PrescQIPP Community Interest Company

Opioid patches

The annual spend in England and Wales on all opioid patches is over £83 million (ePACT May to July 2018). Medicines optimisation projects in this area focus on eliminating inappropriate prescribing of opioid patches as safety concerns include the potential for severe harm or death. They also focus on reducing unnecessary expenditure on opioid patches.

This project should be used in line with '149. Non-neuropathic pain': https://www.prescqipp.info/our-resources/bulletins/bulletin-149-non-neuropathic-pain/

Recommendations

- Only prescribe opioid patches for patients who have previously tolerated opioids.[1] Refer to B149 – management of non-neuropathic pain in primary care. The transdermal route has a slow onset and slow offset of both action and side effects. Do NOT use for acute and/or unstable pain.[2]
- NICE Clinical Guideline (CG) 140 states first-line choice of strong opioid is sustained release (SR) oral morphine, with immediate release oral morphine for breakthrough pain.[1]
- Consider specifying criteria for patients to use opioid patches for pain, e.g. those:
  - Unable to tolerate tablets/capsules due to side-effects, or who have difficulty swallowing (although oral liquids, capsules that can be emptied and sprinkled onto soft or pureed foods and subcutaneous morphine may be suitable alternatives instead of a patch).[3]
  - With compliance issues such as mental health problems, or who are socially isolated with limited access to care.[3]
- Where prescribing is appropriate, prescribe transdermal patches with the lowest acquisition cost for patients in whom oral opioids are not suitable and analgesic requirements are stable; specialist advice should be sought when needed.[1]
- Prescribe opioid patches by brand name for continuity of supply and to avoid confusion for patients and carers. Ensure correct prescribing, dosage frequency, use and disposal of opioid patches due to the potential for serious adverse events, e.g. respiratory depression in opioid-naïve patients.[4] Ensure stock availability.
- Patches should not be cut.[4] Fentanyl patches are available as matrix and reservoir formulations. Cutting reservoir patches can lead to leaking and overdose. The matrix patch is thinner and smaller than the reservoir patch.[5] Patient familiarity with one brand is important.[6]
- Patients with cancer often see several doctors and may receive opioids from more than one clinician. To avoid this happening, it is good practice for one clinician to take the lead role in prescribing.[7]
- Review patients on doses of fentanyl 50microgram/hr or buprenorphine 52.5microgram/hr or greater as the risk of harm outweighs benefits because the equivalent daily dose of morphine is greater than 120mg.[8]

Background

In 1986, the World Health Organisation (WHO) proposed a step-wise approach to the use of medication in cancer related pain. The underlying principle was that medications should be used in an incremental fashion according to the patient's reported pain intensity. The World Health Organisation (WHO) analgesic ladder suggests a stepwise approach to pain management. The WHO recommends the use of strong oral opioids (e.g. morphine or oxycodone) for the management of moderate to severe pain due to cancer, at step three of the analgesic ladder.[7] The Faculty of Pain Medicine states that the analgesic ladder is unhelpful in persistent pain as it has an unpredictable course and may continue for many years. Substantial reduction in pain intensity is rarely an achievable goal.[8]

Opioid patches include fentanyl and buprenorphine patches, which are available as several different brands and formulations. Opioid patches should be reserved for patients unable to take oral medicines. There have been safety concerns highlighted around the use of opioid patches[4] and usage and spend on these products is significant.[1] Transdermal preparations of fentanyl and buprenorphine are not suitable for acute pain or in patients whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose.[9]

Fentanyl is a strong opioid analgesic and a Schedule 2 Controlled Drug (CD POM),[4] which needs to be stored in the CD cupboard and entries made in the CD register for dispensing purposes.[10] A 25microgram per hour (mcg/hr) fentanyl patch equates to daily doses of oral morphine of up to 90mg.[8] Fentanyl patches should only be used in patients who have previously tolerated opioids, because of a risk of significant respiratory depression in opioid-naïve patients. The initial dose should be based on a patient's opioid history. Information on starting doses and dose conversions can be found in the Summaries of Product Characteristics (SPCs), British National Formulary (BNF), British National Formulary for Children (BNFC), Palliative Care Formulary (PCF6) and in local policies and guidance. The NICE Clinical Knowledge Summary (CKS) recommends seeking specialist advice when considering strong opioids other than morphine.[11]

Buprenorphine is a partial opioid agonist. It is a Schedule 3 Controlled Drug (CD No Register POM).[9] Buprenorphine patches need to be stored in the CD cupboard, but no entry is required in the CD register for dispensing.[10]

Prescribers should ensure that they are familiar with the correct use of transdermal preparations as inappropriate use has caused fatalities.[4,5,9]

National guidance

The National Institute for Health and Care Excellence (NICE) CG 140 states that the first-line choice of strong opioid is sustained release oral morphine, with immediate release oral morphine for breakthrough pain.[1] Prescribers are recommended to gain familiarity with one brand of modified release (MR) oral morphine, to reduce the risk of errors from prescribing different brands and formulations. The Department of Health has also recommended brand-name prescribing of modified release morphine.[12]

The NICE CG 140 recommends opioid patches as a treatment option only if oral opioids are unsuitable.[1] It recommends:

- Considering initiating transdermal patches with the lowest acquisition cost for patients in whom oral opioids are not suitable and analgesic requirements are stable, supported by specialist advice where needed.
- Using caution when calculating opioid equivalence for transdermal patches.

