

GUIDELINES FOR THE USE OF TRANSDERMAL OPIOIDS IN PALLIATIVE CARE



1. GENERAL PRINCIPLES

- ➤ Transdermal opioids currently used within palliative care include fentanyl and buprenorphine. ¹⁻⁹
- ➤ Indications for transdermal opioids include: 1-9
 - Stable pain
 - Intolerable, undesirable adverse effects with oral strong opioids e.g. nausea and vomiting, constipation, hallucinations
 - Renal failure (fentanyl and buprenorphine are not renally excreted)
 - Poor compliance with oral medication
 - Patient is unable to take oral medications
 - High risk of tablet misuse / diversion
- ➤ Transdermal opioids should **not** be used for acute pain (transient, intermittent or short term pain) or when there is a need for rapid dose titration for severe uncontrolled pain.^{1,3}
- A variety of fentanyl patch strengths exist from 12 microgram / hr up to 100 microgram / hr with the exception of Fentalis[®] for which there is no 12 microgram dose. ¹⁰
- ➤ There are two different formulations of transdermal fentanyl. Both formulations are usually applied for 72 hours. The maximum recommended dose is 300microgram / hr. ^{5,7,11} [Level 4]
 - *Matrix* patches (e.g. Durogesic D Trans[®] Matrifen[®], Mezolar [®], Victanyl[®] Osmanil[®]) where the fentanyl is evenly distributed throughout an adhesive matrix
 - **Reservoir** patches (e.g. **Fentalis**[®], **Tilofyl**^{®)} where fentanyl is contained within a reservoir and the release is controlled by a rate limiting membrane
- Transdermal buprenorphine is available in two formulations.
 7 day patches (Butrans[®]) 5, 10 and 20 microgram / hr
 4 day patches (Transtec[®]) 35, 52.5 and 70 microgram / hr
- ➤ The maximum licensed dose is 140microgram / hr i.e. two 70 microgram / hr patches worn at the same time.^{8,9,10} [Level 4]
- ➤ In febrile patients the rate of absorption of transdermal opioids increases and can cause toxicity. Absorption may also be enhanced by an external heat source e.g. hot water bottle. Patients should be warned about this and advised to have showers rather than hot baths. ^{5,12} [Level 4]
- ➤ The pharmacology of transdermal opioids explains the indications and restrictions on their use and is summarized in Table 1.1.

Table 1.1 Pharmacology of Transdermal (TD) Opioids 5,10 13,25,26						
	TD Fentanyl	TD Buprenorphine (Transtec [®])	TD Buprenorphine (Butrans [®])			
Opioid Receptor Binding Affinity	Strong µ agonist	Partial μ agonist κ and δ antagonist	Partial μ agonist κ and δ antagonist			
Onset of Action	3-23 hours	21 hours for 35 micrograms/hr patch, 11 hours for 70 micrograms/hr patch	18 -24 hours			
Time to Peak Plasma Concentration	24-72 hours	60 hours	3 days			
Plasma Half Life	13-22 hours ^a	25-36 hours ^a	13-35 hours ^a			
Duration of Action	72 hours for some patients, 48 hours for other patients	4 days	7 days			
Metabolism	Hepatic metabolism via CYP3A4 to inactive compounds mainly excreted in the urine	First pass metabolism in the liver and gastrointestinal mucosa to norbuprenorphine	First pass metabolism in the liver and gastrointestinal mucosa to norbuprenorphine			
Use in Renal Failure	Generally safe in renal failure. Not dialysable	Generally safe in renal failure. Not dialysable b	Generally safe in renal failure. Not dialysable b			

^a The half-life after a patch has been removed and not replaced

2. GUIDELINES FOR THE USE OF TRANSDERMAL FENTANYL

2.1 Initiating Transdermal Fentanyl

- ➤ Transdermal fentanyl should not be used in opioid naïve patients, in those with acute pain, or in those who need rapid dose titration for severe uncontrolled pain. [Level 3]
- ➤ Reservoir patches **should not be cut.** Cutting the patch destroys the controlled release mechanism and allows fentanyl to leak from the patch, with the potential for rapid and excessive absorption. It is also recommended that matrix patches are not cut.^{5,10} [Level 4]
- ➤ There is no strong evidence of a difference in the rate of delivery between different brands of fentanyl patches when used in accordance with the product license. However to avoid confusion it is generally better if only one formulation is prescribed for each patient.¹⁴ [Level 4]
- ➤ Steady state plasma concentrations of fentanyl are generally reached in 36-48 hours. During this period the patient may require more frequent breakthrough doses of immediate release strong opioid, particularly during the first 24 hours. ¹⁰ [Level 4]

^b Caution should be used with all opioids in renal impairment and consideration given to reducing the dose and titrating according to response.

