should be used such as Live Well With Pain's "Opioid Thermometer" (Appendix 12), a tool to aid visualisation of the dose of opioids where risks increase. Tools like this can aid with patient understanding and help inform patient choice, enabling greater clarity around the treatment plan they are agreeing to.

DRAFT

Appendices

Appendix 1 – Harms Associated with Opioids

Potential Harms	Explanation
Gastrointestinal System	The most common side effects of opioid use include nausea, constipation and vomiting.[31]
Respiratory System	Studies suggest that there is a link between chronic opioid use and sleep disordered breathing, such as central sleep apnoea, ataxic breathing, hypoxemia, and carbon dioxide retention.[14] Opioid induced respiratory depression is also one of the most common side effects related to the use of opioid pain relievers.[14]
Cardiovascular System	It has been found that long-term opioid use tends to be associated with increased risk of myocardial infarction and cardiovascular revascularisation.[14] Methadone is associated with prolonged QT interval and arrhythmia.[32] The risk of QTc prolongation tends to be dose dependent (the risk increases with increased methadone dose).[32] Moreover, factors such as gender, age and co-prescribing may increase the risk of QTc prolongation.[32]
Central Nervous System	Long-term opioid use can lead to hyperalgesia[33] – which is *increased* pain sensitivity. Moreover, dizziness and sedation are also common side effects related to the use of opioids. These side effects tend to be associated with an increased tendency to fall.[14]
Musculoskeletal System	Studies have reported increased risk of fracture amongst opioid users. In addition, short-acting opioids tend to be associated with a higher risk of fractures compared to long lasting opioids,[14] which is also relevant to the falls risk.
Endocrine System	Opioids can also have negative effects on the endocrine system. Long-term opioid therapy can lead to sexual dysfunction, fatigue and decreased levels of testosterone (in men and in women).[14]
Immune System	Long-term use of opioids may adversely affect the immune system (immunosuppression), although research in this area is somewhat contradictory. Dose, duration and type of opioid may be relevant.[14, 34, 35]

Appendix 2 - The Polypharmacy Review Process: the '7-Steps' approach to medication review

The following *7-Steps* are intended as a guide to structure the review process and are presented as: **table 2a** an overview of key considerations at each step

N.B. No list can be comprehensive and the reviewers clinical judgement and experience continues to be essential in tailoring the advice given to the needs of an individual patient and to identify other additional medication related problems.

Step 1: (Aim) What matters to the patient?

- Identify aims and objectives of drug therapy by asking the patient ***what matters to you*?**
- Explain any key information such as laboratory markers
- Establish treatment objectives with the patient through shared decision making

Step 2: (Need) Identify essential drug therapy.

- Separate the list of medicines which the patient is taking
- Ensure the patient understands the importance of essential drug therapy
- All medication whether herbal, prescribed or traditional remedies should be included

Step 3: (Need) Does the patient take unnecessary drug therapy?

- For the remaining drugs, it should be verified that each has a function in achieving the therapeutic goals or outcomes that matter most to the patient
- Review preventative treatment to ensure the patient is able to continue taking medicine for required time to gain benefit
- Can lifestyle changes replace any unnecessary drug therapy?

Step 4: (Effectiveness) Are therapeutic objectives being achieved?

- Check treatment choice is the most effective to achieve intended outcomes
- If this is not the case, the possibility of patient non-adherence should be investigated as a potential explanation. Otherwise, the need for dose titration may also be considered. 50% of patients taking four or more medicines don't take them as prescribed (Medication Adherence: WHO Cares?).

Step 5: (Safety) Is the patient at risk of ADRs or suffers actual ADRs?

- The presence of ADRs can sometimes be identified from laboratory data (e.g. hypokalaemia from diuretic use)
- The patient may report such symptoms (including drug-drug and drug-disease interactions, but also the patient's ability to self-medicate)
- Ask the patient specific questions (e.g. about the presence of anticholinergic symptoms, dizziness or drowsiness). If patient is experiencing ADRs, use Yellow Card Reporting

Step 6: (Efficiency) Is drug therapy cost-effective?

- Opportunities for cost minimisation should be explored, but changing drugs for cost reasons should only be considered if effectiveness, safety or adherence would not be comprised
- Ensure prescribing is in line with current formulary recommendations

Step 7: (Patient-centred) Is the patient willing and able to take drug therapy as intended?

- Does the patient understand the outcome of the review?
- Ensure drug therapy is tailored to patient preferences
- Agree and communicate plan with patient and/or welfare proxy
- Even if adult lacks capacity, adults with Incapacity Act still requires that the adult's views are sought. Ensure "Adults with Incapacity Documentation" in place

