COMPASS Therapeutic Notes on the use of Strong Opioids in Chronic Non-Cancer Pain

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Glossary of terms	
Hyperalgesic syndrome	A paradoxical phenomenon whereby a patient receiving treatment for pain may actually become more sensitive to certain painful stimuli
MHRA	Medicines and Healthcare products Regulatory Agency
Neuropathic pain	Pain due to disturbance of the nervous system
NNT	Number Needed to Treat
Nociceptive pain	Pain due to tissue damage; can be either somatic or visceral
RCT	Randomised controlled trial
SmPC	Summary of Product Characteristics
Somatic pain	Pain emanating from muscles, skeleton, skin; pain in the parts of the body other than the viscera.
Visceral pain	Pain relating to any of the large interior organs of the body

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Introduction and background

The use of strong opioids in the management of cancer pain and palliative care is widely accepted. The use of opioids to treat moderate to severe acute pain is also widely accepted. The use of opioids to treat chronic non-cancer pain, however, remains controversial.[1-5] Areas of uncertainty include: [6-8]

- safety and efficacy of opioids in the long-term
- propensity for strong opioids to cause problems of tolerance, dependence and addiction
- type(s) of chronic conditions that should be treated with strong opioids
- patient selection
- clinical goals.

The treatment objectives in chronic non-cancer pain are subtly, but significantly, different and more complex than the goals of opioid therapy in the settings of terminal conditions or acute pain. The objective of the treatment of chronic pain of non-cancer origin includes, when possible, not only management of painful symptoms but an emphasis on maintaining functionality and continued participation in society. These objectives can be thwarted by the use of opioids.

Chronic pain can be treated with a variety of non-pharmacological and pharmacological measures. Non-pharmacological options include:

- physiotherapy,
- heat or cold pack application,
- graduated exercise programmes,
- transcutaneous electrical nerve stimulation (TENS), and
- cognitive behavioural therapy.

It is acknowledged that these interventions may be difficult to obtain in the primary care setting and this may be the reason why, for many patients, the only available option is drug treatment.

Table ONE: Classification of opioids

	Approved name (some proprietary names)	Formulations available
Strong opioids	**Buprenorphine** (Temgesic®, Transtec®, BuTrans®)	Sublingual, transdermal
	Diamorphine	Oral, injection
	Dipipanone (Diconal®)	Oral
	Fentanyl (Durogesic DTrans®, Matrifen®, Effentora®▼, Abstral®▼, Actiq®, Instanyl®▼)	Transdermal, oral transmucosal, sublingual, nasal spray
	Hydromorphone (Palladone®, Palladone®SR)	Oral
	Methadone	Oral, injection
	Morphine (Oramorph®, Sevredol®, MST Continus®, MXL®, Zomorph®)	Oral, rectal, injection
	Oxycodone (OxyNorm®, OxyContin®)	Oral
	Pentazocine	Oral, injection
	Pethidine	Oral, injection
	Tramadol* (Zydol®, Zamadol®)	Oral, injection
Weak opioids	**Codeine**	Oral, injection
	Dihydrocodeine (DF118 Forte®, DHC Continus®)	Oral, injection
	Meptazinol (Meptid®)	Oral, injection

Note: oral formulations can be immediate or modified release

* Tramadol can be a weak or strong opioid, depending on dose

Use of pharmacological options should be based on the analgesic ladder developed by the World Health Organisation (WHO). Treatment should start at the bottom of the ladder and ascend in accordance with response to medication in terms of both efficacy and side effects.

WHO analgesic ladder for chronic nociceptive pain:
Step 1 = non-opioid ± adjuvant
Step 2 = weak opioid ± non-opioid ± adjuvant
Step 3 = strong opioid ± non-opioid ± adjuvant.
(Adjuvants include corticosteroids, antidepressants and anticonvulsants)

How are opioids classified?

Opioids are classified as either strong or weak (see **Table ONE**). Strong opioids differ from weak opioids in having a much broader dose range and a proportionately greater effect can be achieved by increasing the dose in opioid-sensitive pain. Tramadol is considered as either a weak opioid or a strong opioid, depending on the administered dose.[9] The term weak opioid should not encourage lack of caution in prescribing.

Opioid pharmacology

The term "opioid" refers to all compounds that bind to opioid receptors. The term "opiate" can be used to describe those opioids derived from the opium poppy; these include morphine and codeine. Opioids include semi-synthetic opiates, i.e. drugs that are synthesised from naturally occurring opiates (e.g. diamorphine from morphine; oxycodone from thebaine), as well as synthetic opioids such as methadone and fentanyl.

Opioid receptors are widely distributed in the body. When an opioid binds to opioid receptors, analgesia may be accompanied by any of a diverse array of side-effects related to the activation of receptors involved in other functions. These may have an effect on peristalsis

(leading to constipation), may cause itch, or have an effect in the CNS (leading to miosis, drowsiness, or respiratory depression). Activation of other CNS pathways by opioids may also produce mood effects, either dysphoria or euphoria. See **Table TWO**.

Although several types of opioid receptors exist (e.g. mu, kappa and delta), opioid drugs largely produce their analgesic effects via activation of the mu opioid receptors; thus, opioids used for pain are often described as "mu agonists". Mu drugs that have the ability to fully activate opioid receptors are referred to as opioid agonists or full mu agonists (e.g. morphine, oxycodone and methadone). Those opioids that occupy but do not activate receptors are referred to as opioid antagonists (e.g. naltrexone, naloxone); they can reverse the effects of mu opioid agonists. Those opioids with a low activity at opioid receptors are called partial opioid agonists (e.g. buprenorphine) – increases in dose of these agents will only increase effects up to a ceiling point, after which dose increases produce no additional effects.[10,11]

Table TWO: Effects of stimulation of mu, kappa, and delta receptors

Receptor type	Effects of stimulation
Mu	Analgesia (mainly at supraspinal sites), respiratory depression, miosis, reduced gastrointestinal motility
Kappa	Analgesia (mainly in the spinal cord), less intense miosis and respiratory depression, dysphoria
Delta	Uncertain, probably analgesia

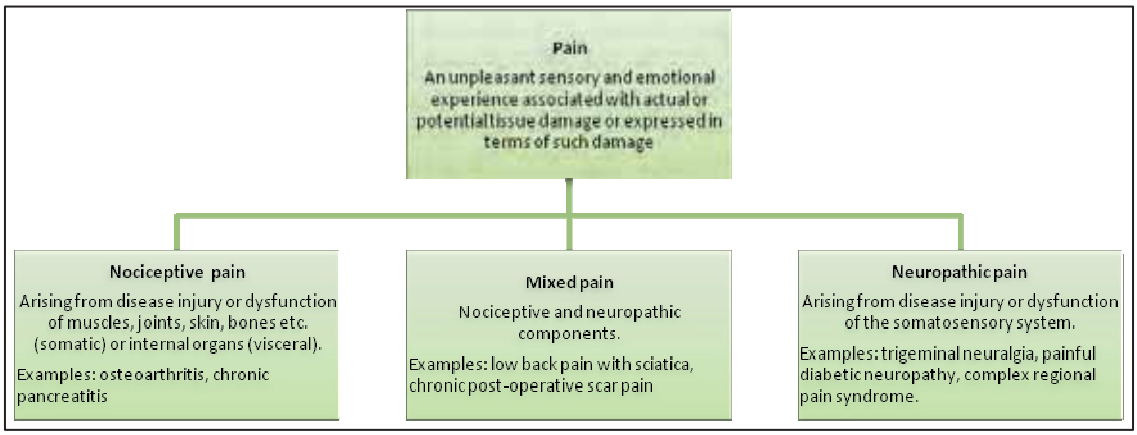
How is pain classified?

