

Fentanyl patches (Durogesic) for chronic pain

FENT-a-nil

Summary

- Oral morphine is preferred when an opioid is required for severe chronic pain, because of its familiarity, availability and the ease of dose adjustment.
- Reserve fentanyl patches for use in opioid-tolerant patients with chronic pain and established opioid needs who cannot take oral morphine, for example in severe renal impairment. Fentanyl patches might also be useful when oral opioids cannot be used because of vomiting or difficulty swallowing.
- Do not use fentanyl patches in opioid-naïve patients with non-cancer pain because of the potential for serious adverse effects. Fentanyl patches have a delayed onset and prolonged duration of action; adverse opioid effects may be difficult to control.
- Monitor serious adverse effects carefully for 24 hours after removal of the patch, as serum concentrations decline slowly.
- Advise patients to replace patches every 72 hours and no earlier.
- Ensure that patients and carers know about the safe use and disposal of fentanyl patches.

PBS listing

Restricted benefit

Chronic severe disabling pain not responding to non-narcotic analgesics.

Restrictions apply for prescribing increased maximum quantities or repeats for opioid analgesics; review by a second medical practitioner is required if opioid therapy extends beyond 1 year.¹

Reason for PBS listing

Fentanyl patches can already be prescribed on the Pharmaceutical Benefits Scheme for chronic severe cancer pain. The listing has changed from August 2006 to include chronic non-cancer pain. Listing was approved on a cost-minimisation basis, that is, transdermal fentanyl was no less effective than oral sustained-release morphine, and for similar cost.

The Pharmaceutical Benefits Advisory Committee recommended that transdermal fentanyl should not be initiated in opioid-naïve patients with non-cancer pain, because of a high risk of adverse events.

Place in therapy

Fentanyl is a strong opioid. The transdermal patch is a long-acting formulation with a delayed onset of effect initially and a prolonged duration of action; plasma concentrations are halved about 17 hours after removal.² It is unsuitable for acute pain. Each patch lasts 72 hours. Fentanyl accumulates to form a 'depot' in the skin below the patch, from where it gradually enters the circulation. A matrix 'drug-in-adhesive'^{*} formulation has replaced the previous gel-reservoir patches, which had problems with leaking[†] and potential for extraction for illicit use.⁴

Oral morphine is generally the first choice when an opioid is required for severe chronic pain, because of its familiarity, availability and range of strengths and formulations that allow greater flexibility in dose titration. Use immediate-release preparations to find the dose that provides effective analgesia

^{*} Matrix patches were introduced in Australia in 2006 and are expected to replace supplies of reservoir patches by August 2006, when the reservoir patches will be discontinued and withdrawn from the market.

[†] Two batches of 50 microgram-per-hour patches were recalled in Australia in October 2005 because of reports of leaking.³

with the most acceptable side effects, then switch to a sustained-release preparation to ensure stable, 'round-the-clock' analgesia.⁵

Reserve fentanyl patches for patients with chronic pain and established opioid needs who are unable to take oral morphine. Fentanyl patches can be useful when morphine cannot be used in severe renal impairment or when the oral route cannot be used because of vomiting or difficulty swallowing.^{6,7} Individual response to opioids varies and some patients might experience uncontrollable adverse effects or poor analgesic response to morphine; in such cases fentanyl is one of several alternative opioids that might be considered.^{6,7} (See *Evidence for fentanyl compared with other opioids* and *Adverse effects*).

Risks in opioid-naïve patients

Opioid-naïve patients are vulnerable to potentially fatal opioid effects such as respiratory depression.

Do not use fentanyl patches in opioid-naïve patients with non-cancer pain.^{2,8} The prolonged duration of action of the fentanyl patch means that adverse opioid effects will be difficult to control; its use in opioid-naïve patients is rarely justified. Oral morphine is preferred because of the relative ease of dose adjustments. Although the approved indication and the PBS listing allow use of the fentanyl patch in opioid-naïve patients with cancer pain, it is still best practice to use oral morphine initially to assess how well patients tolerate the opioid and to find the dose that provides stable analgesia. For some opioid-naïve cancer patients the potential harms with the fentanyl patch may be considered acceptable when balanced with expected benefits — if so, start with the lowest-dose patch (12 micrograms per hour) and monitor closely. Wean other analgesics gradually (see *Dosing issues*).

