The Pharmacological Management of Persistent Non-Malignant Pain in Adults

Prescribing Clinical Network

East Surrey CCG, Guildford & Waverley CCG, North West Surrey CCG, Surrey Downs CCG & Surrey Heath CCG, Crawley CCG, Horsham & Mid Sussex CCG

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INTRODUCTION

- Managing persistent non-malignant pain is a complex area and prescribing patterns both locally and nationally indicate opportunities to optimise medicines use in line with latest evidence. This guidance should be used in conjunction with Clinical Knowledge Summaries (CKS)[9] which is part of the NICE programme of work.
- Persistent Non-Malignant Pain (previously referred to as Chronic Non-Malignant pain) is defined as pain that has been present for more than twelve weeks[1]. It occurs when pain continues after the healing process has occurred, or when pain is associated with a disease process in which healing does not take place.
- Nationally there is increasing acknowledgement of opioid overuse and adverse effects/deaths related to these drugs. The aim is to have judicious use of opioids to ensure maximum benefit and minimise harm.
- It should be emphasised that medicines play only one part in managing pain. Maintaining fitness, pacing activities and a generally healthy lifestyle are also important[1].
- Persistent Non-Malignant pain refers to pain that exists beyond the expected time of healing usually taken as three months[1] or more. It is recognised as a long-term condition in its own right.
- It is a complex bio – psycho – social phenomenon, affecting as many as 20% of the population to some extent[5], recent suggestions of up to 50% of adults[6]. As well as causing a great deal of personal suffering, persistent pain has major economic implications for health service expenditure and for society as a whole[1,2].
- Some patients suffer from pain that does not respond to standard therapies and may require a more in-depth assessment by a specialist chronic pain service[1]. In addition, the patient's expectations of pain management may not be realistic; unfortunately achieving pain free status is not always possible, despite referral to the pain clinic.
- Medications are usually a small part of the pain management plan and should be used in conjunction with non-pharmacological interventions such as advice regarding activity, physiotherapy and an explanation that pain may be resistant to medication and complete relief of symptoms so not a goal of therapy.
- Ensure other medicines and management strategies have been considered and optimised before considering opioids. If opioids are to be considered ensure appropriate goals / expectations and reviews are planned
- Referral to a pain clinic should be carefully considered before starting patients on strong opioids such as morphine and always sought for patients on more than 120mg morphine equivalent in 24 hours[1,8].
- See appendix 1 for the safe prescribing of strong opioid analgesics which are often ineffective for long term pain and have the risk of unintentional overdose, addiction and death.
- Unlike acute pain and cancer pain, persistent pain not-associated with cancer has an unpredictable course and may persist for many years: substantial reduction in pain intensity is rarely an achievable goal.
- Based on advice from the Faculty of Pain Medicine, PCN (like the FPM) does not support the World Health Organisation (WHO) 3-step "Ladder" approach to manage pain in non-cancer patients. It may be rational to use a stepped approach but this should not be determined by reported pain intensity (which is the principle of the analgesic ladder).
- In the management of osteoarthritis PCN advises that the best way to reduce harms of oral NSAIDs is to avoid their use altogether by using alternative pain management strategies. The effectiveness of paracetamol for all types of pain has been questioned. However it's relatively safe and remains a viable option before moving on to oral NSAIDs

- If a medicine after a suitable trial does not work for the patient it should be stopped, the dose should not be increased. Many medications may need to be stopped slowly to avoid withdrawal or undesirable side effects – please see up to date SPC[11] for information
- For patients where pain is having a significant effect on physical functioning and mood who can engage with groups, consider referral to a pain management programme
- NICE Guideline 59[12]- For the management of low back pain, consider oral NSAIDs at the lowest effective dose for the shortest possible period of time. Weak opioids may be considered for managing acute low back pain only if an NSAID is contraindicated, not tolerated or has been ineffective.
- For the management of neuropathic pain see separate guidance on Surrey PAD[7]. This also applies to the management of sciatica. (Also see Clinical Knowledge Summaries – CKS[9]).

PURPOSE

To provide guidance on the pharmacological management of persistent non-malignant pain in adults.

SCOPE

This guideline provides recommendations on the medical management of adults with persistent non-malignant pain.

It does not cover:

- Management of neuropathic pain (See NICE CG96)
- Specialist medicines or medication regimens which will continue to be supplied from secondary care.
- The management of pain in palliative care.
- Migraine/Headache
- Prescribing of analgesics within secure prison services. See the Royal College of GP: Safer Prescribing in Prisons.

GUIDANCE

Prescribers should use this guidance in conjunction with the medication's summary of product characteristics (SPC)[11] British National Formulary (BNF)[10]and Clinical Knowledge Summaries (CKS)[9].

ACKNOWLEDGEMENTS

This guideline has been developed from the East Lancashire CCG non-cancer pain guideline and Derbyshire Joint Area Prescribing Committee Management of non-malignant chronic pain in primary care

SUMMARY OF KEY RECOMMENDATIONS FOR IMPLEMENTATION

Chronic Pain Management

- When considering therapy for patients with persistent non-malignant pain, optimisation of non-opioid pharmacotherapy and non-pharmacological therapy is recommended rather than a trial of opioids. Also optimise treatment of other aggravating factors such as anxiety and depression.
- Ensure type of pain is correctly identified and patients are aware that the drugs will not fully alleviate the pain but should help function better. Manage the expectation from the outset.
- Consider a trial of a strong opioid (see Appendix 1a checklist for opioid prescribing) only when other pharmacotherapy and non-pharmacological therapy is insufficient to manage the patients' condition, except in patients with a history of current or past substance use dependency or severe psychiatric disorders (specialist referral may be necessary).
- Ensure chosen drug is providing benefit and at the optimum tolerated dose before considering adding another. And check compliance at all points in the treatment pathway before dose escalation. Stop drugs not working and remove from repeat prescribing screen.