See **Figure ONE**.

What is meant by "chronic pain"?

Chronic pain is defined by the International Association for the Study of Pain as "pain that persists beyond normal tissue healing time, which is assumed to be three months".[12] A study conducted in a community in the greater London area to quantify the prevalence of chronic pain found that 46.5% of the general population reported chronic pain; low back problems and arthritis were the leading causes.[13]

Figure ONE: Pain Classification



Strong opioids in common use: Morphine, diamorphine, oxycodone, fentanyl and tramadol

Table THREE gives approximate equivalent doses of various opioids.

Morphine

The drug most often associated with potent analgesia within the general population is morphine. Morphine tends to be the standard against which other analgesics are compared. Alternative opioids have not demonstrated advantages that would make them preferable as first-line drugs for moderate to severe pain. Morphine dosage and response can vary widely in the adult population. Older people may require smaller doses due to receptor sensitivity and impaired renal function, whereas the very anxious individual in pain may require a larger-than-expected dose.[14] Sedation, dizziness, nausea and constipation can be problematic (discussed in detail later). These are especially common in the frail or elderly, and when using large doses. Euphoria, dysphoria and itching may also occur with morphine, and important drug interactions are shown in **Table FOUR**. Despite these adverse effects, morphine is a remarkably safe and effective analgesic.

Table THREE: The approximate potency of various opioids[14]

Opioid	Route	Equivalent 24 hour dose
Morphine	Oral	30 milligrams
Codeine	Oral	240 milligrams
Hydromorphone	Oral	6 milligrams
Oxycodone	Oral	10-15 milligrams
Methadone	Oral	30 milligrams
Fentanyl	Transdermal	12 micrograms/hour
Buprenorphine	Transdermal	20-35 micrograms/hour
Tramadol	Oral	120 milligrams
Note: This is only a guide. Since there is considerable interpatient variation in the response to these drugs it is essential to titrate the dose.[15]		

Table FOUR: Common drug interactions with opioids

Opioid	Interacts with:	Effect
All	Domperidone, metoclopramide	Antagonism of GI effect
	CNS depressants	Enhanced depressant effect
	Anticonvulsants	Increased opioid metabolism
	Cimetidine	Reduced opioid metabolism
Methadone	Phenytoin, Rifampicin	Faster elimination of opioid
Morphine	Clomipramine, amitriptyline	Increased bioavailability of morphine
Pethidine	Phenobarbital	Accumulation of norpethidine
	Phenytoin	Faster elimination of opioid
	MAOIs	CNS excitation, hyperpyrexia, convulsions
Tramadol	Cardiac glycosides	Increased risk of digoxin toxicity
	SSRIs	Increased CNS toxicity
	MAOIs	Sympathomimetic pressor response

Prescribing Note: Morphine

For reasons of familiarity, availability and cost (rather than superior efficacy over alternative opioids) **morphine is the first-choice strong opioid.**

Diamorphine

Essentially a prodrug, diamorphine is activated by deacetylation in the plasma to monoacetylmorphine and hence to morphine. Diamorphine is very lipid soluble and rapidly crosses tissue membranes, with a much more rapid onset than morphine. However, the duration of action is also shorter, in the region of two hours. This rapid onset and offset, especially when administered by the intravenous route, greatly increases its addiction potential.

Oxycodone

Oxycodone is licensed for the management of severe pain. It undergoes first-pass metabolism (50%) when taken orally. It is initiated at a dose of 5 milligrams 4-6 hourly.[16] It has similar side-effects to morphine but possibly less sedation. Like morphine, it is available as a modified-release (m/r) preparation (OxyContin®), delivering analgesia for about 12 hours.

In non-cancer pain, m/r oxycodone has been found to be similarly or slightly less effective than morphine.[17,18] Compared to twice daily m/r oxycodone, once daily m/r morphine resulted in significantly better physical function and quality of life.[19] In one study,[20] adverse effects were seen in 88% of patients on m/r oxycodone.

The place in therapy of m/r oxycodone is second-line after morphine, in patients in whom morphine is inappropriate or not tolerated.[21] Use of oxycodone has increased over the last few years and so has its cost to the Health Service. Oxycodone is considerably more expensive than morphine and spend on it is disproportionate to the number of items dispensed. See **Figures TWO(a)** & **(b)**.

Fentanyl

As fentanyl is 500 times more lipophilic than morphine, it can be administered by the sublingual (Abstral®▼), buccal (Actiq®, Effentora®▼), nasal (Instanyl®▼) and transdermal (Durogesic®, Fentalis®, Matrifen®, Mezolar®, Osmanil®, Victanyl®) routes. The efficacy and safety of transdermal fentanyl in the treatment of chronic non-cancer pain for up to 12 months has been evaluated.[22,23] In general, patients reported satisfaction with the treatment, with improvement of quality of life scores and pain.[22,23]

Fentanyl now accounts for a third of the cost of all opioids in Northern Ireland. Almost 90% of this cost is accounted for by prescribing of fentanyl patches although newer buccal and intranasal preparations may change this picture in the future.

Figure TWO(a): Oxycodone and morphine - Number of items dispensed in Northern Ireland

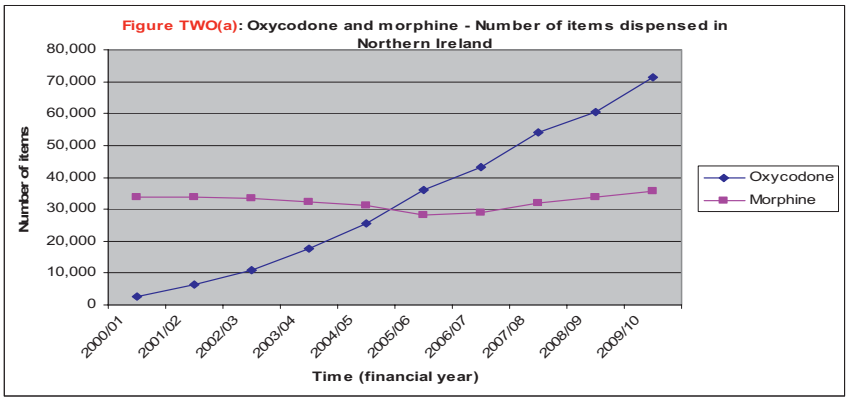
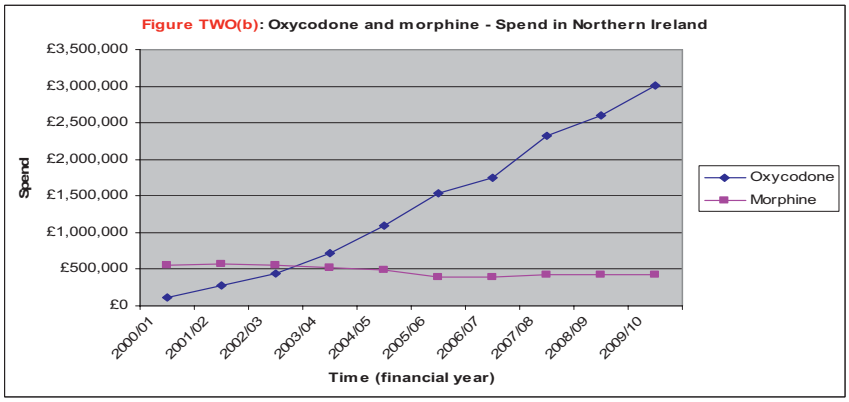