For opioid-tolerant patients, see *Dosing issues* below for equi-analgesic doses of other opioids.

Always use a step-wise approach to analgesia and pain management

Fentanyl should be prescribed within a step-wise approach to analgesia (as for all opioids⁵):

- use non-drug measures as appropriate, such as exercise, physiotherapy and psychological strategies for pain management
- always start with non-opioids: consider starting opioids when regular dosing of non-opioids (paracetamol, NSAIDs) or weak opioids (codeine, tramadol) is ineffective
- titrate to maximum doses before moving to the next drug
- encourage regular (rather than as-needed) use of analgesics.

Diagnose the type of pain as nociceptive (tissue damage) or neuropathic (nerve damage), as this affects treatment choice⁹ (see *Therapeutic Guidelines: Analgesic*⁶).

Discuss and agree on the specific goals of therapy with the patient and document these before embarking on opioid therapy; in non-cancer pain these would include pain relief, functional improvement and quality of life. If goals are not achieved after a reasonable trial, consider stopping the medication.^{10,11}

(See NSW Therapeutic Advisory Group guidelines for further details⁵).

Ideally, refer patients with chronic non-cancer pain to a multidisciplinary pain management clinic, especially when^{6,7}:

- the diagnosis is uncertain
- there is significant disability, mood change or medication difficulties
- there are multiple issues beyond pain alone
- the patient has a history of substance abuse.

Although waiting lists are often prohibitively long, the change in PBS restrictions means that patients can more easily start opioid treatment while awaiting a pain clinic appointment.

Assess ongoing need for opioids through regular review. PBS authority requirements mean that recent review by a second medical practitioner is needed before opioids can be prescribed for more than 12 months. Although this review does not have to be conducted by a pain specialist, early referral to a pain clinic can ensure appropriate review and also fulfill the PBS requirement.

Evidence for fentanyl compared with other opioids

There is little good-quality published trial evidence comparing fentanyl with other analgesics in chronic non-cancer pain, and no blinded trials. Most guidelines are based on clinical experience and consensus.^{7,11,12}

The available evidence suggests no efficacy advantage over standard opioids. A large, randomised open-label trial (n = 680) in patients with chronic lower back pain found similar effects on pain measured with a visual analogue scale (VAS) when transdermal fentanyl was compared with oral sustained-release morphine.¹³ A smaller open-label trial in which patient preference was the primary outcome found small differences in mean VAS ratings, but these were unlikely to be of clinical significance.¹⁴ Some studies have shown that patients prefer fentanyl patches for pain relief over oral morphine, but the lack of blinding means factors other than efficacy cannot be ruled out (e.g. novelty of the delivery mechanism).^{14,15}

Consider the patient's drug and alcohol history

Patients with a history of substance abuse should not be denied effective analgesia for genuine pain. Management is more complex in these patients because:

- previous users of opioids can have high opioid tolerance and may need higher doses for effective analgesia⁶
- concurrent use of alcohol and other central nervous system depressants can have additive effects and place the patient at risk⁸
- there may be a greater risk of dependence in such patients.

Involve pain management or drug and alcohol specialists when possible.

Renal impairment

Fentanyl can be used in severe renal impairment when other opioids are inappropriate. It is metabolised in the liver and does not have active metabolites.²

Safety issues

Safety issues to consider include the following (see the Durogesic product information for a complete list of interactions and precautions).

- Deaths have occurred with use of fentanyl patches in opioid-naïve patients.⁸ Do not use in opioid-naïve patients with non-cancer pain and consider the ratio of benefits to harm before prescribing for cancer pain.
- Elderly patients, in whom there is reduced clearance and a prolonged half-life, may be more sensitive to the effects of fentanyl.
- Do not cut or divide patches.
- Be aware that increased body heat (e.g. fever, humid climate) and direct heat (e.g. from electric blankets, saunas) may increase the rate of absorption.