The BNF states that opioid patches are not suitable for acute pain or in patients whose analgesic requirements are changing rapidly because the long time to steady state prevents rapid titration of the dose.[9]

The European Association for Palliative Care (EAPC) recommend carefully titrating transdermal fentanyl or buprenorphine to account for the long apparent drug half-life (several days), with use of immediate-

release opioids in the interim. Transdermal fentanyl and buprenorphine are alternatives to oral opioids. The clinical trial evidence that was reviewed permits a weak recommendation that either drug may be the preferred step three opioid for some patients.[13] For patients, unable to swallow they are an effective, non-invasive means of opioid delivery.[14]

The Faculty of Pain Medicine states that the risk of harm increases substantially at doses above an oral morphine equivalent 120mg daily dose without an increased risk of benefit. This applies to doses of fentanyl 50microgram/hr (180mg morphine daily dose) and buprenorphine 52.5microgram/hr (126mg morphine daily dose) and any doses above these.

Clinical evidence

Oral morphine compared with fentanyl or buprenorphine patches

The evidence comparing oral morphine with fentanyl or buprenorphine patches is low level and partly indirect. The 2012 European Association of Palliative Care evidence based recommendations about use of opioid analgesics highlights a systematic review of transdermal fentanyl and buprenorphine for moderate to severe cancer pain. The systematic review included the results of one meta-analysis of four randomised, controlled trials (RCTs) that compared oral morphine with fentanyl or buprenorphine, and one RCT with three parallel arms that compared morphine with fentanyl and methadone. No significant differences in efficacy emerged between either of the transdermal preparations and other opioids. However, a difference in favour of transdermal preparations was seen for less constipation and patients' preference. None of these trials were blinded, some were of low methodological quality and two of them were done in patients already taking step three opioids.[13]

Fentanyl

The evidence for the analgesic efficacy of transdermal fentanyl is severely limited. A Cochrane review investigated the analgesic efficacy of transdermal fentanyl for the relief of cancer pain and to assess the adverse events associated with its use. The systematic review found that given the wide use of transdermal fentanyl in the palliative care setting, the evidence base for its use is limited. Rash or pruritus is often quoted as a problem with transdermal fentanyl, but where reported in these studies it occurred at low rates and seemed to improve over time. One of the useful outcomes from the review was to highlight the inherent mortality of patients enrolled in these studies. Most studies included a measure of prognosis to ensure life expectancy exceeded the study length. However, nearly 7% of participants being treated for their primary cancer died over a study period of one month. Studies included in the systematic review were small, generally of poor quality and none reported clinically important primary outcomes. The conclusion was that if patients were able to tolerate the medication and survived to the end of the study, then pain appeared to be improved and the majority of patients would have no worse than mild pain. In terms of side effects, lower rates of constipation were demonstrated with transdermal fentanyl. Further research is needed with improved study design, using clinically important outcome measures, e.g. achieving no worse than mild pain after two weeks of treatment. Clinical decision-making would also need to take into account other factors, such as the balance of cost, preference and speed of response needed (i.e. not for patients who need rapid analgesic titration), when considering treatment for cancer pain.[14]

A Midlands Therapeutics Review and Advisory Committee (MTRAC) review of fentanyl patches concluded that the cost of transdermal fentanyl compared with oral morphine gives it a low place in therapy. Five open-label trials compared transdermal fentanyl with sustained-release (SR) morphine and one double-blind, placebo-controlled trial. Overall transdermal fentanyl was shown to be as effective as morphine SR and more effective than placebo. However, the subjective nature of outcome measures and the open-label design made the trials prone to potential bias.[3]

Fentanyl should not be used in opioid-naïve patients. In the US and Canada, authorities advise that use should be restricted to patients who have been taking the equivalent of at least 60mg daily of oral morphine for at least seven days.[12]

Buprenorphine

Evidence from eight RCTs and nine non-randomised studies (NRS) indicates that transdermal buprenorphine patches provide pain relief in patients with chronic low back pain, osteoarthritis, ischaemic pain associated with vasculopathy, pain related to neuropathic or musculoskeletal disorders and other types of chronic, non-cancer related pain. Effective doses ranged from 5 to 70 micrograms per hour. Transdermal buprenorphine was found to be well tolerated with the most commonly reported adverse events being nausea, vomiting, dizziness, somnolence and non-systemic adverse skin reactions. Three RCTs reported a patient preference for transdermal buprenorphine treatment.[15]

An MTRAC review concluded that the cost of transdermal buprenorphine (patches) compared with oral morphine SR gives it a low place in therapy. The evidence for the efficacy of the buprenorphine transdermal system (patches) was relatively weak. Nine randomised double-blind trials compared patches with placebo and three open-label trials used active comparators, one with morphine sustained-release (SR). The outcome measures were subjective in all trials. The results showed a considerable placebo effect, even in the five trials in which only patients were included who had previously shown a response to transdermal or sublingual buprenorphine. The designs and quality of the trials varied considerably. Transdermal buprenorphine was found to be non-inferior to tramadol for the change in pain score in one trial of patients with osteoarthritis. In a second trial, buprenorphine plus paracetamol was found to be non-inferior to co-codamol in patients with osteoarthritis. The most common adverse events in these trials were nausea, dizziness, somnolence and vomiting occurring in over 20% of patients using transdermal buprenorphine.[16]

A systematic review and network meta-analysis published in 2012 found that buprenorphine patches had similar efficacy and fewer side-effects than fentanyl patches in the treatment of moderate to severe chronic pain. The authors stated a need for further large RCTs to compare buprenorphine to fentanyl patches directly or to the major step three opioids and report sufficient data for inclusion in meta-analyses. These studies should assess relevant outcomes with longer term (at least one year) follow-up and use standardised outcome measures.[17] A summary of the paper by the University of York Centre for Reviews and Dissemination concluded that the short duration and low quality of the included studies mean that the reliability of the results is uncertain.[18]