Prescribing Opioids

- When choosing a strong opioid, modified / sustained release morphine should be considered first line except in patients with severe renal impairment (See Appendix 1 for dosing according to degree of renal impairment) or those that have had previous confirmed intolerance to morphine.
- Prescribers should be aware that other opioids i.e. oxycodone, fentanyl, tramadol and buprenorphine have no evidence of superior efficacy when compared to morphine.
- Refer patients on more than 120mg morphine equivalent in 24 hours to a specialist pain service. Although 120mg is stated in most literature as the dose at which to refer in practice doses above 90mg (due to the greater risk of adverse events may highlight the need for a more regular review.
- Due to concerns of misuse and increase in the number of related deaths The Advisory Council on the Misuse of Drugs (ACMD) recommended the change of tramadol to schedule 3 CD. It should be prescribed with caution and subject to regular reviews (See Appendix 2).
- If a patient is using opioids but the pain is not alleviated, the opioids are not effective and should be discontinued, even if no other drug treatment available.
- Opioid induced constipation should be managed adequately.

Treatment pathway for non-malignant persistent pain in primary care

(see overleaf for lower back pain and osteoarthritis management)

Step 1

REGULAR PARACETAMOL
1g four times a day
<50kg reduce dose – see BNF
+/- **When required NSAID** +
PPI Ibuprofen 200-400mg TDS
or Naproxen 250-500mg BD

Prescribing Notes

- **Explain to patients that the drugs will not fully alleviate pain but should help them function better**
- **Utilise patient agreements for tramadol, buprenorphine and all strong opioids (see Appendix 7)**
- **Start opioids as a trial and STOP if ineffective**
- Ensure chosen drug is actually providing benefit and at optimum tolerated dose before considering adding another
- Check compliance at all points in the pathway before dose escalation
- Make only one change at a time to enable assessment of whether the medication is working
- Risk of harm increases substantially at doses above oral morphine equivalent 120mg/day[1'8] but no increased benefit
- If a patient is using opioids but is still in pain, the opioids are not effective and should be discontinued, even if no other treatment is available.
- A 'Safer Prescribing of NSAIDs' aide memoire is available on the PAD

Step 2

Consider if there is a neuropathic or inflammatory component?
→ Neuropathic – see neuropathic pain guidelines on the PAD
→ Inflammatory – see local CCG joint injection pathways

CONTINUE REGULAR PARACETAMOL
START REGULAR TREATMENT WITH:

- **ORAL NSAID** - Ibuprofen or Naproxen,
  (diclofenac or COX-2 [celecoxib first line COX-2] may be considered as alternatives – see appendix 2)

and/or

- **When required WEAK OPIOID, i.e.** Codeine 30-60mg up to QDS or Dihydrocodeine 30mg up to QDS

METABOLISM

- 6-10% of Caucasian patients cannot metabolise codeine
- Marked increase in morphine toxicity in patients who are ultra-rapid codeine metabolisers (1-2% of Northern Europeans; up to 29% in African / Ethiopian population)

If standard-release dihydrocodeine is not tolerated in these patients, or compliance is an issue, DIHYDROCODEINE SUSTAINED-RELEASE TABLETS may be considered, starting at a low dose

IF CODEINE / DIHYDROCODEINE NOT SUITABLE:

- **Consider Tramadol** (see Appendix 4) in conjunction with completed patient agreement (as with other strong opioids; see Appendix 7) if maximum tolerated dose of codeine / dihydrocodeine is ineffective
- **Consider buprenorphine patches (low dose 5-10 micrograms/hr; locally recommended brand)**. At this dose, buprenorphine has a similar analgesic effect to codeine 120-240 mg/24 hours. **May be of use in patients with frailty / swallowing difficulties**
- **At higher doses**, buprenorphine patch is considered as a strong opioid and consideration should be given to the use of morphine capsules that can be administered with semi-solid food before using higher strength buprenorphine patches.

Step 3

Addition of strong opioids (see page 10)
Confirm that maximum tolerated dose of both codeine or dihydrocodeine is ineffective / no longer effective?
Consider whether all measures have been taken to control side-effects.

REGULAR PARACETAMOL (STOP WEAK OPIOID)
+ START REGULAR TREATMENT WITH:
A strong opioid (**Morphine 1st line**) **+/- NSAID**
(See Appendix 1)
N.B. Routine use of 'when required' opioids is not recommended in the treatment of non-cancer pain.

RENAL IMPAIRMENT

Morphine may be used at lower doses
In severe renal impairment (GFR <10ml/min), seek renal physician advice.
See Appendix 3 if recommended morphine doses are insufficient to manage the patient's pain.

INTOLERANCE TO MORPHINE

A trial **of oxycodone** may be appropriate if intolerant to morphine. Take into consideration dose equivalence
(For patients with swallowing difficulties high dose buprenorphine patch may be considered)

Tapentadol (after assessment by a pain specialist) may be considered in patients not responding to / not tolerating morphine or oxycodone (after a prior trial of tramadol). Prescribers should be aware of the MHRA Drug Safety Update (January 2019) – see page 16

Pharmacological management of osteoarthritis (OA)

- There is a lack of evidence for the effectiveness of most therapeutic interventions for the long term management of OA
- As OA is a long term condition oral NSAIDs should be used with caution, only once the other, safer options have been tried first. Click for aide memoire
- Obtain specialist advice before prescribing stronger opioids for OA

First Line:

- ***Paracetamol*** 1g 3-4 times daily
- <50kg reduce dose – see BNF
- Add codeine 15-30mg if necessary for flare-ups

Second Line:

- ***Topical NSAID*** (e.g. ibuprofen gel, ketoprofen gel) for knee or hand OA
- Two week trial to assess effectiveness

Third Line:

- Consider addition of ***oral NSAID*** *to paracetamol* - ***Ibuprofen*** up to 1200mg daily or ***Naproxen*** up to 1000mg daily (*diclofenac or COX-2 [celecoxib first line COX-2] may be considered as alternatives – see appendix 2*)
- **Use at the lowest effective dose for the shortest possible time.**
- Co-prescribe with a **PPI**, choosing the one with the lowest acquisition cost
- If low-dose aspirin is being used, avoid NSAIDs if possible.

- Topical capsaicin should be considered as an adjunct to core treatments for knee or hand osteoarthritis.
- Intra-articular corticosteroid injections should be considered as an adjunct to core treatments for the relief of moderate to severe pain in people with osteoarthritis of the knee

ALL ***topical rubefacients*** are classified as BLACK due to limited evidence. Patients requesting rubefacients should be encouraged to self-treat and purchase over the counter if necessary.