DRAFT

Table 2a: An overview of key considerations at each step

Domain	Steps		Process
Aims	1	What matters to the patient?	**Review diagnoses and identify therapeutic objectives with respect to:** • What matters to me (the patient)? • Understanding of objectives of drug therapy • Management of existing health problems • Prevention of future health problems
Need	2	Identify essential drug therapy	**Identify essential drugs (not to be stopped without specialist advice):** • Drugs that have essential replacement functions (e.g. levothyroxine) • Drugs to prevent rapid symptomatic decline (e.g. drugs for Parkinson's disease, heart failure)
	3	Does the patient take unnecessary drug therapy?	**Identify and review the (continued) need for drugs:** • With temporary indications • With higher than usual maintenance doses • With limited benefit in general for the indication they are used for • With limited benefit in the patient under review (See: *Drug Efficacy (NNT)* table)
Effectiveness	4	Are therapeutic objectives being achieved?	**Identify the need for adding/intensifying drug therapy in order to achieve therapeutic objectives:** • To achieve symptom control • To achieve biochemical/clinical targets • To prevent disease progression/exacerbation
Safety	5	Does the patient have ADR/Side Effects or is at risk of ADRs/Side Effects? Does the patient know what to do if they're ill?	**Identify patient safety risks by checking for:** • Drug-disease interactions • Drug-drug interactions (see *Cumulative Toxicity* tool) • Robustness of monitoring mechanisms for high-risk drugs • Drug-drug and drug-disease interactions • Risk of accidental overdosing (Yellow Card Scheme) **Identify adverse drug effects by checking for** • Specific symptoms/laboratory markers (e.g. hypokalaemia) • Cumulative adverse drug effects (see *Cumulative Toxicity* tool) • Drugs that may be used to treat ADRs caused by other drugs(*Sick Day Rule* guidance can be used to help patients know what do with their medicines if they fall ill)
Cost-effectiveness	6	Is drug therapy cost-effective?	**Identify unnecessarily costly drug therapy by:** • Consider more cost-effective alternatives (but balance against effectiveness, safety, convenience)
Patient centeredness	7	Is the patient willing and able to take drug therapy as intended?	**Does the patient understand the outcomes of the review?** • Does the patient understand why they need to take their medication? • Consider Teach back **Ensure drug therapy changes are tailored to patient preferences** • Is the medication in a form the patient can take? • Is the dosing schedule convenient? • Consider what assistance the patient might have and when this is available • Is the patient able to take medicines as intended? **Agree and Communicate Plan** • Discuss with the patient/carer/welfare proxy therapeutic objectives and treatment priorities • Decide with the patient/carer/welfare proxies what medicines have an effect of sufficient magnitude to consider continuation or discontinuation • Inform relevant healthcare and social care carers change in treatments across the care interfaces Add the READ code **8B31B** to the patients record so that when they move across transitions of care it is clear their medication has been reviewed

Appendix 3 – Opioid Risk Tool to support the identification of abuse

Opioid Risk Tool(1)(13)

This tool should be administered to patients upon an initial visit prior to beginning opioid therapy for pain management.

A score of 3 or lower indicates **low risk** for future opioid abuse
A score of 4 to 7 indicates **moderate risk** for opioid abuse
A score of 8 or higher indicates a **high risk** for opioid abuse

Mark each box that applies	**Female**	**Male**
Family history of substance abuse		
Alcohol	1	3
Illegal drugs	2	3
Prescription (Rx) drugs	4	4
Personal history of substance abuse		
Alcohol	3	3
Illegal drugs	4	4
Rx drugs	5	5
Age between 16—45 years	1	1
History of preadolescent sexual abuse	3	0
Psychological disease		
ADD, OCD, bipolar, schizophrenia	2	2
Depression	1	1
Scoring totals		

Appendix 4 - Practice chronic pain pain-reliever protocol template

Why have a protocol?
Pain reliever prescribing is continuing to grow. Evidence suggests that over the short term they can be effective in providing symptomatic improvement of many types of pain, however complete relief of pain is rarely achieved, and evidence for use in long term chronic pain (pain lasting > 12 weeks) is lacking. There is increasing evidence that many pain relievers, including opioids, gabapentin and pregabalin, have the potential for harm and abuse. It is therefore imperative to provide a consistent practice approach to the initiation and prescribing of pain relief.
General Principles - Establish diagnosis at first presentation
• Assess patient, determine root cause(s) of pain, ensure BPI Scoring is complete, read code patient as appropriate e.g. Chronic Pain (1M52) and 66n Chronic Pain Review (66n)
General Principles - Develop a clear self-management plan collaboratively with patient
• Ensure expectations are discussed with patient with the aim to achieve a 30% improvement in pain score (1) and/or an improvement in function and quality of life • Ensure non pharmaceutical approaches are encouraged either alone or in conjunction with medicines (physiotherapy, live active, stress and well-being classes, core strengthening classes (yoga/Pilates/tai chi), pain education classes and possibly acupuncture, massage). • Discuss risks, side effects of pain reliever and sign written agreement or contract if required (http://www.paindata.org/documents/guidelines-treatment%20contract%20for%20the%20use%20of%20an%20opioid%20medicine.doc) • Use lowest appropriate dose (considering drug interaction, age, renal function etc) • Review therapy at an agreed interval (e.g every 3 -6 months or annually) for efficacy and tolerability • Agree trials for cessation of pain relief in an agreed time frame to determine ongoing need. This trial must be undertaken and the patient should be made aware of its importance. • Provision of information either in paper or digital form or link to useful websites
General Principles - Practice should agree and adhere to:
• Health Board pain guidelines • Use of pain scoring (BPI) for initial assessment and at ongoing reviews (e.g. every 3-6 months) • When prescribing, discuss practice protocol as outlined and develop a self-management plan between patient and practice. Establish current BPI score. Review medication and trial stop or reduction where appropriate. Agree future review and trial cessation periods • The review of patients newly registered to the practice or who have had contact with secondary or tertiary services (e.g. prison)and already on strong pain relievers. This should happen within a set time period (e.g. 2 weeks) • The STOPPING of all step 2 pain relief before starting step 3 and an agreed maximum daily opioid dose of 90mg of morphine equivalent per day • Set supply quantities of opioid pain relief, and on what type of script (acute or repeat) for different situations i.e. at initiation, post review, for at-risk patients, for patients who DNA • A process on how to perform an opioid risk assessment using an opioid risk tool and if opioid therapy is appropriate then adjust regimen accordingly e.g. dispense weekly

DRAFT

- Consistent procedures to follow for non-attenders of pain reviews i.e. patient will receive no more than 1 week supply at a time and should have a review appointment booked within the week (or at earliest convenience)

Administrative Controls

- Where pain relievers are supplied via repeat, reception staff who print off repeat scripts should be encouraged to monitor potential abuse or oversupply and highlight to a clinician as appropriate

- Regarding patients who request additional supplies of pain relievers (e.g. in event of a lost prescriptions):
  - Patients not to receive further supply without considered authorisation from an appropriate clinician, with due thought being given to potential abuse or diversion
  - Where a prescription has been lost prior to dispensing the medication should always be issued as a re-print rather than a re-issue. To check whether or not the medication has been dispensed contact the ePharmacy Helpdesk and provide the prescription barcode number to determine if the prescription has been dispensed
  - Consideration to be given as to whether the patient requires more frequent monitoring when ordering or whether instalment dispensing would be beneficial

- Monthly (or two monthly) review by admin staff of duplicate repeat items issued is recommended to identify if there are strong opioids, gabapentinoids or other pain relievers frequently occurring. This can serve as an indicator of abuse of the practice systems. A duplicate repeat item is one which has been reissued within three days of its original issue. These items can be identified through the Scottish Therapeutics Utility (STU), Report 3 – Duplicate Issues. For more information about STU go to: http://www.therapeutics.scot.nhs.uk/stu/ or contact your local Primary Care Prescribing Team.