Figure TWO(b): Oxycodone and morphine - Spend in Northern Ireland



Prescribing Note: Fentanyl

The three immediate release products (Abstral®▼ sublingual tablets, Effentora®▼ buccal tablets, and Instanyl®▼ nasal spray) are **not equivalent dose-for-dose**. Each formulation has a different absorption pattern so they are **not interchangeable**. Individual patient dose titration must be carried out if patients are switched between products.

Buprenorphine

As a partial mu agonist, buprenorphine has a ceiling effect on its agonist activity. This partial agonism would presumably yield a ceiling effect for analgesia as well, which would limit the clinical use of the drug in pain management, but there is some question about the extent of this ceiling effect in practice.[24]

Buprenorphine undergoes high first-pass liver metabolism if swallowed, but due to its high lipid solubility (200 times that of morphine) it is readily absorbed from the oral mucosa or through the skin. Thus, it is very effective when administered sublingually (Temgesic®) or as a transdermal preparation (BuTrans®, Transtec®). See later for more information on the use of opioid patches.

Tramadol

Although tramadol has some opioid activity, the majority of its efficacy is through noradrenaline and serotonin reuptake inhibition. Since it lowers seizure threshold it is best avoided if there is a history of epilepsy. Tramadol should be used with caution in patients who concurrently take tricyclic antidepressants, as they have a similar mechanism of action. For the same reason, concurrent use with MAOIs should be avoided.

Tramadol is licensed for moderate to severe pain, but may not be as effective as strong opioids in severe pain.[25] Short term studies in chronic osteoarthritis (OA) or low back pain[26] found that Tramacet® (which contains tramadol 37.5 milligrams and a sub-therapeutic dose of paracetamol 325 milligrams per tablet) was as effective as paracetamol 300 milligrams plus codeine 30 milligrams (both up to 8 or 10 tablets/capsules daily), with similar levels of tolerability.

The most common side effects of tramadol are nausea and dizziness, both occurring in more than 10% of patients.[27] Constipation is also common, occurring in between 1% and 10% of patients.[27] Hallucinations, confusion and convulsions, as well as rare cases of drug dependence and withdrawal, have been reported with tramadol at therapeutic doses.[28] Tramadol is considered to be no more effective than other weak opioid analgesics and its safety profile is problematic.[29] Tramadol has been promoted as a drug to be used between the WHO Step 2 analgesics for moderate pain (such as codeine) and the WHO Step 3 analgesics (strong opioids such as morphine) for severe pain. However, evidence from clinically useful trials (particularly in primary care, chronic pain, and cancer pain) is sparse.[28]

Less commonly used strong opioids: pethidine, methadone

Pethidine

Pethidine was the first totally synthetic opioid. It has approximately one-tenth of the potency of morphine, and like other opioids undergoes extensive first-pass metabolism (47-73%). Convulsions may occur with repeated dosing due to one of the metabolites, norpethidine, which is a proconvulsant. In addition, it should not be administered to patients taking MAOIs as the combination can cause hypertension, hyperpyrexia, convulsions and coma. It was favoured in the past as a drug that avoided smooth muscle spasm in conditions such as renal colic. It is not as popular now and is no longer considered a first-line analgesic due to concerns over adverse reactions, drug interactions (see **Table FOUR**) and norpethidine neurotoxicity.[30]

Methadone

Methadone is a synthetic opioid developed about 50 years ago and has been considered as an option for the management of pain for a number of years, especially chronic pain that is unresponsive to other analgesics. Its long and variable half-life due to extensive tissue binding makes dose titration and switching from other opioids a challenge. The use of methadone for the management of pain appears to be inconsistent among clinicians, with some palliative medicine, oncology and pain management teams using it frequently while others rarely or never using it.[31]

The MHRA issued a warning in 2006 about the risk of QT prolongation with methadone, especially in patients on high doses.[32,33] The recommended usual dose of methadone for the management of pain is 5-10 milligrams given 6-8 hourly, later adjusted to the degree of pain relief obtained.[16] During prolonged use methadone should not be given more frequently than every 12 hours because of its long half-life.[16] Although the half-life of methadone is usually estimated at 15-60 hours, in some reports the half-life is as high as 120 hours.[34] In a patient for whom the methadone half-life is 60 hours, it would take almost 12 days on a stable dose of methadone to approach a steady state. Methadone should therefore be started at low doses and titrated slowly.

Adverse effects of opioid therapy

80% of patients taking opioids will experience at least one adverse effect. The common adverse effects are:[35]

- Constipation
- Nausea and vomiting
- Somnolence or drowsiness
- Itching
- Dizziness or vertigo

Opioid side effects in patients with chronic pain can impair quality of life, increase morbidity, and may cause a patient to use less than the prescribed dose of opioid or to discontinue therapy completely. A systematic review found that 22% of patients with chronic non-cancer pain discontinued opioid therapy because of side-effects.[36]

Tolerance to some side-effects usually occurs within the first few days of initiating treatment; (e.g. nausea and sedation usually become less problematic after 1-2 weeks). However, pruritis and constipation tend to persist and some side effects such as immune and sexual dysfunction are more apparent after long-term therapy.[1] Patients using intermittent dosing schedules may not become tolerant to side-effects.

Prescribers should anticipate, identify and treat common opioid-associated adverse effects and patients should be advised about side-effects and the likelihood of their occurrence before starting opioid therapy.

Constipation

Constipation is one of the most common opioid-related adverse effects.[36] Most patients develop some degree of constipation after opioid initiation or dose increases, and constipation does NOT tend to resolve with continued opioid treatment. Research in a small group of patients with chronic non-cancer pain suggests that constipation is the most bothersome of the opioid side effects, based on its impact on life and the frequency with which it occurs.[37] Thus an effective regimen of laxatives should be initiated at commencement of opioid therapy.

Prescribing Note: Newer laxatives

► Relistor® (methylnaltrexone▼) injection is licensed for the treatment of opioid-induced constipation *only in terminally ill patients* when response to other laxatives is inadequate.[16]

► Resolor® (prucalopride▼) tablets are licensed for symptomatic treatment of chronic constipation in *women* in whom laxatives fail to provide adequate relief.

How should opioid-induced constipation be managed?