Pharmacological Management of low back pain (excluding sciatica)

Consider alternative diagnosis and risk stratification (STarT Back risk assessment tool) to inform decision making.

Non-pharmacological interventions (page 7) should be considered first.

These may include self-management; group exercise programme; psychological therapy which may be combined with physical therapy (for referral see page 7)

Following consideration of non-pharmacological interventions:

- Offer **oral NSAIDs** - ***Ibuprofen*** up to 1200mg daily or ***Naproxen*** up to 1000mg daily (*diclofenac or COX-2 [celecoxib first line COX-2] may be considered as alternatives – see appendix 2*)
- **Use at the lowest effective dose for the shortest possible time.**
- Gastroprotective treatment should also be offered while an NSAID is being used.
- If an NSAID is contraindicated, not tolerated, or ineffective, offer a weak opioid (e.g. ***codeine***) with or without ***paracetamol***, taking into account the risk of opioid dependence and adverse effects such as constipation.
- If the person has muscle spasm, consider offering a short course of a benzodiazepine, such as diazepam 2 mg up to three times a day for up to 5 days, if not contraindicated

- NICE does not recommended SSRI, SNRI, TCA and anticonvulsants (including gabapentin and pregabalin) for managing low back pain
- Do not offer paracetamol alone for managing low back pain
- NICE does not recommend opioids for managing **chronic** low back pain

Non-pharmacological management of persistent non-malignant pain

Non-pharmacological methods are the mainstay in the management of persistent pain. The general principles include:

- **Activity:** This improves both physical and mental well-Being. Being active when in pain can be a challenge and it is therefore important for patients to know that it is safe to be active in spite of pain; provide reassurance that pain does not always indicate harm especially when pain persists for a long time.
- **Psychological approaches:** Pain can be associated with anxiety and stress; therefore it may be helpful to use relaxation techniques and/or psychological approaches Rationale for psychological approaches is not only to treat overlapping or associated mental health issues e.g. anxiety. There is also evidence to suggest that the psychological approach to manage pain can reduce the daily impact of pain. ACT (Acceptance and commitment therapy) and mindfulness can be used in addition to or instead of CBT (such as cognitive behavioural therapy) to help to manage the pain. High levels of anxiety, stress and pain may lead to sleep disturbance; hence, sleep restoration strategies may also be helpful.
- **Encourage self-management** for the control of pain in all clinical and non-clinical settings. This includes ensuring a good understanding of medication and being able to use it both wisely and flexibly as well as using non-pharmacological options. **www.paintoolkit.org**

The above is a very brief overview of non-pharmacological management of Persistent Non-Malignant pain and if the GP requires more detailed assessment and treatment then a referral to specialist services may be necessary. This will vary dependent on the location (see below):

CCG	Services available	Referral Links/Other info
Crawley CCG **Horsham and Mid Sussex CCG**	BSUH Pain Management Sussex Community Foundation trust chronic pain service SASH pain management	https://www.bsuh.nhs.uk/services/pain-management/ https://www.surreyandsussex.nhs.uk/our-services/a-z-of-services/pain-medicine/pain-medicine-outpatient-clinics/ https://www.sussexcommunity.nhs.uk/services/servicedetails.htm?directoryID=17167
East Surrey CCG	Pain clinic at SaSH, IAPT (AQP) which is Surrey wide First Community Health and Care (MSK services	https://www.surreyandsussex.nhs.uk/our-services/a-z-of-services/pain-medicine/pain-management-programme/
Guildford and Waverley CCG	Pain Management Service – RSCH	
North West Surrey CCG	MSK service - ASPH	
Surrey Downs CCG	Medway Back and Pain Clinic Ashtead Hospital (Procedures only) Epsom General Hospital St Helier Hospital Centre for Pain Education -Sutton Hospital Kingston Hospital Raynes Park Health Centre East Surrey Hospital	
Surrey Heath CCG	Surrey Heath Community Pain clinic (Upper Gordon Road Surgery). Advance MSK & Diagnostic service (Upper Gordon Road Surgery).	http://surreypain.org.uk/

Pharmacological management of persistent non-malignant pain

(with exceptions of osteoarthritis and low back pain)

Unlike acute pain and cancer pain at the end of life, persistent pain not-associated with cancer has an unpredictable course and may persist for many years; substantial reduction in pain intensity is rarely an achievable goal. Additionally, persistent pain may be generated by a number of different pathophysiologic mechanisms that may require different approaches to treatment.

Stepped approach

When making medication choices to support patients with persistent pain, the FPM recommend using a stepped approach, but this should not be determined by reported pain intensity (which is the underlying principle of the analgesic ladder). Regardless of pain intensity, it is rational to start with non-opioid drugs, where these have some demonstrated efficacy for the condition being treated. Trials of both weak and strong opioid therapy may be considered for some patients. All drugs prescribed for pain should be subject to regular review to evaluate continued efficacy.

Supporting Principles of Care[1]

a) During the Initial Patient Assessment consider:

- The type of pain
- Its aetiology and severity
- Analgesic history
- Impact on lifestyle & daily activities/ participation
- Common psycho-social problems. The patients' perceptions of the pain and its cause; coping strategies, mood changes, quality of sleep, and anxiety can all impact on perceived pain. Addressing these might reduce the need for analgesics.
- Assessing function and use of functional goals not just pain levels may also help with pain management.
- Pain assessment tools (Appendix 5 & 5a) may help with this process, particularly if patients have difficulty communicating e.g. patients with cognitive impairment or whose first language is not English.

b) Produce a Treatment Plan

- When possible treatment plans should be agreed with the patient, taking into account their concerns and expectations
- The cause of the pain and whether this condition has deteriorated
- Renal function, hepatic function, Respiratory function, Frailty and age of the patient.
- The patient's previous experience of pain analgesics used and any adverse effects or preferences.

c) Discuss with the patient:

- The reason why the treatment is being offered, along with the benefits, titration of dose and potential adverse effects. Coping strategies for pain and for possible adverse effects of treatment.
- Individualised information and advice should be provided if appropriate.