- ➤ Patients may experience opioid withdrawal symptoms e.g. nausea, vomiting, diarrhoea, anxiety and shivering when they are changed from an oral strong opioid to transdermal fentanyl. This is because the majority of opioid is entering the CNS, creating a withdrawal situation in the periphery. Patients can be administered an immediate release oral strong opioid to counteract these symptoms if needed. [Level 3]
- ➤ Transdermal fentanyl is less constipating than morphine, oxycodone or hydromorphone. Consider halving the dose of laxative when converting from another opioid and titrate according to need. (Level 2++)
- Transdermal fentanyl probably causes less nausea and vomiting than morphine or oxycodone. If required prescribe haloperidol 1.5 mg orally as required for the initial 2-3 days after commencing fentanyl. [Level 4]
- Fentanyl patches are normally changed every 72 hours. If the analgesia is not effective for the full 72 hours the correct action is to increase the strength of the patch. However some patients need a shorter application interval to manage increasing pain at the end of the 72 hour period. In this situation the patch can be changed more frequently e.g. every 48 hours. [Level 2+]
- ➤ The analgesic effect of transdermal fentanyl should not be evaluated for at least 48 hours following commencement to allow the gradual increase in plasma fentanyl concentrations. The dose can be adjusted at 72 hour intervals if necessary. It is important to ensure that where a dose increase is intended the calculated dose is safe for the patient.¹⁷ In general the strength increase will be 12microgram / hr. ¹⁰ [Level 4]
- ➤ If the fentanyl dose required exceeds 300 microgram / hr, manufacturers suggest additional or alternative analgesia should be considered.^{7, 11} [Level 4]
- ➤ On removal, fentanyl patches should be folded in half with the adhesive side inwards. Disposal location will vary according to the care setting. In hospitals / hospices this may be a non-hazardous pharmaceutical waste bin or a sharps bin. Health professionals should check their local guidance. In the home setting discarded patches should be placed in the dustbin.^{7,11} [Level 4]
- ➤ Patients should be provided with written information about transdermal fentanyl and the known adverse effects. Patients and carers should be aware of the signs and symptoms of fentanyl overdose (i.e. sedation, confusion, feeling faint.) Patients and caregivers should be advised to seek medical attention immediately if overdose is suspected. ¹² [Level 4]

2.2 Converting to a Fentanyl patch from a different strong opioid ¹⁰ [Level 4]

- > Systemic analgesic concentrations are generally reached within 12 hours. Therefore to convert to a fentanyl patch **from**:
 - 4 hourly oral strong opioid. Give 4 hourly doses of oral strong opioid for the first 12 hours after applying the fentanyl patch.
 - 12 hourly modified release oral strong opioid. Apply the fentanyl patch and give the final dose of modified release opioid at the same time.

- 24 hourly modified release oral strong opioid. Apply the fentanyl patch 12 hours after the final dose of modified release opioid.
- Strong opioid via a continuous subcutaneous infusion. Apply the fentanyl patch, continue the subcutaneous infusion for 12 hours and then discontinue the infusion.

2.3 Discontinuing a Fentanyl patch and converting to an alternative strong opioid ¹⁸ [Level 4]

- A reservoir of fentanyl accumulates in the body and significant blood levels persist for at least 24 hours after discontinuing fentanyl. Therefore to convert from a fentanyl patch **to**:
 - 12 hourly modified release oral strong opioid. Remove the fentanyl patch and after a period of at least 12 hours commence modified release preparation of oral strong opioid. (e.g. Zomorph[®], MST[®], Oxycontin[®] or Palladone[®])
 - 24 hourly modified release oral strong opioid. Remove the fentanyl patch and after a period of at least 12 hours commence oral modified release preparation of strong opioid. (e.g. MXL [®])
 - Strong opioid via a continuous subcutaneous infusion. Remove the fentanyl patch and after a period of at least 12 hours commence the continuous subcutaneous infusion containing an alternative strong opioid.

