

Opioid patches – appropriate prescribing and use

The annual spend in England on all opioid patches is over £94 million (ePACT May 14). QIPP 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.

Recommendations

- Ensure correct prescribing, use and disposal of opioid patches due to the potential for serious adverse events, e.g. respiratory depression in opioid-naïve patients. Only prescribe opioid patches for patients who have previously tolerated opioids.¹ Opioid patches must not be used for acute pain.²
- Extreme care should be taken when starting and stopping therapy with fentanyl patches because of the long duration of action.
- 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.³
- Consider specifying criteria for patients to use opioid patches for pain, e.g. those:
 - » Unable to tolerate tablets due to side-effects, or have difficulty swallowing (although oral liquids and subcutaneous morphine may be suitable alternatives instead of a patch).⁴
 - » With compliance issues such as mental health problems, or who are socially isolated with limited access to care.⁴
- NICE CG 140 recommends initiating 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.³
- If patients are changed from one brand of fentanyl transdermal patch to another (although this is best avoided, to prevent any confusion and patient safety issues), they should receive counselling on the change from their healthcare professional (HCP). This is because interchangeability between different brands of fentanyl patches can not be guaranteed.⁵
- Prescribe opioid patches by brand name for continuity of supply and to avoid confusion for patients and carers. Fentanyl patches are available as matrix and reservoir formulations. Although neither should be cut, cutting reservoir patches can lead to leaking and overdose. The matrix patch is thinner and smaller than the reservoir patch. Patient familiarity with one brand is important.^{2,6}
- 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 person to take the lead role in prescribing.⁷

Background

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.⁴

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,¹ and usage and spend on these products is significant. 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.⁸

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.⁹ A 25microgram per hour (mcg/hr) fentanyl patch equates to daily doses of oral morphine of up to 90mg. 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. 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 (PCF4) and in local policies and guidance.¹ NICE Clinical Knowledge Summaries (CKS) recommend seeking specialist advice when considering strong opioids other than morphine.¹⁰

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

Prescribers should ensure that they are familiar with the correct use of transdermal preparations as inappropriate use has caused fatalities.⁸

National guidance

National Institute for Health and Care Excellence (NICE) CG 140 states the first-line choice of strong opioid is sustained release oral morphine, with immediate release oral morphine for breakthrough pain.³ Prescribers are recommended to gain familiarity with one brand of modified release (MR) oral morphine, to reduce risk of errors from prescribing different brands and formulations. The Department of Health have also recommended brand-name prescribing of modified release morphine.¹¹

The NICE CG 140 recommends opioid patches as a treatment option only if oral opioids are unsuitable.³ 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.

Table 1 below shows approximate equivalence between transdermal fentanyl or buprenorphine with oral morphine. This is from the British Pain Society's *Opioids for persistent pain: good practice consensus statement*.

Table 1: Transdermal opioids – approximate equivalence with oral morphine¹²

Oral morphine equivalent mg/24hrs	10	15	30	45	60	90	120	180	270	360
Transdermal buprenorphine mcg/24 hrs	5	10	20		35	52.5	70			
Transdermal fentanyl mcg/24hrs				12		25		50	75	100

NB. 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.¹²

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 data permit a weak recommendation that either drug may be the preferred step three opioid for some patients. For patients unable to swallow they are an effective, non-invasive means of opioid delivery.¹³

Safety and appropriate prescribing of opioid patches

Fentanyl patches are an effective treatment for malignant and non-malignant chronic intractable pain. However, they must be used correctly and with care.

The Medicines and Healthcare products Regulatory Agency (MHRA) have received spontaneous reports of life-threatening adverse reactions and death after fentanyl overdose.¹

Causes of unintentional overdose include:¹

- Dosing errors (by healthcare professionals, patients or caregivers)
- Accidental exposure (particularly in children)
- Exposure of the patch to a heat source, possibly resulting in increased fentanyl absorption (heat sources can include hot baths, hot water bottles, fever and sunbathing).
- Prescribing in unlicensed indications
- Prescribing in opioid-naïve patients.