- Set realistic expectations of treatment. Achieving a pain free status may not be possible.

d) Review Treatment

- 4-6 weeks after starting or changing treatments and periodically (as appropriate to the patients pain underlying health condition and prescribed medications)
- Each review should assess:
    - pain control, medication concordance, impact on lifestyle, daily activities (including sleep disturbance) and participation, physical and psychological wellbeing, adverse effects, continued need for treatment, the need for specialist pain services input

e) Consider Referral to Specialist Services

PROCESS FOR TRIAL OF STRONG OPIOID (Step 3)

This process should be followed for all patients prescribed a strong opioid e.g. morphine and oxycodone. Consider also for patients prescribed weaker opioids e.g. codeine, buprenorphine (low dose) and tramadol.

Pre-Trial

- Assess pain type and severity and consider whether trial of strong opioid may be appropriate. For example pain assessment tools *see supporting resources document*
- Consider co-existing co-morbidities and drug treatment in the context of strong opioid therapy.
- Assess potential for medication abuse, diversion or accidental ingestion *see Appendix 1 for Checklist for opioid prescribing in persistent non-malignant pain in adults*
- Discuss and develop plan with patient before prescribing and document fully.
    - Set clear objectives and realistic goals e.g. 30% reduction in pain, improved sleep, defined functional improvement
    - Discuss side-effects/potential problems including potential addiction and tolerance and effect on driving – *see Appendix 6*
    - Define review period
    - Explain that if treatment is ineffective it will be stopped, even if there is no alternative treatment available
    - Complete patient agreement form – *See Appendix 7*

Prescribing the Opioid trial – 'Start Low and Go Slow'

Duration of Trial

- In stable constant chronic pain the trail may be concluded within 1-2 weeks
- For intermittent disabling flare ups trial should be long enough to observe effect on 2-3 episodes of pain

Drug, Dose and Formulation

- Use immediate release (IR) morphine tablets or liquid – explore different doses within a specified range e.g 5 to 10mg every 4-6 hours for 1-2 weeks. If 20mg is ineffective as a single dose then opioids are unlikely to be of benefit
- Alternatively use low dose modified release (MR) morphine e.g. Zomorph 10mg bd. Allow time for 1 or 2 dose increases which may take 3 weeks or more.
- Ask the patient to complete a diary recording doses taken and effect on sleep, pain and activities.

Assessing Effectiveness of Opioid Trial and Continued Prescribing

- Compare reported effectiveness with treatment goals and if ineffective taper and discontinue over one week.
- MR preparations are usually more appropriate for persistent pain.
- IR preparations may be suitable for some patients e.g. if pain intermittent and short-lived or infrequent exacerbations.
    - Caution with prescribing for breakthrough doses – IR preparations should not be used routinely
- Maximum dose of morphine 90-120mg/day or equivalent (oxycodone 45-60mg/day) – doses in excess of this are associated with increased risk of harms e.g. overdose and side-effects but are unlikely to provide further pain relief.
- Review patient and their response to the analgesia at least every 3 months with a view to stepping down or discontinuing as soon as possible.
- Consider referral of patients to a pain specialist early in their treatment, in particular those taking doses at or in excess of the maximum recommended dose or if taking for 12 months or more.

Appendix 1 - Checklist for opioid prescribing in persistent non-malignant pain in adults

When initiating opioid therapy consider the following:	
☐	Ensure optimisation of non-opioid pharmacotherapy and non-pharmacological therapy has taken place rather than a trial of opioids
☐	Aggravating factors such as anxiety and depression have been adequately managed
☐	Explain that the evidence for the use of opioids as analgesics is best used in the management of acute pain and opioids are poorly effective for long term pain
☐	Evaluate risk of misuse and harm and discuss risk factors with patient. If patient has a history of current or past substance use dependency or severe psychiatric disorders, specialist referral may be necessary. Consider using an opioid risk tool http://www.cpsa.ca/wp-content/uploads/2017/06/Opioid-Risk-Tool.pdf
☐	Check if the patient has any contra-indications or cautions to the use of opioids e.g. elderly, frail patients, impaired renal and hepatic function, previously poorly tolerated opioid therapy, drug interactions etc.
☐	Assess baseline pain and function and set realistic goals for pain and functional goals that might be achieved based on diagnosis. Discuss the degree of pain relief that might be expected
☐	Discuss the potential side effects of opioid treatment including: sedation, nausea, constipation, effects on hormones, effects on the immune system, effects on the respiratory system, effects on mood, the potential for these drugs to worsen pain and potential for problematic drug use and addiction
☐	Discuss opioids and impairment of driving skills
☐	Discuss the opioid trial
☐	Set criteria for continuing opioids and discuss the circumstances in which opioid therapy will be stopped and the process to discontinue if objectives are not met
☐	Discuss arrangements for review
☐	Complete prescription agreement form

When reviewing opioid therapy consider the following:	
☐	Assess pain and function and compare results to baseline
☐	Evaluate risk of harm or misuse
☐	Ensure optimisation of non-opioid pharmacotherapy and non-pharmacological therapy
☐	Determine medicine taking behaviour
☐	Review appropriateness of therapy and determine whether to continue, adjust, taper, or stop opioids. If opioids have been ineffective they should be tapered/stopped
☐	Refer patients on more than 120mg Morphine MR/SR equivalent in 24 hours to a specialist pain service
☐	Schedule reassessment at regular intervals

Appendix 2 - PAD status and key points relating to drugs within the persistent non-malignant pain guidelines