2.4 Transdermal Fentanyl in the last hours or days of life

- Patients in the last hours or days of life should continue to have their fentanyl patch changed every 3 days unless there is evidence of opioid toxicity. The fentanyl patch should not be discontinued.⁶ [Level 2+]
- ➤ All patients should be prescribed an as required subcutaneous strong opioid e.g. morphine. ¹⁹ [Level 2+] (See Table 2.2.for details of appropriate doses)
- ▶ If a patient requires two or more doses of an opioid for breakthrough pain over a 24 hour period and those doses are effective, consider commencing a continuous subcutaneous infusion with a dose equal to the sum of the breakthrough doses over the preceding 24 hours. The subsequent breakthrough dose may need adjusting to take into account the total opioid dose. (e.g. transdermal fentanyl dose + strong opioid dose contained in subcutaneous infusion) ²⁰ [Level 2+]
- ➤ The continuous subcutaneous infusion should be used **in addition** to the fentanyl patch, which should continue to be changed every 3 days. ¹⁹ [Level 2+]

2.5 Prescribing breakthrough medication for patients using transdermal Fentanyl

➤ Morphine remains the recommended strong opioid for breakthrough pain when using transdermal opioids, unless there are contraindications e.g. previous intolerance of morphine or renal failure. ¹⁸ [Level 4]

- ➤ Appropriate breakthrough medication should be prescribed using equi-analgesic tables. 1,10,20 [Level 4] (See Table 2.2)
- ➤ In some cases adequate analgesia may be achieved or better tolerated with breakthrough doses lower than those recommended in the equi-analgesic tables. This should be assessed on an individual basis. ¹⁸ [Level 4]
- ➤ There is no relationship between the dose of a transdermal fentanyl patch and the transmucosal, buccal or nasal spray fentanyl preparations used for breakthrough pain. If trans mucosal or nasal spray preparations are being used they need to be titrated independently of the transdermal dose. ^{21,22} [Level 4]

Table 2.2 Equi-analgesic Table for Transdermal Fentanyl. 20 [Level 4]

This table is a guide only. The prescriber is ultimately responsible for his/her own actions. Equi-analgesic doses are difficult to ascertain due to wide inter-patient variations, drug interactions and non-interchangeability of products. Initial dose conversions should be conservative. It is preferable to under-dose the patient and use breakthrough medication for any shortfalls.

Transdermal Fentanyl dose (micrograms/hr)	Morphine SR PO bd	Morphine PO PRN dose	Oxycodone SR PO bd	Oxycodone PO PRN dose
12	15mg	5mg	10mg	2.5mg
25	30mg	10mg	20mg	5mg
37	45mg	15mg	30mg	7.5mg
50	60mg	20mg	40mg	10-15mg
62	75mg	25mg	50mg	15-20mg
75	90mg	30mg	60mg	20mg
100	120mg	40mg	80mg	25-30mg

- Doses here are approximated to the most practical, based on current formulations
- This table has been generated using values based on expert consensus which may differ from the manufacturers' recommendations:-Oral morphine 3mg = oral oxycodone 2 mg (oxycodone is more potent than morphine when given by mouth; NB manufacturer states 2:1 ratio)

3. GUIDELINES FOR THE USE OF TRANSDERMAL BUPRENORPHINE

- ➤ When prescribing buprenorphine, opioid naïve patients should be started on the lowest dose buprenorphine patch e.g. 5 or 10 microgram / hr patches. Patients with unrelieved pain (despite maximum step 2 analgesics) should be started on 20 or 35 microgram / hr patches. 8,9,10 [Level 4]
- ➤ The time to reach steady-state plasma concentrations of buprenorphine is approximately 1-2 days for patch strengths less than or equal to 20 microgram / hr but will be longer for higher strengths. During this period the patient may require more frequent doses of immediate release morphine or other strong opioid, particularly during the first 24 hours.^{2,10 [Level 4]}

- ➤ Patients may experience opioid withdrawal symptoms e.g. nausea, vomiting, diarrhoea, anxiety and shivering when changed from another opioid to the transdermal route. This is because the majority of opioid is entering the CNS, creating a withdrawal situation in the periphery. Patients can be administered immediate release morphine or other strong opioid to counteract these symptoms if required. ¹⁰ [Level 4]
- ➤ Buprenorphine is less constipating than morphine. Consider halving the dose of laxative when converting from morphine and titrate according to need. ²³ [Level 1+]
- ➤ Transdermal buprenorphine may cause nausea and vomiting. Consider prescribing haloperidol 1.5 mg orally as required. ¹⁰ [Level 4]
- ➤ In febrile patients the rate of absorption of transdermal opioids increases and can cause toxicity. Absorption may also be enhanced by an external heat source e.g. hot water bottle. Patients should be warned about this and advised to have showers rather than hot baths.^{8,9} [Level 4]
- ➤ On removal, buprenorphine patches should be folded in half with the adhesive side inwards. Disposal location will vary according to setting. In hospitals/hospices this may be a non-hazardous pharmaceutical waste bin or a sharps bin. Health professionals should check their local guidance. In the home setting discarded patches should be placed in the dustbin. ^{8,9} [Level 4]

3.1 Converting to a buprenorphine patch from another strong opioid¹⁰ [Level 4] Note: This applies to both 4 and 7 day patches