Approaches to preventing or treating opioid-induced constipation include:[14,37]

- Use of an opioid-sparing regimen (e.g. adding an NSAID or adjuvant analgesic).
- Use of laxatives - regimens to manage constipation are generally anecdotally based, but it is commonly accepted that both a stool softener and a stimulant are required.[37] The long-term effectiveness and safety of such a regimen is unclear. Bulk-forming laxatives (ispaghula, methylcellulose, sterculia) and osmotic laxatives (lactulose, macrogols) are also commonly employed.
- Use of an opioid antagonist to directly reverse opioid effects. A new product, Targinact®▼ (oxycodone plus naloxone) provides sustained-release oxycodone with naloxone, which has a direct opioid antagonist effect on the bowel (avoiding constipation), but the vast majority of the naloxone is metabolised as it passes through the liver and thus does not have a systemic antagonist effect on the central nervous system, where the opioid works. The Scottish Medicines Consortium (SMC) has not accepted Targinact®▼ for use in Scotland.

Nausea and vomiting

The incidence of opioid-induced nausea and vomiting is estimated to be 10-40% depending on the opioid administered and the disease state studied, although untreated pain itself can induce nausea. Nausea and vomiting are both rated as highly distressing by patients.[38] Gradual dose titration may forestall the occurrence of nausea. Nausea or vomiting tends to diminish over days or weeks of continued opioid exposure. The use of regular cyclizine or prochlorperazine during the first week of treatment minimises this distressing symptom.[14]

Somnolence or drowsiness

Sedation most frequently occurs at initiation of opioid therapy or when a significant dose increase occurs. Symptoms frequently resolve after a few days, in which case reassurance and education (e.g. warning the patient to avoid alcohol and driving) should prove sufficient. Sedation for extended periods may be caused by comorbidities or concurrent medications.

Itching

Pruritus occurs in about 1% of patients after systemic administration of opioids, but its incidence rises to 8% and 46% when epidural or intrathecal routes are employed, respectively.[37] Opioids cause histamine release from mast cells to varying degrees, which may account for the sensation of itch; however, fentanyl has not been shown to cause histamine release, yet it still causes itching.[39] Despite controversy about the role of histamine, opioid-induced pruritus is routinely treated with antihistamines.

Prescribing Note: Long-term opioid-use and driving

Opioids are thought to worsen the performance of tasks such as driving. This may well be the case on starting opioids, but when patients in chronic pain use opioid medication for many weeks, this impression has not been confirmed. In a structural, evidence-based review, there was no evidence of impairment of psychomotor abilities immediately after being given doses of opioids, or any consistent evidence for a greater incidence in motor vehicle violations or accidents in opioid-dependent or -tolerant individuals.[40] Rather than impairing psychomotor tasks, it has been illustrated that test scores significantly improved in patients with chronic back pain during the long-term use of oxycodone or transdermal fentanyl.[41] Long-term therapy with opioids does not inevitably impair complex skills such as driving, but the decision to permit driving must be made in individual cases.

Respiratory depression

Respiratory depression is a much feared complication of the use of opioids for *acute pain*, but it is only likely to be a potential problem in *persistent pain* if there have been major changes in dose, formulation or route of administration. Accidental overdose is likely to be the commonest cause of respiratory depression. Particular caution is necessary for patients taking more than one class of sedative medication and in those with pre-existing disorders of respiratory control, such as obstructive sleep apnoea.[42]

Do the different opioids have different adverse effect profiles?

There is little evidence that (in equi-analgesic doses) commonly used opioids differ markedly in their side-effects. However, because of inter-patient variability, a patient may respond more favourably to one opioid than to another. If a patient fails to achieve useful analgesia or develops intolerable side-effects with their initial opioid regimen, it may be worth trying an alternative opioid.[42]

What is "opioid rotation"?

Opioid rotation exploits differences in efficacy and side-effect profiles of specific opioid molecules. Different opioids have different intrinsic efficacies at opioid receptors. In addition, differences in side-effect profiles may be in part due to individual opioid metabolites. Despite the relatively common practice of opioid rotation, there are no randomised trials that validate its effectiveness.[43]

What are the features of opioid toxicity?

Features of opioid toxicity include:[42]

- Pinpoint pupils
- Sedation
- Depressed respiration
- Visible cyanosis
- Myoclonic jerks
- Snoring
- Agitation
- Confusion
- Vivid dreams, nightmares or hallucinations
- In more severe cases – hypotension, coma, convulsions.

Note: the dose of opioid causing toxicity varies between individuals and depends on medical co-morbidity (particularly renal or hepatic impairment) and concomitant medication therapy, including over-the-counter medications and illicit drug use.

The rise in opioid prescriptions has been paralleled by substantial increases in deaths from opioid-related overdose.[44] Until recently, it was unclear whether these parallel trends were related, but a recent study has provided the first empirical evidence to link prescribed opioids to both fatal and non-fatal overdoses in patients with chronic non-cancer pain.[45] Overdoses were most common at the highest opioid doses (the annual overdose rate was1.8% among patients receiving 100 milligrams per day or more of morphine equivalents), but importantly in public health terms, most overdoses occurred in the larger groups of people receiving lower doses. Most of the overdoses (in both high- and low-dose groups) were medically serious, and 12% were fatal.[45]

When are the features of opioid withdrawal more likely to occur?

Opioid withdrawal occurs when the drug is stopped suddenly, the dose is tapered too rapidly or when an opioid antagonist is given. Signs of opioid withdrawal include:[42]

- Sweating
- Mydriasis
- Piloerection
- Yawning
- Abdominal cramps/vomiting/diarrhoea
- Bone and muscle pain
- Increase in usual pain
- Restlessness
- Anxiety
- Rhinorrhoea
- Lacrimation
- Tremor

Treatment of acute withdrawal includes administration of intravenous fluids, glucose, α-2 adrenoceptor agonists (e.g. clonidine, lofexidine), and antispasmodic drugs.

What are the risks of long-term opioid therapy?

There are currently insufficient data to quantify the risks of long-term opioid therapy.[42] Concerns relate to the effects of opioids on the endocrine and immune systems and the risk of inducing a hyperalgesic syndrome.

Endocrine effects

Influences on both the hypothalamic-pituitary-adrenal axis and the hypothalamic-pituitary-gonadal axis have been demonstrated in patients taking oral opioids. These effects are probably dose-related and can lead to:

- Amenorrhoea, reduced libido, and infertility in women, and
- Erectile dysfunction and diminished libido in men.

Patients should be told about these effects before starting opioids. Endocrine function should be monitored regularly if symptomatically indicated and patients should be referred to an endocrinologist for advice regarding the benefits of hormone replacement.

Immunological effects

Opioids have an immunomodulating effect. Opioids may differ in their propensity to cause immunosuppression. The relevance of this knowledge to the clinical use of opioids is not known.

Opioid-induced hyperalgesia

Opioid-induced hyperalgesia describes the paradoxical phenomenon whereby a patient receiving opioids for the treatment of pain may actually become more sensitive to certain painful stimuli.[46] Clinically, opioid-induced hyperalgesia may be characterised by pain that has become more diffuse and less defined in quality and has a wider distribution than the pre-existing pain state. The management of opioid induced hyperalgesia is opioid dose reduction or changing to an alternative opioid preparation.