Drug	Prescribing Advisory Database (PAD) Status	Key Points
Paracetamol	• Tablets 500mg - **Green** • Oral Suspension 120mg/5ml, 250mg/5ml – **Green** • Dispersible Tablets 500mg – **Green (NOT preferred)** – swallowing difficulties only • Suppository 60mg, 125mg, 250mg, 500mg – **Green (NOT preferred)** – where oral preparations not appropriate • Oral Suspension 500mg/5ml - **Black**	• Paracetamol 500mg/5ml oral suspension is approximately 20 times more expensive than paracetamol 500mg tablets, 6 times more expensive than 500mg soluble tablets and 4 times more expensive than 250mg / 5ml oral suspension. It is not licensed for use in children under 16 years. • **Effervescent or soluble** formulations - No advantage in patients who can swallow tablets, contain high concentrations of sodium and are expensive. Avoid unless difficulty swallowing
Ibuprofen	• Tablets – **Green (1st line)** • Oral Suspension – **Green (1st line)** • Capsules (including modified-release) – **Black** • Orodispersible tablets – **Green (NOT preferred) -** swallowing difficulties only	• A 'Safer Prescribing of NSAIDs' aide memoire is available on the PAD
Naproxen	• Tablets 250mg / 500mg – **Green (1st line)** • Gastro-resistant tablets 250mg/375mg/500mg - **Black** • Naproxen and esomeprazole tablets – **Black** • Naproxen 250mg effervescent tablets – **Green (NOT preferred)** – swallowing difficulties only if ibuprofen suspension ineffective or not tolerated • Naproxen Oral Suspension 125mg/5ml and 250mg/5ml - **Green (NOT preferred)** – swallowing difficulties only if ibuprofen ineffective or not tolerated	• Gastro-resistant tablets offer no additional gastro-protective effect than standard tablets and are more expensive than standard tablets (Drug Tariff June 2018) • **Effervescent tablets** and **oral suspension** are significantly more expensive than ibuprofen equivalent dosage forms (Drug Tariff June 2018). • A 'Safer Prescribing of NSAIDs' aide memoire is available on the PAD
Diclofenac Sodium	• Tablets / capsules – **Green (NOT preferred)** • Diclofenac with misoprostil - **Black**	• For use in certain situations when ibuprofen and naproxen are ineffective / not tolerated • A 'Safer Prescribing of NSAIDs' aide memoire is available on the PAD
Diclofenac Potassium	Tablets - **Black**	More expensive than diclofenac sodium and no evidence of additional benefit

All other oral NSAIDs	Limited place in therapy for treatment of persistent non-malignant pain	PCN (June 2017) have recommended that a review of other oral NSAIDs should be completed separately to determine place in therapy . See PAD for updates • A 'Safer Prescribing of NSAIDs' aide memoire is available on the PAD
Celecoxib	**Green**	• For use in pain and inflammation or ankylosing spondylitis • In pain and inflammation, ibuprofen and naproxen remain the preferred NSAIDs • Celecoxib is the preferred choice of COX-2 inhibitor • A 'Safer Prescribing of NSAIDs' aide memoire is available on the PAD
Etoricoxib	**Green**	• For use in pain and inflammation or ankylosing spondylitis • In pain and inflammation, ibuprofen and naproxen remain the preferred NSAIDs • Etoricoxib is the second-line COX-2 inhibitor due to: ○ Contraindication for use of etoricoxib in people with uncontrolled hypertension (persistently above 140/90 mmHg). ○ The specific requirement for blood pressure to be monitored within two weeks after initiation of treatment with etoricoxib and periodically thereafter. ○ NICE (use in osteoarthritis) recommends that 'When offering treatment with an oral NSAID/COX-2 inhibitor, the first choice should be either a standard NSAID or a COX-2 inhibitor (other than etoricoxib 60 mg).' so the only first choice for the use of etoricoxib is etoricoxib 30mg, which is much more expensive than celecoxib (based on Drug tariff June 2019) • For pain and signs of inflammation associated with acute gouty arthritis, etoricoxib should be considered before celecoxib as it is licensed for this indication • A 'Safer Prescribing of NSAIDs' aide memoire is available on the PAD
Topical NSAIDs	**Green** – for knee or hand osteoarthritis	• Ketoprofen and piroxicam gels are currently least expensive topical NSAIDs (June 2018 Drug Tariff). CCGs may wish to advise on preferred products at a local level. • Topical NSAIDs may be considered as additional pain relief for people with knee or hand osteoarthritis. Topical NSAIDs should be considered before oral NSAIDs • Topical preparations containing piroxicam are not affected by the EMEA restrictions on use of piroxicam • Patients should be advised against excessive exposure to sunlight of area treated in order to avoid possibility of photosensitivity.
Codeine	**Green**	The capacity to metabolise codeine to morphine can vary considerably between individuals; there is a marked increase in morphine toxicity in patients who are ultra-rapid codeine metabolisers (CYP2D6 ultra-rapid metabolisers) and a reduced therapeutic effect in poor codeine metabolisers (estimates indicate that up to 7% of the Caucasian population may have this deficiency). Estimates of prevalence of ultra-rapid metabolisers in different populations are summarized below: Population | Prevalence %

		African/Ethiopian: 29% African American: 3.4% to 6.5% Asian: 1.2% to 2% Caucasian: 3.6% to 6.5% Greek: 6.0% Hungarian: 1.9% Northern European: 1%-2%
Co-codamol	Co-codamol 30/500 **- Green (NOT preferred)** Co-codamol 8/500 – **Green/Black**	• Fixed dose combination products (e.g. **Co-codamol 30/500mg**) - Limited role as do not allow titration to the most effective analgesic dose. • **Effervescent or soluble** formulations - No advantage in patients who can swallow tablets, contain high concentrations of sodium and are expensive. Avoid unless difficulty swallowing • Low-dose combination products (e.g. Co-codamol 8/500mg) still lead to opioid adverse effects and no evidence to show more effective than paracetamol alone. • See codeine section above for information regarding CYP2D6 ultra-rapid metabolisers
Dihydrocodeine	Standard release tablets – **Green** Sustained-release tablets - **(NOT preferred)**	Sustained-release tablets may be considered if standard release dihydrocodeine not tolerated or compliance is an issue
Co-dydramol	Co-dydramol 10/500 – **Green (NOT preferred)**	Low-dose combination products (e.g. Co-dydramol 10/500) still lead to opioid adverse effects and no evidence to show more effective than paracetamol alone. May have a limited place in therapy.
Co-proxamol	**Black**	• No longer licensed in the UK. • Not recommended in line with NHS England guidance on *Items which should not routinely be prescribed in primary care*
Tramadol	**Green (NOT preferred)**	• To be used in conjunction with a patient agreement • Tramadol is neither more effective nor better tolerated than other weak opioid analgesics for moderate to severe pain and its safety profile is problematic. • Co-prescribing of high doses of tramadol and amitriptyline should be avoided due to the increased risk of CNS toxicity with this combination. • Lowers the seizure threshold, is associated with psychiatric reactions and has the potential to produce serotonin syndrome when co-prescribed with tricyclic antidepressants or selective serotonin reuptake inhibitors (SSRIs). • In renal and/or hepatic insufficiency the elimination of tramadol is delayed therefore it's prolongation of the dosage interval should be carefully considered and the use of modified release preparations avoided. • Schedule 3 controlled drug
Tramacet	**Black**	• Contains Tramadol 37.5mg and a subtherapeutic dose of paracetamol 325mg