See the NSW Therapeutic Advisory Group Analgesic Skin Patches alert at www.nswtag.org.au.

Adverse effects

Respiratory depression (hypoventilation) is the most serious potential opioid effect, and accidental overdose may be fatal.¹⁶ Respiratory depression can occur throughout the therapeutic range.⁸

Common opioid adverse effects include nausea, vomiting, constipation, drowsiness and hypotension. Fentanyl may cause less constipation, nausea and vomiting than other opioids, but laxatives are often still required.^{2,17} In one large trial, constipation occurred less frequently with fentanyl than with morphine but was still the most frequent adverse effect reported with each drug (52% and 65% of adverse events reported, respectively¹⁵). Prescribe prophylactic laxatives for all patients taking regular opioid analgesics, including transdermal fentanyl.^{2,6}

The patch adhesive may cause erythema or skin irritation.

Monitor serious adverse effects carefully for 24 hours after removal of the patch, as serum concentrations decline slowly.

Potential for accidental and deliberate misuse

Used patches contain high quantities of residual fentanyl (about 60% of the intended dose¹⁸). The matrix patches contain higher quantities of fentanyl to achieve the same delivery rate (60–70% more than the reservoir patches).^{8,19}

Advise consumers to store and dispose of the patches safely (see *Information for patients*). In institutions, appropriate disposal processes should apply.

Like all opioids, fentanyl carries a risk of dependence and misuse. Addicts may seek out new or used patches. Deaths have occurred with reservoir patches through overdose, application to sites other than skin, and ingestion through various methods. The new matrix patch formulation patches may eliminate some means of misuse that existed with reservoir patches but the potential for 'creative' misuse remains.

The risk of addiction developing is considered low in most patients using opioids for pain relief, but may be higher in patients with a history of substance abuse.² Nonetheless, such patients should not be denied effective analgesia for genuine pain (see *Consider the patient's drug and alcohol history*).

Report adverse events to increase knowledge of fentanyl patches

Report suspected adverse reactions to the Adverse Drug Reactions Advisory Committee (ADRAC) online (see www.tgasime.health.gov.au) or by using the 'Blue Card' distributed with *Australian Prescriber*. For information about reporting adverse drug reactions, see the Therapeutic Goods Administration website (www.tga.gov.au).

Dosing issues

On first application it usually takes 24–72 hours for serum concentrations of fentanyl to reach a peak, so it may not be until the second patch has been applied that a steady-state concentration is reached. Break-through analgesia may be required initially. Wean other analgesics slowly after the first patch.² The patch should be changed every 72 hours.

Fentanyl matrix patches are available in several dosages expressed as the number of micrograms delivered per hour — 12, 25, 50, 75 and 100 micrograms per hour. The older reservoir patches were labelled according to the amount of fentanyl contained in the patch (2.5 mg, 5 mg, 7.5 mg, 10 mg); however, because the matrix patches contain more fentanyl to achieve the same hourly dose, delivery rate rather than total content is now used, to avoid confusion.

If required, titrate the dosage using 12 or 25 microgram-per-hour patches at 72-hour intervals (not less).⁸ Estimate needs from doses of breakthrough analgesia required over several days, but exclude the first patch from this assessment.^{6,8}

Opioid-naïve patients

Ideally all patients should have had recent strong-opioid exposure before starting fentanyl patches. Do not prescribe to opioid-naïve patients with non-cancer pain. If prescribing to opioid-naïve patients with cancer pain, always initiate therapy with the lowest strength patch (12 micrograms per hour). (See above *Risks in opioid-naïve patients*).

Opioid-tolerant patients

Dosing should be individualised. People vary in their rate of absorption of fentanyl from the patches⁶, in their ability to tolerate the drug⁸ and in analgesic response.