Opioids in specific conditions

Osteoarthritis (OA)

A summary of the guidance given by various bodies is given in **Table SIX**.

The efficacy of open-label extended-release **morphine** in a 26 week trial in OA patients has been evaluated.[47] Reductions in pain intensity and improved sleep measures were observed. However, improvements were NOT observed in physical function. Constipation and nausea were the most frequent adverse effects reported in over 80% of the patients. Controlled-release **oxycodone** therapy has also been shown to be safe and effective for patients with chronic, moderate to severe osteoarthritis-related pain.[48]

Table SIX: Use of Opioids in Osteoarthritis

Body/Guideline	Summary of recommendations
NICE[49]	• Offer paracetamol for OA pain if non-drug core interventions are inadequate. • If paracetamol or topical NSAIDs are insufficient, then one suggested option is addition of an opioid analgesic. The guideline makes no distinction between weak and strong opioids. • States that the evidence for using opioids in the condition is "poor", with virtually no good studies using opioids in peripheral joint OA, and little evidence to suggest that dose escalation is effective. It also states that there are few data comparing different opioid formulations or routes of administration.
Osteoarthritis Research Society International[50]	Weak opioids "can be considered" for refractory pain from OA of the knee or hip, where non-drug and drug options have been ineffective, or are contraindicated. Stronger opioids should only be used for severe pain in exceptional cases, in addition to non-drug treatments, and that surgical treatment should be considered in these circumstances.
European League Against Rheumatism[51,52]	Opioid analgesics (without specifying weak or strong opioid) are useful alternatives for those patients with OA of the hip or knee in whom NSAIDs are contraindicated, ineffective or poorly tolerated.
Joint guidance from the Pain Society, Royal College of Anaesthetists, Royal College of General Practitioners and Royal College of Psychiatrists[42]	Hospital-based services should not start long-term opioid therapy without support from a multidisciplinary pain management service and liaison with the patient's primary care team.

Neuropathic pain

Pharmacological treatment of neuropathic pain usually involves antidepressants or anticonvulsants; however, effective analgesia is achieved in less than half of patients.[53] The role of opioids in neuropathic pain has been under debate in the past, but is nowadays more widely accepted.[54-57] Unfortunately, there is great variability in the trials of opioids in neuropathic pain, leading to conflicting and often confusing results. Overall, higher opioid doses are often needed for treatment of neuropathic pain than for nociceptive pain.[58] Opioids have efficacy in neuropathic pain that is similar to that of the tricyclic antidepressants and gabapentin. However, as opioids result in more adverse effects, they are not considered to be first-line treatments for neuropathic pain.[59,60] A substance that might be specifically interesting in this type of pain is **tramadol**. It has shown efficacy in a variety of neuropathic pain settings, with an NNT of 3.8.[61] Further advantages are the low abuse potential, non-controlled drug status, availability as generic preparations and a reduced rate and severity of constipation. **Buprenorphine** also shows a potential benefit in improving neuropathic pain symptoms, possibly due to its specific pharmacological profile.[62]

In its recent clinical guideline for management of neuropathic pain,[63] NICE recommends oral **tramadol** only as a third-line option and recommends that treatment with opioids other than tramadol should not be started without assessment by a specialist pain service.[63]

Chronic back pain

Opioids seem to have limited, if any, value in chronic low back pain.[5] A Cochrane review of opioids in chronic low back pain found that **tramadol** was more effective than placebo but that neither **morphine** nor **oxycodone** were significantly better than naproxen for relieving pain or improving function.[3] One study[64] showed that sustained-release morphine significantly improved pain relief and quality of life for patients who remained in the study for 56 weeks. However, use of concomitant strong short-acting opioids for "breakthrough" pain was required in 50% of patients.

The NICE clinical guideline on low back pain[65] advises that strong opioids should only be considered for short-term use in people with severe low back pain and that referral for specialist assessment should be considered for those people who may require prolonged use of strong opioids.[65]

Opioids and problem drug use

"The patient uses opioids to relieve pain and maintain a normal relationship with the real world; the addict takes opioids to escape from reality."[66]

What is meant by "problem" use?

Evaluation of problem drug use in relation to prescribed opioids for pain relief has been hampered by confusion regarding the terms **tolerance**, **dependence** and **addiction**. Terminology for patients using opioids medicinally has been clarified by a consensus statement from the American Pain Society, the American Academy of Pain Medicine and the American Society of Addiction Medicine (See **Table FIVE**).These definitions distinguish between expected sequelae of opioid therapy, including physical dependence and tolerance, and the

Table FIVE: Tolerance, dependence, pseudoaddiction and addiction[14,67]

Tolerance A reduction in response intensity and duration following the repeated administration of a drug; this includes the side-effects as well as the beneficial effects. Analgesic response generally improves with an increase in dose. Although this is a normal pharmacological response, the dose should not have to be increased on multiple occasions.
Physical dependence This is a normal physiological response. Receptors become dependent on the presence of an exogenous agonist. The sudden withdrawal of an agonist or the use of a substance with antagonistic properties will precipitate a withdrawal response. Physical dependence symptoms abate when an opioid is tapered slowly.
Pseudoaddiction If inadequate analgesia is provided, the patient seeks further analgesia. In this situation, despite the patient asking for increasing doses of analgesia (because of inadequate pain relief), they tend to use their medication as prescribed.
Addiction True drug addiction is the overwhelming desire to continue to use the same or greater dose of a substance with psychomimetic properties. The desire is over and above that for analgesia and involves both psychological as well as physical factors.

more biologically and behaviourally complex syndrome of addiction. The term "pseudoaddiction" has been coined to describe behaviours such as drug hoarding, attempts to obtain extra supplies and requests for early prescription or increased dose that might be mistaken as signs of addiction but are an attempt to obtain better pain relief. When pain is relieved, these behaviours cease.[42]

How big a problem is misuse of prescribed opioids?

The estimated risk of addiction to prescribed opioids is variably reported. Most data are derived from studies of analgesic efficacy that are usually of too short a duration to identify problems relating to aberrant drug use. Longer term data are available, but these require caution in interpretation as study populations are not consistent with respect to diagnosis and previous history, and because reported prevalence varies depending on the criteria used to define addiction. Rates of addiction in non-cancer pain patients are reported as occurring in 0-50% of patients[42,68-73]

Is it possible to predict which patients are likely to be at risk of addiction to prescribed opioids?

A number of factors are thought to indicate a risk of addiction to prescribed opioids. These include:[42,74]

- Current or past history of substance misuse, including alcohol
- Family member with history of substance misuse
- Male gender
- Younger adults
- Poor social support
- Co-morbid psychiatric disorders
- Longer use of opioids

Note: the presence of risk factors should not be a reason for denying a patient opioid therapy if opioids are the appropriate management of the painful condition. Identification of risk should help the prescriber determine the degree of monitoring and support needed to prescribe opioids safely. Discussions should be clearly documented and communicated to other members of the patient's healthcare team. If the clinician has concerns about how the patient is taking his/her medication, frequency of review should be increased.[42]

It is preferable that a person on a strong opioid attend the same healthcare professional for follow-up and repeat prescriptions.[75] A simple protocol such as that shown in **Table SEVEN** can be valuable in providing good patient care while minimising short- and long-term problems.