- Systemic analgesic concentrations are usually reached within 12-24 hours but levels can continue to rise for 32-54 hours. Therefore to convert to a buprenorphine patch from:
 - 4 hourly PO strong opioid. Give 4 hourly doses for the first 12 hours after applying the buprenorphine patch
 - 12 hourly modified release oral strong opioid. Apply buprenorphine patch and give the final dose of modified release strong opioid at the same time
 - 24 hourly modified release oral strong opioid. Apply buprenorphine patch 12 hours after the final dose of modified release oral strong opioid
 - Strong opioid via a continuous subcutaneous infusion. Apply buprenorphine patch and continue the subcutaneous infusion for 12 hours then discontinue the infusion

3.2 Discontinuing a buprenorphine patch and converting to an alternative strong opioid ^{2, 18} [Level 4]

A reservoir of buprenorphine accumulates in the body and significant blood levels persist for at least 24 hours after discontinuing fentanyl. Therefore to **convert from a buprenorphine patch to**:

- 12 hourly modified release oral strong opioid. Remove the buprenorphine patch and after a period of at least 12 hours commence the modified release preparation. (e.g. Zomorph®, MST®, Oxycontin® or Palladone SR®)
- 24 hourly modified release oral strong opioid. Remove the buprenorphine patch and after a period of at least 12 hours commence the modified release preparation. (e.g. MXL[®])
- Strong opioid via a continuous subcutaneous infusion. Remove the buprenorphine patch and after a period of at least 12 hours commence the subcutaneous infusion.

3.3 Transdermal Buprenorphine in the last hours or days of life

- ➤ Patients who are in the last hours or days of life should continue to have the buprenorphine patch changed every 7 days (Butrans^{®)} or 4 days (Transtec^{®)} unless they have toxic opioid side effects. It **should not** be discontinued. ¹⁰ [Level 4]
- ➤ All patients should be prescribed an "as required" subcutaneous strong opioid e.g. morphine. ¹⁸ [Level 4]
- ➢ If a patient requires two or more doses of a strong opioid for breakthrough pain over a 24 hour period and those doses are effective, consider commencing a continuous subcutaneous infusion (CSCI) with a dose equal to the sum of the PRN doses over the preceding 24 hours. The PRN dose may need adjusting to take into account the total opioid dose (i.e. transdermal buprenorphine+ CSCI strong opioid)¹¹0 [Level 4]
- ➤ The CSCI should be used in addition to the buprenorphine patch, which continues to be changed every 4 or 7 days dependent on the brand. ¹⁰ [Level 4]

3.4 Prescribing breakthrough medication for patients using transdermal Buprenorphine

- ➤ It is appropriate to use pure opioid agonists such as morphine for breakthrough pain without loss of analgesia. Antagonism does not occur at normal clinical doses.

 [Level 2+]
- ➤ Appropriate breakthrough medication should be prescribed using an equi-analgesic table to determine the correct dose. ¹⁴ [Level 4] (See Table 1.3)

Table 1.3 Equi-analgesic Table for Transdermal Buprenorphine [Level 4]

This table is a guide only. The prescriber is ultimately responsible for his/her own actions. Equi-analgesic doses are difficult to ascertain due to wide inter-patient variations, drug interactions and non-interchangeability of products. Initial dose conversions should be conservative. It is preferable to under-dose the patient and use breakthrough medication for any shortfalls.

Transtec [®] Patch 96 hourly	Morphine PO 4 hourly	Morphine SR PO BD	Butrans [®] patch weekly
	2.5mg -5 mg	10mg -20 mg	10 micrograms
	5mg -10 mg	20mg -30 mg	20 micrograms
35 micrograms	10mg -15 mg	30mg -50 mg	
52.5 micrograms	15mg -25 mg	50mg -75 mg	
70 micrograms	20mg -30 mg	60mg -100 mg	

Note: Buprenorphine equi-analgesia with oral morphine varies in the literature from 75:1 to 115:1. The values in the table reflect this.

4. STANDARDS

- 1. All patients prescribed a transdermal opioid should have the reason clearly documented in the case notes. ¹⁸ [Grade D]
- 2. All patients receiving transdermal opioids should have an appropriate strong opioid prescribed for breakthrough analgesia.¹⁸ [Grade D]
- 3. Each care setting should have a policy for the safe administration of transdermal opioids. ¹² [Grade D]
- 4. Patients who are treated with transdermal opioid patches for pain control should have these continued in the dying phase. [Grade D]
- 5. A patient who has a transdermal opioid patch in situ in the dying phase, and who requires two or more doses of a strong opioid for breakthrough pain over a 24 hour period, should be commenced on an appropriate dose of a strong opioid via a continuous subcutaneous infusion over 24 hours. 10,19 [Grade D]

5. REFERENCES

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