Practical considerations

A ceiling effect has been shown with buprenorphine for respiratory depression (200mcg/70kg IV) and other effects, e.g. euphoria (4-8mg sublingually) but not for analgesia. Buprenorphine does slow intestinal transit, but possibly less so than morphine. Constipation may be less severe than morphine. There are few practical differences in the use of the buprenorphine or fentanyl matrix patches and similar safety considerations apply, e.g. not exposing to external heat sources. There may be differences in adherence. Compared with fentanyl, transdermal buprenorphine (as Transtec®) adheres better. Patch removal with buprenorphine is associated with more persistent erythema (and/or localised pruritus) and sometimes a more definite dermatitis. This is generally caused by the adhesive, but occasionally by the buprenorphine itself. Careful removal of patches minimises skin irritation.[2]

Retrospective analysis suggests that compared with transdermal fentanyl, patients receiving transdermal buprenorphine (as Transtec®) have a slower rate of dose increase and longer periods of dose stability. This requires confirmation in an RCT. Systematic reviews have highlighted a lack of high quality studies of transdermal buprenorphine.[2]

Converting between opioids

Use a recognised conversion rate.[12] Conversion ratios vary and these figures are a guide only. Determine dosage based on the patient's opioid history. Refer to tables in the Palliative Care Formulary,[2] Faculty of Pain Medicine[8] and BNF.[9]

Dosing instructions including conversion from a different opioid, initiation in opioid naïve patients and titration to the effective dose are included in the individual summaries of product characteristics (SPCs) and should be followed.

Careful monitoring during conversion is always necessary, especially when high doses are used, as conversion ratios are only an approximate guide and there is wide inter-individual variation.[12]

Buprenorphine

Conversion rates between transdermal buprenorphine and oral morphine vary, with transdermal buprenorphine 70-115 times more potent than oral morphine.[2] Table 1 below shoes the approximate equivalence for buprenorphine to oral morphine based on BNF and the faculty of pain medicine conversion rates.[8,9] Dose equivalences with available preparations are also shown. When switching due to possible opioid-induced hyperalgesia, the calculated equivalent dose of the new opioid should be reduced by one-quarter to one-half. Morphine equivalences for transdermal opioid preparations have been approximated to allow comparison with available preparations of oral morphine.[9]

Table 1: Approximate equivalence of buprenorphine patches and 24 hour doses of oral morphine and suggested dose with available products[8,9]

Morphine daily dose		Buprenorphine daily dose	Dose with available morphine product Note: For some strengths dose may be more than one tablet
Morphine salt 12 mg daily	≡	Buprenorphine '5' patch (7 day patch)	Morphine MR 5mg twice daily (total daily dose 10mg morphine salt) This is also equivalent to codeine 30mg four times a day
Morphine salt 24 mg daily	≡	Buprenorphine '10' patch (7 day patch)	Morphine MR 10mg twice daily (total daily dose 20 mg morphine salt)
Morphine salt 36 mg daily	≡	Buprenorphine '15' patch (7 day patch)	Morphine MR 15mg twice daily (total daily dose 30mg morphine salt)
Morphine salt 48 mg daily	≡	Buprenorphine '20' patch (7 day patch)	Morphine MR 20mg twice daily (total daily dose 40mg morphine salt)
Morphine salt 84 mg daily	≡	Buprenorphine '35' patch (twice weekly)	Morphine MR 40mg twice daily (total daily dose 80mg morphine salt)
Morphine salt 126 mg daily	≡	Buprenorphine '52.5' patch (twice weekly)	Morphine MR 60mg twice daily (total daily dose 120 mg morphine salt)
Morphine salt 168 mg daily	≡	Buprenorphine '70' patch (twice weekly)	Morphine MR 80mg twice daily (total daily dose 160 mg morphine salt)

Fentanyl

Fentanyl equivalences are documented below for patients on well tolerated opioid therapy for long periods; for patients who are opioid naive (in certain circumstances, for example, patients with severe dysphagia, renal failure or who are living in social circumstances where there is a high risk of diversion and tablet misuse[3]) or who have been stable on oral morphine or other immediate release opioid for

only several weeks.[9] Table 2 states the approximate equivalence of 72 hour fentanyl patches to 24 hour doses of oral morphine given in the BNF compared to those recommended by the Faculty of Pain Management.[8,9] Prescribers should familiarise themselves with and use just one conversion chart to ensure safe prescribing.

Table 2: Approximate equivalence of fentanyl patches and 24 hour doses of oral morphine[8,9]

BNF conversion[9]	Fentanyl patch dose	Faculty of Pain Medicine[8]
Morphine salt 30 mg daily	fentanyl '12' patch	Morphine salt 45 mg daily
Morphine salt 60 mg daily	fentanyl '25' patch	Morphine salt 90 mg daily
Morphine salt 120 mg daily	fentanyl '50' patch	Morphine salt 180 mg daily
Morphine salt 180 mg daily	fentanyl '75' patch	Morphine salt 270 mg daily
Morphine salt 240 mg daily	fentanyl '100' patch	Morphine salt 360 mg daily

As with buprenorphine, conversion rates between fentanyl patches and oral morphine can vary considerably. Table 3 highlights the fentanyl to morphine equivalence stated in the SPCs for two specific brands of fentanyl (Durogesic® and Fencino®[5,19]) which give different conversions to both the BNF and FPM (table 2).

Table 3: SPC Fentanyl to morphine equivalence[19]

Oral 24 hour morphine (mg/day)	Fentanyl dose (microgram/hour)
<90	12
90-134	25
135-224	50
225-314	75
315-404	100

Safety and appropriate prescribing of opioid patches

After the application of any patch there is a delay of many hours before therapeutic levels of a drug are reached. Also, after removal of a patch, there is a delay of many hours before circulating levels of a drug drop to a sub-therapeutic level, i.e. there is a slow onset and slow offset of analgesia and of side effects.