		• Prescribing of this product is not recommended as it offers little advantage in terms of efficacy, adverse effects or convenience over standard analgesics, in line with NHS England guidance on *Items which should not routinely be prescribed in primary care*
Buprenorphine	Patches - **Green (NOT preferred)** – in patients who are unable to tolerate oral medications or if morphine is contra-indicated Buccal / sublingual tablets - **BLUE** – in patients who are unable to tolerate oral medications or if morphine is contra-indicated	• Transdermal buprenorphine patches are not suitable for acute pain or in those patients whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose. • Transdermal patches are available as 72-hourly, 96-hourly and 7-day formulations; prescribers and dispensers must ensure that the correct preparation is prescribed and dispensed. • Patch formulations must be worn for at least 3 days until maximal effect is achieved • Consult product literature before initiating or switching between products. <u>Moderate, non-malignant pain</u> • Butec® patches (check with your CCG if this is the locally agreed brand) are licensed for use in moderate pain and are changed every 7 days • Prescribe by brand (CCGs may choose a locally preferred brand); • For use in the limited number of patients who are unable to tolerate oral medications or if morphine is contra-indicated • Patients not previously receiving opioids should start on 5 or 10 microgram/hr patches. <u>Severe Pain unresponsive to non-opioid analgesics</u> • Higher dose buprenorphine patches are not included in the pathway within this guidance and have a limited place in therapy for persistent non-malignant pain • At higher doses, buprenorphine patch is considered as a strong opioid and consideration should be given to the use of morphine capsules that can be administered with semi-solid food before using higher strength buprenorphine patches • When high doses of buprenorphine are used, in patients who are dependent on other opioids, it may precipitate withdrawal symptoms including pain. <u>Buccal / sublingual formulations</u> • Limited place in therapy in patients who are unable to tolerate oral medications or if morphine is contra-indicated
Morphine	**Green 1st line**	• Morphine is considered as the first choice strong opioid • Prescribe by brand for MR formulations (CCGs may choose a locally preferred brand) • Zomorph® capsules can be opened up for patients who cannot swallow
Oxycodone	**Green 2nd line (NOT preferred)**	• Efficacy and side-effect profile similar to that of morphine. • No advantages in using oxycodone but may be tried if patient intolerant to morphine.

<table>
<tr><td></td><td></td><td>Oxycodone has an efficacy and side-effect profile similar to that of morphine but is much more expensive.
Note: oxycodone is twice as potent as morphine so dose should be adjusted accordingly.
CQC (Preventing Harm From Oral Oxycodone) recommends that oxycodone should only be used as a second-line strong opioid, if morphine is not suitable or cannot be tolerated. The specialist pain or palliative care team should be consulted for advice in cases of complex pain management.
There are significant risks of overdose when a fast acting product of short duration is used in error for the slow acting, longer duration products.
Oxycodone should be prescribed by brand – see Surrey PAD for most cost effective brands recommended or ask your MMT Pharmacist</td></tr>
<tr><td>Targinact (oxycodone / naloxone)</td><td>Black</td><td>Not recommended in line with NHS England guidance on Items which should not routinely be prescribed in primary care
This product is considerably more expensive than oxycodone prescribed as a single component.
Naloxone added to counteract opioid induced constipation but opioid use may not be the only cause of constipation</td></tr>
<tr><td>Tapentadol</td><td>Blue</td><td>Tapentadol (after assessment by a pain specialist) may be considered in patients not responding to / not tolerating morphine or oxycodone
Due to the similar mode of action and relative efficacy of tapentadol compared with tramadol, it would be appropriate to have tried tramadol before initiating tapentadol.</td></tr>
<tr><td colspan="3"><u>MHRA Drug Safety Update (January 2019)</u>
Prescribers should be aware that tapentadol may increase seizure risk in patients taking other medicines that lower seizure threshold, for example, antidepressants and antipsychotics.

Serotonin syndrome has also been reported when tapentadol is used in combination with serotoninergic antidepressants.

The following advice has been issued for healthcare professionals:
as for all opioid medicines, tapentadol can induce seizures
tapentadol should be prescribed with care in patients with a history of seizure disorders or epilepsy
tapentadol may increase seizure risk in patients taking other medicines that lower seizure threshold, for example, antidepressants such as serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), tricyclic antidepressants, and antipsychotics
serotonin syndrome has been reported when tapentadol is used in combination with serotoninergic antidepressants (see typical presenting symptoms below)
withdrawal of the serotoninergic medicine, together with supportive symptomatic care, usually brings about a rapid improvement in serotonin syndrome
report suspected adverse drug reactions, including those resulting from interactions between drugs, on a Yellow Card</td></tr>
</table>

Fentanyl	Fentanyl Patches - **Blue** Immediate Release Fentanyl (unlicensed indications) - **Black**	• Fentanyl patches have a very limited place in therapy in persistent non-malignant pain and should only be prescribed on advice of a relevant specialist (e.g. renal physician) • Brand name prescribing is recommended to reduce the risk of confusion and error in dispensing and administration • **Should not** be prescribed under any circumstances for opioid naïve patients. Take care with calculation of dose equivalents. • Should be changed every 72 hours • Fever or external heat may increase absorption. Sweating may reduce the adhesion and absorption. See Medicines Compendium for Patient Information leaflet for up to date information on application. • Immediate Release fentanyl is considered BLACK in line with NHS England guidance on *Items which should not routinely be prescribed in primary care.* There is an exception for use in cancer patients in line with licensed indications
Pregabalin / gabapentin	**Black** – for persistent non-malignant pain **Green (4th line)** – for neuropathic pain **Blue** – for epilepsy	Not recommended as treatment options for persistent non-malignant pain (including low back pain)
SSRIs, SNRIs, TCAs, other anticonvulsants	**N/A**	• Not recommended for persistent non malignant pain. • Due to the use of these drugs in other indications (including neuropathic pain) it is recommended that no traffic light status is given for persistent non malignant pain due to the potential confusion when presented on the PAD.
Meptazinol	**Black**	Associated with rebound pain and an unacceptable level of side effects and therefore is not recommended to be prescribed routinely.