Familiarity is important for safe prescribing of opioids. Fentanyl patches are not suitable for opioid-naïve patients and are best reserved for patients with stable opioid requirements.¹¹ 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:²

- Fluconazole, ketoconazole, itraconazole
- Erythromycin, clarithromycin
- Ritonavir, nelfinavir
- Aprepitant
- Cimetidine
- Diltiazem
- Verapamil.

In contrast fentanyl concentrations are reduced by potent CYP3A4 inducers and this may lead to loss of analgesia. Examples are:²

- Carbamazepine
- Phenytoin
- Phenobarbitone
- Rifampicin.

When fentanyl patches are prescribed it is important to ensure that patients and/or their carers understand how to use them correctly.¹¹ 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.⁴

Opioid toxicity has been reported with inappropriate prescribing of transdermal fentanyl. In addition owing to limitations in patch size, small increments in dose are not possible. The dose is effectively doubled when increasing from 25mcg/hr to 50mcg/hr patches, and clinical problems have been reported with this dose increment.⁷ 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).¹⁴

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.¹²

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). Alternatively it may be a formulary consideration driving this decision.¹⁵

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 patient's report of pain until adequate analgesia is obtained). This is because fentanyl concentrations fall gradually after the fentanyl patch is removed. It takes 17 hours or more for the fentanyl serum concentrations to decrease 50% and the range can be 13 - 22 hours. As a general rule, the discontinuation of opioid analgesia should be gradual, in order to prevent withdrawal symptoms (nausea, vomiting, diarrhoea, anxiety and muscular tremor).^{5,16-22} If the patient is on a high strength patch, then gradual downward titration (through the available strengths) is recommended to avoid withdrawal symptoms.²⁰

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.²³⁻²⁵

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 adhesive surfaces inwards, place back in 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.²⁶

An 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. The MHRA have received three Yellow Card reports so far 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 remind 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.²⁷

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. A systematic review of transdermal fentanyl and buprenorphine for moderate to severe cancer pain includes the results of one meta-analysis of four randomised, controlled trials (RCTs). This 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 this 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.²⁸

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 of 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.²⁸

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.⁴

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 7 days.¹¹

Buprenorphine

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.²⁹

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. 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.³⁰

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.³¹

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. Compared with fentanyl, buprenorphine (Transtec) adheres better. However, after patch removal it is associated with more persistent erythema (and/or localised pruritis) and sometimes a more definite dermatitis. This is generally caused by the adhesive, but occasionally by 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