As stated, opioid patches are an effective treatment for malignant and non-malignant chronic intractable pain. However, they must be used correctly and with care. Familiarity of patches is important for safe prescribing of opioids.[12]

The Medicines and Healthcare Products Regulatory Agency (MHRA) have received spontaneous reports of life-threatening adverse reactions and death after fentanyl overdose. Factors identified as possibly related to unintentional overdose include dosing errors (by healthcare professionals, patients, or caregivers); accidental exposure (particularly in children and pets); and exposure of the patch to a heat source, possibly resulting in increased fentanyl absorption.[4]

Causes and outcomes of unintentional overdosing and underdosing with buprenorphine patches are listed below.[20] Some of these are also applicable to fentanyl.

Error/cause		Potential risks
Dosing errors	Initiating a patient on too large a dose of transdermal buprenorphine.	Patient drowsiness due to inappropriately high dose of transdermal buprenorphine.
	Applying a buprenorphine patch licensed to be changed every 72 hours (three days) and leaving it in situ for 96 hours (four days) or seven days.	Breakthrough pain for patient and unlicenced use of buprenorphine patch.
	Prescribing a higher strength patch in error to a patient previously on a seven day 20 microgram per hour patch.	Risk of serious side effects due to large increase in buprenorphine dose.
	Applying a buprenorphine patch licensed to be changed every seven days and adding directions of 'change twice a week'.	Waste of NHS resources, and risk of side effects and higher than intended dose being given to the patient.
	A higher strength patch labelled as 'Apply two patches weekly' rather than 'Apply one patch twice a week'.	Potential confusion in application frequency.
Failure to remove a buprenorphine patch when applying a new buprenorphine patch.		Patient drowsiness due to increase in buprenorphine dose.
Administering fentanyl patches in error for buprenorphine patches.		Patient receives incorrect medication.
Increased release of buprenorphine from the patch due to excessive heat (heat sources can include hot baths, hot water bottles, fever and sunbathing).		Patient drowsiness and increased risk of side effects due to increase in buprenorphine dose.
Accidental exposure (particularly in children).		
Prescribing in unlicensed indications.		
Prescribing in opioid-naïve patients.[1]		

Fentanyl patches

Fentanyl patches are not suitable for opioid-naïve patients and are best reserved for patients with stable opioid requirements.[12] Transdermal fentanyl is used in the management of chronic severe pain, particularly in cancer. Steady-state plasma concentrations of fentanyl are generally achieved after 36-48 hours, but this is sometimes longer.[2]

Fentanyl is metabolised by CYP3A4 so fentanyl plasma concentrations may be increased by CYP3A4 inhibitors such as: fluconazole, ketoconazole, itraconazole, erythromycin, clarithromycin, ritonavir, nelfinavir, aprepitant, cimetidine, diltiazem and verapamil. In contrast fentanyl concentrations are reduced by potent CYP3A4 inducers and this may lead to loss of analgesia. Examples are carbamazepine, phenytoin, phenobarbitone and rifampicin.[2]

When fentanyl patches are prescribed, it is important to ensure that patients and/or their carers understand how to use them correctly.[12] The patch must be pressed firmly in place for at least 30 seconds to ensure adherence. Fentanyl is a reasonable option for patients with renal impairment or renal failure.[2] Pain not relieved by morphine will generally not be relieved by fentanyl. If in doubt seek specialist advice before prescribing fentanyl patches.[2]

Opioid toxicity has been reported with inappropriate prescribing of transdermal fentanyl. Where the dose is effectively doubled when increasing from 25mcg/hr to 50mcg/hr patches, clinical problems have been reported with this dose increment.[7] However, Mezolar Matrix is available as 37.5 microgram/hr and two patches of different strength (i.e. 25microgram/hr and 12 microgram/hr can be used to escalate the dose slowly (by e.g. 50%).[9] Ensure that where a dose increase is intended that the calculated dose is safe for the patient (e.g. for oral morphine in adult patients, not normally more than 50% higher than the previous dose).[21]

Buprenorphine patches

There are two groups of buprenorphine patches, lower strength and higher strength as detailed in tables 1 and 2 and table 4 below.

Table 4: Licensed indications of buprenorphine[9]

Strength of patch	Licensed indication	Frequency of patch application
Lower strength 5 micrograms, 10 micrograms, 15 micrograms and 20 micrograms per hour	Treatment of non-malignant pain of moderate intensity when an opioid is necessary for obtaining adequate analgesia	Apply a new patch every seven days
Higher strength 35 micrograms, 52.5 micrograms and 70 micrograms per hour	Treatment of moderate to severe cancer pain and severe pain which does not respond to non-opioid analgesics	Either (depending on brand): Apply a new patch every 72 hours (three days) or Apply a new patch after up to 96 hours (four days). SPCs suggest bi-weekly dosing, e.g. Tuesday and Friday

Transdermal patches are available as 72-hourly, 96-hourly and seven day formulations; prescribers and dispensers must ensure that the correct preparation is prescribed and dispensed – see tables 6 and 7.[9]

Table 5: Frequency of prescribing of different brands of buprenorphine patches[9]

72 hours	96 hours	7 days
Hapoctasin®	Bupeaze®	Bupramyl®
Prenotrix®	Buplast®	Butec®*
	Relevtec®	Busiete®
	Transtec®	BuTrans®*
		Panitaz®
		Reletrans®
		Sevodyne®

*Butec® and BuTrans® products are identical

Table 6: Current brands of buprenorphine patch and frequency of application[9]