Practice	Date Created	Review Date (2 yearly)
Complete parts in italics	***Insert Date***	***Insert Review Date***
Written by:	***Insert Name***	
Agreed by:	***Insert names of all practice prescribers who agree to policy***	

When establishing a diagnosis:

- Use BPI Scoring: BPI
- Investigations (if clinically indicated): ***physical examinations, bloods, weight, x-ray, imaging***
- Specialist referral (if clinically indicated): ***pain services, rheumatology, mental health***
- Read code to be used: **Chronic Pain (1M52)**

Developing a self management plan with the patient

- Discuss patient expectations
- Clarify aim: A 30% improvement in pain score and/or an improvement in function / quality of life
- Use BPI Scoring (initial and follow up reviews): BPI and record on EMIS chronic pain template
- NHS Fife Pain Self Management Leaflet provides a good example for printing
- Newly registered patients already on strong pain relief / patients returning to practice following contact with secondary / tertiary services e.g. prison to be reviewed within ***X weeks***

• Direct to Pain Concern website for chronic pain resources/ideas

Non-pharmaceutical approaches to be considered:	
Approach	Access via (web / e-mail / telephone)
Core strengthening classes (yoga, Pilates, tai chi) ***Live Active*** ***Physiotherapy*** ***Stress / well being classes*** ***Pain education classes*** ***(where relevant – acupuncture, massage)***	*Add information e.g. local resource available to practice, including mental health resource*

When using pharmacotherapy
• Follow Health Board Guidelines: *Insert guideline link* • Discuss risks and side effects • Use lowest dose appropriate to patient e.g. accounting for age, renal function, interactions, etc • Stop all Step 2 opioids prior to starting strong opioids • Agree upper limits of prescribing i.e. daily morphine equivalent 90mg per day • Prescribing Checklist • Opioid Risk Tool

On new initiation of pharmacotherapy
• Initial trial to be given for a period of ***1-2 weeks prescribed on Acute prescription only*** • Review and trial cessation or therapy reduction to take place after ***X weeks*** • Read code to be used: **Chronic Pain Review (66n) via chronic pain template**

At Risk Patients
• Supply to be limited to ***X weeks prescribed on Acute prescription only*** • Consideration to be given to supplying as 'dispense weekly' • Patient review to take place every ***X weeks***
• Patient agreement to be completed: Patient Agreement

Ongoing reviewing of pharmacotherapy		
• Supply to be limited to ***X weeks*** prescribed on Acute / Repeat script (under x circumstances if repeat) • Patient review to take place every ***X weeks***(consider trial cessation / reduction). Assess using BPI / PADT • Read code to be used: **Chronic Pain Review (66n) via chronic pain template**		
Pharmacotherapy choices (*Refer to HB Formulary for options)*	Lowest Dose (based on SPC)	
Step 1		
List Step 1 Drugs Here	***List Doses Here***	
Step 2		
List Step 2 Drugs Here	***List Doses Here***	
Step 3		
List Step 3 Drugs Here	***List Doses Here***	
Neuropathic Pain		
List Neuropathic Pain Drugs Here	***List Doses Here***	
Local Guidelines Available At:		
Insert link		

DRAFT

Appendix 5 – Adapted from SIGN 136 Management of Chronic Pain - pathways[2]

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

	Define and discuss how the trial will work
	
	• Set a timescale; discuss the expected duration of trial, frequency of review.
	• Set a dose; including upper dose limit; aim for lowest effective dose.
	• Agree stopping rules with the patient before starting:
	  ○ if treatment goals are not met
	  ○ if there is no clear evidence of dose response
	  ○ if rapid tolerance develops necessitating high dose opioids. In this situation proceed to reduction and cessation or consider specialist referral/advice.
	• Consider opioid rotation if the pain is opioid responsive but efficacy and dose titration is limited by side effects.
	
	The suggested dose conversion ratios table (page 28) is for guidance only and should be used with caution.
	
	If the patient is on a high dose before conversion, consider phased conversion to avoid withdrawal. Short acting opioids may need to be used during conversion until the correct dose is established.

Starting a strong opioid	**Factors to consider** • Route of administration; oral or transdermal are the main routes for chronic non-malignant pain. • Choice of opioid (see section on choice of opioid and suggested dose conversion ratios). • Dose; there is considerable variability in the dose needed to effectively treat pain. Careful titration to the lowest effective dose, balanced against side effects requires regular review.
	There are two potential options for starting strong opioids: • Start with low dose of long-acting preparation. If the patient is already on co-codamol or dihydrocodeine, then they are not opioid naive, particularly if they are on the maximum dose or more than one of these agents. OR • While establishing dose, use an immediate release preparation for short term use, only to determine approximate dose range, then convert to equivalent long-acting preparation as soon as possible. This may be more appropriate if the patient has multiple comorbidities. Aim to establish the patient on long-acting opioid with no immediate release opioid if the chronic pain is stable. For patients with mild 'breakthrough pain' consider non-opioids (e.g. paracetamol, NSAIDs) or weak opioid.
Monitoring opioid trial	**Monitor adverse effects** • Gastrointestinal: ○ nausea/vomiting; tolerance usually develops. Consider use of an antiemetic at initiation of therapy. Due to the abuse potential of cyclizine, avoid if possible.