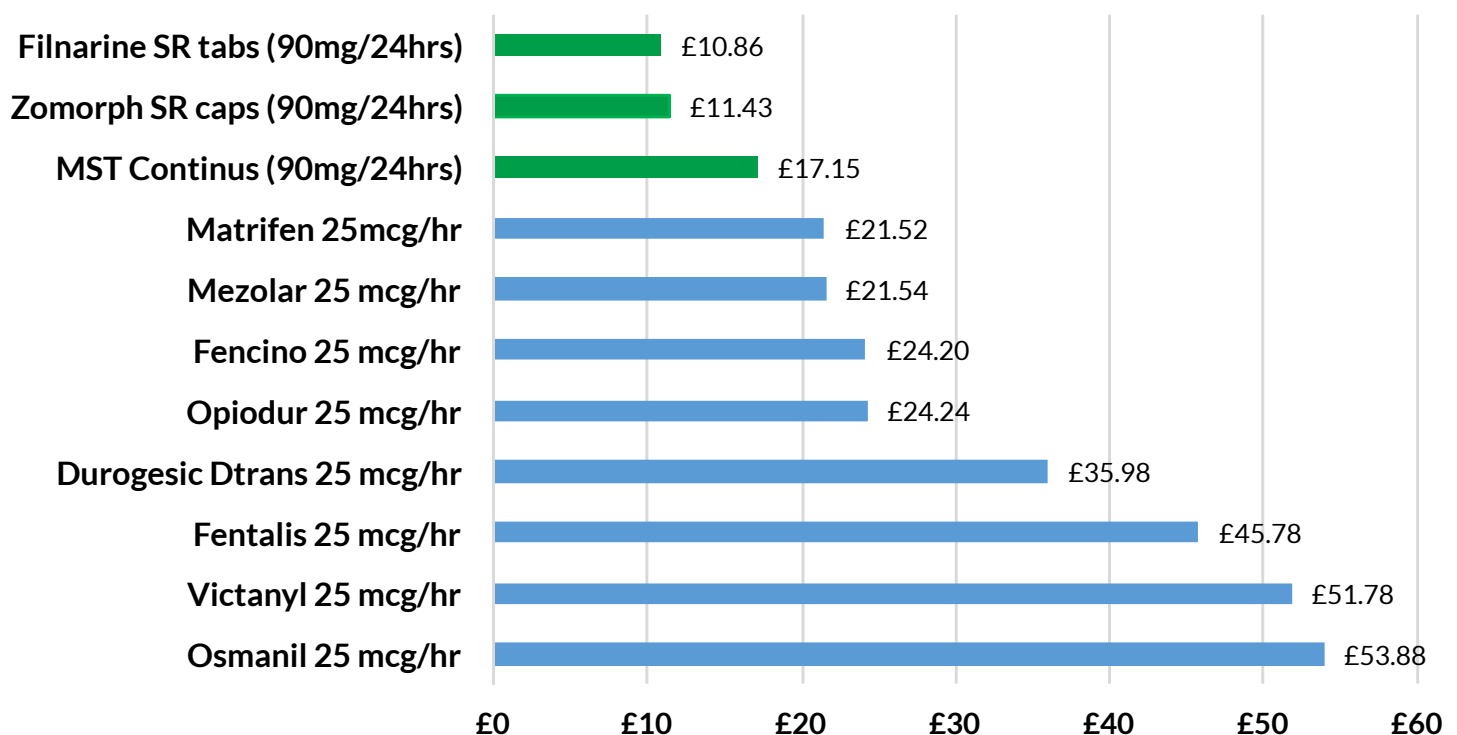
Costs

Chart 1 shows the 28 day cost of fentanyl 25mcg/hr patches, changed every 72 hours (3 days) equating to use of 10 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 British Pain Society has been used.¹² The cost of 90mg SR oral morphine is demonstrated using the cost of 30mg + 60mg Filnarine SR® tablets, 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 Fentails patches, which are not available as a 12mcg/hour patch. Treatment for 28 days with Osmanil® patches is almost five times more costly than the equivalent dose of oral morphine as Filnarine® SR tablets (the largest cost difference). Patients that are suitable for oral morphine treatment should be using that route of administration.

Chart 1: Comparison of 28 day cost of fentanyl patches (blue) to SR oral morphine (green)³² using British Pain Society equivalent doses¹²