	5mcg/hr	10mcg/hr	15mcg/hr	20mcg/hr	35mcg/hr	52.5mcg/hr	70mcg/hr	Frequency of administration
Bupramyl®	x	x		x				7 days
Busiete®	x	x		x				7 days
Butec®	x	x	x	x				7 days
BuTrans®	x	x	x	x				7 days
Panitaz®	x	x		x				7 days
Reletrans®	x	x	x	x				7 days
Sevodyne®	x	x		x				7 days
Bupeaze®					x	x	x	96 hours
Buplast®					x	x	x	96 hours
Relevtec®					x	x	x	96 hours
Transtec®					x	x	x	96 hours
Hapoctasin®					x	x	x	72 hours
Prenotrix®					x	x	x	72 hours

Frequency of transdermal buprenorphine patch removal and renewal

Patients should be appropriately counselled on the frequency of patch removal and renewal dependent on the individual preparation dispensed. They should be encouraged to keep a record of when the patch was removed and when it was replaced, for example by using the manufacturer provided record areas on the product packaging. Some clinical teams use transdermal patch application forms to record where a patch has been placed, confirm that the old patch has been removed and ensure that patches are changed at appropriate times on a new area of skin.[2] Errors have occurred in primary and secondary care because of confusion in the correct renewal frequency between three day, four day and seven day patches. Labelling should make the frequency of patch removal and renewal clear e.g.:

- Apply ONE patch every SEVEN days. Remove and discard old patch before applying new patch.

Labelling added to the package during dispensing should be applied carefully so that it does not obscure useful information for the patient. When reviewing a patient using buprenorphine patches, healthcare professionals should consider the following questions:

- Which manufacturers' version of transdermal buprenorphine patch does the patient apply and what is the licensed frequency of removal and renewal?
- What is the strength of the buprenorphine patch?
- When was the buprenorphine patch last applied and when is it due for replacement?
- Have all the old buprenorphine patches been removed?
- Does the patient understand how to use buprenorphine patches appropriately?[20]

Prescribing by brand

It is important to stick to the same brand of product for individual patients. If necessary to switch, switching between products of the same strength, but made by different manufacturers, should not cause a significant change in dose for the patient.[5] Prescribers should however be aware that breakthrough pain or excessive drowsiness may occur and advise the patient how to manage this.[20]

Escalation of doses

To increase the dose, a larger patch should replace the patch that is currently being worn, or a combination of patches should be applied in different places to achieve the desired dose. It is recommended that no more than two patches are applied at the same time,[9] e.g. BuTrans® up to a maximum total dose of 40 microgram/hour.[22] If doses are escalated by no more than 50%, it may be necessary to use patches of different strengths.

Check individual SPCs for the time interval of when the new patch should not be applied to the same area, for example:

- BuTrans® - a new patch should not be applied to the same skin site for the subsequent 3-4 weeks.[22]
- Fentanyl 72 hour patches - several days should elapse before a new patch is applied to the same area of the skin.[5,19,23-28]
- Hapoctasin®, Transtec® - at least one week should elapse before a new transdermal patch is applied to the same area of skin.[29,30]

Patients should be carefully and regularly monitored to assess the optimum dose and duration of treatment.[22] After an increase in dose, it may take up to six days for the patient to reach equilibrium on the new dose level. Therefore, after a dose increase, patients should wear the higher dose patch through two 72-hour applications before any further increase in dose level is made.[5]

Long term effects of opioids

Long term administration of opioids is associated with endocrine impairment in men and women with consequent hypogonadism and adrenal insufficiency. Studies have also demonstrated that opioids can cause immunosuppression, although each may differ in their effects on the immune system. Prolonged use of opioids may lead to a state of abnormal pain sensitivity or 'hyperalgesia', which is more diffuse than the pre-existing pain and less defined in quality. The management of opioid-induced hyperalgesia is opioid dose reduction or changing to an alternative (opioid) preparation.[8]

Discontinuation/switching of opioid patches

Occasionally there is a clinical situation where it is in the patient's best interests to switch from transdermal opioids to a different opioid or route of administration (e.g. in hyperalgesia).[8]

Discontinuation/switching of fentanyl patches

If discontinuation of fentanyl patches is necessary, any replacement with other opioids should be gradual, starting at a low dose and increasing slowly (according to the patient's report of pain until adequate analgesia is obtained). This is because fentanyl concentrations fall gradually after the fentanyl patch is removed. It may take 20-27 hours or more for the fentanyl serum concentrations to decrease 50%. In general, the discontinuation of opioid analgesia should be gradual in order to prevent withdrawal symptoms (nausea, vomiting, diarrhoea, anxiety and muscular tremor); consequently patients who have experienced serious adverse events should be monitored for at least 24 hours after removal of the patch, or more, as clinical symptoms dictate.[5,19,23-28]

If the patient is on a high strength patch, then gradual downward titration (through the available strengths) is recommended to avoid withdrawal symptoms.[26]

Discontinuation/switching of buprenorphine patches

After removal of buprenorphine patches, serum concentrations decrease gradually. It takes about 30 hours for buprenorphine concentrations to decrease by 50% once a Transtec® patch is removed (range 22-36 hours) and 12 hours (range 10-24 hours) with a BuTrans® patch. This should be considered when therapy is to be followed by other opioids. As a general rule, a subsequent opioid should not be administered within 24 hours after removal of a buprenorphine patch.[22,29,30]

Appropriate disposal of opioid patches

Used patches can still contain residual opioid in them and should be disposed of carefully and out of the reach of children to avoid accidental exposure. Advise patients to fold patches with the adhesive surfaces inwards, place back in the sachet and discard in a dustbin.[2]