Rubefacients	**Black**	• Not recommended for the treatment of osteoarthritis (NICE CG 59).
		• Prescribers should:
		  ○ NOT initiate rubefacients for any new patient
		  AND
		  ○ De-prescribe rubefacients in all patients in line with NHS England guidance 'Items which should not routinely be prescribe in primary care: Guidance for CCGs'

Intra-articular hyaluronic injection	**Black**	• Not recommended for the treatment of osteoarthritis (NICE CG 59). • It may be suitable for individual patients for whom other pharmacological options have been intolerable or ineffective and who are unable to undergo surgery. Hyaluronic acid for these patients should be made available on an individual basis at the Acute Trust (this is not a Payment by Results Excluded drug and in individual cases GPs should not be asked to prescribe

Lidocaine Plasters – for persistent non-malignant pain	**Black**	• Not recommended for the treatment of osteoarthritis (NICE CG 59).
		• Primary care prescribers should:
		  ○ NOT initiate lidocaine plasters for any new patient;
		  AND

		○ De-prescribe lidocaine plasters in all patients with specialist support if appropriate, in line with NHS England guidance 'Items which should not routinely be prescribe in primary care: Guidance for CCGs' • In exceptional clinical circumstances for all indications (expect symptomatic relief of neuropathic pain associated with previous herpes zoster infection), where a patient has trialled all other treatments and the specialist pain or palliative care team consider there is a clinical need for lidocaine plasters to be prescribed in primary care, there should be an informed discussion between the specialists and the primary care prescriber about prescribing for individual patients.
Glucosamine and Chondroitin	**Black**	• Not recommended for the treatment of osteoarthritis (NICE CG 59). • Prescribers should: ○ NOT initiate glucosamine and chondroitin in any new patients AND ○ De-prescribe glucosamine and chondroitin in all patients, in line with NHS England guidance '*Items which should not routinely be prescribe in primary care: Guidance for CCGs'*

Appendix 3 - Definitions of Degrees of Renal Impairment including doses of Morphine

	GFR (mL/min)	Dose of morphine
Mild renal impairment	20-50	75% normal dose
Moderate renal impairment	10-20	Use small doses, e.g. 2.5–5mg and extended dosing intervals. Titrate according to response
Severe renal impairment	<10	Seek renal physician advice for options in severe renal impairment. Use small doses, e.g. 1.25-2.5mg and extended dosing intervals. Titrate according to response

(Source: The Renal Handbook Third Edition)

An immediate release preparation given at longer intervals than normal is more appropriate than using a modified release preparation in these patients.

	GFR (mL/min)	Dose of oxycodone
Mild renal impairment	20-50	Dose as in normal renal function
Moderate renal impairment	10-20	Dose as in normal renal function
Severe renal impairment	<10	Seek renal physician advice for options in severe renal impairment. Start with small doses and gradually increase according to response

(Source: The Renal Handbook Third Edition)

The Faculty of Pain Medicine has produced useful resources for patients and healthcare professionals to support prescribing of opioid medicines for pain. This web based resource has received contributions from several medical royal colleges. NICE, Royal pharmaceutical society, the British Pain Society, Public Health England, NH England, the CQC and the NHS Business Services Authority

Appendix 4 - Tramadol prescribing in primary care

The Medicines Management Team advise cautious prescribing of tramadol and regular patient reviews.

Aims:

- Promote safe and appropriate prescribing of tramadol, and ensure regular review.
- Raise awareness of the potential harms associated with the misuse and dependence of tramadol
- Reduce the risk of patients having adverse drug reactions and interactions.

Tramadol:

- Tramadol is licensed for the treatment of moderate to severe pain. But has not been shown to be more effective or better tolerated than other weak opioid analgesics such as codeine.
- Produces analgesia by two methods: an opioid effect and enhancement of the serotonergic and adrenergic pathways.
- The Advisory Council on the Misuse of Drugs (ACMD) recommended the change to schedule 3 CD due to concerns of misuse and increase in the number of related deaths.

Key Prescribing Points:

- Tramadol treatment should be short and intermittent and only used for moderate and severe pain.
- Maximum dose should not exceed 400mg in 24 hours. If using for persistent pain, prescribe tramadol as modified release as immediate release preparations are more associated with tolerance and problem drug use.
- Tramadol is a schedule 3 CD. Department of Health guidance is for prescriptions to be limited to a supply of up to 30 days' treatment. If the prescription is issued for a longer period, the prescriber must justify that there is a clinical need and will not cause an unacceptable risk to patient safety and document this in notes.
- Patients discharged on tramadol for acute pain from secondary care should be reviewed after discharge, and treatment discontinued where appropriate to ensure they are not continued on treatment for longer than necessary.
- Patients initiated on tramadol should be supplied as acute prescription and reviewed at three months to discourage long-term use for patients with acute pain. After 3 months, there is evidence to suggest that the pain is no longer acute and has become a chronic condition. If no other alternative analgesic is considered suitable, and tramadol is considered to be appropriate as part of the pain management plan, and there are no contra-indications then tramadol should be reviewed every 3 to 6 months.
- Review should consider: How and when it is taken? Have alternatives been tried? (both medication and non-medication approaches). Can it be stepped down or stopped gradually?
- Only prescribe tramadol if first-line opioids/opioid combination products (codeine, co-codamol) are not appropriate or not tolerated.
- Tramadol should not be co-prescribed with other opioids/ opioid combination products.
- Vigilance needed: patients requesting extra or interim prescriptions of tramadol, as this may indicate that the patient's pain is not being managed appropriately, or that the patient is stockpiling or diverting supplies.
- Avoid abrupt withdrawal after long-term treatment. The dose must be reduced slowly to ensure patient safety and to minimise the risk of withdrawal symptoms and/or adverse reactions

.