DRAFT

	○ constipation: tolerance often does not develop to this. Use stool softeners/stimulant laxatives or a combination. Consider opioid preparations less likely to cause GI effects. • Central nervous system: *If these do not resolve, then either dose reduction or rotation will be needed.* ○ impaired memory, concentration ○ hallucinations, milder visual disturbance ○ sedation, confusion, cognitive impairment ○ myoclonic jerks. • Other: ○ sweating ○ reduced libido, fertility; consider stopping, testosterone replacement, possible opioid rotation; may need endocrine review ○ respiratory depression; stop opioid until resolves; consider factors contributing to event ○ tolerance; rotate opioid or reduce and stop ○ opioid induced hyperalgesia - rotate opioid or reduce and stop; seek specialist advice.
	Assess pain relief • If there is good pain relief on a stable dose of opioid without unacceptable side effects continue with at least annual review. • If pain relief is inadequate due to: ○ dose titration not being possible due to adverse effects, try opioid rotation ○ no/minimal evidence of opioid responsiveness, reduce and stop opioid ○ intolerable side effects, try opioid rotation. Short-acting opioids may need to be used during the conversion both to reduce physical withdrawal and while optimum dose is being established. If the patient is on a large dose of opioid, consider phased conversion (e.g. reduce the current opioid dose by 50% and introduce the new opioid dose at less than the morphine equivalent dose replacement dose (because of incomplete cross-reactivity). Continue with reduction of the old opioid and increase in new opioid as indicated by response.
	At all times before and during opioid treatment signs of iatrogenic substance misuse should be sought and if problems arise, then consider early specialist advice/referral.
Continuing opioid therapy	**Regular review, ideally with one prescriber:** • At least annual, more frequently if problems arise. • Have a clear plan for flare-up management (including availability/accessibility to out of hours service)

Up-to-date SMC advice on these drugs is available from their website, www.scottishmedicines.org.uk

DRAFT

Choice of Opioid		
OPIOID	**ROUTE**	**COMMENTS**
Morphine	Oral	Most commonly used; very variable bioavailability (15 - 65%), no evidence that it is better than other opioid; active metabolites can accumulate in renal impairment, some may cause hyperalgesia.
Tramadol	Oral	Weak Mu Opioid Receptor (MOR) agonist with additional effects on noradrenergic and serotonergic systems. Potency approximately 1/6th that of morphine. Metabolism is via the Cytochrome P450 enzymes, with one of the active metabolites: O-desmethyltramadol having considerably more potency at the MOR.
Oxycodone	Oral	More reliable bioavailability than morphine (60 - 87%); metabolism involves both cytochrome P450 enzymes and glucuronidation.
Fentanyl	Transdermal	Useful if problems with oral administration.
Buprenorphine	Transdermal	Useful if problems with oral administration; minimal active metabolite accumulation in renal impairment.
Hydromorphone	Oral	Potent strong opioid, metabolised in the liver. Wide inter-individual patient variability.
Tapentadol	Oral	New opioid with additional activity on the noradrenergic systems; may have a role in neuropathic pain; some evidence of improved side effect profile and drop-out rates from RCTs compared to other strong opioids.
Oxycodone/ Naloxone	Oral	Combined preparation where naloxone binds preferentially to MORs in the GI tract, with potential reduction in opioid-related adverse GI effects. Maximum recommended dose 80 mg oxycodone/40 mg naloxone.
Methadone	Oral	Very unpredictable pharmacokinetics with considerable inter-individual variation. NOT recommended for use without specialist advice.

DRAFT

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

DRAFT

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

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

** The conversion ratios of oral morphine: transdermal fentanyl specified by the manufacturer(s) vary from around 100:1 to 150:1

DRAFT

Appendix 6 – Opioid Care Bundle to assist in review and audit of opioid prescribing

Opioid CARE Bundle

Practices will randomly sample 10 patients per quarter who have been prescribed opioid* derived pain relief in the past 3 months, to see if they are reliably receiving the following care:

1. Is there a clear indication documented and coded?
2. Is there a clear management plan linked to patient goals, including non-pharmacological strategies?
3. Is there evidence that the pain relief has been used in accordance with local pain guidance prior to the patient being prescribed a moderate to strong opioid derived pain relief?
4. Is initial prescription an acute and for no more than 30 days' supply and are lost or over-ordered prescriptions dealt with in accordance with prescribing policy (if applicable)?
5. Has clinical review occurred effectively prior to the second prescription being issued?

Key Area	Measure	To meet criteria	Rationale
Indication	Is there a clear indication documented and coded?	Clear indication for the opioid use should be documented in the patient notes (handwritten or computerised) If the patient has had pain for more than 12 weeks the read code 1M52. Should be added to their notes if not coded already.	Coding for chronic pain will allow audit and review and begin the process of implementing and measuring other improvements.
Management Plan	Is there a clear management plan including non-pharmacological strategies?	Evidence of clear pharmacological plan and signposting for non-pharmacological strategies/self-management approach	SIGN 136 recommends exercise and exercise therapies, regardless of their form and self-management for patients with chronic pain.
Assessment	Is there evidence that the pain reliever has been used in accordance with local pain guidance prior to the patient being prescribed a moderate to strong opioid derived pain relief ?	Evidence of trials of weak opioids and Non-opioid pain relief if appropriate Evidence of assessment to rule out neuropathic pain Evidence of conforming to local formulary choices	Although effective in short-term pain relief, there is little or no evidence for the effectiveness of long-term use of strong opioids in chronic pain, and these should only be initiated with caution after a discussion about realistic treatment goals, the potential side effects and longer-term risks.
Prescription Management	Is initial prescription an acute and for no more than 30 day supply and are lost or over-ordered prescriptions dealt with in accordance with prescribing policy (if applicable)?	Must meet both aspects if applicable to meet criteria	The Department of Health and Scottish Government have issued strong recommendations that the maximum quantity of opioids should not exceed 30 days
Review	Has clinical review occurred effectively prior to the second prescription being issued?	The patient must have been formally reviewed by GP or Specialist within the planned timeframe and consultation recorded with clear record of response/benefit to Opioid.	SIGN 136 recommends "Strong opioids should be considered as an option for pain relief for patients with chronic low back pain or osteoarthritis, and only continued if there is ongoing pain relief. Regular review is required."