A case in the United States highlights this issue. A two year old boy died after accidental exposure to a used fentanyl patch, which hadn't been disposed of safely. The medical examiner determined that he died from a lethal dose of fentanyl, absorbed through his oral mucosa. The theory to the two-year old's death was that while visiting his great grandmother and playing with his toy truck, he may have run over a used fentanyl patch. Later he may have removed the patch from the truck's wheel and stuck the fentanyl patch in his mouth.[31]

A MHRA Drug Safety Update was published in July 2014 as a reminder of the potential for life-threatening harm from accidental exposure to fentanyl patches, especially in children. A recent EU-wide review emphasised the need for safe handling of patches. When this report was written, the MHRA had received three Yellow Card reports describing accidental contact with or transfer of fentanyl patches; two of these concerned children. They are particularly at risk because children may touch, suck, chew, or swallow a patch that has not been disposed of properly. They also have a lower threshold for fentanyl overdose than adults. The MHRA reminds healthcare professionals to advise patients and caregivers to follow the instructions on the patch carton and leaflet. If a patch is transferred to another person, it should be removed and that person should seek medical help immediately. If a patch is swallowed, again that person should get immediate medical help. Any cases of accidental exposure where harm or suspected side effects have occurred should be reported via the Yellow Card scheme to the MHRA.[32] A further MHRA safety aert was issued in October 2018, which reiterated this advice due to receiving a further five reports of fatal incidents specifying accidental exposure, accidental overdose, or product adhesion issue.[33]

Costs

Chart 1 on the next page shows the 28 day cost of fentanyl 25mcg/hr patches, changed every 72 hours (three days) equating to the use of ten patches in total, in comparison to the equivalent total daily dose of 90mg of SR oral morphine. For the purposes of the cost comparison chart the equivalent dose given by the Faculty of Pain Medicine has been used.[8] The cost of 90mg SR oral morphine is demonstrated using the cost of 30mg + 60mg Zomorph® SR capsules and MST Continus® tablets although this would not work well in practice as it would not be dividing the dose equally every 12 hours.

The 25mcg/hour strength of fentanyl patch was chosen to include Fentalis® and Tilofyl® patches, which are not available as a 12mcg/hour patch. Treatment for 28 days with Osmanil® and Tilofyl® patches is almost five times more costly than the equivalent dose of oral morphine as Zomorph® MR tablets (the largest cost difference). Patients that are suitable for oral morphine treatment should be using that route of administration.

Note: Fentalis® is the only fentanyl reservoir patch, all the other products are matrix patches. Generic morphine sulphate SR capsules prices are the same as Zomorph® SR capsules.

The BNF dose conversion for fentanyl 25mcg/hr changed every 72 hours is equivalent to a total daily dose of 60mg SR oral morphine. Costs for morphine given at the lower BNF conversion ratios would be lower. In this case, the 28 day cost would only be, £7.75 for Zomorph® SR capsules.[9]

Chart 1: Comparison of 28 day cost[9] of 25 microgram/hour fentanyl patches to SR oral morphine using Faculty of Pain Medicine equivalent doses[8]

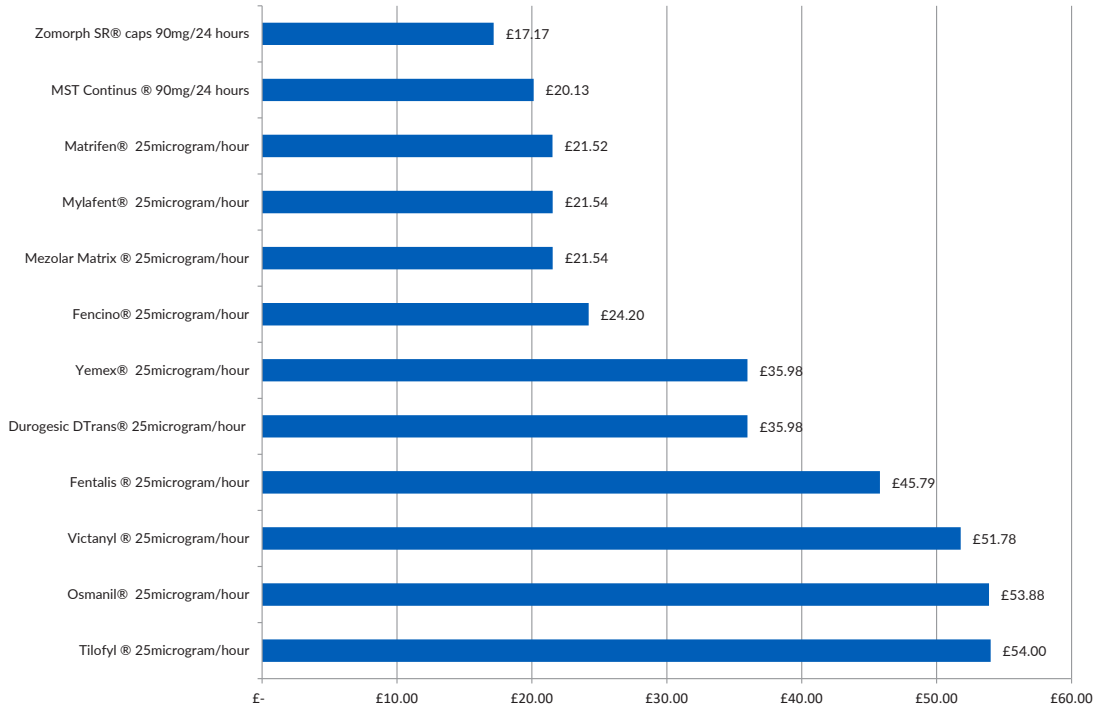


Chart 2 shows the 28 day cost of buprenorphine 20mcg/hr changed every seven days (4 patches total). Buprenorphine 20 microgram/hr is equivalent to the total daily dose of SR oral morphine 48mg as stated by FPM and the BNF.[8,9] A 40mg dose of oral morphine (MST and Zomorph 20mg twice daily) has been used as a cost comparison. Treatment with BuTrans® 20mcg/hr is significantly more expensive than MST. Patients that are suitable for oral morphine treatment should be using that route of administration.