Prescribing Note:
Opioid dose escalation

Need for increased dose of opioids is not always indicative of problem drug use.[42]
Dose escalation may result because of:

- Increase in intensity of underlying pain condition (disease progression)
- Development of an additional painful condition
- Opioid tolerance
- Opioid induced hyperalgesia

Table SEVEN: Considerations for prescribing strong opioids in severe, chronic pain[14]

- Perform an initial assessment, including motor function and activity levels.
- Explain the reasons for using strong opioids.
- State clearly that pain will be modified but rarely completely controlled.
- Discuss side-effects and interactions.
- An opioid trial can be useful (see later).
- If possible use the oral route of administration.
- Use only one opioid at a time.
- Agents with toxic metabolites, e.g. pethidine, should be avoided.
- Analgesic/antiemetic combination products should be avoided.
- Regular dosing as opposed to "as-required" prescribing should be used.
- Long-acting opioids or sustained-release preparations are preferred.
- Changes in dosage should be made promptly to gain rapid control of pain.
- Regular follow-ups should be arranged.
- Ensure that documentation is clear and complete.

Transdermal opioids/ opioid patches

Prescribing Note:
Opioid patches

►**Buprenorphine** patches are available as either **4-day** or **7-day** patches. Transtec® are 4-day patches. BuTrans® are 7-day patches.

►**Fentanyl** patches are **3-day** patches. Various brands including Durogesic DTrans®, Fentalis®, Matrifen®, Mezolar®, Osmanil®, Tilofyl®, and Victanyl are available.

►Opioid patches should be reserved for patients with swallowing difficulties.

►Heat therapy is often recommended as a non-pharmacological option for treatment of chronic pain. However, patients should be counselled NOT to use items such as heating pads, electric blankets and heat lamps on the area where the patch is.

►Skin irritation is reported to occur in about 9% of patients using transdermal opioids.[35]

Fentanyl and buprenorphine patches release a lipid-soluble opioid through the skin into the subcutaneous fat from where it is absorbed into the systemic circulation.[76] These drugs are very potent but plasma levels take some time to become therapeutic (see later). Likewise, when the patch is removed, a depot of the drug remains in subcutaneous fat continuing to have an effect for a further 12-24 hours. When a new patch is applied it should be at a different site to the previous one.

It is important when using transdermal opioid preparations to be aware of opioid load in terms of equivalent daily morphine dose.[42] **Table EIGHT** shows approximate equivalent potencies of commonly used transdermal opioids.

Effect of skin temperature on opioid patches

Skin temperature affects peripheral blood flow so it is important to be aware that a sustained rise in ambient or body temperature can increase the drug uptake substantially – a rise in body temperature of 3°C will result in an increased absorption rate of 30%.[14]

Fentanyl 3-day patches

Fentanyl patches give up to three days of potent analgesia. Since the transdermal fentanyl preparations are available as a reservoir or matrix formulation, it is best to prescribe the patches **by brand** as bioavailability may vary between products.

If a patient is started on a transdermal fentanyl patch, evaluation of the analgesic effect should not be made before the system has been worn for 24 hours. This allows for the gradual increase in fentanyl concentration. If necessary, dose should be adjusted at 48-72 hour intervals in steps of 12-25 micrograms/hour. Previous analgesic therapy should be phased out gradually from time of first patch application.

When use of fentanyl patches is stopped and the patch is removed it may take up to 25 hours for the plasma fentanyl concentration to decrease by 50% - replacement opioid therapy should be initiated at a low dose and increased gradually.

Prescribing Note: Fentanyl patches

Prescriptions for fentanyl patches can be written to show the strength in terms of the release rate and it is acceptable to write "fentanyl 25 patches" to prescribe patches that release fentanyl 25 micrograms per hour. The dosage should be expressed in terms of the interval between applying a patch and replacing it with a new one, e.g. "one patch to be applied every 72 hours".[77]

Buprenorphine 4-day or 7-day patches

If a patient is started on a transdermal buprenorphine patch, evaluation of the analgesic effect should not be made before the system has been worn for 72 hours for the 7-day patch and 24 hours for the 4 day patch. This allows for the gradual increase in buprenorphine concentration. Previous analgesic therapy should be phased out gradually from time of first patch application.[77]

Absorption varies depending on the application site of the patch and the plasma concentration of buprenorphine can be up to 26% higher when applied to the upper back compared to the side of the chest. The clinical relevance of this is unknown.

BuTrans® patches are available in three patch strengths. Their daily dose equivalents to codeine, dihydrocodeine and tramadol are shown in **Table NINE**. The BuTrans® SmPC gives some specific instructions regarding use of the patch:

- Apply the patch to non-irritated, intact skin of the upper arm, upper chest, upper back or the side of the chest, but not to any parts of the skin with large scars.
- The site of application should be relatively hairless. If the site is not hairless, the hair should be cut with scissors, not shaven.
- Do NOT use soaps, alcohol, oils, lotions or abrasive devices to clean the skin prior to application. The skin must be dry prior to application.
- Apply the patch immediately after it is removed from the sealed sachet.
- The patch should be worn continuously.
- After removal of a patch, a new patch should not be applied to the same site for the subsequent 3-4 weeks.

Buprenorphine patches have become highly popular in the last 5 years with a steady continuing growth in prescribing and costs. In 2010, £4million was spent in Northern Ireland on these patches. Can this large growth in use be justified in terms of evidence and cost-effectiveness? The main problem with these patches is lack of good comparative information versus other active drugs. We don't know if they are as effective and we don't know if they are better tolerated.

Table EIGHT: Transdermal opioids – approximate equivalence with oral morphine[42]

Oral morphine (mg/24 hours)	10	15	30	45	60	90	120	180	270	360
Transdermal buprenorphine (micrograms/hour)	5	10	20		35	52.5	70			
Transdermal fentanyl (micrograms/hour)				12		25		50	75	100

Note: Published conversion ratios vary and these figures are a guide only. Morphine equivalences for transdermal opioid preparations have been approximated to allow comparison with available preparations of oral morphine.

Table NINE: Approximate dose equivalents of buprenorphine patch and oral opioid analgesics

	Buprenorphine 5mcg/hour patch	Buprenorphine 10mcg/hour patch	Buprenorphine 20mcg/hour patch
Tramadol	<50 milligrams/day	50-100 milligrams/day	100-150 milligrams/day
Codeine	~30-60 milligrams/day	~60-120 milligrams/day	~120-180 milligrams/day
Dihydrocodeine	~60 milligrams/day	~60-120 milligrams/day	~120-180 milligrams/day

Note: these doses do not imply equi-analgesia; they should be used as a rough guide to estimate a safe starting dose of buprenorphine. Patients must be treated on an individual basis and carefully titrated to pain control.

Cost considerations

See **Table TEN**.