*Includes any medication containing: Tramadol, Tapentadol, Morphine, Oxycodone, Fentanyl, Buprenorphine.

DRAFT

Appendix 7 – Considerations for opioid reviews for Health Care Professionals

Assessing suitability - {To be done prior to initiation, or at review}

- Establish the aims and objectives – decide these with the patient
- Assess pain (e.g. using BPI's); risks (ADRs etc); risk of misuse
- Assess for Frailty and comorbidities that predispose to higher risk of harm
- Assess effectiveness of previous treatments including any non-pharmaceutical approaches
- Record diagnosis and any reviews which take place
- Set goals, ensure patient is informed in order for them to make their choices

Starting a strong opioid

- Consider route, choice and dose
- Aim to "*start low and go slow"*
- Titrate to agreed therapeutic goals or up to where there are limiting side-effects
- Monitor/review within 2-4 weeks
- Ensure patient clear about dosing & has a "flare-up" plan in place

Monitoring a strong opioid

- At initiation; depending on patient/circumstances, review within 2-4 weeks
- Monitor for effectiveness and side-effects – review essential and unnecessary medication, make extensive use of non-pharmaceutical approaches
- Review at least annually (more frequently if this is required)
- Maintain vigilance for any misuse

Continuing opioid therapy

- Maintain ongoing review and assessment - 7 step review process
- Initial review should be **2-4 weeks**, review ongoing use 6 monthly to **annually** - depending on individual circumstances
- Monitor and assess "flare-up" plan, continue to monitor for effectiveness and side-effects, and to review essential and unnecessary medication, and any non-pharmaceutical treatments

Reducing and stopping strong opioids

- Aim to reduce/stop if therapeutic goals not reached or side-effects become unacceptable – **avoid abrupt discontinuation**
- Review to aim to reduce even if stable - to assess need for ongoing therapy
- Agree the "hows" with the patient: how fast, how much, how to manage a "flare-up" during this period, how to manage symptoms of withdrawal, how to manage the supply

DRAFT

Appendix 8 – Clinical Opiate Withdrawal Scale

For each item, write in the number that best describes the patient's signs or symptom. Rate on just the apparent relationship to opiate withdrawal. For example, if heart rate is increased because the patient was exerting self just prior to assessment, the increase pulse rate would not add to the score.

Patient's Name:_____ Date: _____				
Times:				
Resting Pulse Rate: (record beats per minute) *Measured after patient is sitting or lying for one minute* 0 pulse rate 80 or below 1 pulse rate 81-100 2 pulse rate 101-120 4 pulse rate greater than 120				
Sweating: *over past ½ hour not accounted for by room temperature or patient activity.* 0 no report of chills or flushing 1 subjective report of chills or flushing 2 flushed or observable moistness on face 3 beads of sweat on brow or face 4 sweat streaming off face				
Restlessness *Observation during assessment* 0 able to sit still 1 reports difficulty sitting still, but is able to do so 3 frequent shifting or extraneous movements of legs/arms 5 Unable to sit still for more than a few seconds				

DRAFT

Pupil size 0 pupils pinned or normal size for room light 1 pupils possibly larger than normal for room light 2 pupils moderately dilated 5 pupils so dilated that only the rim of the iris is visible				
Bone or Joint aches *If patient was having pain previously, only the additional component attributed to opiates withdrawal is scored* 0 not present 1 mild diffuse discomfort 2 patient reports severe diffuse aching of joints/ muscles 4 patient is rubbing joints or muscles and is unable to sit still because of discomfort				
Runny nose or tearing *Not accounted for by cold symptoms or allergies* 0 not present 1 nasal stuffiness or unusually moist eyes 2 nose running or tearing 4 nose constantly running or tears streaming down cheeks				
GI Upset: *over last ½ hour* 0 no GI symptoms 1 stomach cramps 2 nausea or loose stool 3 vomiting or diarrhea 5 Multiple episodes of diarrhea or vomiting				
Tremor *observation of outstretched hands* 0 No tremor 1 tremor can be felt, but not observed 2 slight tremor observable 4 gross tremor or muscle twitching				
Yawning *Observation during assessment* 0 no yawning 1 yawning once or twice during assessment 2 yawning three or more times during assessment 4 yawning several times/minute				

DRAFT

Anxiety or Irritability 0 none 1 patient reports increasing irritability or anxiousness 2 patient obviously irritable anxious 4 patient so irritable or anxious that participation in the assessment is difficult				
Gooseflesh skin 0 skin is smooth 3 piloerrection of skin can be felt or hairs standing up on arms 5 prominent piloerection				
Total scores **with observer's initials**				

Score:
5-12 = mild;
13-24 = moderate;
25-36 = moderately severe;
more than 36 = severe withdrawal

DRAFT

Appendix 9 – Examples of Symptomatic Relief in Opioid Withdrawal

Suggestions for prescription, noting variations in local formularies (also see BNF):

Drug	Comment
Lofexidine	0.2mg-0.4mg, 2 - 4hourly, up to maximum of 2.4mg in 24 hours (**Monitor pulse and BP: If systolic BP <90mmHg, or 30mmHg drop from baseline: or pulse <55; withhold until normalises.** Should also be reduced gradually if used over several days due to risk of rebound hypertension).
Metoclopramide	10mg, 8 hourly, up to maximum of 30mg in 24 hours (oral or im)
Ibuprofen	400mg oral, 4 - 6 hourly, up to maximum of 2.4g in 24 hours
Loperamide	2mg oral, as required for diarrhoea, up to maximum of 8mg in 24 hours
Buscopan (Hyoscine butylbromide)	20mg as required, up to maximum of 80mg in 24 hours – note that this should ideally be injected.
If sleep problems, consider **trazodone 50mg** or **zopiclone 7.5mg.**	Do not prescribe a benzodiazepine. If prescribed as inpatient, medication for sleep should NOT continue post-discharge, and if initiated in Primary Care, any prescription should be reviewed as quickly as possible. Sleep problems patient information leaflet self-help guide to sleep problems.