Chart 2: Comparison of 28 day cost of 20mcg/hr buprenorphine patches[9] to 40mg daily SR oral morphine[8]

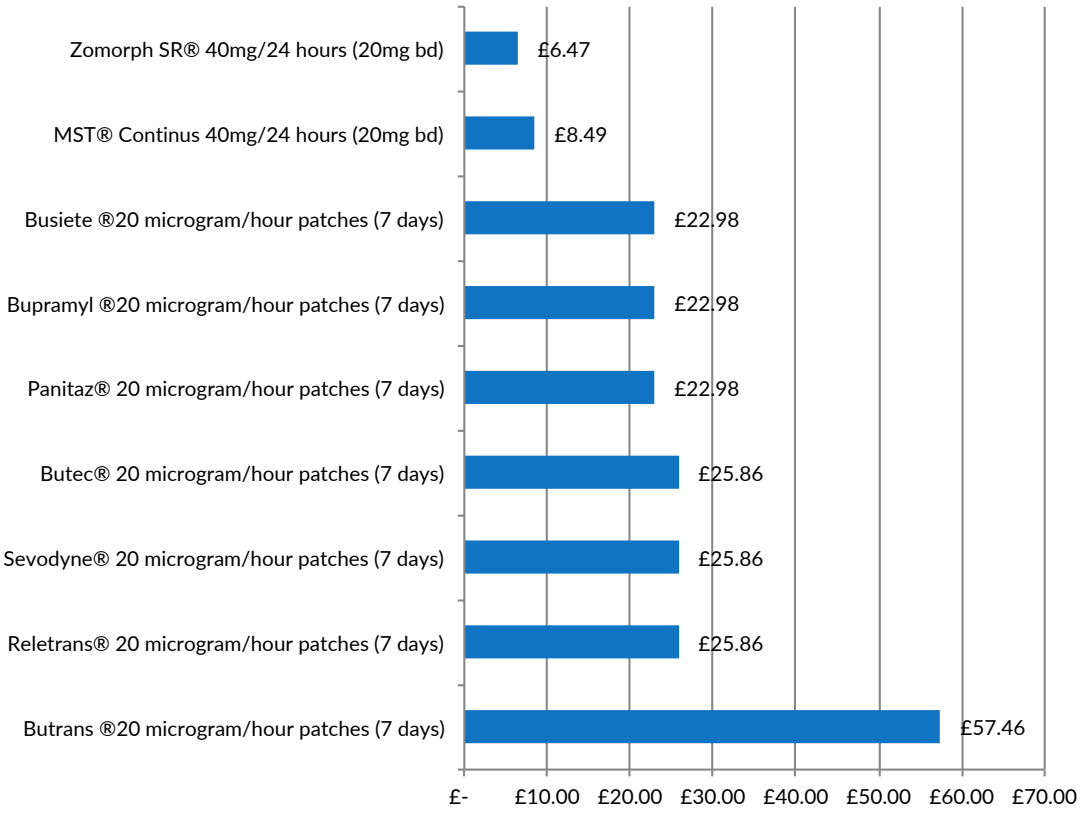
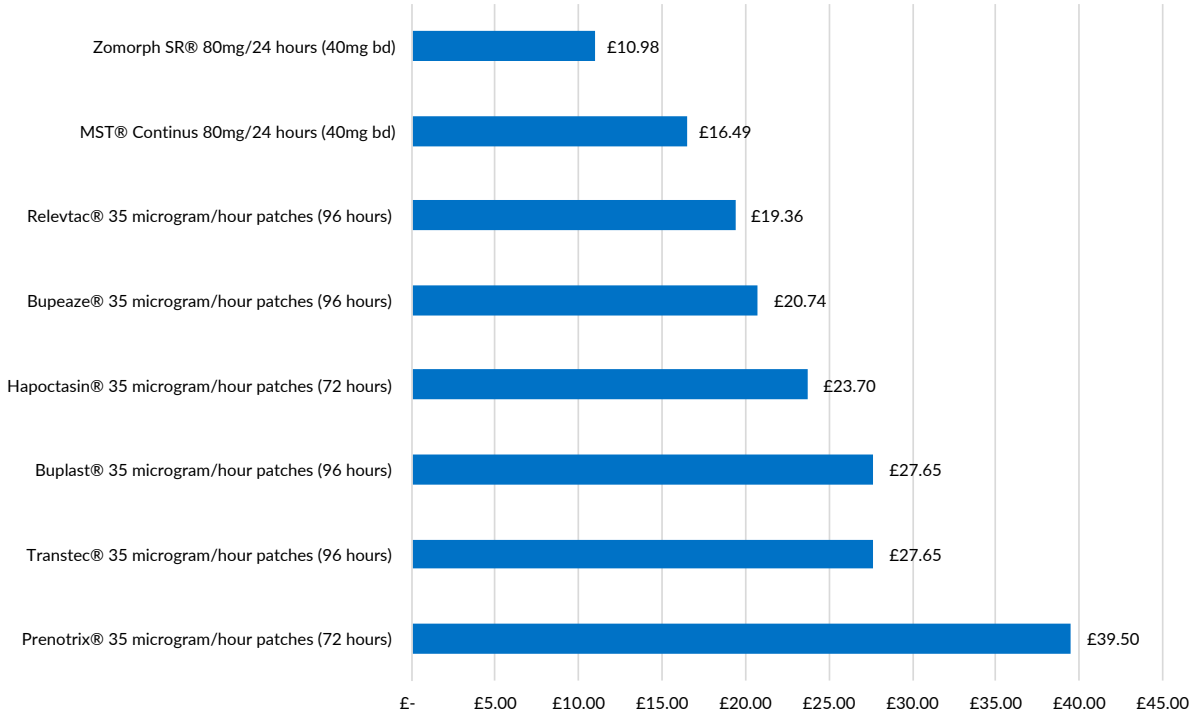