Dose equivalence in opioid-tolerant patients

When changing patients from another opioid to fentanyl, remember that drug equivalence information is often based on single-dose studies, and **there is substantial individual variation in response**.^{2,7} The dose-conversion ranges provided by the manufacturer are only a guide (Tables 1 and 2).⁸ Consider using a lower-dose patch initially then titrating upwards.²

If the patient has been using an analgesic other than morphine, estimate the morphine-equivalent dose of their previous analgesic using the equi-analgesic doses in Table 1, then use this to estimate their previous 24-hour equivalent oral morphine requirement.

1. Assess current 24-hour opioid requirement.

Example: the patient has been taking oxycodone 30 mg tablets, 4 times daily, that is, 120 mg daily.

2. Convert this to a 24-hour oral morphine equivalent dose.

Example: the patient has been taking oxycodone 120 mg/day orally. In Table 1, oral oxycodone 30 mg is equivalent to oral morphine 30 mg (assuming repeated dosing). So oxycodone 120 mg/day orally is equivalent to oral morphine 120 mg daily. This is the 24-hour morphine-equivalent dose. Use this value in Table 2.

Table 1: Equipotency of opioid analgesics to oral morphine 30 mg*

Drug (oral only)	Equianalgesic dose (mg) to oral morphine 30 mg
Morphine	30 (assuming repeated dosing)
Oxycodone	30
Codeine	200
Buprenorphine	0.8 (sublingual)

* This chart shows the dose of oral opioids considered equivalent to 30 mg oral morphine (as a regular dose).

3. Based on estimated 24-hour equivalent oral morphine dose, look up the recommended fentanyl patch dose in Table 2 below.

Example: with an estimated 24-hour-equivalent oral morphine daily dose of 120 mg, the equivalent fentanyl patch is 25 micrograms per hour.

Table 2: Recommended Durogesic dose based on daily oral morphine dose

Oral 24-hour morphine (mg/day)	Fentanyl patch (Durogesic) dose (micrograms/hour)
< 135	12–25*
135–224	50
225–314	75
315–404	100

* The manufacturer advises that the 12 microgram-per-hour patch is considered approximately equivalent to oral morphine 45 mg daily.¹⁸

Stopping fentanyl patches

Drug effects continue after removing the patch as fentanyl concentrations fall slowly, decreasing to 50% after 17 hours.⁸ The decline in serum concentrations is slower than with subcutaneous fentanyl because release continues from the depot accumulated in the skin.² Withdrawal symptoms may occur; if possible taper slowly to minimise these.

Information for patients

Ensure that patients know how to use and dispose of fentanyl patches. Patches should be folded with the sticky sides together, wrapped and disposed of either by returning to the pharmacist, or placing in the garbage well out of reach.

Suggest or provide the Durogesic consumer medicine information (CMI) leaflet. Illustrated leaflets explaining how to use the patches are available to doctors, pharmacists and patients from Janssen-Cilag.

Advise patients to be aware of the following when they use fentanyl patches^{2,8,16}:

- Avoid drinking alcohol or using other central nervous system depressants while using a fentanyl patch.
- Apply to a non-hairy part of the upper torso or arms. Hair may be cut before application but not shaved, as this may remove some skin and increase absorption.
- Remove each patch after 72 hours. Date the patch using a marker pen — either the date of application or the date of removal may be used, but be consistent about which is written. Remove the old patch before applying a new one. Apply the new patch to a different site and do not re-use the old site for several days.
- Do not cut or divide the patch or use when damaged.
- Heat may increase the release of drug from the patch and hot skin may absorb the drug faster, both increasing the risk of adverse effects.
 - Patients should not expose the body to external increases in body temperature, especially on the application site — for example electric blankets, saunas, heat lamps, wheat packs, hot water bottles, sunbathing or very hot baths.
 - Patients should seek advice from their doctor if they develop a fever.
- Store unused patches and dispose of used patches out of the reach of children. Do not allow children to come into contact with the adhesive, and prevent situations in which the patch may accidentally stick to them (e.g. while sleeping).

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The information contained in this material is derived from a critical analysis of a wide range of authoritative evidence. Any treatment decisions based on this information should be made in the context of the clinical circumstances of each patient.

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