DRAFT

Appendix 10 – Considerations when reducing strong opioids

Guidance for HCPs, based on Oxford Pain Management Clinic:[27]

a. Education: explain the value of reducing opioids.
The patient can engage best when there is an understanding and recognition of opioid side effects that are personally relevant, and of the importance of reducing opioids.

b. Engagement: give the patient as much choice as possible around how to reduce their opioids.

Overall, it does not matter how the opioids are reduced as long as the overall daily dose continues to decrease, and that there is an understanding that the opioid doses should not increase once reduced. Giving the patient choice over how this is achieved gives more control and ownership of the process, improves engagement and is more likely to succeed.

c. Effecting the weaning plan:
Note:
Rate and size of reduction (taper tool): this will vary between patients. Minimising opioid withdrawal symptoms and allowing short term pain flares to settle between dose reductions should be the aim. At very high doses the size of the reduction may be better tolerated, with consideration given to smaller, slower reduction towards the lower end of the dose range.

Short term pain flare: Manage with simple pain relievers, non-pharmacological approaches, and reassurance that this usually settles. But be very clear that this is normal and manageable.

Opioid withdrawal: Patients and HCPs may find it difficult to identify withdrawal symptoms as distinct from the symptoms associated with their chronic pain, but it is important to do so. Symptomatic relief can be used (Appendix 8 for examples). Ideally reducing in smaller increments and/ or more gradually over time will avoid this, unless there is a need for more rapid reduction (e.g. safety). Other practical suggestions are: switch liquids to tablets; stick to agreed plans in using tapering or reducing templates; and ensure that equivalent doses are switched to the opioid which is the **one to be reduced** e.g. switch oxycodone to morphine, then reduce the *morphine* as per a tapering tool.

DRAFT

d. Emotional impact: Anxiety is to be expected during opioid reduction.

If a patient has taken opioids for many years they may have a sense that they won't be able to cope without them. Anxiety and depression often worsen during an opioid reduction, either because the long term opioids have suppressed noradrenaline and dulled usual emotions (in which case the increased anxiety then settles back down again), or because the reduction unmasks pre-existing psychopathology. If not managed well, this can derail the opioid reduction. Psychological support with psychologists, counsellors or access to psychological therapies will be helpful. Note – do not manage anxiety with benzodiazepines, due to the risk of respiratory depression.

e. Expectations: ensure the patient understands that the pain is likely to worsen in the short term during opioid weaning.

Despite slow reductions, patients may also experience withdrawal symptoms together with increased anxiety and depression. For this reason it is important that there is engagement, understanding and support from friends and family during the process. Patients should also be encouraged to develop non-drug techniques (relaxation, distraction, music, DVDs, walks etc., as discussed in Appendix 10) to manage their pain and reduce the reliance on pharmacological treatment. It can take 4-6 months after the cessation of opioids before feeling back to normal, i.e. for the pain, anxiety and depression to reduce. In the longer term, the pain will reduce to a degree due to the reversal of opioid induced hyperalgesia (where long-term opioids *increase* sensitivity to pain, rather than decrease it). For patients with abdominal pain, this pain will also improve as the opioids will have been contributing to gut dysmotility.