CPD into action: Audit of prescribing of opioid patches

Suggestion – identify patients in your practice who are being prescribed opioid patches. Do they have swallowing difficulties? Are they taking opioids orally concurrently? Consider the appropriateness of ongoing treatment with patches.

Table TEN: Cost* of strong opioid analgesics licensed for non-cancer pain[77]

Drug†	Dose	Cost of 28 days treatment*
Buprenorphine patch	5-20 mcg/hour, 7-day patch (BuTrans®)	£17.60 to £57.16
	35-70 mcg/hour, 4-day patch (Transtec®)	£27.51 to £55.00
Buprenorphine sublingual tablet	200-400 mcg every 6-8 hours	£8.62 to £22.98
Fentanyl patch	12-100 mcg/hour, 3-day patch (non-branded or Durogesic DTrans®)	£35.52 to £162.90
Morphine modified release oral preparations	12-hourly capsules (Zomorph®), 10-200mg, twelve hourly	£3.47 to £51.30
	24-hourly capsules (MXL®), 30-200mg daily	£10.91 to £46.15
Oxycodone	Immediate-release capsules (OxyNorm®) 5-100mg, 4-6 hourly	£22.72 to £682.05
	Modified-release tablets (OxyContin®) 10-200mg, every 12 hours	£24.92 to £498.32

* Costs are based on prices quoted in BNF60, September 2010
† Other formulations of these drugs may be available, but are not licensed in non-cancer pain.

Which type of patients may benefit from opioids?

Proper management of opioids in well-selected patients with no history of substance addiction or abuse can lead to long-term pain relief for some patients with a very small (though not zero) risk of developing addiction, abuse, or other serious side effects. However, the evidence supporting these conclusions is weak, and longer-term studies are needed to identify the patients most likely to benefit from treatment.[73]

Which types of pain may benefit from opioids?

Opioids are not effective in every patient with pain. No criteria have been identified that predict good response to opioids in any particular condition. Therefore each patient who is considered for treatment with opioids needs to be assessed for both efficacy and safety. Pain of both nociceptive and neuropathic origin may respond to opioid therapy.[4,35,78] There are no conditions under which opioid therapy is contraindicated, but prescribers must be aware of the likely efficacy of a range of interventions for a given condition and use this information to guide management.

Key Point: In most situations, for most patients and most pains, opioids should not be considered as the first-choice treatment.[42]

Use of opioids for chronic non-cancer pain remains controversial. Data on the long term effectiveness of opioids for chronic non-cancer pain are sparse, with inconclusive or mixed results.[79] Although extensive clinical experience suggests that opioids can improve pain and function in some patients,[4,35] a significant proportion experience no improvement or worsening of symptoms,[64] and opioid use is associated with a variety of potentially serious adverse outcomes, including harms related to drug abuse and diversion.[36,80]

Choice of drug

The choice of drug depends on clinical circumstances, local experience and expertise.[42] There are no high quality RCTs that compare different opioids in the management of persistent non-cancer pain. Clinical experience suggests that pethidine is particularly *unsuitable* for patients with persistent pain.[42] Its high lipid solubility and rapid onset/offset may predispose patients to problem drug use. Its active metabolite norpethidine can lead to serious side effects. It does not produce less smooth muscle spasm than equipotent doses of other opioids and so confers no advantage for patients with visceral pain.[42]

Choice of route of administration

Opioids may be administered orally or transdermally. Injectable opioids should not be used in the management of patients with persistent non-cancer pain except in extraordinary circumstances and then only after consultation with a specialised multidisciplinary pain management service.[42]

An important goal of analgesic therapy for chronic pain is to provide sustained analgesia; therefore, regular administration is required to ensure the next dose of analgesic is given before the effects of the previous dose have dissipated. Consequently, many patients benefit from an extended-release analgesic that can be administered once or twice a day.[81] Extended-release analgesics can provide prolonged, more consistent plasma concentrations of drug compared with short-acting agents and minimise fluctuations that could contribute to end-of-dose breakthrough pain. In addition, extended-release analgesics may provide better night-time pain control with less need for night-time dosing.

Key point: The use of immediate-release opioids is NOT encouraged in chronic non-cancer pain. Where possible, oral, modified-release opioids administered at regular intervals should be used. Long-acting opioid formulations generally last 8 to 72 hours, making them appropriate for patients with persistent chronic non-cancer pain that requires stable, around-the-clock dosing.[82]

Prescribing Note: Oxycodone preparations

► Oxy**Norm**® are immediate-release oxycodone capsules. One capsule is taken every 4-6 hours.

► Oxy**Contin**® are modified-release oxycodone tablets. One tablet is taken every 12 hours.

Drug dose

Pain treatment with opioids should start with a low dose that is titrated upwards according to analgesic effect and side effects.[42] The patient must be warned that it may take some days to determine whether the drug is going to be effective.[42] The doses of opioids used for chronic non-cancer pain in well conducted controlled trials usually equate to less than 180 milligrams of morphine equivalent in 24 hours.[42] There are no high quality data published that inform prescribers of the safety and efficacy of higher doses.[42]

A major concern with repeated dosing of any opioid is psychological dependence. In chronic pain, it is important to achieve pain control within a week or so.[14] If this is not achieved, the withdrawal of the opioid and the use of an alternative treatment should be considered.[14] Despite this, it is not unreasonable to use an escalating opioid regimen with an agreed plan and goals over several weeks to establish efficacy.[14] The continued need for an escalating dosage after the first few weeks indicates that tolerance may be occurring and that specialist support should be sought.

Prescribing Note: Opioid dose

If patients do not achieve useful relief of pain symptoms at daily doses between 120 – 180 milligrams morphine-equivalent, referral to a specialist in pain medicine is strongly recommended.[42]

Trial of opioid therapy

A closely monitored trial of opioid therapy is recommended before deciding whether a patient is prescribed opioids for long term use.[42] The patient may need two or three upwards adjustments of opioid dose (if tolerated) before effectiveness can be evaluated.[42] If after reasonable dose titration, useful pain relief is not achieved or intolerable side effects occur, the trial of opioid therapy should be considered unsuccessful.[42] If opioid therapy is not to be continued, the dose of opioid should be stopped by gradual decrements.[42]

How should a person be assessed prior to prescribing an opioid?

A minority of patients with chronic non-cancer pain have quite unrealistic expectations.[14] It is therefore essential to discuss not only the diagnosis of their problem and the therapeutic options but also realistic goals. Failing to do so can result in regular attendances at the surgery in an attempt to gain a complete return to normality.

It is good practice when assessing the patient in pain to elicit a mental health history, including screening questions relating to:[42]

- Current/past history of depression or anxiety
- Current/past history of substance misuse
- Family history of substance misuse

A history of depression or anxiety, and substance misuse (by the patient or a family member) may be risk factors for problematic opioid use. This information is needed to determine the degree of monitoring and support needed to prescribe opioids safely.

The goals of therapy should be agreed before starting opioid treatment and assessed at each review. These goals should be clearly documented. Adverse effects should be documented at every assessment.