Use with Caution in:

- Patients taking other interacting drugs e.g. warfarin, SSRIs, TCAs, mirtazapine, venlafaxine, antipsychotics, epilepsy medications and other medication that can lower the seizure threshold.
- Patients with a history of addiction or dependence.
- Patients with a history of depression.
- Patients with a history of epilepsy or those susceptible to seizures: only prescribe in these patients if there are compelling reasons.
- Use with caution in patients with impaired hepatic and/or renal function. In patients with renal and/or hepatic insufficiency the elimination of tramadol is delayed. In these patients prolongation of the dosage intervals should be carefully considered according to the patient's requirements. In cases of severe renal and/or severe hepatic insufficiency tramadol is not recommended.

Recommendations:

- Audit and review patients currently prescribed tramadol with a view to stepping down and gradually stopping treatment.
- Ensure regular analgesic review as withdrawal symptoms and dependence have been reported with prolonged administration of tramadol.
- Review quantities prescribed and frequency of ordering including potential overuse by patients.
- Do not routinely use tramadol and do not start new patients on tramadol.
- Ensure optimal use of other non-opioids and weak opioids.

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- Tramadol SPC: http://www.medicines.org.uk/emc/medicine/30906

Acknowledgement to: Thurrock Medicines and Safety Group

Appendix 5 - Opioid Dose Conversion[15]

Be cautious when switching and monitor regularly. Withdrawal symptoms (such as sweating, abdominal cramps and yawning) occur if an opioid is stopped/reduced abruptly. The chart below shows opioid dose conversion chart:

NB: Dose conversion ratios are approximate as there is a lack of definitive trial data to demonstrate dose- equivalence. They are intended as a guide and may be subject to individual variation. Prescribers should use with caution, particularly in the elderly, if there are significant co-morbidities or polypharmacy.

If switching opioids it is prudent to reduce the calculated dose of the new opioid. In most cases when switching between different opioids, the calculated dose-equivalent must be reduced to ensure safety. The starting point for does reduction from the calculated equi-analgesic dose is around 25-50%.

Approximate equi-analgesic potencies of opioids for oral administration

Opioid	Potency Ratio	Equivalent dose to 10mg oral Morphine
Codeine Phosphate	0.1	100mg
Dihydrocodeine	0.1	100mg
Morphine	1	10mg
Oxycodone	2	5mg
Tapentadol	0.4	25mg
Tramadol	0.15	67mg

Transdermal buprenorphine changed at weekly intervals

Buprenorphine	5mcg/hr	10mcg/hr	20mcg/hr
Codeine phosphate mg/day	120mg	240mg	
Tramadol	100mg	200mg	400mg
Morphine	12mg	24mg	48mg

Fentanyl

Fentanyl patch strength (micrograms/hr)	Oral Morphine (mg/day)
12	45
25	90
50	180
75	270
100	360
300	1120

Ref: https://www.rcoa.ac.uk/node/21126

Appendix 6 - Drugs and Driving[21]

On 2 March 2015 8 general prescription and 8 illicit drugs were added into new regulations that came into force in England and Wales. Regulations on amphetamine came into force on 14 April 2015. Following a report from a panel of experts and a drug driving consultation the government decided to take:

- a zero tolerance approach to 8 drugs most associated with illegal use, with limits set at a level where any claims of accidental exposure can be ruled out
- a road safety risk based approach to 8 drugs most associated with medical uses
- a separate approach to amphetamine that balances its legitimate use for medical purposes against abuse

  The government is unable to provide any guidance on what amounts of dosage would equate to being over the specified limits. There are too many variables, where each person will metabolise the drug at different rates. Eating or drinking will also have an effect on the blood concentration

Table of drugs and limits

'Illegal' drugs ('accidental exposure' – zero tolerance approac	**Threshold limit in microgrammes per litre of blood (µg/L)**	**'Medicinal' drugs (risk based approach)**	**Threshold limit in blood**
benzoylecgonine	50µg/L	clonazepam	50µg/L
cocaine	10µg/L	diazepam	550µg/L
delta-9-tetrahydrocannabinol (cannabis)	2µg/L	flunitrazepam	300µg/L
ketamine	20µg/L	lorazepam	100µg/L
lysergic acid diethylamide	1µg/L	methadone	500µg/L
methylamphetamine	10µg/L	morphine	80µg/L
Methylenedioxymethamphetamine (MDMA)	10µg/L	oxazepam	300µg/L
6-monoacetylmorphine (heroin)	5µg/L	temazepam	1,000µg/L
amphetamine	250µg/L		

Appendix 7 – Prescription agreement

This is for you to adapt for your patient(s). Please ensure that you customise the text highlighted in yellow so that the information is appropriate. Please also ensure that once you have made your amendments, any important information isn't split across two pages, or that an instruction to continue on to a second page is added.

Prescription agreement

Patient name	[add patient name]
Prescriber name	[add prescriber name]

Please read the information below and complete and sign it once you are happy that you fully understand the information. Please ask your prescriber to explain anything that you do not understand.

I understand that I will receive pain management therapy (opioids) from [insert prescriber name] as part of the management plan to treat my pain condition. This medicine is only one item amongst a range of options for my care.

This medicine is intended to:

- Improve my level of mobility and ability to perform daily tasks.
- Improve my quality of life.
- Reduce (but not eliminate) my intensity of pain.

I have read and understand the potential side effects (provide for patient).	☐
I understand that this medication if misused can cause grave harm to myself or any other individual who may have access to it.	☐

Therefore I will;

Keep the medicine in a safe place and not share it with others.	☐
Take the medicine as it has been prescribed to me by [insert prescriber name]	☐
If I require potent medication from another source I will inform my GP	☐
Agree not to take/use recreational drugs during this treatment	☐
Note that this medicine may be withdrawn if the intended benefits are not obtained or abuse of prescription is suspected	☐
Patient name	[add patient name]
Patient signature	

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