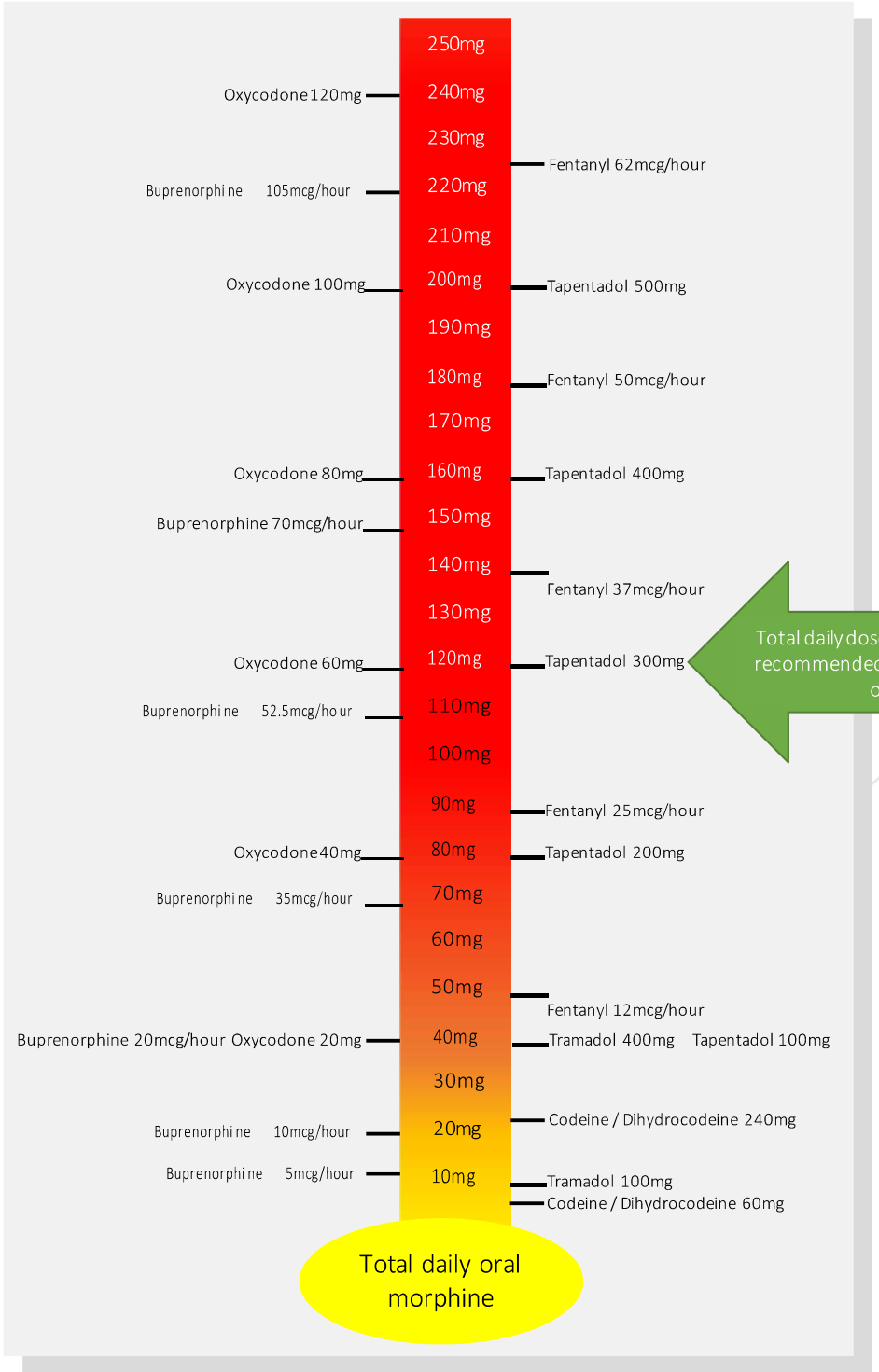
DRAFT

Appendix 11 – Non-pharmaceutical support – resources

Link	Comment
SIGN Guideline for Patients	Lists useful resources and websites.
NHS Education for Scotland website	Includes various self-management related resources and handouts (including information about pain, physical activity, exercise and pain, flare-ups, goal setting, sleep, and relaxation) developed for patients, their carers and the public as well as professionals with an interest in chronic pain.
NHS Inform website	Includes different lifestyle strategies such as pacing yourself or doing things that you enjoy, to manage pain.
Pain Association Scotland	Self-management pain education
Pain Concern	Extensive tools for management of pain
Versus Arthritis	For arthritis care information
Back Care	For back pain information
Pain UK	Aims to improve the quality of life for people living with pain in the UK.
ReConnect2Life	This will help patients to learn more about their pain and how to improve their quality of life.
The Live Well with Pain website	Contains an extensive selection of resources for clinicians on how to support people who suffer from chronic pain to self-manage their condition effectively, and how these strategies can help when coming off medication.
The Pain Toolkit	Website has various information leaflets and tools.
Pain Data	Also has advice for patients on self-management and resources that patients can download such as mindfulness mp3s.
Moodcafé	The Moodcafé website contains information about relaxation, mindfulness and improving sleep.
Beating the Blues	Online CBT programme.
Living Life	CBT website.

The opioid thermometer below is a useful tool for highlighting equivalent opioid dosing, the need for regular medicine reviews and the need to discuss non medicinal ways to live with persistent pain. It highlights doses above 120mg oral morphine equivalent per day are associated with little additional pain relieving benefit but significantly higher risks of harm, however expert consensus has identified 90mg oral morphine equivalent per day as the threshold at which higher risks of harm occurs, with little additional pain relieving benefit takes place above this dose [10].

DRAFT



How does the opioid prescribing in your practice measure up? Is it too hot to handle?

- There are increasing concerns about the number of prescriptions for opioid medicines being issued each year for people living with persistent pain.
- The evidence does not support the use of opioids for long-term, non-cancer pain, and there are risks of harm increasing with the dose prescribed and the duration of use.
- Doses above 120mg oral morphine equivalent per day are associated with little additional pain relieving benefit but significantly higher risks of harm.

  So how does the prescribing in your practice measure up? Use the thermometer to take the temperature of opioid prescriptions you issue.
- If you co-prescribe opioids, then it can be easy for the opioid temperature to creep up without realising.
- People taking opioid medicines should have a review at least every year.
- Advice on non-medicinal ways to live with persistent pain should be provided at every opportunity.
- For useful resources to help you advise your patients with persistent pain in other ways, visit: **www.livewellwithpain.co.uk**

The opioid thermometer is intended for illustrative purposes and should not be used to assist with conversions between opioid medicines. All equivalences are approximate; there can be significant inter-patient variability.