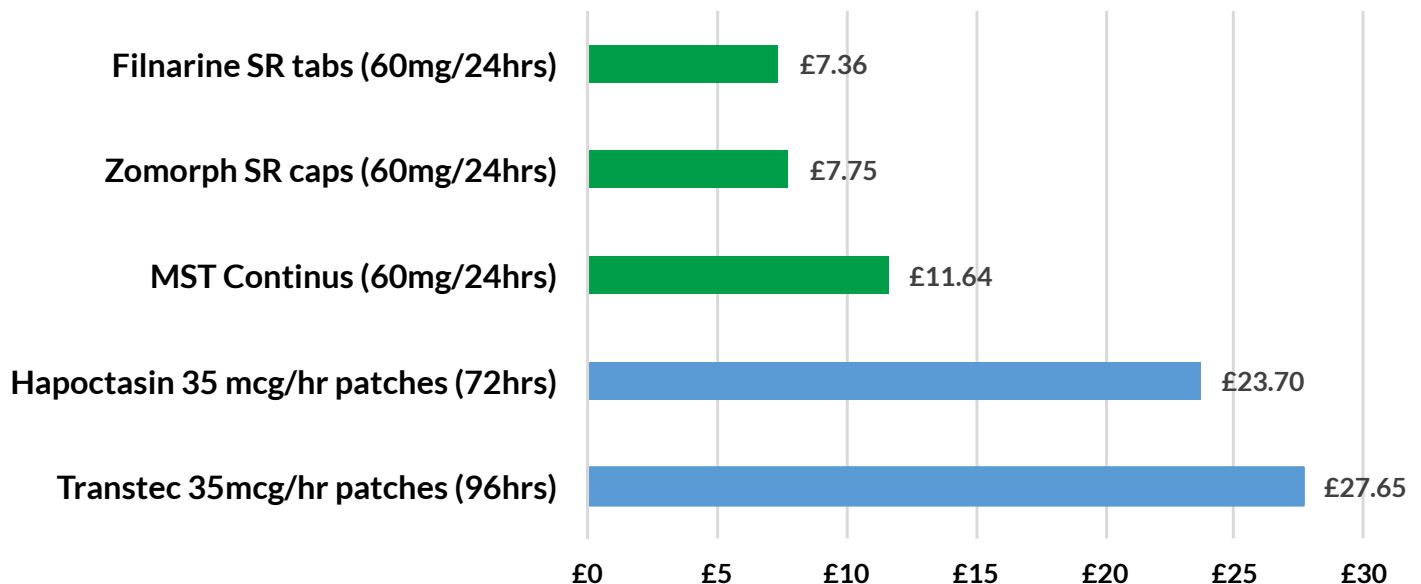


Note: Fentails is the only fentanyl reservoir patch, all the other products are matrix patches. Generic morphine sulphate SR capsules prices are the same as Zomorph SR capsules.

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 £7.36 for Filnarine® SR tablets, £7.75 for Zomorph® SR capsules and £11.64 for MST Continus® tablets.⁸

Chart 2 below shows the 28 day cost of buprenorphine patches 35mcg/hour, changed every 72 hours (3 days) for Hapoctasin® patches, (10 patches in total) and every 96 hours (4 days) for Transtec®, (7 patches in total). This is in comparison to the equivalent total daily dose of SR oral morphine of 60mg. Costs for Filnarine® SR tablets, Zomorph® MR capsules and MST Continus® tablets 30mg every 12 hours have been used. Treatment for 28 days with Transtec 35mcg/hour patches is 3.75 times more costly than oral morphine as Filnarine 30mg SR tablets every 12 hours (the largest cost difference). Patients that are suitable for oral morphine treatment should be using that route of administration.

Chart 2: Comparison of 28 day cost of buprenorphine patches (blue) to SR oral morphine(green)³²



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 is over £94 million in England (ePACT May 14). This equates to around £166,440 per 100,000 patients. Reviewing the appropriateness of transdermal opioid patch therapy **could save approximately £47 million per year in England (assuming a 50% reduction in prescribing). This equates to over £83,000 per 100,000 patients.**

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 £35 million in England. The annual spend on lower acquisition cost fentanyl patches is nearly £8 million in England. A change in prescribing to lower acquisition cost fentanyl after appropriate patient review **could result in savings of up to £13 million annually which equates to £22,954 per 100,000 patients.**

If at review the patient is able to take morphine sulphate tablets, assuming there is a 50% reduction in prescribing of fentanyl patches, **this would result in savings of around £21.5 million per year which equates to £38,048 per 100,000 patients.**

Buprenorphine patches

Currently the annual spend on all buprenorphine patches is over £51 million in England, so more than on fentanyl patches. This equates to a cost of over £90,000 per 100,000 patients. If at review the patient is able to take morphine sulphate tablets, assuming there is a 50% reduction in prescribing of buprenorphine patches, **this would result in savings of around £25.5 million per year which equates to £45,172 per 100,000 patients.**

Summary

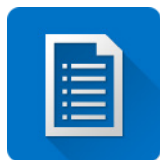
- Improved safety and significant savings can be implemented by ensuring appropriate prescribing and use of opioid patches, in patients previously tolerating oral opioids.
- Oral morphine (sustained release) is the first line choice of strong opioid and has a lower acquisition cost than opioid patches. 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 matching 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



Data pack



Audit

Available here: <http://www.prescqipp.info/resources/viewcategory/258-opioid-patches>

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