Chart 3 below shows the 28 day cost of buprenorphine patches 35mcg/hour, changed every 72 hours, (10 patches in total) and every 96 hours (7 patches in total). The Faculty of Pain Medicine equivalent total daily dose of SR oral morphine is 84mg daily so we have used an 80mg daily dose as a comparison (Zomorph® bd or MST® 40mg bd).[8]

Chart 3: Comparison of 28 day cost[9] of 35mcg/hr buprenorphine patches to 60mg daily SR oral morphine[8]



Note: Generic morphine sulphate SR capsules prices are the same as Zomorph® SR capsules.

Savings available

All opioid patches

The annual spend on all opioid patches across England and Wales is over £83 million (ePACT May to July 2018). This equates to around £133,929 per 100,000 patients. Reviewing the appropriateness of transdermal opioid patch therapy **could save approximately £41.7 million per year in England and Wales (assuming a 50% reduction in prescribing). This equates to £69,178 per 100,000 patients.**

- Specify criteria for patients to use opioid patches for pain:
  - Unable to tolerate tablets/capsules due to side-effects, or who have difficulty swallowing (although oral liquids and subcutaneous morphine may be suitable alternatives instead of a patch; the contents of Zomorph® can be administered directly in semi-solid food (puree, jam, yoghurt) or via gastric or gastrostomy tubes of a diameter of more than 16 F.G. with an open distal end or lateral pores. It is sufficient to rinse the tube with 30ml to 50ml of water.[2,34]
  - Have compliance issues such as mental health problems, or who are socially isolated with limited access to care.[2]

There would be some additional costs if patients still required analgesic treatment. However, this would vary depending on the treatment that the patient was switched to and would be offset by the savings made.

Fentanyl patches

Currently the annual spend on higher acquisition cost fentanyl patches is just over £15.7 million in England and Wales. A change in prescribing to lower acquisition cost fentanyl after appropriate patient review **could result in savings of up to £8.2 million annually which equates to £13,546 per 100,000 patients.**

If a fentanyl patch needs to be prescribed, they should be prescribed by brand name using the most cost-effective brands e.g. Matrifen®, Mylafent®, Mezolar Matrix® or Fencino®. Ensure stock availability locally before making formulary choices.

If, at review the patient is able to take morphine sulphate capsules/tablets, assuming there is a 50% reduction in prescribing of fentanyl patches, **this would result in savings of around £18.3 million per year, which equates to £30,483 per 100,000 patients.**

Buprenorphine patches

Currently the annual spend on all buprenorphine patches is over £46.6 million in England and Wales. This exceeds expenditure on fentanyl patches. This equates to a cost of over £74,907 per 100,000 patients. Patients should be reviewed for suitability to reduce and stop treatment, switch to morphine sulfate oral treatment or switch to a more cost effective brand of buprenorphine patches.

If, at review the patient is able to take morphine sulphate capsules/tablets, assuming there is a 50% reduction in prescribing of buprenorphine patches, **this would result in savings of around £23.3 million per year which equates to £37,453 per 100,000 patients.**

A change in prescribing to lower acquisition cost buprenorphine patches after appropriate patient review **could result in savings of up to £22.9 million annually, which equates to £36,817 per 100,000 patients.**

If a buprenorphine patch needs to be prescribed, they should be prescribed by brand name using the most cost-effective brands considering the dose range available, e.g. at current April 2018 prices:

- For 5mcg/hr or 20mcg/hr, consider Panitaz®, Bupramyl® or Busiete®
- For 35mcg/hr patches, consider Relevtec® or Bupeaze®

Ensure stock availability before making formulary choices.

For patients on long term buprenorphine 5 microgram/hour review and where appropriate switch to codeine 30mg four times a day.

Summary

- Improved safety and significant savings can be implemented by ensuring appropriate prescribing and use of opioid patches, in patients previously tolerating oral opioids.
- Oral morphine (sustained release) is the first line choice of strong opioid and has a lower acquisition cost than opioid patches. Opioid patches should be reserved for patients who are unable to tolerate the side-effects of oral morphine or have difficulty swallowing, have compliance issues, or renal impairment/failure.
- If patches are required in patients satisfying the above criteria, then initiating prescribing by brand of the lowest acquisition cost product will release considerable savings and ensure that patients remain on the same brand of patches whenever their treatment is dispensed.
- Switching opioid patches must be undertaken very carefully. Ideally only consider a switch after a break in treatment with opioid patches, or where the patient will be carefully monitored after the switch. If there are any safety risks such as patient or carer confusion then a switch should not be considered. If a patient has been prescribed patches generically, ensure their prescription is changed to a brand (ideally the lowest acquisition cost patch).

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Additional PrescQIPP resources

 Briefing  Implementation resources - Audit

Available here: https://www.prescqipp.info/our-resources/bulletins/bulletin-215-opioid-patches/

 Data pack

Available here: https://pdata.uk/#/views/B215_Opioidpatchesupdate/FrontPage?:iid=1

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