LiveWell with pain

Thermometer and text: ♥ *LiveWell with Pain 2019*

References

1. The Scottish Government, Quality Prescribing for Chronic Pain: A Guideline for Improvement 2017-2020 [Internet] 2018. Available from: www.therapeutics.scot.nhs.uk/wp-content/uploads/2018/03/Strategy-Chronic-Pain-Quality-Prescribing-for-Chronic-Pain-2018.pdf
2. Scottish Intercollegiate Guidelines Network, Management of chronic pain. SIGN 136. 2013 (Updated 2019).
3. The Scottish Government, Polypharmacy Guidance Realistic Prescribing, 3rd edition 2018
4. Bohnert ASB, Valenstein M, Bair MJ, Ganoczy D, McCarthy JF, Ilgen MA, et al. Association between opioid prescribing patterns and opioid overdose-related deaths. JAMA - J Am Med Assoc. 2011;
5. Edlund MJ, Austen MA, Sullivan MD, Martin BC, Williams JS, Fortney JC, et al. Patterns of opioid use for chronic noncancer pain in the veterans health administration from 2009 to 2011. Pain. 2014;155(11):2337–43.
6. Zin CS, Chen LC, Knaggs RD. Changes in trends and pattern of strong opioid prescribing in primary care. Eur J Pain (United Kingdom). 2014;18(9):1343–51.
7. Torrance N, Mansoor R, Wang H, Gilbert S, Macfarlane GJ, Serpell M, et al. Association of opioid prescribing practices with chronic pain and benzodiazepine co-prescription: a primary care data linkage study. Br J Anaesth. 2018;120(6):1345–55.
8. Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, et al. Pharmacotherapy for neuropathic pain in adults: A systematic review and meta-analysis. Lancet Neurol. 2015;14(2):162–73.
9. Vowles KE, Ashworth J. Is opioid withdrawal necessary within comprehensive pain rehabilitation programs? Pain. 2011. p. 1948–50.
10. US Dept of Health – Centres for Disease Control and Prevention, Checklist for Prescribing Opioids for Chronic Pain. 2016.
11 Royal College of Anaesthetists. Opioids Aware: A resource for patients and healthcare professionals to support prescribing of opioid medicines for pain. [Internet]. Available from: https://www.rcoa.ac.uk/faculty-of-pain-medicine/opioids-aware
12 UK Guidelines on Clinical Management, Drug misuse and dependence. 2017
13. IASP Statement on Opioids [Internet] 2018. Available from: http://www.iasp-pain.org/Advocacy/Content.aspx?ItemNumber=7194
14. Castro MMC, Daltro C, Kraychete DC, Lopes J. The cognitive behavioral therapy causes an improvement in quality of life in patients with chronic musculoskeletal pain. Arq Neuropsiquiatr [Internet]. 2012;70(11):864–8. Available from: http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0004-282X2012001100008&lng=en&tlng=en
15 Lawrence R, Mogford D, Colvin L. Systematic review to determine which validated measurement tools can be used to assess risk of problematic analgesic use in patients with chronic pain. In: British Journal of Anaesthesia. 2017. p. 1092–109.
16. Webster LR, Webster RM. Predicting aberrant behaviors in opioid-treated patients: Preliminary validation of the opioid risk tool. Pain Med. 2005;6(6):432–42.
17. A. B, M. von K, E.H.B. L. A review of potential adverse effects of long-term opioid therapy: A practitioner's guide. Prim Care Companion J Clin Psychiatry [Internet] 2012;14(3). Available from: http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L365397934%0Ahttp://article.psychiatrist.com/?ContentType=START&ID=10007908%0Ahttp://dx.doi.org/10.4088/PCC.11m01326
18. Adams LL, Gatchel RJ, Robinson RC, Polatin P, Gajraj N, Deschner M, et al. Development of a self-report screening instrument for assessing potential opioid medication misuse in chronic pain patients. J Pain Symptom Manage. 2004;27(5):440-59.
19. Butler SF, Budman SH, Fernandez K, Jamison RN. Validation of a screener and opioid assessment measure for patients with chronic pain. Pain. 2004;112(1–2):65–75.
20. Butler SF, Budman SH, Fernandez KC, Houle B, Benoit C, Katz N, et al. Development and validation of the Current Opioid Misuse Measure. Pain. 2007;130(1–2):144–56.
21. Brummett CM, Waljee JF, Goesling J, Moser S, Lin P, Englesbe MJ, et al. New persistent opioid use after minor and major surgical procedures in us adults. JAMA Surg. 2017;152(6).
22. Brat GA, Agniel D, Beam A, Yorkgitis B, Bicket M, Homer M, et al. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: Retrospective cohort study. BMJ. 2018;360.
23. Sun EC, Dixit A, Humphreys K, Darnall BD, Baker LC, MacKey S.

Association between concurrent use of prescription opioids and benzodiazepines and overdose: Retrospective analysis. BMJ. 2017;356.
24. Krebs EE, Gravely A, Noorbaloochi S. Opioids vs Nonopioids for Chronic Back, Hip, or Knee Pain-Reply. Jama. 2018;320(5):508–9.
25. Chou R, Turner JA, Devine EB, Hansen RN, Sullivan SD, Blazina I, et al. The effectiveness and risks of long-term opioid therapy for chronic pain: A systematic review for a national institutes of health pathways to prevention workshop. Annals of Internal Medicine. 2015. p. 276–86
26. Kalso E, Edwards JE, Moore RA, McQuay HJ. Opioids in chronic non-cancer pain: Systematic review of efficacy and safety. Pain. 2004. p. 372–80.
27. Oxford Pain Management Clinic. Guidance for Opioid Reduction in Primary Care. Available from: https: www.ouh.nhs.uk/services/referrals/pain/documents/gp-guidance-opioid-reduction.pdf
28. Interventions for the reduction of prescribed opioid use in chronic non-cancer pain. Cochrane Libr.
29. Frank JW, Lovejoy TI, Becker WC, Morasco BJ, Koenig CJ, Hoffecker L, et al. Patient outcomes in dose reduction or discontinuation of long-term opioid therapy: A systematic review.Annals of Internal Medicine 2017p.181–91
30. Turn the Tide Rx. Treatment Option [Internet]. Available from: https://turnthetiderx.org/treatment/
31. Porreca F, Ossipov MH. Nausea and vomiting side effects with opioid analgesics during treatment of chronic pain: Mechanisms, implications, and management options. Pain Medicine. 2009. p. 654–62.
32. McCance-Katz EF, Sullivan LE, Nallani S. Drug interactions of clinical importance among the opioids, methadone and buprenorphine, and other frequently prescribed medications: A review. American Journal on Addictions. 2010. p. 4–16.
33. Colvin LA, Fallon MT. Editorial: Opioid-induced hyperalgesia: A clinical challenge. British Journal of Anaesthesia. 2010;104(2):125–7.
34. Hutchinson MR, Watkins LR. Why is neuroimmunopharmacology crucial for the future of addiction research? Neuropharmacology. 2014. p. 218–27.
35. Boland JW, McWilliams K, Ahmedzai SH, Pockley AG. Effects of opioids on immunologic parameters that are relevant to anti-tumour immune potential in patients with cancer: A systematic literature review. British Journal of Cancer. 2014. p. 866–73.