Long term opioid prescribing

If the opioid trial (as outlined above) is a success the patient may wish to continue taking opioids. Treatment may be continued until:[42]

- The painful condition resolves
- The patient receives a definitive pain relieving intervention (e.g. joint replacement)
- The patient no longer derives benefit from opioid treatment
- The patient develops intolerable side-effects
- Use of opioids becomes problematic.

Is there evidence that opioids are useful in the long-term for chronic non-cancer pain?

The efficacy of opioids for chronic non-cancer pain has been demonstrated in short-term trials,[35] but little is known about whether these agents continue to be effective over the longer duration of treatment typical for chronic non-cancer pain. Concerns have also been raised about adverse effects that may arise with long-term use, including the development of addiction or abuse, or both.[73] At best the evidence for the effectiveness of long-term opioids in reducing pain and improving functional status for six months or longer in chronic non-cancer pain is variable.[73,79,83]

During long term therapy with an opioid, how often should the patient be reviewed?

During long-term opioid treatment, reviews should be conducted at least monthly in the first six months after stable dosing has been achieved. Frequency of review thereafter can be clinically determined by the complexity of the case, but should be at least biannually.[42] If opioids have been started in secondary care, there should be agreement between the hospital and the patient's GP regarding where and by whom the patient will be assessed.[42] Monitoring should include documentation of pain intensity and level of functioning, assessment of progress toward achieving therapeutic goals, presence of adverse events, and adherence to prescribed therapies.[84] Risks and benefits of opioids do not remain static over time due to changes in the severity of the underlying pain condition, development or progression of medical or psychiatric comorbidities, and other factors. Regular monitoring of an array of outcomes is therefore critical to assess the therapeutic response.[85]

Prescribing quantities

The DHSSPSNI has issued a strong recommendation that, as good practice, the quantity of Schedule 2, 3 and 4 Controlled Drugs prescribed should not exceed a 30 day supply. If more than a 30 day supply is prescribed, the prescriber should record the reasons for doing so in the patient's notes and be prepared to justify their decision. Whilst it remains legal to dispense a prescription for more than a 30 day supply, pharmacists should ensure that there is a genuine clinical need and that such prescribing does not pose an unacceptable risk to patient safety.

Generic prescribing

There is a general consensus that it is best NOT to switch between differing preparations of potent opioids, especially transdermal and sustained-release preparations, as bioavailability may differ to a clinical extent. In Northern Ireland, the Health and Social Care Board has listed the following strong opioids as UNSUITABLE for generic prescribing:[86]

- Buprenorphine patches (BuTrans®, Transtec®)
- Fentanyl patches (Durogesic DTrans®, Fentalis®, Matrifen®, Mezolar®, Osmanil®, Tilofyl®, Victanyl®)
- Morphine modified-release oral preparations (Morphgesic® SR, MST Continus®, Zomorph®, MXL®)
- Oxycodone oral preparations (OxyNorm®, OxyContin®).

Websites

- Action on Pain: www.action-on-pain.co.uk
- British Pain Society: www.britishpainsociety.org
- Chronic Pain Policy Coalition: www.paincoalition.org.uk
- International Association for the Study of Pain: www.iasp-pain.org
- Pain Concern: www.painconcern.org.uk
- Pain Support: www.painsupport.co.uk
- The Pain Relief Foundation: www.painrelieffoundation.org.uk

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Lynn Keenan BSc(Hons) MSc MPS
Medicines Management Information Pharmacist
COMPASS Unit
Pharmaceutical Department
HSC Business Services Organisation
2 Franklin Street, Belfast
BT2 8DQ.

With thanks to the following for kindly reviewing this document:

• **Professor GD Johnston**, Consultant Physician. Belfast Health and Social Care Trust. Professor of Therapeutics and Pharmacology. Queen's University Belfast.

• **Dr Pamela Bell**, Lead Clinician Chronic Pain Services.
Belfast Health and Social Care Trust.

The editorial panel for this edition of COMPASS Therapeutic Notes:

Ms Kathryn Turner (Medicines Management Lead, HSCBSO).

Dr Bryan Burke (General Practitioner)

Dr Grainne Crealey (Health Economist, CRSC)

Miss Veranne Lynch (Medicines Management Advisor, Belfast LCG)

Dr Ursula Mason (General Practitioner)

Ms Joanne McDermott (Medicines Governance Pharmacist, Western Office)

Mrs Stephanie Sloan (Community Pharmacist)

Dr Thérèse Rafferty (Medicines Management Information Analyst, HSCBSO).

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COMPASS THERAPEUTIC NOTES ASSESSMENT
Strong Opioids in Chronic Non-cancer pain

COMPASS Therapeutic Notes are circulated to GPs, nurses, pharmacists and others in Northern Ireland. Each issue is compiled following the review of approximately 250 papers, journal articles, guidelines and standards documents. They are written in question and answer format, with summary points and recommendations on each topic. They reflect local, national and international guidelines and standards on current best clinical practice. Each issue is reviewed and updated every three years.
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Successful completion of these assessment questions equates with **2 hours** Continuing Professional Development time. Circle your answer TRUE (T) or FALSE (F) for each question. When completed please post this form to the relevant address shown overleaf. Alternatively, you can submit your answers online:

- **Doctors and nurses** should submit their answers at: **www.medicinesni.com**
- **Pharmacists** should submit their answers at: **www.nicpld.org**

1	**Morphine:**			
	a	Morphine tends to be the standard against which other analgesics are compared.	T	F
	b	Older people may require larger doses of morphine than younger people.	T	F
	c	A daily oral dose of 30 milligrams of morphine is approximately equivalent to a daily oral dose of 240 milligrams of codeine.	T	F
	d	Morphine is considered to be the first-line choice of strong opioid.	T	F
2	**Fentanyl:**			
	a	Fentanyl sublingual tablets, buccal tablets and nasal spray are directly interchangeable dose-for-dose.	T	F
	b	Fentanyl patches provide 3-days of analgesia.	T	F
	c	Fentanyl patches should be prescribed generically.	T	F
	d	If a patient is started on a transdermal fentanyl patch, evaluation of the analgesic effect should not be made before the system has been worn for 24 hours.	T	F
3	**Buprenorphine:**			
	a	Buprenorphine is available in both 4-day and 7-day patches.	T	F
	b	Buprenorphine patches should be applied to the upper arm, upper chest, upper back or side of the chest.	T	F
	c	If the area is hairy, the skin should be shaved before applying the patch.	T	F
	d	Buprenorphine patches can cause skin irritation.	T	F
4	**Adverse effects of opioid therapy:**			
	a	Opioids are well tolerated and seldom discontinued due to adverse effects.	T	F
	b	Nausea and sedation usually become less of a problem after 1-2 weeks of treatment with a strong opioid.	T	F
	c	Constipation does not tend to resolve with continued opioid treatment.	T	F
	d	Itching occurs in about 1% of patients taking an opioid.	T	F
5	**Prescribing strong opioids in chronic non-cancer pain:**			
	a	In general, strong opioids are first-line.	T	F
	b	Pethidine is considered to be particularly useful in chronic pain.	T	F
	c	If an opioid is considered necessary, an oral, modified-release opioid administered at regular intervals should be used.	T	F
	d	When stopping an opioid, the dose should be tapered slowly.	T	F